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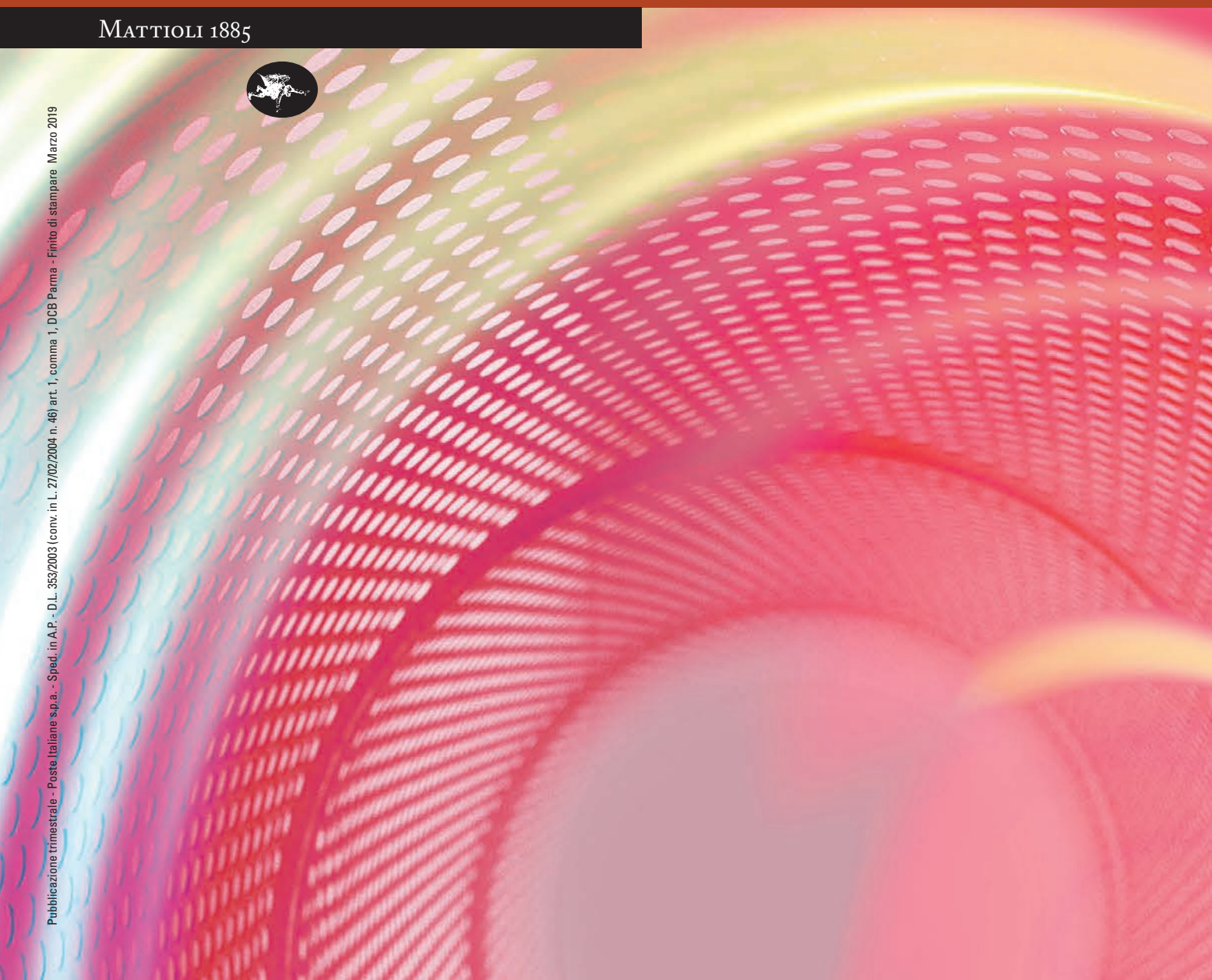

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Review

Contact dermatitis due to transdermal therapeutic systems: a clinical update

Paolo Romita[1], Caterina Foti[1], Gianfranco Calogiuri[2], Stefania Cantore[3, 4, 5], Andrea Ballini[3, 4], Gianna Dipalma[3, 4, 5], Francesco Inchingolo[3, 5]

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Summary. Transdermal therapeutic systems (TTS) have become a popular method of drug delivery because they allow drugs to be delivered in a rate-controlled manner, avoiding first-pass metabolism and the fluctuating plasma concentrations encountered with oral medications. Unfortunately, TTS may provoke adverse skin reactions as irritating contact dermatitis and allergic contact dermatitis: TTS seem to be ideally suited to produce sensitization because they cause occlusion, irritation, due to the repeated placement of the allergen in the same skin location. Since TTS consist of an adhesive, an active pharmaceutical drug and enhancing agents, sensitization may develop owing to one of these three agents. The purpose of this manuscript is to review known responsible allergens of contact dermatitis due to TTS. (www.actabiomedica.it)

Key words: allergic contact dermatitis, drugs, excipients, rubber, transdermal therapeutic systems

Introduction

Transdermal absorption of pharmacological active ingredients has been carefully studied in the last 40 years as the skin, being the most extended and most easily accessible organ of the body, represents an attractive alternative to oral administration. Transdermal administration is of easy execution, compared to the intramuscular or intravenous methods, and it assures a constant absorption of the drug during the day, which is preferibile to the pulsed bioavailability caused by oral adminstration. Moreover, transdermal administration often succeeds in obviating the annoying and badly tolerated gastrointestinal side effects, typical of oral admnistration.

Beginning from the introduction of the first transdermal patch made of scopolamine, in 1979, successively numerous transdermal systems were created using several active principles. Currently, the most used ones are made of scopolamine, estrogens, nitroglycerin and clonidine. The drug, in order to be absorbed through the skin, must possess such properties to cross the corneous layer. The permeation of the active principle through the corneous layer is, in fact, the limiting phase of such modality of administration, since it consists of the processes of partitioning and diffusion through the lipophilic and then hydrophilic phase of the superficial layers of the epidemis, which are opposed to the last passage of diffusion in the capillary net of the derma. A candidate drug for transdermal transport must therefore possess both lipophilic and hydrophilic characteristics, so that the moderated hydrophilicity does not prevent the partition through the lipid-rich corneous layer, and the moderated lipophilicity does not obstacle the diffusion in the lower watery layers of the epidermis and beyond. In order to estimate the partitioning of a compound through the skin, the coefficient of division in octanol/water is used (1).

The application of transdermal patches is not free from disadvantages. In fact, irritant contact dermatitis (ICD) provoked by the adhesive, the active principle or the excipients may often appear, and also allergic contact dermatitis (ACD), consequent to sensitization to the administered active principles.

Methods

The literature was searched via the Medline/PubMed database (http://www.ncbi.nlm.gov/pubmed) combining transdermal therapeutic systems and transdermal patches with contact dermatitis and skin reaction.

Allergic contact dermatitis and TTS

ACD is a type IV cell-mediated hypersensitivity reaction that usually presents with lesions that can vary from erythema and papules to vesicles and bullae. ACD to TTS can be caused by all the components of TTS that are an active drug, an adhesive and excipients; moreover, different kinds of TTS are currently available. Among these, the most common are matrix TTS that are characterized by a single-layer adhesive, active drug and other components that get in contact with the skin. Other kinds of TTS are local-action transcutaneous TTS and reservoir TTS: the former is similar to matrix TTS, except for a non-woven polyester backing that supports the active drug; the latter is characterized by a rate-controlling membrane that releases the active drug contained in a depot. Nowadays, ACD to TTS can be considered rare; conversely, irritant reactions are more common. Patients should follow simple recommendations to avoid these latter: TTS should be applied daily by rotating the application site and should be removed carefully; moisturizers and gentle cleansings are recommended, topical corticosteroids should be used only if necessary (2, 3). Irritant contact dermatitis to TTS may present with skin lesions similar to ACD ones (table 1). For this reason, patch testing is required in all cases of skin reaction onset after application of TTS.

ACD to TTS

Nitroglycerin

The use of transdermal patches made of nitroglycerin represents a common antianginous treatment. In literature, numerous cases of ACD to transdermal patches made of nitroglycerin are reported (4-8). Kounis et al. (9) have demonstrated that the reactions to such patches are mostly irritative and only minimally allergic. In the suspicion of ACD to patches made of nitroglycerin, it is indispensable to carry out a patch test with the active principle in order to define the type of reaction (9).

Scopolamine

Scopolamine, also known as hyoscine, is used for the prevention of the symptomatology of motion sickness, generally in the form of transdermal patches to be

Table 1. Characteristics of ICD and ACD from TTS (modified from (2))

	ICD	ACD
Morphology	Erythematous-papular/vesicular/bullous lesions sharply circumscribed to the area of contact.	Erythematous-papular/vesicular/bullous lesions (vesiculation is more typical) circumscribed to the area of contact but with ill-defined limits. Dissemination of the lesions can occur
Symptoms	Burning, stinging, itching	Burning, stinging, itching
Resolution	Characterized by decrescendo phenomenon following patch removal; typically within 48 h	Characterized by crescendo phenomenon. Resolution is slower than ICD
Clinical diagnosis	On the basis of lesions and clinical course	Patch testing with the individual components of the TTS

applied for 72 hours behind the ear. Numerous cases of ACD due to such patches are reported in literature (10-12). Gordon et al. have evidenced that 10% of the crew of a ship, formed by 164 people, all using transdermal patches with scopolamine, showed eczematous reactions in the application area of the support (13). These patients, who underwent a patch test with the same transdermal patch, without the active principle, did not show any positivity, suggesting that scopolamine was responsible for the allergic reaction.

Nicotine

Transdermal patches made of nicotine are used as an aid to the interruption of the smoking habit. Although nicotine is a weak sensitizer, when transmitted through transdermal patches, it can provoke ACD (14-18).

Testosterone

Transdermal devices made of testosterone are used in clinical practice for the treatment of dysfunctional pathologies, correlated to the deficit of the hormone. Very rarely, also this drug can provoke ACD cases (19-21). However, the prevailing cutaneous reactions to such patches turn out to be irritative (17).

Estradiol

Commonly used for treating the symptoms of menopause, transdermal patches made of estradiol have been reported as a cause of sensitization towards such hormone (22-26). Moreover, Lamb and Wilkinson have assumed that the sensitization to topically applied estradiol can represent a risk factor for the development of ACD to corticosteroids (23). However, patients sensitized to estradiol seem to be able to take the same active principle orally, without the appearance of any cutaneous reactions.

Clonidine

Clonidine, a drug usually taken orally for the treatment of hypertension, can be successfully transmitted through transdermal patches kept in the area for a period of application of 7 days, which is a longer period, compared to the other active principles. Even if clonidine does not seem to possess a high sensitizing capability, probably due to the long period of application, the ACD for such drug is rather frequent (27-29). Maibach et al. (30) have pointed out the role of transdermal administration in causing allergic sensitization by comparing a group of 103 patients, who underwent a topical application of clonidine 9% in vaseline, with a group of 92 patients, who underwent the application of transdermal patches with clonidine. The results showed that after 3 weeks 4.3% of patients belonging to the 2nd group turned out sensitized to clonidine, while no case of sensitization was found among the patients in the 1st group.

Rotigotine

Rotigotine is a drug used for the treatment of the first stage of Parkinson's disease. The treatment includes the application of a patch containing 2 mg of the active principle every 24 hours, paying attention to reapply it each time in a different place. Among the most common side effects, there are nausea, sleepiness, dyspepsia and asthenia. Adverse cutaneous reactions are considered rare; however, during the last few years two cases of ACD due to transdermal patches containing rotigotine were reported in literature (31, 32).

Rivastigmine

Rivastigmine is a cholinesterase inhibitor, used to improve cognitive functions in dementia forms of Parkinson's disease and Alzheimer's disease. Rivastigmine has been commercialized since 2007 also as a transdermal patch, in order to eliminate the gastrointestinal side effects of oral administration (vomiting, nausea and diarrhea). Recently, some cases of adverse reactions to transdermal patches made of rivastigmine were reported (33-35) (Fig. 1). Moreover, Makriset et al. (35) have studied the usefulness of the desensitizing therapy in a patient with Alzheimer's dementia, who had developed ACD to the rivastigmine contained in the transdermal patch used for the therapy. In this case it was possible to demonstrate how, once an adequate desensitizing therapy was carried out, it was possible

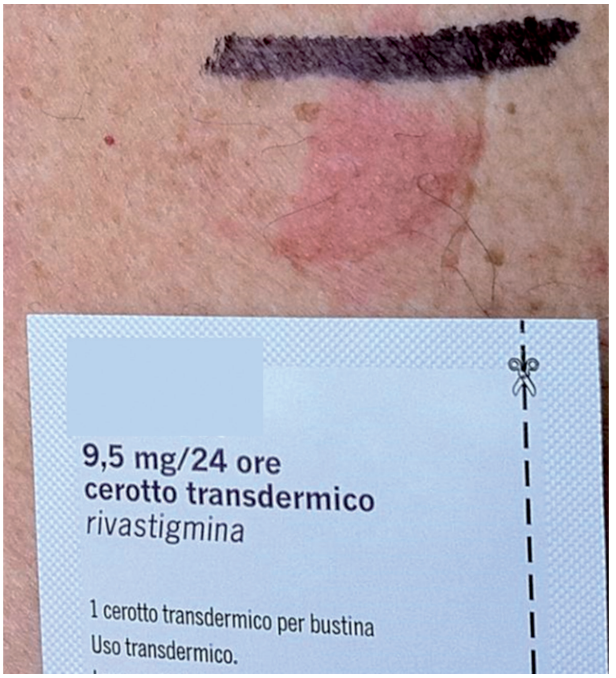

Figure 1. Positive patch test to a transdermal therapeutic system containing rivastigmine

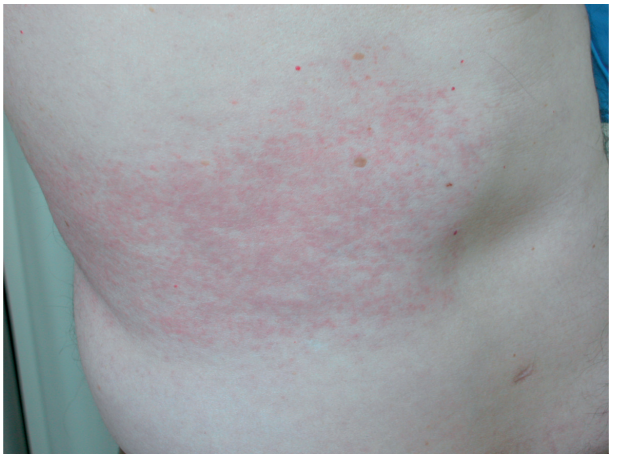

Figure 2. Allergic contact dermatitis to a transdermal therapeutic system with flurbiprofen for lumbar pain. The culprit allergen was menthol, an excipient used to facilitate the penetration of the active drug

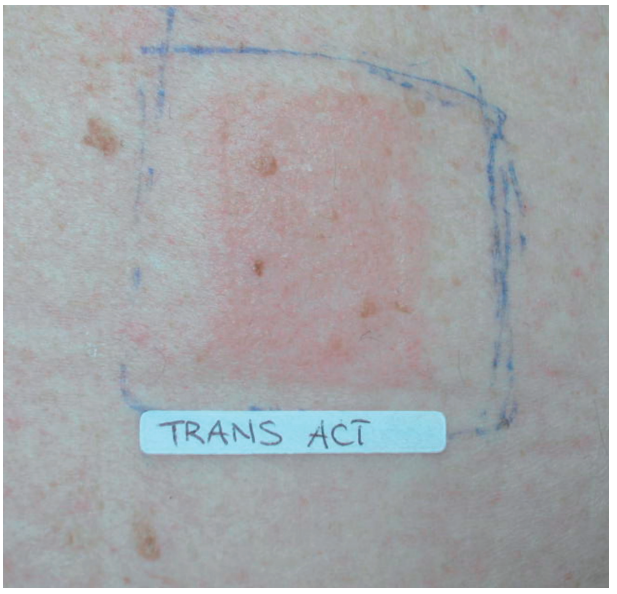

Figure 3. Positive patch test to a transdermal therapeutic system caused by an excipient (menthol)

to administrate rivastigmine orally once again to patients previously sensitized because of the contact with the same active principle contained in transdermal patches.

Adhesives and excipients

ACD to transdermal patches, besides the active principles and excipients they contain, can also be caused by the adhesive substances that guarantee the adhesion of the support to the skin: rosin, rosin esters and silicone derivatives. In case of ACD to medicated patches, it is important, therefore, to carry out a patch test with a placebo patch, that is, a support identical to that constituting the transdermal system, devoid of the active principle, in order to verify the eligibility of the support in the determination of the reaction (9, 10, 36, 37).

Among the excipients responsible for ACD to patches, menthol is reported (Fig. 2, 3). An active principle contained in mint oil, it is a strongly aromatic, bitter compound, known for its anti-inflammatory, analgesic and vasodilatory effects. In the light of its properties, it is used in transdermal systems in order to facilitate the penetration of the active principle they contain. Menthol is a weak sensitizing agent and only very rarely it provokes ACD. However, cases of allergies due to contact with menthol can likely occur as a consequence of the metabolization of the menthol in mentone, a more powerful sensitizing agent. In literature, cases of ACD provoked by the use of cigarettes,

tooth-pastes and scents made of menthol are reported (38), and also subsequent to the use of patches containing menthol as an excipient (39).

Conclusion

In conclusion, the majority of skin reactions to TTS are irritant reactions that self-heal once the exposure to the patch is avoided. On the basis of the reports on sensitization to TTS, there is sufficient evidence to confirm that such therapeutic systems can also cause ACD, being an ideal environment to elicit contact allergy. Skin reactions are usually mildly characterized by erythematous-vesicular lesions that heal in a few days, once exposure to patches is avoided, thanks to topical therapy with corticosteroids. Rarely, systemic skin reactions can be observed. Patients should be educated to properly use them and immediately seek evaluation by dermatologists in case of suspected skin reactions. ACD to TTS can be caused by drugs, or excipients and adhesives. Patch tests should be therefore performed with the same TTS, with active principles and with excipients, to perform a correct differential diagnosis versus irritant ICD. Further studies in this area are required as TTS become more widespread among several diseases.

Conflict of interest: None to declare

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Review

Diagnostic techniques and multidisciplinary approach in idiopathic granulomatous mastitis: a revision of the literature

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Summary. Idiopathic granulomatous mastitis (IGM) is a chronic benign inflammatory disease of the breast that may mimic breast cancer. It is most common in parous young fertile women, although it can occur in nulliparous women and in men. IGM is an idiopathic disease due to the influence of some environmental factors in genetically predisposed subjects. Several pathogenic hypothesis have been proposed in the last years (autoimmune, hormonal, infective genesis). IGM presents as a painful palpable mass located in one of the two udders. The skin is usually normal but could present signs of inflammation with or without lymph nodes involvement. Ultrasonography, mammography, magnetic resonance can be diagnosed an IGM, but pathognomonic radiological signs has not yet reported in literature. Biopsy findings show granulomatous lesion centered on the breast lobule, as in granulomatous mastitis induced by tuberculosis or sarcoidosis. The aim of this review of literature is to verify the development of new advanced diagnostic techniques and multidisciplinary approach for this condition. In the last years innovative approaches have modified IGM diagnosis and therapy, avoiding surgery in most of cases, introducing a more conservative medical approach based on recent etiopathological hypothesis. (www.actabiomedica.it)

Key words: breast cancer, chronic benign inflammatory disease, idiopatic mastitis

Introduction

Idiopathic granulomatous mastitis (IGM), also known as idiopathic granulomatous lobular mastitis, is a chronic benign inflammatory disease of the breast with unknown etiology. It was first described by Kessler and Wolloch in 1972 (1-10).

IGM is most commonly seen in parous young women, often within a few years of pregnancy, although it can occur in nulliparous women and in men (6, 11, 129.

Although most articles have mentioned that IGM is rare, numerous recent studies with large number of patients, that are continuously published especially in developing countries, make a doubt about the rarity of IGM. This could be due to under-diagnosis or misdiagnosis or due to a possible increasing prevalence among developing nations (3).

There is no increased risk of subsequent breast cancer in IGM patients, but, clinically and radiologically, it may mimic breast cancer and awareness of surgeons, pathologists, and radiologists is essential to avoid unnecessary mastectomies (14, 15). For these reasons, although IGM is considered a benign condition, most of studies has been concentrated on disease management, which is still very controversial (2, 16-18).

Our review has the aim to verify how, in the last 30 years, the development of new advanced diagnostic techniques and multidisciplinary approach, have modified IGM diagnosis and therapy, avoiding surgery in most of cases.

In this work, literature was reviewed from 1972, when IGM was discovered, until now. In general, reported cases were represented by young adult fertile female patients (mean age 35 years), multiparous. A few percent of cases was represented by over 50 patients. In rare cases, IGM was described in an 11-year-old female patient, in an 80-year-old woman and in some male patients. Interestingly, in almost all reported cases, patients delivered five year before, and interrupted breastfeeding one year before disease diagnosis (10-12, 16, 19). Usually, IGM presents as a painful palpable mass located in one of the two udders. The skin is usually normal but could present signs of inflammation with or without lymph nodes involvement. Diagnosis is bases on ultrasonography (US), mammography, magnetic resonance (MR), fine needle aspiration cytology (FNAC), fine needle ago-biopsy (FNAB) (20-24). In this review, IGM medical and surgical treatment options were evaluated (16-18, 25-28).

Discussion

IGM represents a benign inflammatory disease of the breast. It is an idiopathic disease due to the influence of some "environmental stimulus" in genetically predisposed subjects. Some authors proposed that a local granulomatous inflammatory response to epithelial damage describes the pathogenesis of IGM (29). However, the trigger in the development of the epithelial damage remains unknown. Although several triggers have been proposed, the etiologic association of neither of them has been documented with IGM. It has been postulated that extravasated lactational secretions may be responsible for eliciting a granulomatous inflammatory response (30).

To date, three main hypotheses have been postulated to explain IGM (31):

1) autoimmune genesis;
2) infectious disease;
3) hormonal disorder.

Currently, the most accredited hypothesis recognizes IGM as an *autoimmune disease*; in many studies, some IGM patients could be also affected by erythema nodosum and arthritis, a lymphocyte-rich immunohystochemicl pattern, and present a good clinical response to steroid or immunosuppressant administration (32).

Hormonal disorder hypothesis rises from the evidence of high prolactin serum levels in IGM patients; furthermore, prolactin could affect disease severity and prognosis and increase disease relapse rate. IGM presents frequently in fertile female patients, especially in those who use oral contraceptives or are near to delivery or breastfeeding. However, IGM is uncommon during pregnancy. To date, few are hyperprolactinaemia-related cases and new studies should be aimed to clarify the role of this hormone in IGM pathogenesis and analyse its prognostic significance to better address treatment (15). Cases of IGM have been recognized in patients submitted to Selective Serotonine Reuptake Inhibitors (SSRI). Interestingly, it has been reported that antipsychotic therapy can be associated with hyperprolactinemia and that the onset of breast enlargement can occur during chronic antidepressant therapy (33, 34), suggesting a possible side effect of SSRI. Maione et al demonstrated that SSRI could exert a perturbation in dopamine secretion, counteracting its role in repressing prolactin gene expression, leading finally to hyperprolactinemia and associated IGM. In this regard, it seems worthy of noting the findings about a functional crosstalk between serotonin and dopamine receptors (35). In a study on 18 patients, Ehran et al. used prolactin serum levels to address the IGM treatment: they performed surgery + steroids when IGM relapsed and prolactinaemia was in normal range, whereas they used medical therapy alone when prolactin serum levels where higher (34).

Infectious hypothesis is not supported by a causality relation between IGM and infectious agents; however, a granulomatous inflammation is typical in response to specific strains of bacteria, fungi and parasites. Corynebacterium is the most recognized bacterium of the breast granulomatous diseases, unfortunately its etiologic role in IGM has not been yet established. Some cases of IGM in developing Countries could be associated to tuberculous bacterial infections (36-39).

IGM may present as a peripheral inflammatory breast mass; it can also present as multiple simultaneous areas of peripheral (and rarely central) infection with abscesses and/or overlying skin inflammation and ulceration (2, 4-8). Nipple retraction, sinus formation, peau d'orange-like changes, and axillary adenopathy may accompany these findings (1, 11, 19, 38). Some patients have extramammary signs and symptoms, while others have disease confined to the breast(s). IGM patients could develop repeated abscesses over weeks to months. These findings may be confused with breast abscess or malignancy (4).

There are not pathognomonic signs on US, mammography and MR. Irregular tubular hypoechoic lesions, lobulated hypoechoic masses, parenchymal irregularities without a mass, fistulisation to skin or axillary lymphadenopathies, could be recognized on US. Typically, US examination demonstrates a solid mass, often with one or more abscesses. Multiple irregular hypoechoic masses and collections with tubular connections with fingerlike aspects and skin fistulae in patients with breastfeeding history, suggests IGM rather than carcinoma (39).

A focal asymmetric opacity, enhancement of density, diffuse enhancement of fibroglandular mass density, an irregular mass, ellipsoid mass, retraction and heterogeneity of breast parenchyma, could be identified on mammography. Cases with micro-calcifications are confused with cancer (40, 41). In IGM, radiology findings are nonspecific and mammography may be easily suggestive of malignancy (39, 41-45).

A pathognomonic imagination for IGM on MR has not yet been reported in the literature. Yildiz et al. described T2-weighted hyperintense masses in 4 out of affected patients but no conclusions were reached because of the short amount of cases (39).

Overtime, excisional biopsy has acquired a diagnostic and therapeutic role. Biopsy findings typically show granulomatous lesions centered on the breast lobule (14, 23, 24). The biopsy should be sent for acid-fast bacilli and fungal stains in addition to histopathology; other diseases such as tuberculosis or sarcoidosis may induce a granulomatous mastitis. However, biopsy is the gold standard for its diagnosis and should be taken in any patient even with a mild suspicion of cancer (20, 46). On the other side, some Authors have introduced a more conservative medical approach, against a more or less aggressive surgical approach (16-18, 25, 27, 28). Due to its possible autoimmune aetiology, immunosuppressors have been proposed for the treatment of IGM. There is no role for steroid use; systemic glucocorticoid therapy and local depot steroid injections have been used for the treatment of IGM, although there are no randomized controlled trials that demonstrate their efficacy (4, 26, 42, 47, 48). Altintoprak et al reviewed the effect of topical steroids in patients with IGM characterized by skin changes (49). Methotrexate is another option (31, 50-53). In the experience of Sheybani et al., 16 out of 22 patients (72.7%) suffering from IGM took advantages from a combined treatment of prednisone and methotrexate (31). Discontinuation of these drugs has been associated with rebound inflammation.

IGM is a self-limiting inflammatory condition but commonly takes 9 to 12 months to resolve (54), that is why its therapeutical management is still controversial: recent studies showed that expectant conservative management with no medical or surgical treatment resulted with high rates of spontaneous remission in IGM patients as well (54-56). Therefore, there exists different valid management options for these patients (56, 57). When considering the high success rates of nonsurgical modalities for IGM, it seems that surgical treatment might be reserved for those in whom other modalities are not effective or who ask to have a rapid amelioration (49).

Conclusion

To date, IGM has lost its surgical identity (except for rare cases of relapsing or complicated disease) and it could be considered a medical condition. Taking into account the three main aetiological hypotheses, the treatment can be oriented to different targets (immune system, endocrine system or infectious agents) in a multimodal fashion. Therefore, involved drugs vary from immunosuppressors to steroids to those medications which interact with endocrine system. Because of its multimodal and complex therapeutic management, IGM has been identified as a complex, multifactorial disorder that should involve different specialized

figures, such as endocrinologists, radiologists, immunopathologists, infectivologists. Only addressing the right aetiology it is possible to address the right treatment, avoiding invasive decisions and reducing hospital stay and social costs.

Conflict of interest: None to declare

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Computer-assisted surgery in total knee replacement: advantages, surgical procedure and review of the literature

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Summary. *Introduction:* Total knee replacement (TKR) is one of the most frequent orthopaedic procedures performed every year. At the same time 20% of patients who underwent TKR are not satisfied with the outcome. The reasons are unknown; we think that a mechanical alignment beyond 3° of varus-valgus can represent the most important cause of failure of TKR and consequently patient dissatisfaction. *Materials and Methods:* Neutral mechanical alignment is the main goal in every TKR: this can be achieved through different tools, such as extramedullary and intramedullary guides, patient-specific instrumentation (PSI) and computer-assisted surgery (CAS). The aim of this review is to compare the different alignment techniques in TKR, to describe CAS procedure and CAS results in recent literature. *Results:* Regarding the intramedullary guide, there is an increased risk of fatty embolism; there are great limitations on its use, or even impossibility, in cases of bone deformity and sequelae of trauma. Regarding the extramedullary guide, it becomes more difficult to use in cases of great obesity or increased soft-tissue volume around the tibia. PSI for TKR has been introduced to improve alignment, reduce outliers, operation time and the risk of fatty embolism by avoidance of intramedullary canal violation. Recent randomized controlled trials and meta-analysis proved no advantage of PSI in improving mechanical axis and implant survivorship. *Discussion:* CAS has provided to be a useful tool in assisting the surgeon to achieve more accurate post-operative mechanical axis through precise and reproducible bone cuts and ligament balancing. Two meta-analyses definitively proved that CAS technique improves mechanical axis and implant survivorship and one recent meta-analysis demonstrated that CAS provides better mechanical alignment and higher functional scores at short-term follow-up. (www.actabiomedica.it)

Key words: computer, TKR, knee, prosthesis, robot, knee replacement, technology

Introduction

Total knee replacement (TKR) is one of the most frequent orthopaedic procedures performed every year. The number of TKRs carried out in the United States is estimated to increase by 673% before 2030 (1). At the same time 20% of patients who underwent TKR are not satisfied with the outcome (2, 3). The reasons are unknown but we think that a mechanical alignment beyond 3° of varus-valgus can represent the most important cause of mechanical failure of a TKR and consequently patient dissatisfaction.

Restoring the mechanical axis in TKR is a key factor to optimize the load sharing and prevent the eccentric loading through the prosthesis, which could avoid implant loosening, instability or early failure (4, 5). The concept of mechanical axis was introduced by Insall et al. (6) in 1985: it requires that both femoral and tibial cuts must be perpendicular to the mechanical axis of the femur and tibia. The purpose is to create equal load distribution on the new joint line.

Although Parratte et al. (7) found that a post-operative mechanical axis of 0° did not improve the rate of survival 15 years post-operatively, several authors

suggested that restoration of a neutral mechanical axis improves durability following TKR (8-10).

Nowadays, neutral mechanical alignment is considered the "gold standard" and the primary aim in every TKR. This can be achieved through different surgical techniques, such as extramedullary and intramedullary guides, patient-specific instrumentation (PSI) and computer-assisted surgery (CAS), each one with advantages and disadvantages. Regarding the intramedullary guide, there is an increased risk of fatty embolism (11), there are great limitations on its use, or even impossibility, in cases of bone deformity, sequelae of trauma or presence of osteosynthesis material that obliterates the medullary canal. Regarding the extramedullary guide, it becomes more difficult to use in cases of great obesity or increased soft-tissue volume around the tibia. PSI for TKR has been introduced to improve alignment, reduce outliers, operation time and the risk of fatty embolism by avoidance of intramedullary canal violation. Recent randomized controlled trails and meta-analysis proved no advantage of PSI in improving mechanical axis and implant survivorship (12, 13).

In the late 1990s, two teams, one led by Picard and Leitner in France (14), the other led by Krackow in Buffalo, New York (15), concurrently developed the technology for modern imageless computer-assisted TKR. Approved by the FDA in 2001, these systems utilize infrared communication to track the spatial positioning of patient anatomy and surgical equipment. The system's subsequent calculations allow the surgeon to evaluate bony cuts prior to their execution and also allow the surgeon to check these cuts after they are performed.

Different recent meta-analyses (references) has provided CAS to be a useful tool in assisting the surgeon to achieve more accurate post-operative mechanical axis through precise and reproducible bone resection and ligament balancing (16). CAS for TKR has been reported to provide more precise component placement in coronal, sagittal and rotational alignment; more accurate bone cuts and better restoration of coronal limb alignment (17-19). In a meta-analysis of 29 studies comparing CAS with conventional technique, Mason et al. (20) demonstrated 90.4% of patients with a femoral varus/valgus alignment within 2° of the femoral mechanical axis (versus 65.9% in the conventional group) and 95.2% of patients with a tibial varus/valgus alignment within 2° of the tibial mechanical axis (versus 79.7% of the conventional group).

Operative technique

Since 1998, in our department, different systems based on computer-assisted navigation systems without use of computed tomography (CT) have been used in >1.000 joint replacements (knee and hip), and according to these navigation systems, all data have been acquired in the operating theater during the procedures.

Step 1. Prepare the surgical field according to your preferences. However, the patient should be in supine position just with the feet outside allowing the knee to be easily flexed at 90°. Place a support by the side of the thigh to maintain lower limb position even with the knee flexed. The surgeon is supposed to be in front of the patient and able to check the mechanical axis constantly.

Step 2. We always position a metal locator in the center of the hip as further limb alignment reference during the surgery in order to keep a constant check on axial adjustment and on the correct positioning of the prosthetic femoral component (a x-ray of the hip should give you the position of the metal locator).

Step 3. With the patient under anesthesia, the surgeon should evaluate clinically the limb deformity and how much can be reduced manually acting on the knee.

Step 4. The skin incision with the limb flexed at 90° should not exceed 12–14 cm in a median or paramedian medial direction. Then the surgeon should perform knee arthrotomy and should evaluate all compartments and confirm or not surgical indication.

Step 5. Insert the screws for the infrared reflecting diodes (LED) of the computer scanner with tiny skin incision of <1 cm. One diode should be located on the femur and one on the tibia both 10 cm away from the joint line. Proceed with the lower limb data acquisition using the computer. Just moving the limb and using mathematical models, the navigator determines the axis, which goes through the rotation center

of the femoral head, the center of the knee and ankle. Acquire the deepest point in the more damaged tibial plateau with a mobile pointer, the center of the tibial plateau, both posterior femoral condyles, the superior femoral cortex, and medial and lateral epicondyles, always according to the indications on the screen step by step.

Step 6. With the data reported on the screen, the surgeon can recalculate with numbers the deformity and how much can be corrected. Data processing empowers the system to produce onscreen information related to the mechanical function in frontal and lateral projection within the entire given range of movement (Figure 1). It suggests implant size, amount of bone according to the deformity and tridimensional implant alignment.

Step 7. The deformity should always be reducible manually; otherwise, the surgeon should proceed with a slight release of the ligaments under the direct control of the system.

Step 8. Position the tibial cut guide and connect with a mobile diode to the computer. The height of the resection is based on the concept of "minimum bone cut": this is a simple rule we have been experimented since 2001. The amount of bone to be resected is given by the difference between prosthesis thickness and arthritic knee deformity. For example, if a patient had a valgus deformity of 8° and assuming a total thickness prosthesis of 19 mm, the planned minimum bone to be resected is 11 mm (19-8=11. Figure 2).

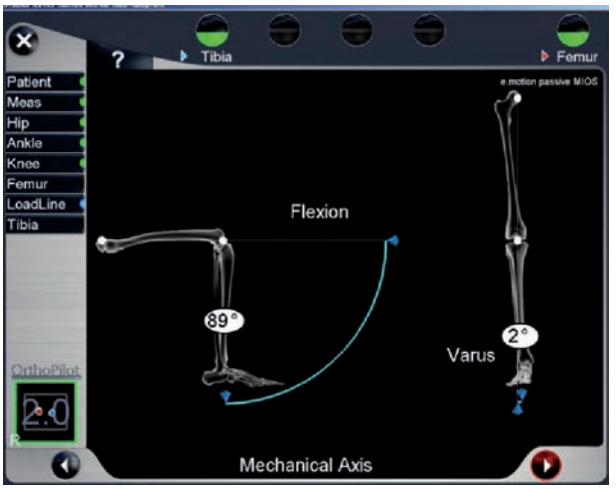

Figure 1. Flexion and extension mechanical axis

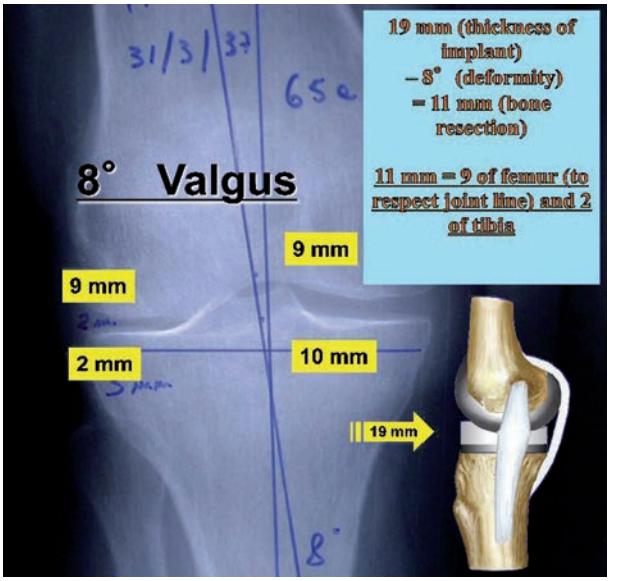

Figure 2. Eight degrees valgus knee. The minimum bone cut: the entity of bone resection is given by the difference between prosthesis thickness and axial deviation angle. We have to cut 9 mm of femur because it drives the joint line

Then you should plan tibial cut orientation (varus–valgus) and checked it on the display (Figure 3). The slope will be according to the implant slope. After fixing the guide, use a blade for the horizontal cut.

Step 9. The femoral cuts have been already planned according joint space in flexion and extension,

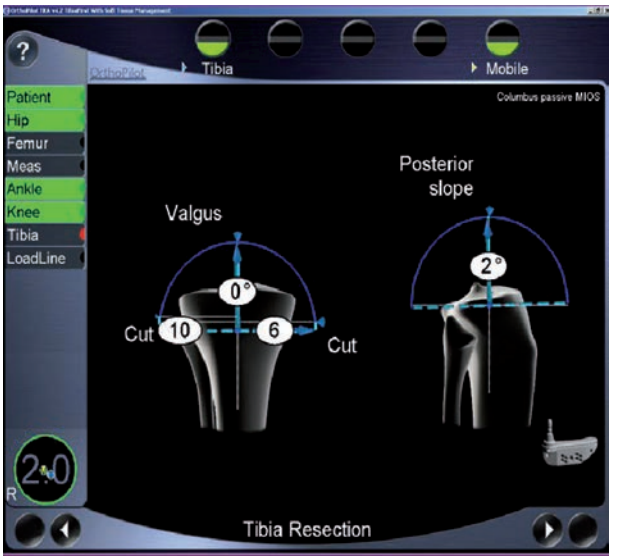

Figure 3. Navigated tibial cut

both in the medial and lateral compartment, using spreaders (Figure 4).

If gap balancing is not correct, you have to plan femoral cuts, rotation of the femoral component, size of prosthesis and polyethylene thickness in order to equalize the gaps (Table 1). In difficult cases with deformities >10 degrees, you have to perform ligament release to equalize the gaps. In impossible cases, you have to use hinge prosthesis.

Step 10. Then you perform distal femoral cut and check it on the screen. Position the chamfers of the corresponding size, with adequate femoral rotation, planned and checked on the screen. Perform the remaining cuts (Figure 5).

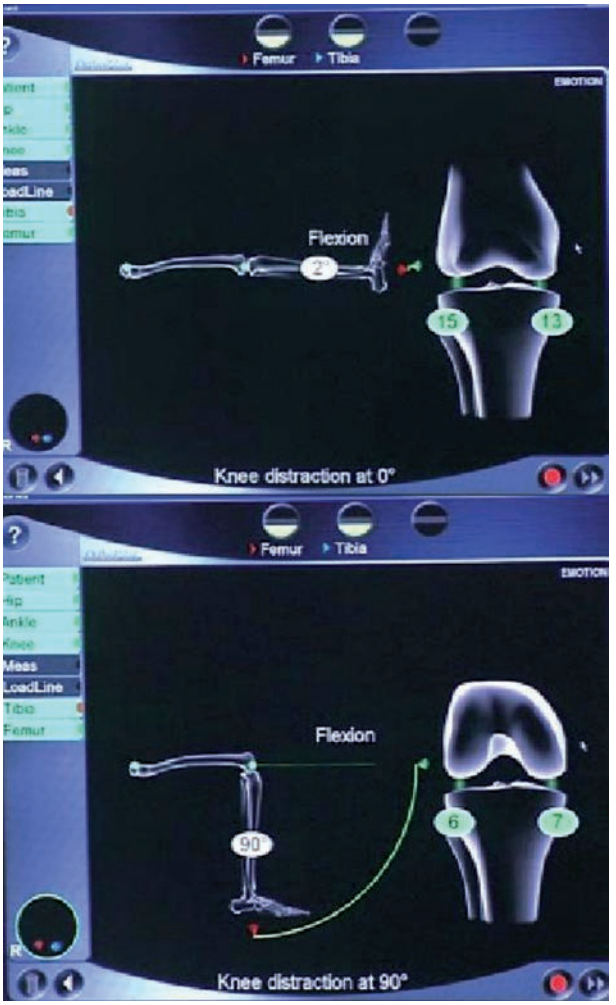

Figure 4. Gap balancing in extension (0 degrees) and flexion (90 degrees)

Step 11. Position the tibial and femoral trial components with polyethylene thickness, check the mechanical axis and the ligament balance in full range of motion, always reading the values and the morphology of the inferior limb in motion on the computer screen.

Step 12. We first implant the tibial component and then the femoral one; the limb should be extended and compressed securely against the chest of the operator to complete the operation. Final recording of data is performed for the personal computerized patient file charts.

Step 13. Wound suture and post-operative x-ray. This is the only check for those who do not use CAS.

Discussion

Several studies have reported significant difference in implant survivorship when a traditional safe zone of 0-3 degrees was used to define aligned versus malaligned knees respect to a neutral mechanical axis. For example, Berend et al. (8) reported a statistically increased rate of failure of tibial components positioned in >3.9° of varus. Ritter et al. (9) found an increased rate of failure in knees with a femoral component in >8° of anatomical valgus and in those with a varus tibial component relative to the tibial axis. Collier et al. (10) reported a significantly greater loss of thickness of polyethylene in the medial compartment when the limb was aligned in >5° of varus.

On the other hand, some authors have found no statistically significant differences in survivorship between aligned versus malaligned knees respect to a neutral mechanical axis. One of the most influential studies is reported by Parratte et al. (7), who retrospectively reviewed the clinical and radiological data of 398 TKRs. They found that a post-operative mechanical axis of 0° did not improve the rate of survival 15 years post-operatively and stated that the description of alignment as a dichotomous variable (aligned versus malaligned) provided little value in regards to durability. Neverthless, they concluded that "until additional data can be generated to more accurately determine the ideal post-operative limb alignment in individual patients, a neutral mechanical axis remains a reasonable target and should be considered as the standard for

Table 1. Gap balancing algorithm in TKR

TKR	Extension space balanced	Extension space is thight	Laxity in extension space
Flexion space balanced	PERFECT	Release posterior capsule Increase distal femoral cut with the same polyethylene thickness Removal of osteophytes and posterior condyles	Distal femoral wedges Increase tibial slope with higher polyethylene thickness Decrease femoral size component with higher polyethylene thickness
Flexion space is thight	Undersize femoral component with the same poly Release PCL in CR implant Increase tibial slope with the same poly thickness	Increase tibial cut with the same polyethylene thickness	Decrease femoral size with higher polyethylene thickness Distal femoral wedges and increase distal cut and/or tibial slope
Laxity in flexion space	Increase tibial cut and decrease tibial slope with higher polyethylene Increase femoral size with the same polyethylene thickness Increase distal femoral cut with bigger polyethylene	Increase distal femoral cut with bigger polyethylene thickness Increase femoral size component and/or augmentation with posterior femoral wedges with the same polyethylene thickness	Bigger polyethylene thickness

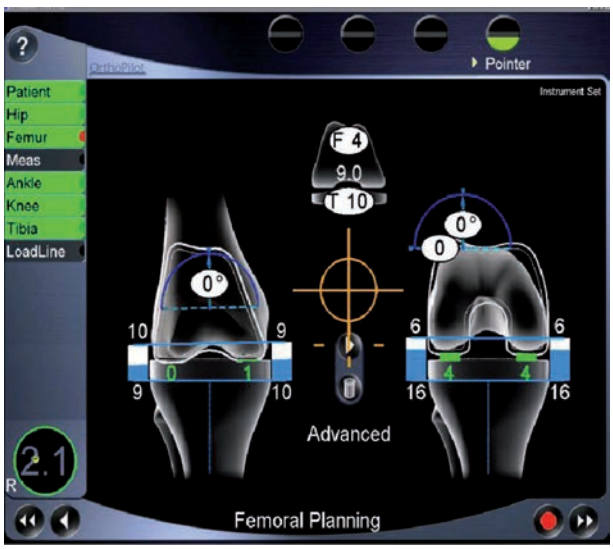

Figure 5. Navigated femoral planning

comparison if other alignment targets are introduced". Similar to Parratte et al. (7), also other authors found that the relationship between coronal alignment and survivorship was weak (21-23).

The precision with which the implants are placed directly affects patient outcome as implant position and alignment influence the stability, durability and patellar tracking. Evaluating the alignment in total knee arthroplasty and functional outcome with respect to the alignment is the need of the hour.

Orthopaedic surgeons have different tools to achieve these targets, such as conventional techniques (intramedullary or extramedullary guides), PSI and CAS. Although intra- and extramedullary alignment are used worldwide, several errors have been reported, due to variations in bony anatomy, visual misjudgement by the surgeon or limitations of the technique.

Several studies reported that with conventional technique the percentage of malaligned knees is between 20% and 30% (24-28). It has been shown that only 70-80% cases would obtain the ideal positioning of the prosthesis when using the intramedullary system (29). Recently, navigation systems have been developed to improve the accuracy of align- ment of the components in TKR. So far, only a few studies have been published, reporting the results of computer-assisted TKR.

Computer navigation has the potential to play a role in improving mechanical alignment and outcomes in TKR. In our Department we started using CAS in 1999, both in unicompartmental knee replacement (UKR) and TKR, then in association with patellofemoral replacement, bi-UKR and tri-UKR. CAS is also a teaching tool in TKR, especially in inexpert hands. In 2010 we published a paper in which we demonstrated that surgeons with different experience in CAS and knee surgery could perform TKRs with similar mechanical alignment (179.2° vs 178.1° with no statistical significant difference), proving CAS as teaching tool to train inexpert surgeons in knee replacement surgery (30). Then, in 2012 we demonstrated that a beginner can reproduce the results of an expert TKR surgeon by means of navigation after a learning curve of 16 cases; this represents the break-even point after which no statistically significant difference is observed between the expert surgeon and the beginner utilizing CAS (31). In 2012 we checked usefulness of CAS in post-traumatic knee arthritis comparing a group of CAS TKR performed in traumatic knee arthritis with CAS TKR in atraumatic knee arthritis. We found no statistical significant difference between the two group in terms of functional outcomes (32).

CAS in TKR provides more accurate bone cuts, more precise component placement in the coronal, sagittal and rotational planes, better restoration of coronal limb alignment and lower gap asymmetry (33-37).

Two recent meta-analyses definitively proved that CAS technique provided better mechanical axis and implant survivorship (38-39), but only Rebal et al. definitively demonstrated that CAS improves clinical outcomes at short-term follow-up (40). This meta-analysis collected only randomized controlled studies with two groups, CAS versus conventional technique in TKR: twenty-one papers were analysed, with the hypothesis that imageless computer navigation improves TKR short-term functional outcomes scores by producing superior post-operative alignment. They concluded that TKR performed with computer navigation was more likely to be within 3° of ideal mechanical alignment (87.1% vs 73.7%, P<0.01) and had a higher increase in Knee Society Score at 3-month follow-up (68.5% vs 58.1%, P=0.03) and at 12-32 month follow-up (53.1% vs 45.8%, P<0.01). The mean operative time for CAS TKR was 101.6 minutes vs 83.3 for conventional TKR (P< 0.01) (40).

These results demonstrate that CAS is a useful and teaching tool in TKR, even in inexpert hands; it allows reproducible results, providing better mechanical alignment and superior functional outcomes in the short-term follow-up. This increase requires the investment of additional and financial resources (40).

Additional operating time is needed when using navigation systems in TKR. However, after an initial learning curve, the computer-assisted surgical procedure took only 10-15 minutes longer to perform. This additional time is acceptable in clinical practice. In future, it may be reduced by an improvement of the computer-assisted workflow and by the development of specific navigation-adapted instruments.

Conflict of interest: None to declare

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Original article

Public health and burnout: a survey on lifestyle changes among workers in the healthcare sector

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Summary. Burnout Syndrome is a condition which could most commonly be associated with negative effects on the quality of work and life. Some occupations are more likely to suffer from this syndrome, for example workers in the health sector. This survey was therefore conducted among hospital workers of the Marche Region in order to analyze levels of Burnout and any possible correlation of these levels with lifestyle changes. Methods: The survey was carried out using a self-administered, anonymous questionnaire in two sections: the first consisted of the Maslach Burnout Inventory (MBI) and the second contained questions about the healthcare operator's lifestyle. The MBI investigates levels of Emotional Exhaustion (EE), Depersonalization (DP) and finally of Personal Accomplishment (RP) in respondents. Survey results were processed using descriptive statistics, applying the Chi-square statistic and an Odds Ratio ($p<0.05$). *Results:* 53.4% of the questionnaire was duly completed. The scale with the highest incidence among interviewees was Depersonalization. Even though the high-level percentage for the DP and EE scale was equal to 22.3%, when adding the high-level percentage to the medium level percentage, the difference between low and medium-high level was found to be around 20% for all areas. Analyzing the correlation between lifestyle choices, and in particular the consumption of alcohol and smoking with Burnout Syndrome, a statistically significant Odds Ratio was observed in the DP scale vs alcohol (OR=4.67), the RP scale vs cigarette smoke (OR=2.50), and finally in the EE area vs cigarette smoke (OR=2.92). *Conclusion:* Our results are in line with other studies which show increasing levels of EE and DP in healthcare workers. Healthcare workers who have been in the same job for a considerable amount of time (15+ years) show the highest levels of EE and DP. Subjects with high levels of Depersonalization show a worrying exposure to alcohol abuse, while those with high levels of Emotional Exhaustion tend to make use of both alcohol and tobacco, demonstrating negative lifestyle choices; in spite of this, results for personal accomplishment being relatively low and therefore not cause for worry, subjects still show high levels of exposure to cigarette smoke. (www.actabiomedica.it)

Key words: burnout, public health, lifestyle, workers

Introduction

Over the past 20 years, professional quality of life has changed for many occupational groups. If, on one hand, work conditions have improved in some aspects, these changes have also caused new conditions to emerge, such as psychological disturbances linked to occupational stressors (stress, mobbing and burnout) (1).

In particular, some occupations linked to the public health sector seem to be more exposed to this type of problem, since prolonged psychophysical exhaustion, Emotional Exhaustion and a lack of personal fulfilment can have a negative influence on the quality of work and mental health of the healthcare professional (2-9).

Burnout Syndrome, in particular, has been recognized as the condition most commonly associated

with negative personal behavior in people who work in healthcare and education. The individual suffering from burnout can no longer appreciate the specific meaning attached to a role or the purpose of a job and lose interest in the people who are being taken care of (10, 11). It is difficult to respond to this syndrome in an appropriate manner, particularly when it comes to healthcare professionals (2, 12). The number of healthcare professionals showing signs of depression, passivity, loss of confidence in their ability, loss of professional identity and self-confidence are on the rise. These issues are reflected in a loss of professional presence which reflects on the organization and its clients.

This study aims to examine the correlation between burnout, self-esteem and quality of life in healthcare professionals employed in the hospital units of the Marche Region (Central Italy), also in relation to lifestyle changes caused by the use of alcohol, drug abuse and cigarette smoking (13-17).

Methods

The study was carried out in the following hospitals of the Marche region: Ancona, Ascoli Piceno, Camerino, Fermo, Jesi and Pesaro, as well as INRCA (Scientific Institute for Hospitalization and Health Care) and the Salesi (children's hospital) in Ancona.

A self-administered anonymous questionnaire survey was distributed. It was in two sections: the first contained the Maslach Burnout Inventory (MBI) and the second consisted of questions about the healthcare operator's lifestyle (18).

The "Maslach Burnout Inventory" has been validated at international level and consists of 22 items which appear as affirmations describing personal feelings and attitudes. The term 'user' refers to the sort of person treated by the healthcare professional. The healthcare professional can answer each item by using a value scale from 0 to 6, based on the strength of his/her feeling on the subject. Each one of the three subscales evaluating burnout, that is to say *Emotional Exhaustion (EE)*, *Depersonalization (DP)* and *Personal Accomplishment (RP),* contain references which are spaced unevenly throughout the questionnaire so as not to influence answers in any way.

Before the questionnaire was distributed participants were informed about the aim of the survey and its importance and utility were stressed. The study was conducted in agreement with the latest version of the Declaration of Helsinki.

Excel and Access for Windows were used to archive data and to perform descriptive statistics. Statistical analysis was performed with X-Lstat software (19).

Descriptive statistics were used to analyze the distribution of variables. Qualitative data were described using frequencies and percentages. The Chi-square analysis and the Odds Ratio were applied to evaluate the differences between use of alcohol, smoking and drug abuse. The level of statistical significance was set at $p<0.05$.

Results

Of 4.150 questionnaires distributed, 2.216 (corresponding to 53.4%) were duly completed and the characteristics of the sample have been summarized in Table 1.

An initial analysis of results shows that feelings of Depersonalization (DP) are high in all respondents (35.6%) as well as levels of Emotional Exhaustion (EE), which can be seen in 23.6% of respondents. The percentage of those who display high levels of DP and EE is equal to 22.3% of the sample. Results obtained for all levels of Emotional Exhaustion show an overall balance between the percentage obtained for low and high levels. Furthermore, adding the percentages for medium and high levels shows that they exceed low levels by 22.5% (Fig. 1). Regarding Depersonalization, medium-high levels exceed low levels by 18.5% (Fig. 1).

However, when it came to Personal Accomplishment, the vast majority of respondents reports no issues. Even by adding medium and high levels, the percentage (35.9%) does not exceed low levels (Fig. 1).

Emotional Exhaustion

Comparing levels of EE with the age of respondents, it can be seen that 56.1% of respondents over 50 years of age show high levels, while younger people

Table 1. Sample characteristics

Age group	Male no.	Male %	Female no.	Female %	n.a. gender no.	n.a. gender %	Total no.	Total %
Sample characteristics								
≤ 30	48	7.69	148	9.4			196	8.84
31-40	134	21.47	553	35.11			687	31.00
41-50	152	24.36	496	31.49			648	29.24
51-60	160	25.64	211	13.40			374	16.88
61-70	5	0.80	6	0.38			11	0.50
> 70	5	0.80	0	0.00			5	0.23
n.r.	120	19.23	161	10.22	14	100.00	295	13.31
Total	624	100.00	1575	100.00	14	100.00	2216	100.00

	no.	%
Main activity		
General practitioner	18	0.81
Physician	244	11.01
Biologist	16	0.72
Official	67	3.02
Administration	38	1.71
Employee	22	0.99
Social worker	80	3.61
Healthcare assistant	1271	57.36
Nurse	36	1.62
Psychiatric nurse	35	1.58
Obstetrician	10	0.45
Psychologist	18	0.81
Therapist	30	1.35
Head nurse	94	4.24
Intermediate care technician	6	0.27
Pharmacist	126	5.69
Technical health worker	12	0.54
IT specialist	6	0.27
Trainee	12	0.54
Dietician	2	0.09
Community worker	21	0.95
Telephone operator	6	0.27
Ophthalmologist	46	2.08
n.a.		
Time operating		
≤5	260	11.73
6-10	388	17.51
11-20	698	31.50
21-30	568	25.63
>30	215	9.70
n.a.	260	3.93
Time employed		
≤5	638	28.79
6-10	457	20.62
11-20	577	26.04
21-30	331	14.94
>30	122	5.50
n.a.	91	4.11

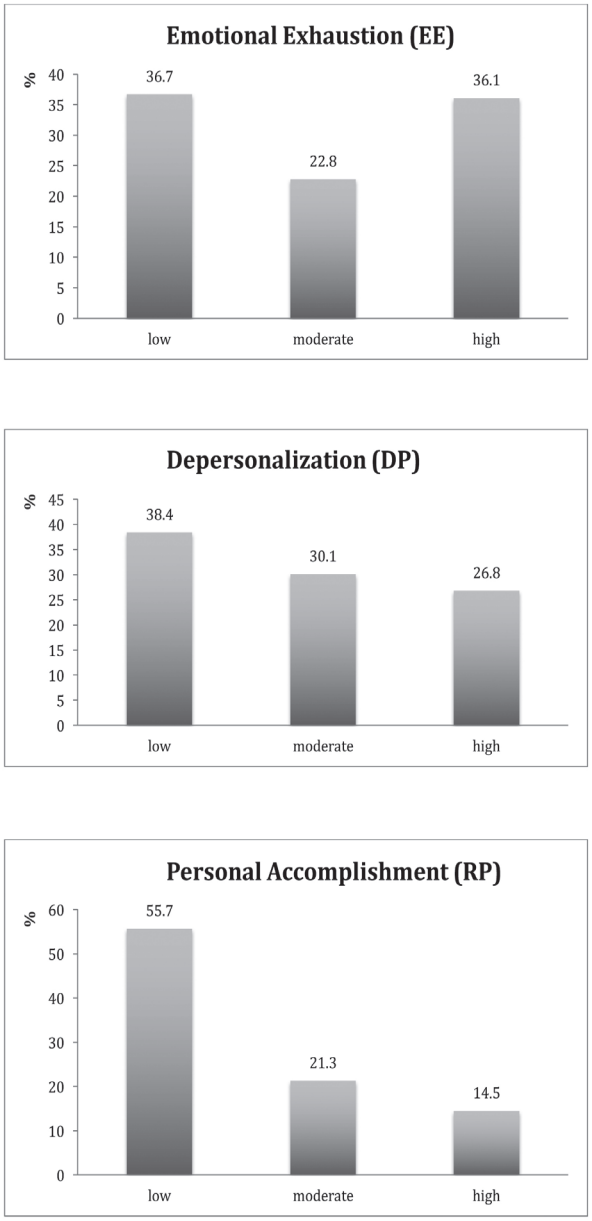

Figure 1. Percentage of overall levels of Burnout for all scales

(from 20 to 30 years of age) have lower levels of EE (43.8%).

Moving on to "how long" respondents have been in their current position, it is noted that the highest levels of EE are found in those who have been in the same job for more than 15 years (42.9% of cases).

Emotional Exhaustion can be seen in the extreme tiredness a worker might feel at the end of a day's work and this was found in 35% of healthcare workers; physical exhaustion concerns 50% of respondents. This is emphasized by feelings of having "worked too hard", as seen in about 35% of respondents.

Feelings of exhaustion are exacerbated by the fact that over 30% of respondents already feel tired when they get up in the morning and have to face another day at work; the percentage of those who feel unable to carry on (15%) is relevant. More than 25% of respondents admit to being 'stressed out' by their job, a situation which can easily lead to feelings of frustration, as evidenced in over 20% of the sample.

Depersonalization (DP)

No differences can be observed between those who have been in the same role for a long or shorter period. More than 20% of the sample worry that their profession might, over time, desensitize them to clients' requirements.

Personal Accomplishment (RP)

Results relating to Personal Accomplishment show that high levels prevail, thus showing an ability to make and maintain interpersonal relations, qualities of social openness and disinhibition and the ability to reach important goals. Furthermore, these respondents exhibit fewer symptoms of psychophysical distress and are more likely to give increasing importance to the social aspects of their job, such as relationships with colleagues and clients, as well as recognizing stimulating elements which are part of their activity.

If we look at the length of time the respondents have operated in the healthcare sector, it becomes obvious that levels of RP lessen as time goes by, with percentages equal to 62.7% and 65.93% in those who have been employed for 1-5 years or over 15 years respectively. An analysis of lifestyles, particularly alcohol and tobacco consumption, shows the possible existence of feelings of discomfort or unease which are potentially connected to Burnout Syndrome.

38.4% of respondents are smokers and, of these, 66.8% show low levels of job satisfaction; while 57.0% regularly consume alcohol. Specifically, regarding the category measuring EE levels, subjects showing high

scores are compared to subjects from the same category with low scores pertaining to exposure to cigarette smoke and alcohol. An analysis of data shows that exposure to cigarette smoke and alcohol is significantly higher in subjects with high levels of EE compared to those with low levels of EE (Table 2). The same can be said for alcohol abuse, with a slight difference in the Odds Ratio, in the RP scale. The highest significance for exposure to alcohol is seen relative to DP levels, while exposure to cigarette smoke is not significant (Table 2).

Conclusions

Our results show that worrying levels of Emotional Exhaustion, as well as medium/high levels of Depersonalization, can be seen in healthcare workers. Our results are in line with other studies which show increasing levels of EE and DP in healthcare workers, who compared to other work categories are known to be exposed to stressful procedures at work (2). On the contrary, data pertaining to Personal Accomplishment show that our sample is characterized by medium/low levels of stability. A possible explanation for this result could depend on the fact that when answering questions on psycho-physical health, respondents easily admit to feeling distressed but, when faced with questions on Personal Accomplishment, prefer not to admit that psychological distress might have a negative influence on their performance at work.

Healthcare workers who have been in the same job for a considerable amount of time (15 + years) show the highest levels of EE and DP. As shown by other studies, this can be linked to the high levels of emotional exhaustion connected to long-term exposure to suffering in patients (20, 21).

Concerning lifestyle choices, some studies have shown that among the different work categories, healthcare workers show the highest percentage relating to substance abuse. Tobacco and alcohol abuse can be seen as a choice which is made to help tackle feelings of exhaustion related to work issues. It must also be said that the search for personal satisfaction does not necessarily depend on adverse working conditions. However, a situation of constant stress can lead healthcare workers to abuse alcohol, which is used as relaxant, tranquilizer and even as a form of evasion (22-24).

In light of these results, we believed it necessary to look deeper into the correlation between alcohol and tobacco abuse within MBI categories. In accordance with the literature, specifically, the highest levels of tobacco and alcohol consumption were found in subjects with high levels of EE and DP (25, 26). Subjects with high levels of Depersonalization show a worrying exposure to alcohol abuse, while those with high levels of Emotional Exhaustion tend to make use of both alcohol and tobacco, demonstrating lifestyle choices which aggravate a partially compromised psychophysical condition. It is interesting to note that, though results for personal realization are not worrying, subjects still display high levels of exposure to cigarette smoke.

To conclude, it could be said that working patterns for healthcare workers, which are in many cases more stressful than for other occupations, can generate feelings of unease which deplete emotional resources. Objective conditions and the type of work that is

Table 2. Odds Ratio: correlation of alcohol and cigarette consumption with EE, DP and RP levels.

Variables	Smoking (OR)	P-value	95% CI	Alcohol (OR)	P- value	95% CI
Emotional Exhaustion (EE) high *vs* low	**2.92***	0.0365	1.06 to 8.06	2.35	0.0000	2.01 to 2.76
Personal Accomplishment (RP) low *vs* high	**2.50***	0.0343	1.04 to 6.02	1.97	0.0124	1.15 to 3.37
Depersonalization (DP) high *vs* low	1.66	0.0005	1.24 to 2.21	4.67*	0.0000	3.01 to 7.24

*P-value correlation significant ($\alpha<0.05$)

done still seem to be the main culprits for an insurgence of conditions which lead to Burnout Syndrome. In healthcare workers, Burnout should not be underestimated: many factors associated with the onset of this syndrome, such as organizational issues or conflict between working hours and family duties, might be modified in order to increase emotional stability in subjects whose occupation is characterized by marked emotional involvement (27-30).

Conflict of interest: None to declare

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Original article

Plate fixation in periprosthetic femur fractures Vancouver type B1: preliminary report of macroscopic evaluation of the cement mantle and short literature review

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Summary. The goal of our preliminary report is to investigate hip stem stability and intra-operative cement mantle integrity after screw insertion in plate fixation of periprosthetic Vancouver B1 femur fractures. From a cohort of 50 patients with a periprosthetic femur fracture treated in our department from February 2012 until February 2017, we included in our study patients with a periprostethic Vancouver B1 femoral fracture in cemented hip arthroplasty and hemiarthroplasty, operated with ORIF using a 4.5/5.0 LCP Proximal Femoral Hook Plate ® (Synthes, Switzerland) with at least one screw perforating the cement mantle. Anteroposterior and lateral femur views and pelvis X-rays were performed preoperatively. The stability of the hip implant and the cemented mantle integrity was evaluated intra-operatively in a macroscopic way and with a post-operative X-ray in anteroposterior and lateral views. Only 7 patients satisfied the inclusion criteria; no lesion/break of the cement mantle occurred intra-operatively at any step during drilling or screw insertion, also confirmed with C-arm assessment. No cases of stem mobilization were found and cement mantle integrity was maintained in every case. Insertion of screws around a cemented stem for plate fixation in periprosthetic femur fractures Vancouver type B1 could be considered a safe procedure. However, further and more extended studies are necessary for proving additional knowledge at the evaluation of the cement mantle in osteosynthesis procedures. (www.actabiomedica.it)

Key words: cement mantle; periprosthetic Vancouver B1 femur fractures; hip stem stability

Introduction

The incidence of periprosthetic fractures after hip arthroplasty is continuously rising because of an increasing number of hip joint replacements and an enhanced survivorship of the eldery population. Previously reported studies showed an increased risk of periprosthetic femoral fractures in uncemented stems compared to cemented implants (1, 2). Currently, cemented stems are still considered to be one of the most reliable materials available for the treatment of osteoporotic hip fractures. Periprosthetic femoral fractures represent a serious complication for elderly patients (1, 2). Plate fixation in Vancouver type B1 periprosthetic femur fractures with cemented stem is a very common approach for the elderly (3-7). The use of screws perforating the cement mantle is a common treatment option when a plate fixation is performed. The goal of this preliminary report is to investigate hip stem stability and intra-operative cement mantle integrity after screw insertion in plate fixation of periprosthetic Vancouver B1 femur fractures.

Material and methods

We retrospectively evaluated the treatment results in a cohort of 50 patients with a periprosthetic femur fracture treated at San Carlo Borromeo Hospital from February 2012 until February 2017.

The informed consent of all the patients was obtained about the use of clinical data for scientific publication.

The periprosthetic femoral fractures in this study were classified according to the Vancouver classification. Inclusion criteria of the study were: (1) Periprostethic Vancouver B1 femoral fractures (a fracture around or just below to a stable stem) in cemented hip implants, including both total hip arthroplasty and hemiarthroplasty, operated with (2) ORIF using a 4.5/5.0 LCP Proximal Femoral Hook Plate® (Synthes, Switzerland) (3) with screws (one at least) perforating the cement mantle.

The exclusion criteria were (1) periprosthetic fractures on uncemented hip implants and (2) Vancouver B femoral fractures with no screws perforating the cement mantle.

The X-rays of the patients were obtained from the Picture Archiving and Communication System (PACS) of our Institute. Anteroposterior and lateral femur views and pelvis X-rays were performed for each patient preoperatively.

The stability of the hip implant and the cemented mantle integrity was evaluated intra-operatively by performing a mobilization test of the involved femoral stem by using a farabeuf or a lambotte clamp. In the post-operative X-ray in anteroposterior and lateral views, subjective loosening signs of the femoral stem was investigated.

All patients were in supine position on a radiolucent table. Mainly extended lateral approach to the femur was performed with minimal invasive plate osteosynthesis (MIPO) technique used in some cases. A 4.3 mm or a 3.2 mm drill was used to perforate the femoral bone and the cement mantle. Cephazoline (2 gr) was administered 30 minutes prior to skin incision for infection prophylaxis. For thromboembolic prophylaxis we administered low molecular weight heparin subcutaneously (according to the patient's weight) until the full weight bearing was reached.

Results

The final cohort of our study consisted of 7 patients who actually satisfied the inclusion criteria, specifically 6 women and 1 man, with a mean age of 85.6 years (range 58-97) at the time of surgery. 4 monocortical screws and 10 bi-cortical screws were implanted in the cement mantle. All bi-cortical screws were positioned distal to the stem, 3 mono-cortical screws were placed around the stem and the 1 remaining was put proximal to the stem. Time from admission to surgery was on average 5.8 days (range 2-7 days).

Intraoperative fluoroscopy with C-arm and direct macroscopic evaluation was used to assess the stability of the hip implant and the cement mantle integrity. Follow-up anteroposterior and lateral X-rays were done postoperatively.

No lesion/break of the cement mantle occurred intra-operatively at any step during drilling or screw insertion, also confirmed with C-arm assessment. No cases of stem mobilization were found and cement mantle integrity was maintained in every case (Figg. 1a, 1b, 1c, 1d).

Discussion

First reports on periprosthetic femoral fractures (PFF) predate the modern Total Hip Replacement (THR) designs. First publication was a 70 patient follow-up in 1954 (8). Complications related to use of metal in bones was published in 1957, where the importance of mechanical stresses and strains as contributors to metal loosening or failure was noted (9). The first successful cemented THR system created by Charnley in 1962 was the golden standard for many years coming (10-12). The incidence of periprosthetic fractures around the femur continues to rise due to increasing numbers of primary and revision THRs performed each year (13). Relative and established risk factors for periprosthetic fractures include age, sex, gender, index diagnosis, presence of osteolysis, presence of aseptic loosening, specific type of implant used and revision THR (14-16).

Current surgical treatment options of PFF are widely based on the Vancouver classification system

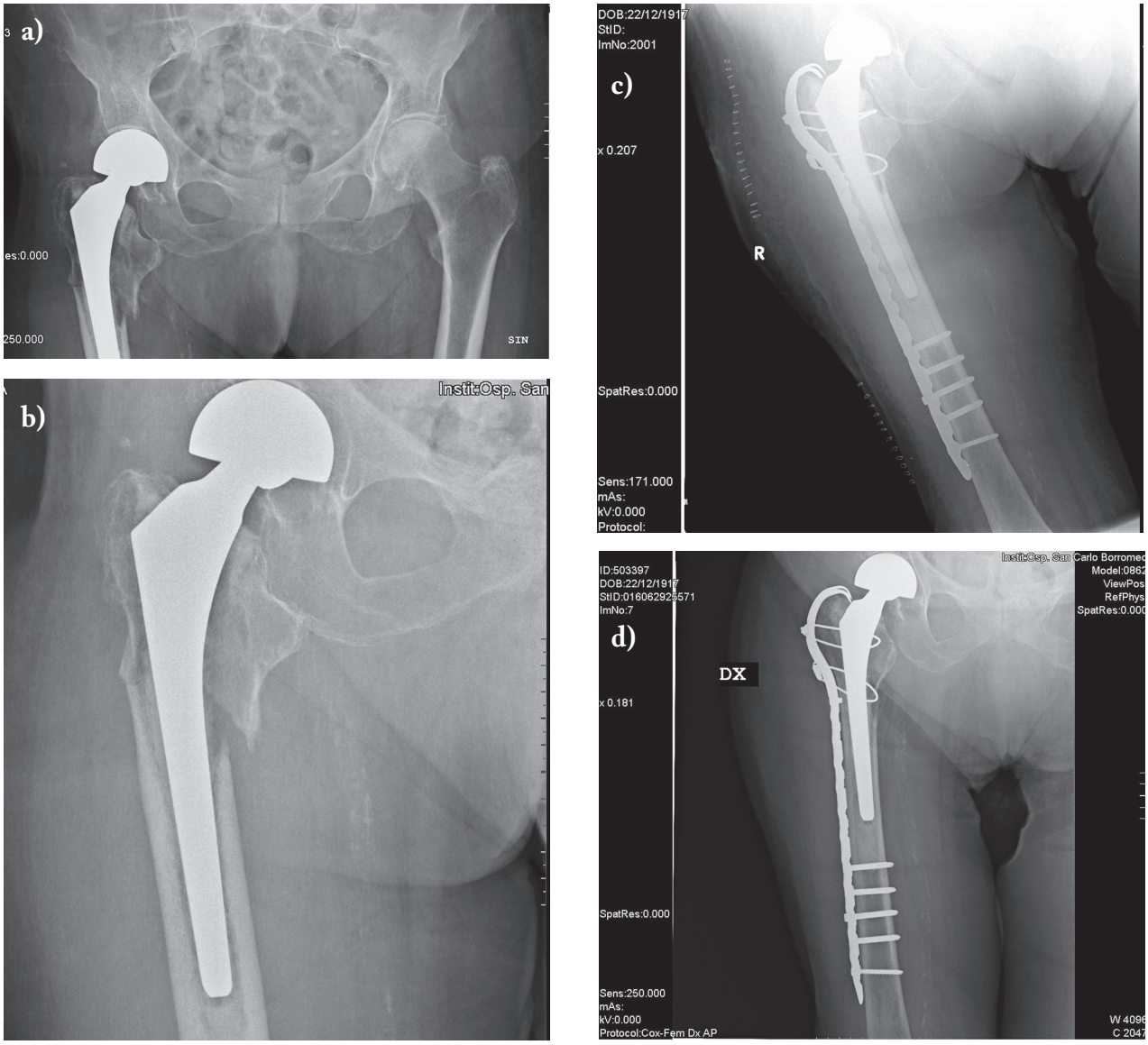

Figure 1. a, b) Preoperative images of a 98 years old female patient with a periprostetic fracture with suspect of subsidence and stem loosening. Only after intra-operative evaluation of the stem's stability the fracture was classified as Vancouver B1. c) After the insertion of one bicortical and one unicortical screw around the cement mantle, intra-operative macroscopic evaluation didn't reveal stem's instability. d) X-rays at 8 months follow-up show a stable cemented stem with a hook plate and screws

(17). Vancouver type B fractures divide to subgroups depending on the stability of the femoral stem and bone stock. Unfortunately it is not always possible to assess the stability of the stem prior to surgery. In 2009, a study was published revealing 20% unstable femoral stems on initially diagnosed Vancouver Type B1 fractures (18). Many publications recommend the use of plate osteosynthesis for Vancouver Type B1 fractures as opposed to revision of stem for unstable Type B2 and B3 types (19-22). Different types of plates were tested over the past 2 decades with combination of cables, cerclages, locking screws, hook plates etc., with

no widely accepted guidelines of our knowledge. Debates are focused on the different types of fixation to proximal femur as the stable stem can be compromised from the use of screws.

Biomechanical studies also were conducted to assess the stability of different types of plate osteosynthesis. Lever et al. utilized 12 pairs of human cadaveric femurs for 3 different plate fixation systems and concluded that screw plate fixation systems provided more mechanical stability compared to cable plate systems (23). Kampshoff et al. assessed the cement mantle integrity after screw insertion and concluded that bicortical screws passing through the cement cause cracks and further can destabilize the stem (24). The authors noted that the use of a unicortical screw is a much safer option with lower pullout resistance.

Giesinger et al. conducted another biomechanical study on 17 synthetic femurs and found no cracks in cement mantle after bicortical screw insertion (25). Difference is that they used same diameter drill bit and screw inserted right after the screw size was measured. The biomechanical studies conclude that longer clinical trials are needed in vivo to investigate long-term stem stability. New plate designs with variable-angle locked plates with bicortical proximal screws showed significantly greater load-to-failure ratios when compared to unicortical or cable fixation types (26). The screw holes in this system are placed outside the midline of the plate allowing angling of the screws and bicortical purchase. Weak points of this study were the use of synthetic bones and cementless stems.

Lewis et al. conclude in a recent biomechanical study that proximal femoral stability of cemented periprosthetic fracture is improved with tangentially directed bicortical locking screws as compared to unicortical screw or cable fixation (27). Further prospective studies with big samples and long term follow-up will help in choosing the correct algorithm of treatment and establish guidelines for clinical practitioners.

In our experience, osteosynthesis around cemented prostheses is very challenging to manage, as it is difficult to achieve a placement of bicortical screws around a cemented stem. The difficulty of screw placement has lead to the development of new plate designs allowing angular positioning of the screws and the use of cerclages and cables has been controversial. Screw placement around a cemented stem sometimes gives excellent grip but it may compromise the cement mantle and may lead to cement fragmentation and failure with subsequent mobilization of the femoral stem.

Summarising, the use of unicortical screws alone or together with cables provide additional resistance to lateral bending or torsion when a plate is used, compared to cables alone. It is easier to place unicortical screws around the cement mantle rather than adjusting them around a cemented stem and this concept should be further investigated. If rigid proximal fixation is required, an effort should be made to obtain bicortical fixation. Newly designed implants are necessary to obtain bicortical locking screws directed tangentially to the hip stem. A major concern is the loosening of the construct, caused by screw penetration and cracking of cement mantle.

Moreover, clinical experience of intraoperative procedures should be reported in the studies, as only a few are available, basically reporting the results of drilling and screwing the femoral cement mantle around prosthesis. Many Authors performed the evaluation of the cement mantle in periprosthetic femur fractures. We underline that our preliminary report is the first one that evaluates in vivo the integrity of the cement mantle in plate fixation of periprosthetic femur fractures. It's very important, as these fractures are becoming more common due to increase of average life expectancy.

In our study we had no cases of macroscopic cracks in the cement mantle or stem mobilization, even when bicortical screws were used. Unfortunately, only 7 patients met our inclusion criteria; another remark is that we probably need at least a 1 year follow up after plate fixation, to check what happens after weight bearing.

In the future we expect the development of higher speed drills, which may also help in this process.

Conclusions

The use of screws around a cemented stem for plate fixation in periprosthetic femur fractures Vancouver type B could be considered a safe procedure. However, further and more extended studies are necessary

for proving additional knowledge at the evaluation of the cement mantle in osteosynthesis procedures.

Conflict of interest: None to declare

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Original article

Evaluation of alpha-1-antitrypsin levels in blood serum of patients with chronic obstructive pulmonary disease

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Summary. *Introduction:* Chronic obstructive pulmonary disease (COPD) is a disease that causes obstructed air flow from the lungs. The disease also has a dramatic role in increasing rate of mortality and morbidity in recent years. Air pollution, long-term exposure to particulate matter and irritating gases, especially cigarette smoke, genetic inheritance which has an impact on the initial forced expiratory volume one in second (FEV_1), and alpha-1-antitrypsin (AAT) deficiency are among common COPD risk factors. The objective of this study is to evaluate parameters and serum AAT levels in COPD patients. *Materials and Methods:* Having taken the approval of local ethical committee, this cross-sectional study was performed with adult patients diagnosed with COPD, whose serum AAT levels were measured through nephelometric analysis in Kars Harakani State Hospital where secondary health care is served. The study evaluated ATT levels in patients' serum in relation to their age, gender, body mass (BMI), exposure to cigarette smoke, FEV_1 percentage, hospitalization in pulmonology or intensive care unit through a year, mortality status, white blood cell (WBC), c-reactive protein (CRP) and blood gases. *Results:* The average age of the 243 patients included in the study was 68.41±11.52 and 160 (65.8%) of them were male. The age and BMI of the female patients were higher. Of the all patients only a single patient's serum AAT level was below the reference value. AAT levels were similar in both genders irrespective of their being exposed to cigarette smoke or being discharged or being exitus at their first admission to hospital, being exitus in the first year of disease diagnose, and being hospitalized in intensive care unit. AAT levels were reasonably correlated with WBC and CRP in a positive way ($p<0.001$ $r=0.289$ for WBC; $p<0.001$, $r=0.295$ for CRP). AAT levels were seen to significantly increase along with COPD stages which go up with FEV_1 percentages ($p<0.001$). CRP was watched to have increased to Stage III COPD (severe COPD). However, it was watched to have decreased in Stage IV (very severe COPD) ($p=0.179$). *Conclusion:* In the study, AAT serum levels of COPD patients were examined. The levels and their relations in various parameters of the patients were evaluated. (www.actabiomedica.it)

Key words: serum alpha-1 antityrpsin level, chronic obstructive pulmonary disease

Introduction

COPD is a substantial reason of morbidity and mortality world-wide (1). COPD is the 5th most common cause of death and also 10th heaviest burden disease according to the World Health Organization (2). COPD is one of the chronic diseases which have critically increased mortality in recent years. Global Initiative for Chronic Obstructive Lung Disease (GOLD) describes the disease as: it is a disease which increases patients' clinic severity, which bears significant extrapulmonary effects, and which can be prevented and cured. It causes not fully reversible airflow limitation in lungs (1). The airflow limitation caused by COPD

is usually progressive and the limitation is related to the abnormal inflammatory response in lungs, which is caused by noxious particles or gases (1). Even if it may differ in general population, the risk factors are divided into two as endogenous or host and exogenous or environmental. (1). Air pollution, long-term exposure to particulate matter and irritating gases especially cigarette smoke, genetical inheritance, having an impact on FEV1, and AAT, the major serum serine protease inhibitor are known risk factors for COPD (1).

AAT is a well-known glycoprotein which weighs 52-kDa and includes three N-glycosidically linked complex oligosaccharides and belongs to the serpin family (3). AAT automosol dominant is inherited and, coded by SERPINA1 gene placed in the long arm of 14th (14q31–32.3) chromosome (4). AAT variations are divided into four groups: a) Levels of common alleles, normal variants and nephelometric serum are between 80-220 mg/dL; b) in deficient variations, nephelometric serum levels are below and in some alleles functional activity of AAT molecule are reduced; c) rare alleles are null variations characterized by AAT, which exists in serum as a result of transcriptional or translational errors in protein synthesis; d) dysfunctional variants are characterized with abnormal function of AAT (4). AAT deficiency is most frequently identified with nephelometric measurement especially serum levels are below 100 mg/dL (4).

The role of AAT is to neutralize neutrophil elastase enzyme and to preserve connective tissue of the lung from degeneration by elastase released from neutrophils (3). AAT is an acute phase reactant produced by mainly liver, macrophages and monocytes whose concentration amount increases also in plasma during malignancy, inflamination and infection (3). Plasma level of AAT in a healthy individual is between 0,9-2 g/L (5). However, it may multiply 4 to 5 times in some cases such as acute inflammation and infection (5). Apart from its acute phase response, it increases in the third trimester of pregnancy and in a parallel way to ageing (5). Deficiency of functional AAT may cause early beginning emphysema, bronchial asthma, bronchiectasis, panniculitis, systemic vasculitis, spontaneous cervical artery dissections, type 2 diabetes mellitus, spontaneous abortions and human immunodeficiency virus (HIV) type 1 (5).

The objectives of this study are to evaluate age, gender, BMI, exposition to tobacco, smoke, percentage of FEV_1 and degree of airflow obstruction in relation to those percentages, hospitalization in pulmonology and intensive care unit in a year, mortality status, WBC, CRP and blood gases of COPD patients in a secondary service hospital; and to evaluate serum AAT levels measured through nephelometric analysis in relation to patients' parameters.

Materials and methods

This cross-sectional study was conducted with the approval of the local ethical committee, between the dates 01.01.2013-31.12.2015, in adult patients diagnosed with COPD in Kars Harakani State Hospital, Kars, Turkey.

People who were included in the study are; adult patients formerly diagnosed with COPD and present to the emergency room or pulmonology with any reason as ambulant between the specified dates or hospitalized to intensive care unit, and adults whose serum AAT was examined as external examination. Patients who hadn't been diagnosed with COPD before admission to hospital and ones whose serum AAT levels weren't examined were not included in the study. Data belonging to patients; a) age, gender, length (metre), kilo (kilogram), BMI (kilo/length), exposition to tobacco smoke ; b) percentage of FEV_1, measured with spinometer after bronchodilator and degree of airflow limitation in relation to those percentages (Stage I: Mild- FEV_1 percentage ≥80%, Stage II: Moderate-50% ≤FEV_1 <80%, Stage III: Severe-30% ≤ FEV_1 <50%, Stage IV: Very Severe-FEV_1 <30% (6)); c) number of hospitalization to pulmonology and history of hospitalization to intensive care unit, result of existing admissions (discharge or exitus) and to be mortality in a year; d) reference WBC (10^3/ul), reference CRP (mg/L), reference pH obtained from blood gas, partial pressure of oxygen (PaO_2-mmHg), partial pressure of carbon dioxide ($PaCO_2$-mmHg); e) serum AAT level measured with nephelometric analysis (mg/dl) (reference levels 88-174 mg/dL(Ankalab Laboratories, Ankara, Turkey) were evaluated. Data obtained from the study were analyzed through "SPSS for Windows ver.

22.0" packet program. Continuous variables average ± with standard deviation and frequency data (%) were described with numbers. In statistical analysis, the convenience of all measurable variables to normal distribution was evaluated with histogram and Kolmogorov-Smirnov test. Since data didn't adjust to normal distribution, "Kruskal Wallis Test" was used in comparison of more than two groups. In doublet comparison of groups, "Bonferroni correction Mann-Whitney U Test" was used. Relations between variables were evaluated with analysis of Sperman Correlation. In comparison of data gained through enumeration, "Chi square test" , "Fisher's exact test" and "Linear- by-linear association" were used. Existence of dependent effects of hospitalization to intensive unit care and mortality variables was evaluated with "Binary Logistic Regression" analysis. Value of foreseeing AAT levels in hospitalization to pulmonology and intensive unit care and one-year-mortality was done with ROC analysis. In all tests, level of statistical relevance was accepted as $p<0.05$.

Results

Average age of the patients was 68.41±11.52 and distribution of ages was seen to be normal. 160 (65.8%) of the patients were male. Weight values of the both male and female patients were similar but levels of age and BMI were higher in females whereas length level was shorter (Table 1).

Only one of the 243 patients included in the study had 25,5 mg/dL level of serum nephelometric AAT and it was below the value of reference. AAT levels were 205.08±58.09 in females, and 205.08±58.09 in males. The levels were similar in both genders (p=0.426). AAT levels of patients exposed to tobacco smoke were 210.61±59.18, whereas AAT levels of patients not exposed to tobacco smoke were 205.15±58.73. The levels were similar in both groups (p=0.214). AAT levels of patients who were discharged from hospital at their existing admission were 208.75±59.15, whereas they were 198.33±53.96 in exitus patients. The levels were similar in both groups (p=0.709). AAT levels in patients who became exitus in the first year were 209.04±58.89 while they were 208.14±59.06 in non-exitus patients. The both groups were similar (p=0.387). AAT levels of patients who were hospitalized to intensive unit care in a year were 207.44±52.32 whereas levels of patients not have been hospitalized to intensive unit care were 208.50±60.24. They were similar in both groups (p=0.491).

Table 1. Distribution of age, length, weight and BMI as to gender

	Kadın	Erkek	p
Age, (year)	71.53±10.84	66.79±11.57	**0.003**
Length , (m)	1.54±0.12	1.64±0.15	**<0.001**
Kilo, (kg)	71.60±19.09	71.43±18.04	0.974
BMI, (kg/cm^2)	30.35±8.44	27.37±11.06	**<0.001**

AAT level was correlated with WBC and CRP in a positive way ($p<0.001$, $r=0.289$ for WBC; $p<0.001$, $r=0.295$ for CRP). It was seen that AAT levels significantly increased along with COPD stages which rise in regard to percentages of FEV1($p<0.001$). However, it was seen that CRP increased till Stage III and decreased at Stage IV ($p=0.179$).

Discussion

AAT is a protein which inhibits neutrophil elastase, whose deficiency is hardly seen and prevalence of its deficiency shows variety as regard to population study (7). Patients usually get the diagnosis of AAT deficiency at approximately 45 and unfortunately almost 85% of patients don't have a diagnosis along all their lives (7). One of the patients included in the study had serum nephelometric level which was below the range of reference value. The patient was a 53-year-old tobacco user. Considering the low serum level of the patient, the patient was thought to have AAT deficiency and genotypic analysis was done. Homozygous allel PI*ZZ was identified in the patient. Similar to the age and gender of this patient, in the study of Piras et al, AAT deficiency in males was higher in smokers and the age of diagnosis of this deficiency was approximately 47±14.7 (8). In the study age average of COPD patients was 68.41±11.5 and distribution of ages was normal. Most of the patients were male (65.8%). In the studies of Zillmer et al and Barrecheguren et al, the

Table 2. FEV_1 percentages and demographic features of the patients as to COPD stages and laboratory data

	Stage I (n=9, 3.7%)	Stage II (n=57, 23.5%)	Stage III (n=117, 48.1%)	Stage IV (n=60, 24.7%)	P
Age (Year)	64.78±12.48	65.32±13.89	70.93±10.35	66.97±10.17	0.007*
Gender					0.241**
Female	3 (33.3%)	22 (38.6%)	42 (35.9%)	16 (26.7%)	
Male	6 (66.7%)	35 (61.4%)	75 (64.1%)	44 (73.3%)	
Length (m)	1.61±0.13	1.58±0.15	1.60±0.16	1.65±0.12	0.062*
Kilo(kg)	73.78±13.25	73.40±19.73	72.12±18.68	68.08±16.95	0.371*
BMI(kg/m^2)	29.11±7.62	29.85±9.65	29.13±11.92	25.43±6.99	**0.048***
Levels of AAT	193.89±45.95	199.44±59.29	211.01±63.16	212.22±51.26	**<0.001***
Negatif	-	-	1 (0.9%)	-	0.097**
Reference range	3 (33.3%)	22 (38.6%)	31 (26.5%)	14 (23.3%)	
Positive	6 (66.7%)	35 (61.4%)	85 (72.6%)	46 (76.7%)	
Exposure to tobacco					0.660**
Yes	6 (66.7%)	27 (47.4%)	58 (49.6%)	34 (56.7%)	
No	3 (33.3%)	30 (52.6%)	59 (50.4%)	26 (43.3%)	
WBC	7.89±1.42	10.47±4.88	10.38±5.15	10.69±4.11	0.245*
CRP	1.61±1.17	3.70±4.13	5.49±7.12	5.22±6.61	0.179*
pH	7.43±0.08	7.42±0.06	7.42±0.08	7.40±0.11	0.419*
pCO2	41.22±8.39	41.06±9.47	43.25±11.48	47.54±12.29	0.056*
pO2	46.67±12.12	49.56±14.77	46.09±11.39	43.10±13.44	0.194*
Number of hospitalization in a year, median	1±0.87	1.84±1.66	2.52±2.42	2 (0-15%)	**0.024***
Exitus in hospital					**0.049****
Yes	-	1 (1.8%)	3 (2.6%)	5 (%)	
No	9 (100%)	56 (98.2%)	113 (97.4%)	54 (91.5%)	
Exitus in the first one year					0.193**
Yes	2 (22.2%)	7 (12.3%)	35 (23.7%)	14 (23.7%)	
No	7 (77.8%)	50 (87.7%)	81 (69.8%)	45 (76.3%)	
Hospitalization to intensive unit care in the first one year					**0.008****
Yes	-	5 (8.8%)	24 (20.7%)	15 (25.0%)	
No	9 (100%)	52 (91.2%)	92 (79.3%)	45 (75.0%)	

* Kruskall-Wallis test; **Ki-kare test

age average of the patients was 68.5±9.6, 52.6±16.3. 45.3% and 55.5% of the patients were male (9, 10).

Even though in the study the number of the male patients was more than the females, the age average and BMI of the females were higher. Similarly, in the study of Harik-Khan et al done with COPD patients, at first admission of the females to the hospital, age and BMI respectively was 55.4±4.2 and 25.4±3.5, which was higher when compared to the males (11). Different from all those studies, Senn et al, Ferrarotti et al studied the relation of serum AAT with BMI; and Senn et al showed that there occurred a negative relation between those two parameters whereas Ferrarotti et al displayed that AAT didn't get affected from age, gender and BMI (12,13). In this study, it was released that AAT levels in both genders were seen to be similar in patients no matter they were exposed to tobacco or not. It was seen that serum level which belongs to this protein wasn't affected from gender and exposure or non-exposure to tobacco. In the study of Barrecheguren et al, approximate serum AAT level was 150.9±34.2 and that was higher in smokers compared to former smokers, which

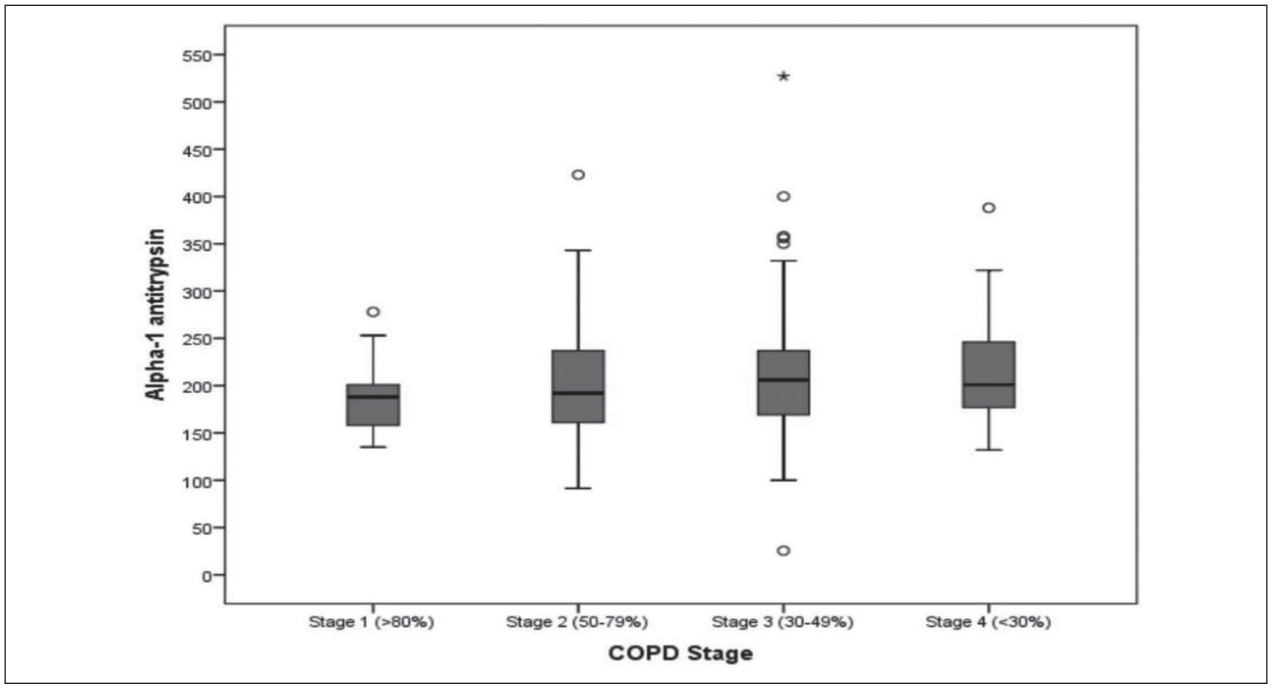

Figure 1. Box plot graphs AAT and COPD Stage

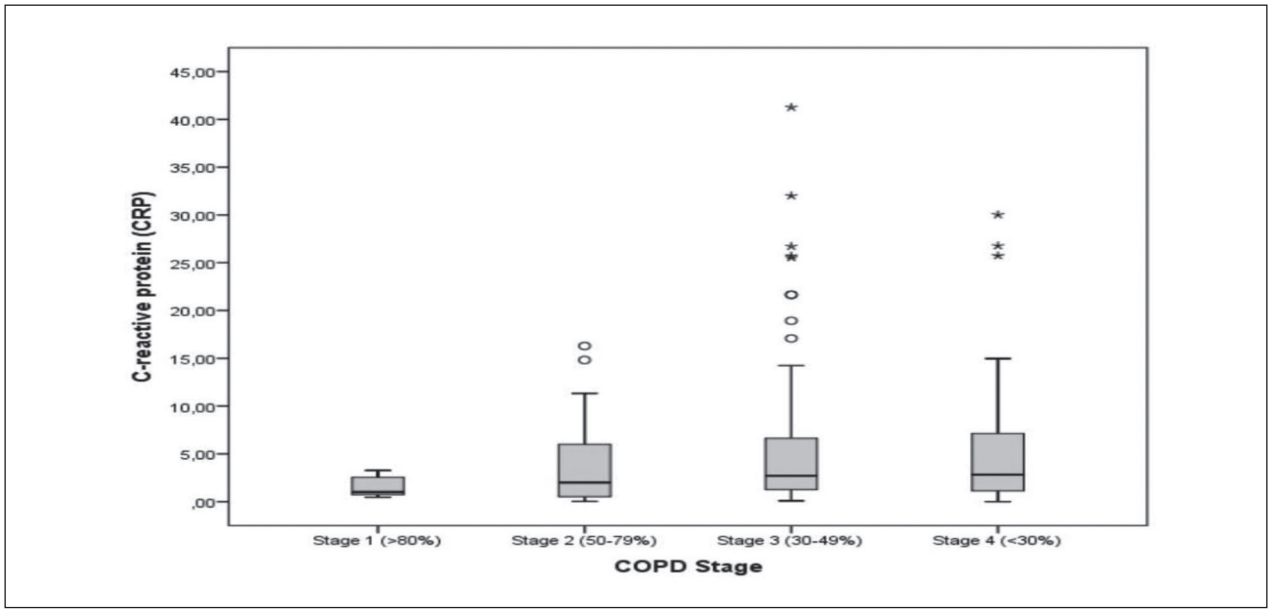

Figure 2. Box plot graphs of CRP and COPD Stage

showed that exposure to tobacco smoke affected level of AAT (10). In the studies of Senn et al, AAT levels were positively related to males and postmenopausal female age group; it depended on rising dose in patients with exposure to tobacco (12). Serum AAT level in the study of Ferrarotti et al didn't get affected from smoking status (13). In the study, AAT levels were similar between groups of patients who were discharged from

hospital or became exitus at their existing admission to hospital, who became exitus or not in the first year, who were hospitalized to intensive care unit or not in a year. Those results showed that AAT serum levels didn't affect to be discharged from hospital, mortality in a year and hospitalization to intensive unit care. In the studies of Nuijens et al, serum elastase-AAT complex was an significant prognostic factor and was higher in groups of patients who became exitus than patients who survived (14). The AAT Deficiency Registry Study Group informed that serum levels which increased with intravenous AAT augmentation therapy increased survivability (15). In the studies of Li et al, concentration of serum AAT significantly affected (16). In the studies of Sclar et al, serum AAT levels which increased with augmentation therapy provided longer life span (17). Carey et al showed that after liver transplantation, patients with AAT deficiency displayed normalizing AAT serum levels and together with that the rate of survivability for a year increased to 90 % (18). On contrary to those studies, in the studies of Simpsons et al, survivability day was 300 days more in the group with low level of AAT. (19).

In this study, serum AAT level was reasonably correlated in a positive way with WBC and CRP, which is a marker of inflammation. In studies of Nuijens et al, serum elastase-AAT complexes levels weren't correlated with number of WBC and on the contrary, AAT level was significantly high in patients whose WBC number was low (14). According to Senn et al, factors which are related to serum AAT levels didn't get affected from CRP and CRP itself was positively related to Serum AAT level (12). According to Ferrarotti et al, serum AAT levels didn't get affected from CRP levels (13).

Since the beginnings of 1980, patients with AAT deficiency have been given purified human AAT concentration and their serum levels have been increased. Additionally, in those patients whose serum levels were increased and cured, it was seen that there was a less decrease in their FEV_1percentages (20). In the study, it was seen that approximate AAT levels significantly increased along with seriousness of COPD stages which raised percentages of FEV_1. CRP increased till Stage III and it decreased at Stage IV. According to Senn et al, since there was an absence of adjustment, serum AAT level was inversely associated with FEV_1 (12). Serum levels which increase with The AAT Deficiency Registry Study Group intravenous AAT augmentation therapy didn't have a general affect on FEV_1 decrease ratio. However, patients predicted with FEV_1values of 35 to 49% were stated to have a slower decrease in values (15). According to Sclar et al, predicted FEV_1 which increased with AAT augmentation therapy was decreasing (17).

Conclusion

In the study, in a secondary care serving hospital where limited examinations can be done, AAT serum levels as external examination of patients diagnosed with COPD were studied. Only one of the patients included in the study was seen to have AAT deficiency and genotypic analysis was done. Relations of AAT serum levels and relations of parameters belonging to patients were evaluated. The limitations of the study are not to be able to reach laboratory results of some patients, and to be able to measure only serum AAT levels. Studies in which especially AAT levels are examined and advanced research to be done are significantly needed.

Conflict of interest: None to declare

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Original article

Proposal of a study protocol of a preliminary double-blind randomized controlled trial. Verifying effects of selenium supplementation on selenoprotein p and s genes expression in protein and mRNA levels in subjects with coronary artery disease: selenegene study

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Summary. *Background:* Selenium is the component of selenocystein amino acid, which itself is the building block of selenoproteins having diverse effects on various aspects of the human health. Among these proteins, selenoprotein P is the central to the distribution and homeostasis of selenium, and selenoprotein S as a transmembrane protein is associated with a range of inflammatory markers, particularly in the context of cardiovascular disease. It is known that selenium status outside of the normal range is considered to confer different benefits or adverse cardiovascular risk factors. Therefore, for the first time, we aimed to verify effects of Selenium supplementation on Selenoprotein P and S Genes Expression in Protein and mRNA Levels in Subjects with Coronary Artery Disease (CAD). *Methods:* This is the study protocol of a double blinded randomized clinical trial on 130 subjects with angiographically documented stenosis of more than 75% in one or more coronary artery vessels. In this 60-day study, 65 patients in each group received either a 200mg selenium yeast or placebo tablets once daily. During the study, subjects were followed by phone calls and visited our clinic twice to repeat baseline measurements. We hypothesized that our finding would enable a more basic and confirmed understanding for the effect of selenium supplementation by investigating its effect on gene expression levels in people with CAD. *Discussion:* Upon confirmation of this hypothesis, the beneficial effect of inflammation regulation by supplementation with micronutrients could be considered for subjects with CVD. (www.actabiomedica.it)

Key words: selenium, supplementation, gene expression, metabolic syndrome, coronary artery disease, randomized controlled trial

Background

Selenium is a vital trace element for humans and is part of the unusual amino acids selenocysteine and selenomethionine (1-4). It is involved in the mechanisms that form part of tissue inflammation and oxidative stress (5).

To date, almost 25 different selenocysteine-containing selenoproteins have been detected in human cells and tissues (6). Since a lack of selenium deprives

a cell of its ability to synthesize selenoproteins, many health effects associated with a low selenium intake are believed to be caused by the deficiency of one or more particular selenoproteins (7). On the other hand, it is important to note that too much selenium in the diet causes toxic effects and leads to selenium poisoning (8).

The threshold between essential and toxic concentrations of this element is rather narrow: the factor is in the range of 10-100 (8).

A noticeable geographical variety is found in its dietary intake from plants, which is low in Europe because of contrasts in its bioavailability. In a few sections of the world, for example, the UK, China, and Russia, its extensively decreased admission can be principally brought on by the brought down imports of wheat developed in the northern selenium-rich high-protein soils for making bread. Its inadequacy has been every now and again reported in areas where most nourishment is privately developed and expended (9).

Recently, the level of blood selenium has been determined by measuring the amount of selenoprotein P (SELP). The latter is the most common selenoprotein found in the plasma (10), which contains ten selenocysteine residues and functions as a selenium supply protein (11). In addition, it is suggested that there is an association between the level of SELP and an abnormal glucose metabolism. Moreover, previous studies have shown that SELP plays a part in the development of cardiovascular risk factors, such as obesity, diabetes, and atherosclerosis (12).

Another selenoprotein is selenoprotein S (SELS), which was recently, described as an endoplasmic reticulum (ER) and plasma membrane-located selenoprotein that is involved in the physiological adaptation to ER stress (13, 14). The SELS gene is known to be expressed in a wide variety of tissues and cell types, including those of the former that are important for glycemic control, such as adipose tissue, muscle, and liver (15, 16). In omental adipose tissue from diabetic subjects, gene expression of SELS was increased compared with that of non-diabetic controls, while in both groups, SELS expression correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) (17). In HepG2 cells, SELS expression is inhibited by glucose; meanwhile, SELS has been suggested to be involved in glucose homeostasis in an animal model of type 2 diabetes mellitus (18) and in human diabetic subjects (19). Additionally, in HepG2 and intestinal epithelial cells, pro-inflammatory cytokines activate the transcription of SELS (20). In the past, genetic analyses of SELS in various cohorts have been performed (21) and associations between SELS polymorphisms and inflammation (22), and hard end points in cardiovascular disease (23,24), have been found. However, there is no previous study showing how selenium supplementation changes the expression of SELP and SELS genes in the level of mRNA and protein in subjects with documented coronary artery disease.

Main objective

Our hypothesis in the present study is that Se supplementation will alter the expression of SELP and SELS genes in mRNA and protein levels. Our aim is to estimate the effects of Se intake on changes in the expression of these genes.

Specific objectives

1. To compare the level of selenium in both intervention groups, before and after the study.
2. To compare the level of expression of SELP and SELS in both intervention groups.
3. To estimate the effect of selenium intake on quality of life.
4. To describe nutritional status and selenium feeding habits.

Methods

Ethical considerations

The trial was approved by the Isfahan University of Medical Sciences and Research Ethics Committee and conforms to the standards currently applied by the Iranian Registry of Clinical Trial (IRCT=10252). An external data safety monitoring board monitored the trial to guarantee its quality. An option was in place for the trial protocol to be altered, with confirmation from this committee, if interim analyses demonstrated statistically significant differences in the primary end point between the groups. If significantly beneficial ef-

fects of Se supplementation were found, Se treatment would have been offered to those patients who were randomized to the placebo group.

Study design and settings

This was a single-center; double-blind, placebo-controlled, superiority-randomized clinical trial. All participants had coronary artery disease, which was documented by angiography. In total, 160 patients were enrolled in the study after fulfilling inclusion and exclusion criteria. The subjects were referred to our research center from referral heart hospitals in Isfahan, Iran.

Participants

1. Having angiographically documented stenosis in one, two or three vessels. These should have confirmed coronary artery disease angiographic diagnosis, based on the stenosis, of more than 75% in each vessel.
2. Aged between 30 and 65 years.
3. Living in Isfahan province for more than 5 years.

Exclusion criteria

1. Pregnancy or breastfeeding.
2. Having diabetes mellitus or being under treatment by metformin.
3. History of hormone therapy, Cushing's syndrome, inflammatory bowel disease and other inflammatory disorders, gastrointestinal disease and lactose intolerance, and/or use of any type of selenium supplements.
4. History of liver disease, kidney disease, gout, rheumatoid artery, thyroid disorders, adrenal and parathyroid dysfunction, women's diseases, cancer, cardiovascular disease including arrhythmias, uncontrolled advanced congestive heart failure (CHF), severe valvular disease, pericarditis and/or myocarditis.
5. Under medical prescription of vitamins or supplements
6. Participating as a volunteer in other clinical investigations with interventions.
7. Having conditions that may result in low protocol adherence.

Patients who met the inclusion criteria were invited to participate in the study and informed consent was obtained from them. Participants underwent an initial interview. The initial interviews and tests included a questionnaire to collect demographic data, medical history, stress levels, physical activity, smoking habits, quality of life, anthropometric measurements, and detailed information for a nutritional profile, including selenium intake in diet and biochemical laboratory measurements.

Intervention

Patients received either 200 mg selenium yeast tablets or placebo tablets orally after a meal, once daily for 60 days. The placebo tablets had the same color, form and texture as the selenium tablets. At each visit, patients in both groups received the number of tablets needed to be taken until the next scheduled appointment. If, for any reason, a treatment interruption occurred, the treatment duration was to be extended until the volunteer had taken 60 tablets.

Selenium_yeast was provided in commercial form by the Nature company, while Amin pharmaceutical company was responsible for providing the placebos. Adverse events were to be recorded.

Measurement of Gene Expression in RNA level

Total RNA (2 μg) was treated with DNase I and reverse transcribed using random hexamers and Super Script II reverse transcriptase (Invitrogen Ltd, UK). Primers were designed using Primer3 software and synthesized by Sigma-Aldrich, Ireland. PCR was carried out in a 50 ml mix containing 0.5 ml of Taq polymerase (Invitrogen) and 1 ml of cDNA. PCR products were then run on 2% agarose gel with a parallel 100 bp DNA ladder (Promega, UK). Real-time PCR was carried out according to the manufacturer's instructions using the Light Cycler RNA SYBR Green 1 Amplification Kit (Roche Applied Science). All measurements were independently repeated six times (n=6). The maximum concentration of total RNA template used was 0.5 μg ml-1. Data are presented as cycle thresholds

(Ct), and in quantitative analysis, the Ct method was performed using the LightCycler version 4.0 software. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression levels were used to normalize.

Determination of Selenoprotein P and S

Each selenoprotein was determined considering similar strategies described as follows: Total plasma selenoprotein concentration was measured at baseline and at the 8 week of follow-up in 130 participants who were participated in this study by commercial kit Hangzhou Eastbiopharm Co.,Ltd (China). This kit used a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of Human selenoprotein in samples. Then, the selenoprotein was added to the selenoprotein pre-coated monoclonal antibody Enzyme. Selenoprotein antibodies labeled with biotin were then added and combined with Streptavidin-HRP to form an immune complex. The incubation was carried out and washed again to remove the uncombined enzyme. Chromogen solutions were then added which the liquid color was finally turned from blue to yellow due to the effect of the acid. The chroma of color and the concentration of the Human selenoprotein of samples were positively correlated.

Outcomes

1. To compare the average concentration of serum protein products and mRNA levels of SELP and SELS in target groups before and after the trial.
2. To determine the selenium level before and after supplementation.

Secondary putcome

Changes in components of metabolic syndrome, such as diabetes, hypertension, and central obesity after supplementation.

Follow-up

Participants were followed every two weeks by phone calls and answered brief questions on the occurrence of any adverse events. Four weeks after the initial visit, they were invited to visit Isfahan Cardiovascular Research Institute and interviews and non-laboratory evaluations similar to the baseline were performed. Moreover, all evaluations including blood tests were repeated eight weeks after the baseline visit.

All examination results were recorded and stored in digital media to do later analysis at an EPI with software SPSS (Version 15)

Sample size

We estimated a minimum sample size of 130 volunteers (65 in the placebo group and 65 in the Se group). In this calculation, we considered anα error of 0.05, a β error of 0.20, and a difference in progression risk of 50%.

Randomization

The 130 subjects were randomly allocated into two groups in a 1:1 ratio. Placebo pills that looked similar to selenium were provided by the pharmacist. The tablets were packaged by pharmaceutical companies in the same numerical packages and were recognized with four different codes. Executives and interviewers were both unaware of the coding. The latter decided which set of participants would form the placebo group and which would be the intervention group by flipping a coin. As volunteers were recruited by the medical staff, they were assigned a number that sequentially corresponded to a treatment box. In this way, a strategy of numbered boxes was used for sequence concealment.

Blinding

Patients, interviewers, and staff involved in outcome assessment were blinded to treatment. The blinding was conducted using the same strategy of allocation concealment by numbered boxes. In brief, numbers were assigned to volunteers' treatments, but only one pharmacist, who was not involved in the tasks, was aware of what was in each numbered box.

Minimum sample size estimation

The type of analysis that was of the greatest interest was the intention-to-treat analysis. At baseline, both intervention groups were compared concerning information that may have modified disease progno-

Table 1. Clinical Characteristics of Iranian Population Participants in the Selengene Study

Demographic characteristics	Non MetS	MetS	P Value
Women (%)	11 (15.5)	21 (32.3)	0.021
Age	55.9±7.52	55.6±6.41	0.798
FBS (mg/dL) (Mean ±SD)	96.3±11.0	106.7±14.1	<0.001
Chol (mg/dL) (Mean ±SD	153.7±39.7	158.6±40.3	0.479
TG (mg/dL) (Mean ±SD)	139.1±86.5	198.5±122.0	0.003
HDL_C (mg/dL) (Mean ±SD)	43.0±9.52	37.8±9.67	0.003
LDL-C (mg/dl) (Mean ±SD)	81.4±32.2	80.8±32.9	0.913
BMI (Kg/m2), Mean +SD	26.8±3.67	28.8±4.01	0.003
Waist circumference\Mean +SD	97.9±9.78	106.7±14.1	<0.001
SBP (Mean ±SD)	125.8±17.6	141.4±19.7	<0.001
DBP (Mean ±SD)	78.4±9.78	83.0±10.3	0.009
Diabetic			<0.001
Normal	51 (71.8)	18 (29.0)	
Pre diabetic	18 (25.4)	27 (43.5)	
diabetic	2 (2.8)	17 (27.4)	
Hypertension			<0.001
Normal	17 (23.9)	5 (7.7)	
Pre hypertensive	34 (47.9)	23 (35.4)	
hypertensive	20 (28.3)	37 (56.9)	
Central Obesity			
Residency (Urban)	65 (91.5)	64 (98.5)	0.118
Education Years (%)			
illiterate(%)	7 (9.9)	10 (15.4)	0.754
<9	39 (54.9)	35 (53.8)	
9-12	14 (19.7)	10 (15.4)	
13<	11 (15.5)	10 (15.4)	
Family history of Cardiovascular disease (%)	6 (8.5)	8 (12.3)	0.460
Lifestyle			
Smoking (%)	14 (19.7)	11 (16.9)	0.674
Intake of food items			
Red Meat Intake (times/week)	6.58±2.39	7.23±4.23	0.269
Fats	2.01±3.68	1.51±2.59	0.583
Fruit and vegetables	49.0±28.0	43.5±19.2	0.182
Nuts	3.95±4.10	3.46±2.81	0.435
Beans	1.76±0.85	1.88±0.96	0.462
Diary	13.5±4.62	14.8±5.00	0.119
Cereals	21.8±6.67	23.1±6.06	0.244

SePP1: Selenoprotein P, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, Chol: Total Cholesterol, TG: Triglyceride, LDL-C low density Cholesterol, HDL_C: High density Cholesterol, FBS: Fasting Blood Suger

Table 2. SELS and SELP gene expression in subjects with MetS versus subjects without MetS

Gene	Variantes	MetS ΔCt	Non MetS ΔCt	2^(-ΔCt)	P value
SELS	VIMP I(MEDIAN (IQR))	8.85 (7.93-12.2)	8.99 (7.49-11.48)	1.02	0.948
	VIMP II(MEDIAN (IQR))	7.64 (4.06-9.05)	6.82 (5.28-9.56)	1.60	0.863
SELP	SELPI(Mean ± SD)	2.75±4.21	2.04±3.40	0.61	0.56

sis, to check whether random allocation was working properly at that time. Analysis was conducted by adjusted regression as per protocol. This analysis was mainly conducted on the understanding that random allocation did not fulfill its purposes at baseline.

Stopping rules

All important harmful or unintended effects in each group, such as nausea, vomiting, nail changes, loss of energy, and irritability.

Ethics

The study protocol was explained to all who agreed to enroll in the study and sign the agreement. All potential side effects were described.

Results

A total of 65 subjectswith MetS and 71 subjects without MetS were included in this study. No significant differences were observed between both groups in age 55.6±6.41 vs. 55.9±7.52 P=0.798) and sex (female, 32.3% vs. 15.5%, P=0.021), respectively. Mean of FBS is higher among subjects with MetS (106.7±14.1vs, 96.3±11.0, P<0.001). Mean of TG is higher among MetS+ 198.5±122.0 vs. 139.1±86.5, P=0.003) Mean of systolic and diastolic blood pressure, BMI, WC, were higher among subjects with MetS (P=0.05). There was no significant difference in the family history of cardiovascular disease between two groups (P=0.388). Also, there were no significant differences between smoking and nutritional habits (such as using beans, dairy, all types of meats, cereals, nuts, fruits, and vegetables) between the two groups (P<0.05) (Table 1). Median and interquartile for the expression of different variants in our study groups are shown in table 2. The level of VIMP II was lower in MetS+ compared to the MetS- subjects; however it was not a significant difference (P <0.05). We found no significant differences in quantitative expression of VIMPI in both groups. There are no significant mean differences between both variants in subjects with MetS (2.74±1.61, P=0.109). There is no significant difference in the quantitative expression of SELP in subjects with MetS versus subjects without MetS (2.75±4.21, 2.04±3.40, p=0.56).

Discussion

If the hypothesis is confirmed, it will constitute a new contribution to the improvement of the healthcare of the affected population; in Iran, this equates to approximately 1 million sufferers. Supplementation with micronutrients is simple and has been widely employed using oral administration (25). In many countries, including the US and France, selenium is considered a supplement rather than a medicine. According to the Brazilian Agency of Sanitary Inspection, 100 micrograms of selenium is considered medicinal, because it is up to 100% of the recommended 34 microgram daily intake. However, the daily level in our trial was within the limits considered to be safe (200 micrograms; Secretariat of Health Surveillance, Ministry of Health (SVS/MS) Ordinance 40/1998). The organic form of selenium (selenium-yeast) was chosen because it has been proven to prevent and improve cardiovascular disease. If the microgram treatment in this trial turns out to be beneficial, a new and affordable treatment strategy for cardiovascular disease would be suggested which require further multicentral trials to support and confirm our mentioned possible trial results.

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Conflict of interest: None to declare

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Original article

Topical Fisionerv® is effective in treatment of peripheral neuropathic pain

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Summary. *Background:* Management of neuropathic pain (Neu P) is complex and difficult. Although there are several therapeutic options, treatment with Neu P is often inadequate, which led to undertreated patients. Thus, it would be desirable, for Neu P treatment, further multimechanistics approaches. *Objective:* The aim of the present study was to evaluate, in Neu P management, the effectiveness of "FISIONERV, a gel for topical use. *Setting:* This study was conducted in the "Rehabilitation Unit of N. Melli's Hospital, Brindisi, Italy". *Patients and intervention:* In this study a double- blind randomized controlled clinical trial was conducted over 8-week treatment on 58 outpatients affected by Neu P caused by lumbar sciatica or lumbar disk herniation and/or lumbar canal stenosis (31 subjects), or with carpal tunnel syndrome (27 subjects), randomly assigned to the following two groups: Group A; n=29, received (*fisionerv*® gel, 3 times/day) added to physiotherapy (forty minutes-daily session). Group B; n=29 received a vehicle gel (placebo, 3 times/day) added to physiotherapy (forty minutes-daily session). *Measurements:* Pain was assessed by a visual analogue scale (VAS). Neuropathic symptoms frequency (pain, burning, paraesthesiae and numbness) were scored at baseline and at the end of the treatment. Treatment compliance and safety were also evaluated. *Results:* Both groups experienced a significant reduction in VAS and neuropathic symptoms after 8-treatment weeks. However, a significant ($p<0.05$) improvement was observed in group A (VAS mean 5.3 (1.10) with respect to group B (VAS mean=6.17 (0.80), already after 4 weeks of treatment. A further VAS reduction was recorded at 8 treatment weeks, with significant difference between the treatments (group A: VAS mean=1.89 (0.77); group B: VAS mean=3.79 (1.20) ($p<0.001$). In addition, more patients of the group A, than in group B, reported an improvement of their neurophatc pain ($p<0.01$). No adverse drug reaction was observed. Conclusion: Use of *fisionerv*®, in combination with physiotherapy, resulted a useful approach to NP treatment. *Clinical rehabilitation impact:* These preliminary observations suggest that some interesting goals (better pain control and physical wellbeing) could be achieved by a multimodal therapy in NP patients. (www.actabiomedica.it)

Key words: peripheral neuropathies, *fisionerv*® emulgel, physiatric treatment, neuropatic pain

Introduction

Aim of the study

Neuropathic pain (NeuP) is a symptom which occurs as a result of injury or dysfunction of the nervous system caused by a lot of conditions affecting the peripheral or central nervous system. Compared to other types of pain, it is debilitating, both physically and psychologically. It could be constant or intermittent, spontaneous or induced by a trigger stimulus and could give allodynia or hyperalgesia. The cause could be due to the pathological changes or damages in neurons which can disrupt the normal pain signaling process causing sensitization or stimulation of spontaneous neuronal activity which is perceived as pain. Because of the complex nature of Neu P and, since the treatment of the underlying pathophysiogy causing neurophaties may not be always possible, a multidisciplinary and integrated approach is often used to manage the pain mainly improving the patient's quality of life. Valid drugs today available for Neu P treatment result often inadequate, considering that only 40-60% of treated patients may report an adequate pain relief and comorbidities whereby polidrugs intake could appear an unbearable situation (1). Furthermore, several guidelines have been published for the pharmacological management of Neu P which underline the importance of drugs efficacy, patient comorbidities, potential side effects and drug interactions, as well as abuse potential and costs (2-5). Other additional drugs like *capsaicin or lidocaine* could be used topically to relieve pain in a specific area of the body or to relieve particularly severe pain for shorts period of time, primarily in patients which cannot or don't prefer to intake drugs due to their interference with the ongoing treatment. Capsaicin preparations (cream or ointment) have shown some effectiveness on pain. Derivated from "*capsicum chili pepper*", capsaicin has been used for centuries as a topical analgesic. It is a selective agonist of TRPV1 receptors (transient receptor potential vanilloid receptor 1) expressed in afferent neuronal "c" fibers. Local activation of TPRV1 by heat, ph changes or endogenous lipids, normally leads to nerve depolarization propagated to spinal cord and brain thus causing local heat stinging and itching sensation. Prolonged activation of TPRV1 by capsaicin results in loss of receptor functionality, causing impaired local nocyneception for extended period. The therapy also involves the use of neuroprotective drugs, such as alpha-lipoic or tioctic acid, which have antioxidant action, in order to improve nerve conduction speed and endoneural blood flow and thereby reducing pain. *Fisionerv* ® is an ozolipoil gel containing stabilized ozonized oil together with a dynamic pool of functional molecules to release bioperoxides and ozonides, in synergic action with tioctic acid plus Vitamin E, capsaicin, panthenol, arginine, valine, isoleucine, leucine and glutamine. Generally, although the neuropathic pain poorly responds to treatment with NSAIDs or pure analgesics, such classes of drugs are however equally and widely used in these diseases. Our aim is to demonstrate the validity of *fisionerv*® to ameliorate the painful state of the treated patients and to significantly improve the suffering pain with respect to the control group. The important aspect put on evidence in this procedure is the lack of needing other concomitant pharmacologic therapies during the treatment with *fisionerv*®. Their quality of life obtained a significative improvement with a long-lasting pain reduction during the walk, the upright posture and during sleep, especially in supine position.

Formulation: *fisionerv*® emulgel is packed in 100 ml aluminum tube. The emulgel is constituted of Carbopol 990 Polymer which produces the gelling water and Carbopol Ultrez 20 which emulsifies the ozonized olive oil, previously stabilized with alpha lipoic acid and Vitamin E acetate.

Materials and methods

Study design

Consecutive outpatients (Department of Physical and Rehabilitative Medicine, N. Melli's Hospital, Brindisi, Italy) with clinical features of Neu P from November 2015 to June 2016 were invited to participate in this 8-week, randomized, controlled, clinical trials. A total of 76 consecutive outpatients affected by low back pain with leg pain (24 women and 22 men) or carpal tunnel syndrome (16 women and 14 men) were screened for eligibility. This study, conducted in com-

pliance with the "*ethical principles for medical research involving human subjects*" of the Declaration of Helsinki and *in accordance with Italian laws and regulations*. The informed consent of all the patients was obtained prior the begin of the study.

Inclusion criteria: The enrolled patients were suffering neuropathies for more than six months, with chronic pain from moderate to severe (VAS>4) and with little or absent response to systemic or local analgesic therapy.

Exclusion Criteria: Were excluded from the study pregnant or breastfeeding patients, spinal tumor, major organ transplantation, uncontrolled major depression or psychiatric disorder, acute or uncontrolled medical illness (malignancy or active infection), chronic severe condition that could interfere with interpretation of the outcome assessments. Also allergy to study drugs and placebo were taken into consideration as exclusion criteria. On the total number of admitted outpatients, only 58 patients were enrolled in the present study: (low back pain=31; 17 women and 14 men; carpal tunnel syndrome=27; 14 women and 13 men; mean age=63,5 years , SD=7.1) (Table 1).

Enrolled patients, all over 18 years old, were informed about the reasons and objectives of the present study, releasing an informed consent as spontaneous adhesion to the study.

Study protocol and treatments

All the enrolled patients (58) were randomized by an independent investigator, using a computer generated-random-number table to the following treatment groups:

Group A (treated group); n=29, received *fisionerv®* gel, three times/day) added to physiotherapy (forty minutes-daily session);

Group B (control group); n=29 received a vehicle gel (placebo, three times /day) added to physiotherapy (forty minutes-daily session).

Dosage: *fisionerv®* for topical use was administered 3 times a day.

Assessment: Before starting the study, all the patients underwent a screening included medical history and physically examination gender, age and occupation were documented, as well as other clinical characteristics such as the diagnosis, time since first diagnosis, diagnostic tests performed and concomitant treatments.

All the patients were asked, by a blinded interviewer, for neuropathic pain according to the original Scott- Huskisson scale with score from 0 ('no pain') to 10 (unbearable pain) (6).

Table 1. Baseline demographic and clinical characteristics of participants with neuropathic pain in groups. A and B

Characteristics	Group A (n= 29)	Group B (n= 29)	*p*
Age	57.09 [(16.40) 50.00-64.18]	51.65 [(12.23) 46.36-56.94]	*0.21*[a]
Range	27-78	31-78	
Time since onset of pain (mo)	6.95 [(1.06) 6.49-7.41]	7.22 [(1.20) 6.69-7.74]	*0.44*[a]
Range	6-9	6-10	
Sex (female/male) No (%)	16/13	15/14	*1.00*[b]
Type of neuropathic pain (NeuP) No (%)			
Low back pain with leg pain (female/male) No (%)	9/7	8/7	*1.00*[b]
Tunnel Carpal Syndrome (female/male) No (%)	7/6	7/7	*1.00*[b]
***VAS** score* Low back pain	8.26 [(0.70) 7.87-6.78]	8.00 [(1.00) 7.44-8.55]	*0.40*[a]
***VAS** score* Tunnel Carpal Syndrome	7.66 [(1.17) 7.01-8.31]	7.36 [(1.04) 6.77-7.94]	*0.45*[a]

Values are means [(SD: standard deviation) 95% CI: 95% confidence interval unless otherwise specified;
VAS: Visual Analogic Scale (0-10 point);
[a] As determined by an independent 2-sample t;
[b] As determined by Fisher's exact test.

All outcomes before treatment (T0) and at the scheduled follow-ups (T1=4-treatment-weeks and T2 =8-treatment-weeks were assessed by a third blinded independent observer.

Neuropathic symptoms frequency (pain, burning, paraesthesiae and numbness) were also scored at baseline and at the end of the treatment.

The compliance of the patients with the study was assessed by checking whether the patients followed the physiotherapy sessions that were prescribed at the start of the study and recording adverse reactions, intolerance, or "lack of efficacy" as perceived by the patients.

Both experimental groups were composed by 29 patients: treated group: (**Group A**)=16 women and 13 men, control group (**Group B)=**15 women and 14 men (table 1).

On these two groups of patients we have studied the effectiveness of our galenic topic preparation "*fisionerv*"®, compared to a similar gel but without ozonides used in placebo group.

Patients were not allowed to take any other analgesic compound for the entire duration of the study.

Statistical evaluation: The results are reported as descriptive statistics: quantitative parameters are reported as median, minimum, maximum and standard deviation; qualitative parameters are reported as absolute and relative frequencies. Comparisons were made with a chi-squared test for qualitative parameters and with an unpaired Student's t test for quantitative ones.

Two-way analyses of variance (ANOVAs) for repeated measures of VAS scores were performed with group (treatments) as the between-subjects factor and time and group interactions × time as the within-subjects factors. Post hoc comparisons were made by Bonferroni multiple comparisons test. Statistical analysis was performed according to the principle of intention to treat, with missing data imputed with the "last observation carried forward" technique. All analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). Computed *P* values were 2-sided and $p<0.05$ was used to determine statistical significance.

Results

As shown in table 1, the participants' baseline characteristics did'nt show statistically significant differences between the experimental groups.), Of the 58 patients with Neu P, 38 (65.5%) had numbness and 20 (35%) had tingling and touch hypoesthesia at baseline. Repetead measure Two way Anova for VAS scores showed a significant effect of Treatment: F=3.01 df=1/56; p<0.0001 and a significant treatment-time interaction: F=3.67; df= 2/112, p<0.0001. A significant change in VAS score over time also was observed in both groups: F=75.88; df=2/112. The effect on pain relief was perceptible-at 4-treatment-weeks (T1) versus baseline (T0) in both groups although it was more evident in group A than in group B with a statistically difference between treatment groups (p<0.05). Comparing VAS scores at 8 weeks of treatment (T2 versus T1), the difference between the treatments resulted more significant (p<0.001) Table 2.

In addition, more patients of the group A reported that their neurophatic pain was significantly improved with respect to the patients of the group B ($p<0.01$; *Chi square test).* No drug reaction was observed.

Table 2. Time course of VAS scores in Treatments groups at the baseline and follow-ups: T1 (4 treatment- weeks); T2 (8 -Treatment weeks);Tukey Multiple comparisons test between treatment groups

	Group A (n= 29)	Group B (n= 29)	p
T0	8.26 [(0.70) 7.62-8.38]	7.69 [(1.03) 7.29-8.08]	n.s.
T1	5.31 [(1.10)4.89-5.73]°	6.17 [(0.80) 5.86-6.47]#	<0.05*
T2	1.89 [(0.77) 1.60-2.19]°	3.79 [(1.21) 3.33-4.25]#	<0.001**

* p<0.05 T1 group B vs T1 Group A
** p<0.001 T2 group B vs T1 Group A
° p<0.001 vs baseline and T1
# p<0.001 vs vs baseline and T1

Conclusions

Previous studies with ozolipoil were made in 2015 by Inchingolo et al (11) in order to test, on actinic ulcers of patients receiving radiation therapies, a mixture with a formulation containing, other than ozolipoile, several natural active ingredients. Although there are several therapeutic options, Neu P treatment results often inadequate leaving patients undertreated thus, a better use of available options and multimechanistics approaches to Neu P management, based on the patient's characteristics, may result beneficial. Multiple factors are involved in the pathophysiology of peripheral neuropathies and it is very difficult to pinpoint the right treatment. For this reason new treatments are desired. In this context, *fisionerv*® represents a topical gel which encloses, in its formulation, a wide range of active ingredients related with different mechanisms involved in peripheral neuropaties. Results clearly demonstrate a significant pain improvement in the group treated with *fisionerv*® with respect to placebo group. The important aspect put on evidence in this procedure is the lack of needing other concomitant pharmacologic therapies during the treatment with *fisionerv*®. Their quality of life obtained a significative improvement with a long-lasting pain reduction during the walk, the upright posture and during sleep, especially in supine position. However, further studies and larger groups of patients are needed to validate these preliminar data in order to confirm our encouraging results.

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Conflict of interest: None to declare

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Original article

Physicians' perception of the importance of ethical and deontological issues in a major Italian Province: pilot questionnaire and its validation

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Summary. *Background and aim:* This study aims at validating a questionnaire on physicians' knowledge and perception of deontological and ethical rules that guide the medical profession, in a major Italian Province. *Methods:* We designed an on-line survey questionnaire. Participants (N=200) were asked to fill in information regarding their demographic features and knowledge of the deontological code. *Results:* Concerning the preliminary data, the median total score on knowledge of the deontological code was 0.50. A significant difference in the total score was observed among education groups. Specifically, the median total score among subjects with a specialist qualification was significantly lower than among those with only a medical degree. *Conclusions:* The tested instrument and methodology appear to be efficacious and reliable. Our preliminary data indicate that knowledge of the rules concerning medical deontology and the related principles of medical ethics seems to be very limited. Therefore, the authors plan to implement a second phase of the study, which will consist of the questionnaire' distribution to a broader and more representative sample. (www.actabiomedica.it)

Key words: code of medical deontology; medical ethics; ethical principles; physicians' knowledge; pilot questionnaire

Background

In their clinical practice, physicians are increasingly called upon to deal with complex situations that may be a source of ethical dilemmas and deontological problems. This requires knowledge of the ethical principles included in the Code of Medical Deontology (here in after CMD).

The Italian CMD contains a series of rules of conduct which are inspired by fundamental ethical principles shared by the medical community. Physicians enrolled in the professional registry are obliged to observe these rules in their professional practice (1, 2). Whereas in the Anglo-Saxon world the first CMD dates back to the beginning of XIX century, in Italy the first national edition of the CMD dates back to 1924. Subsequently, various revisions were undertaken, including that of 1935-37 (fascist version) and those of republican history date back to 1958, 1978, 1989, 1995, 1998, 2006 and 2014 (currently in force) (3).

Constant revision of the CMD, together with the development of courses of training and updating in medical ethics, medical deontology and bioethics, provides physicians with the coordinates needed in order to orientate their professional practice towards informed and responsible choices (4).

To date, no studies in Italy have investigated physicians' knowledge of deontological rules that guide the medical profession, their update, and their perception of the importance of ethical and deontological issues in their profession.

For this reason, we deemed it important to draw up and validate a cognitive instrument, in the form of a questionnaire, to survey the above mentioned knowledge among doctors and dentists enrolled in their respective professional registries. This need is particularly compelling in the light of ongoing work to draw up a European code of medical ethics capable of laying the foundations for the common implementation of medical practice (5). The present pilot study is to be extended, in the second phase, not only to all the others physicians from Genoa, but also to the entire nation in order to obtain more representative data that may confirm, or confute, the preliminary data gathered during the validation phase of the study.

Materials and Methods

The questionnaire

A preliminary draft of a questionnaire containing closed and semi-closed questions pertaining to various aspects, such as general knowledge of the deontological code and doctors' attitudes towards bioethical issues, was created in Italian. In order to determine whether the questions were clear, the preliminary draft was submitted to a panel of experts in clinical and psychometric properties.

After slight modification of the first draft, the final version of the questionnaire, comprising 12 closed and semi-closed questions, was administered by means of a Google Form Survey (*see Appendix 1*). Demographic characteristics, such as gender, nationality, religion, year of graduation, type of degree and healthcare sector (public or private), were also recorded during the Google Form Survey. The system automatically generated a web-link to the final version of the survey. This, together with a cover letter containing information on the aim of the study, the organization behind the study and assurance that respondents would remain anonymous, was sent via email to the participants (n=200). The survey was sent on February 4th, 2016 and could be completed by participants online, with their answers being automatically and anonymously stored in an Excel file generated by the system. The questionnaire was again administered to participants on March 4th, 2016 by means of the same modalities as the first administration.

Participants

The study involved a sample of 200 medical doctors belonging to the Provincial Order of Physicians and Surgeons of Genoa, Italy. Some respondents possessed only a medical degree conferred between 1970 and 2014, while others also held a post-graduate qualification, such as a specialty degree, doctorate, or a diploma attesting completion of a course of updating or general medicine. In addition, the sector in which the individual worked (public, private or both) was also recorded. Only doctors who had completed the questionnaire during both sessions of administration were included in the analysis.

Data processing

A score from 0 to N (where 0 was assigned to the first answer and N was the number of possible answers per question) was assigned to the answers to questions Q1, Q4, Q5, Q6 Q9 and Q10. The answers to question Q3 were grouped into 5 classes. Specifically, class 1 comprised subjects who did not know any bioethical principle, and classes 2, 3, 4 and 5 were made up of subjects who knew 1, 2, 3, or 4 bioethical principles, respectively. Answers to Q7 were grouped into 3 classes; the first class was formed of subjects who answered that the ethical perspective provided "no solution" or "a normative solution" or "a normative solution and a critical methodology", class 2 comprised subjects who answered "Don't know", and class 3 comprised those who answered that the ethical perspective provided a critical methodology. Regarding question Q8, the answers were grouped into class 1 (subjects did not know bioethics), class 2 (subjects' bioethical knowledge came from 1 information source), class 3 (subjects obtained bioethical information from 2 sources) and so on up to class 5 (subjects obtained information from 4 sources).

Answers to question Q11 were grouped into 4 classes, where classes 1, 2, 3, and 4, respectively, comprised subjects who: (I) had never been faced with a bioethical issue, (II) took an independent decision on bioethical issues, without seeking help, (III) needed help to decide on a bioethical issue, and (IV) took a decision on bioethical issues after seeking help. Thus, questions Q1 to Q8 provided information on doctors' general knowledge of the deontological code, questions Q9 and Q10 provided some information on doctors' feelings towards bioethical issues, and question Q11 provided information on attitudes adopted in managing bioethical issues.

Statistical analysis

Continuous variables are reported as means and Standard Deviations (SD); categorical variables as number and/or percentage of subjects. Data were normalised by using the feature-scaling formula; a section total score was then obtained, indicating values in knowledge domains. To identify and describe the underlying latent construct of the questionnaire, Exploratory and Confirmatory Factorial Analyses were carried out by selecting the factors based on the number of eigenvalues greater than 1 and using the "varimax" rotation method. Reliability analysis was performed by using Cronbach's alpha. Items with Cronbach's alpha coefficients greater than 0.70 were considered acceptable.

To identify problematic items, the Cronbach's alpha improvement or worsening was studied by removing one by one items from the analysis.

Moreover, the stability test-retest was done asking the respondent to complete the questionnaire again 1 month after the first administration (Spearman's test for correlation between items). Differences in scores across groups were evaluated by means of the non-parametric Mann-Whitney test or the Kruskal–Wallis test, as appropriate, whereas any significant associations between continuous variables and scores were assessed by means of Spearman's rank-order correlation coefficient. *Post hoc* analysis was performed by means of the Mann–Whitney U-test, and p-values were adjusted for multiple comparisons by using the Bonferroni correction method. Differences with a p-value <0.05 were deemed significant and data were acquired and analysed in R 3.2.2 software environment (6).

Results

A total of 200 medical doctors were asked to fill in the questionnaire; two questionnaires were subsequently excluded, as these respondents had failed to complete the second questionnaire administration. A total of 196 questionnaires (from 124 males and 72 females) were therefore analysed. The median age of respondents was 52 years (range=25-70). 116 (59.18%) subjects worked in the public sector, 20 (10.20%) in the private sector, and 60 (30.61%) in both sectors. The median year of graduation was 1988 (range=1970-2014). The majority of subjects (N=152; 77.55%) were Catholic, 38 (19.39%) were atheist and 6 (3.06%) were of other religions (2 Jewish and 4 Orthodox). The median duration of employment was 27.5 years (range=2-46). Forty-eight subjects had a medical degree, 116 had a medical specialization and the remaining 32 had both a medical specialization and another post-graduate qualification.

Regarding the doctors' views of bioethical issues (Table 1: Questions 9 and 10), about 51% (N=100) declared that they had had to consider ethical issues before continuing a procedure. The majority (N=58) of these 100 subjects reported that they had sometimes had difficulty in solving ethical problems. 88 subjects (45%) claimed that they had not had to consider ethical issues before continuing a procedure, while the remaining subjects answered "Don't know". Regarding the attitude adopted in managing bioethical issues, 16% had decided independently, 29% had needed help to decide, and 19% had decided after seeking help. Seventy subjects (36%) had never been faced with a bioethical issue. Regarding question Q8, the majority of subjects (N=96) obtained bioethical information from 1 source, while 52, 32 and 8 subjects answered that they learned about bioethics from 2, 3 and 4 sources, respectively. Two subjects answered "Don't know". More than half of the subjects declared that they had no or very little knowledge of the CMD (Q1: 25.51% and 28.57%, respectively). Forty-four subjects stated that they knew only a few points of the

CMD, while 36 stated having fair knowledge. Only 10 subjects (5.10%) claimed to know the CMD. All the CMD's ethical principles (Q3) were known to 24.45% of the subjects (N=48), while 27.55% (N=54) had no knowledge of these principles. 32, 30 and 32 subjects, respectively, knew one, two or three ethical principles (16.33%, 15.31% and 16.33%). Regarding the field of bioethics, ethics and medical ethics (Q5), 38.78% (N=76) of the subjects believed that bioethics, ethics and medical ethics had the same field of interest, while 39.8% (N=78) did not; 42 subjects declared that they did not know. Moreover, a high percentage (Q4: 64.29%) answered that did not know the difference among these disciplines; 24 subjects claimed that there was no difference, and 46 that there was. Analysis of the items designed to investigate the kind of perspective offered by bioethics with regard to morally difficult cases (Q7) showed that, in the view of 29.9% (N=58) of the subjects, the ethical perspective provided no solution or a normative solution, while 38.14% (N=74) answered that the ethical perspective provided a critical methodology. Sixty-two subjects (31.96%) answered "Don't know".

Regarding question Q2, most subjects (52.04%) said they did not know whether the current CMD fully covered the issues related to the medical profession; 32.65% (N=64) thought that it did so sufficiently, while 7.14% replied that it fully covered the issues, and another 7.14% felt it did so only slightly. Only two subjects (1.2%) responded negatively. Regarding the autonomy of the patient and physician (Q6), 58 subjects (29.59%) believed that the current CMD was balanced; 24 (12.24%) replied that the CMD was tilted in favor of patient autonomy, while only two subjects (1.02%) replied that the CMD was tilted in favor of the autonomy of the physician. The majority of subjects (57.14%) selected "Don't know".

The need for an organization to provide advice and guidance on bioethical issues (Q12; Ethics Committee) had been felt very often by 12 (6.12%) subjects, and sometimes by 74 (37.76%); 56 (28.57%) subjects declared that they had never felt this need, while 54 (27.55%) rarely had.

Concerning general knowledge of the deontological Code, the Exploratory Factor Analysis (FA), with a reduction to three-factor solutions, explained 52% of the total variance. Factor 1 grouped Q4 and Q5, while Factor 2 regarded Q3, and Factor 3 combined Q1 and Q8. The subsequent confirmatory FA showed no significant underlying latent constructs (p-value=0.6247). Regarding the reliability analysis (*Internal consistency*), an acceptable Cronbach's alpha value of 0.71 was observed for the total score (Table 1: reliability analysis); the items were therefore combined in the further analysis. Significant Spearman Rho correlation coefficients were observed in the test-retest analysis (Table 1: stability analysis. p-values <0.05). Specifically, the median Rho was 0.90, with a range from 0.33 to 0.99 for Items 7 and 6, respectively. The median total score was 0.50 (range=0.08-0.96), indicating that knowledge of the deontological code was around 50%.

For what concerns the effect of demographic characteristics and professional training on the general knowledge of the CMD, a significant difference in the total score emerged among education groups (Table 2: p-value=0.0103). Specifically, the median total score among subjects with a specialist qualification was significantly lower than among those with only a medical degree (adjusted Mann-Whitney p-value=0.0122).

Discussion

This article describes the development and evaluation of a questionnaire aimed at studying physicians' knowledge of deontological rules that guide the medical profession, their update, and their perception of the importance of ethical and deontological issues in their profession.

One of the major challenges with surveys aimed at understanding the human beings, is that the population characteristics of interest may not be directly measured via single question. Factor analysis helps address this issue (7). Even if the exploratory factor analysis, performed on our data, showed possible underlying latent constructs, the subsequent confirmatory factor analysis demonstrated no significant results (p-value=0.6247) underlining that the hypothesized structure adequately did not fit the observed data.

Adequate evaluation of the reliability of a specific questionnaire involves analysis to determine internal consistency and test-retest reliability for all of the

Table 1. Reliability and stability analysis
N(%) = number of observations with percentage; Mean (SD) = Mean with Standard Deviation of the normalised and raw data for Reliability and Stability analysis, respectively; Cronbach's α = Cronbach's α is item delated; Rho = Spearman's coefficient; p-value = p-value of the correlation test.

		Reliability Analysis		Stability Analysis			
Knowledge questions	Subjects (%)	Mean (SD)	Cronbach's α	Mean (SD) at T0	Mean (SD) at T1	Rho	p-value
Q1		0.36 (0.29)	0.63	1.49(1.20)	1.56(1.27)	0.90	<0.0001
No	50 (25.51%)						
very little	56 (28.57%)						
just a few points	44 (22.45%)						
enough	36 (18.37%)						
Yes	10 (5.1%)						
Q3		0.49 (0.39)	0.59	1.94(1.56)	2.01(1.55)	0.91	<0.0001
no one	54 (27.55%)						
One	32 (16.33%)						
Two	30 (15.31%)						
three	32 (16.33%)						
Four	48 (24.49%)						
Q4		0.75 (0.36)	0.59	1.52(0.71)	1.53(0.68)	0.94	<0.0001
No	24 (12.24%)						
Yes	46 (23.47%)						
I don't know	126 (64.29%)						
Q5		0.51 (0.44)	0.66	1.01(0.89)	0.96(0.85)	0.88	<0.0001
Yes	76 (38.78%)						
I don't know	42 (21.43%)						
No	78 (39.8%)						
Q7		0.53 (0.41)	0.71	1.08(0.83)	0.86(0.80)	0.33	0.0011
no critical	58 (29.9%)						
methodology	62 (31.96%)						
I don't know	74 (38.14%)						
critical methodology							
Q8		0.43 (0.23)	0.64	1.73(0.90)	1.68(0.91)	0.74	<0.0001
no one	2 (1.05%)						
One	96 (50.53%)						
Two	52 (27.37%)						
three	32 (16.84%)						
Four	8 (4.21%)						
Other questions							
Q2				1.42(1.55)	1.53(1.52)	0.88	<0.0001
I don't know	102 (52.04%)						
No	2 (1.02%)						
Very little	14 (7.14%)						
Enough	64 (32.65%)						
Yes	14 (7.14%)						

(continued)

Table 1 *(continued)***.** Reliability and stability analysis
N(%) = number of observations with percentage; Mean (SD) = Mean with Standard Deviation of the normalised and raw data for Reliability and Stability analysis, respectively; Cronbach's α = Cronbach's α is item delated; Rho = Spearman's coefficient; p-value = p-value of the correlation test.

		Reliability Analysis		Stability Analysis			
Knowledge questions	Subjects (%)	Mean (SD)	Cronbach's α	Mean (SD) at T0	Mean (SD) at T1	Rho	p-value
Q6				1.03(1.34)	0.97(1.29)	0.99	<0.0001
I don't know	112 (57.14%)						
the CDM is in favour of the patient	24 (12.24%)						
the CDM is in favour of the doctor	2 (1.02%)						
balanced	58 (29.59%)						
Q9				1.47(0.58)	1.45(0.58)	0.95	<0.0001
I don't know	8 (4.08%)						
No	88 (44.9%)						
Yes	100 (51.02%)						
Q10				1.77(0.87)	1.70(0.89)	0.85	<0.0001
Never	6 (6.12%)						
Rarely	16 (16.33%)						
sometime	58 (59.18%)						
very often	18 (18.37%)						
Q11				1.32(1.15)	1.31(1.19)	0.91	<0.0001
Never confronted	70 (35.71%)						
Self-decision	32 (16.33%)						
Help request	56 (28.57%)						
Self-decision with help request	38 (19.39%)						
Q12				1.21(0.93)	1.29(0.92)	0.86	<0.0001
Never	56 (28.57%)						
Rarely	54 (27.55%)						
Sometime	74 (37.76%)						
Very often	12 (6.12%)						

psychometric measures. The internal consistency of a specific questionnaire is evaluated according to each domain, assuming that individual questions in each domain correspond to the same topic. It is known that the internal consistency coefficient increases as the number of questions for a specific domain increases (8), and that the internal consistency coefficient is best evaluated by means of Cronbach's alpha coefficient. An optimum Cronbach's coefficient should range between 0.70 and 0.80. In the present study, this coefficient was 0.71 for the total score of knowledge, which can be considered satisfactory. Looking at the omitted item Cronbach's alpha coefficient (Table 1: Reliability Analysis), the Cronbach's alpha increases from 0.59 to 0.71, when questions Q1 Q3, Q4, Q5, Q7 and Q8 were respectively removed from the analysis one by one. These results suggest that questions Q1 Q3, Q4, Q5, Q7 and Q8 are the best indicators of the general knowledge of the deontological Code.

In the context of surveys, test-retest is usually in the form of an interview-reinterview procedure, where the survey instrument is administered on multiple

Table 2. Descriptive statistics
Result are expressed in median with range or the Spearman's rank-order correlation coefficient for categorical and continuous characteristics, respectively. Characteristic = variable taken into account; p-value = p-value of the Spearman's rank-order correlation test for continuous variables or p-value of the non-parametric Kruskal–Wallis test (marked with *) or Wilcoxon test (marked with **) for categorical variables.

Characteristic	Descriptive statistics	Knowledge Total Score	p-value
Median (Range)		*0.50 (0.08 : 0.96)*	
Working time	27.5 (2 : 46)	rho = -0.15	0.1381
Age	52 (25 : 70)	rho = -0.13	0.2140
Gender			0.7397 **
Male	62 (63.27%)	0.50 (0.08 : 0.96)	
Female	36 (36.73%)	0.50 (0.12 : 0.83)	
Religion			0.2741 *
catholic	76 (77.55%)	0.50 (0.08 : 0.92)	
Althea	19 (19.39%)	0. (0.17 : 0.96)	
Other	3 (3.06%)	0.42 (0.17 : 0.42)	
Education			0.0103 *
Degree	24 (24.49%)	0.67 (0.12 : 0.88)	
Specialist	58 (59.18%)	0.46 (0.08 : 0.96)	
Specialist and other	16 (16.33%)	0.48 (0.38 : 0.92)	
Job			0.5823 *
Public	58 (59.18%)	0.50 (0.08 : 0.96)	
Private	10 (10.2%)	0.44 (0.21 : 0.83)	
Public and private	30 (30.61%)	0.52 (0.21 : 0.92)	

occasions (usually twice), and the responses on these occasions are compared (9). In the present study, the test-retest analysis, based on comparing results of the first questionnaire administration with those obtained 1 month later, shows excellent correlation coefficients. In particular, the majority of questions were highly correlated (Table 1: Stability Analysis), suggesting that the respondents tended to interpret the questions and response categories in the same way. These data provide generally consistent results and they show that questionnaire is able to reveal physicians' knowledge of deontological rules that guide the medical profession, their update, and their perception of the importance of ethical and deontological issues in their profession.

The scant knowledge of the deontological rules and ethical principles, as it comes out from the preliminary results, has a negative connotation that suggests that a fundamental instrument such as CDM is not perceived by physicians as an essential guide to everyday clinical practice. The knowledge of the rules and their update is, for instance, absolutely mandatory also because of the existence of disciplinary sanctions. These critical points may stem from a lack of attention, during university training, to the importance that the deontological Code has in the professional life of the doctor. The substantial inability of the respondents to provide a precise answer regarding the ability of the current CMD to fully cover the issues facing the medical profession confirms these major gaps in knowledge.

A key point is the opportunity to investigate the fundamental principles on which medical ethics is based (10) and which are amply agreed upon by the international medical community. All medical professionals should be aware of these principles, which inspire the profession to which they belong. Indeed, the technical and scientific knowledge that underpins the services provided by the physician should be accompanied by knowledge of these ethical principles, which

are able to guide the medical practice by a moral perspective. These principles above all focus the doctor-patient relationship, stressing a good communication in order to highlight the central position of the patient and, at the same time, the physician's independence with also regard to controversial issues, such as ethically or scientifically sensitive issues (11, 12). In addition, the ethical knowledge can be interpreted as a fundamental instrument to recognize a global vision of the patient as essential element to achieve the treatment' goals (13, 14). The fact that this situation seems to be equally widespread in the various healthcare settings, both public and private, is also cause for concern. This interpretation also seems to be confirmed by our analysis of the replies concerning physicians' opinions of the stance taken by the CMD with regard to the degree of autonomy of the patient and of the doctor in the therapeutic relationship. Indeed, over half of the respondents were unable to answer the question. However, of those who did provide an answer, it is interesting that the majority judged these two types of autonomy (doctor-patient) to be correctly balanced, while only a small percentage deemed that this relationship was excessively tilted in favour of the patient (15, 16).

A possible explanation for this finding may lie in the steady increase in cases of claims for damages in recent years (17), especially those involving lawsuits (18), which may have fostered the perception that the patient is excessively safeguarded by the law. A different reading of this finding, however, may be that the patient is perceived as being particularly vulnerable and, consequently, requiring greater attention and protection on the part of both the CMD and the law (19)

Interestingly, the preliminary data revealed that knowledge of the CMD was greater among subjects who had only a medical degree than among those with specialty or other postgraduate qualifications. This might be because the CMD is more familiar to younger individuals, who have entered the world of work more recently and who probably maintain a closer link with their academic background. Indeed, in Italy in recent years, ethical and deontological issues have received greater emphasis in medical faculties than in the past, though the situation is still partial and heterogeneous (20). Another possibility is that "young" professionals may be more inclined to acquire knowledge of deontological rules in order to have a source of reference that can orientate their everyday medical practice, while their "older/more expert" counterparts may tend to believe that they have already absorbed the principles of medical morality, and therefore act autonomously.

Although 50 out of 196 respondents were aware that medical ethics, bioethics and medical deontology cover overlapping areas of intervention, more than half admitted that they did not know the differences among them. This can probably be ascribed to two main factors:

1. frequent confusion regarding the key terms of these disciplines;
2. the lack, as mentioned above, of thorough and homogeneous teaching of these disciplines in degree courses in medicine, during which emphasis is chiefly placed on technical and scientific aspects. Moreover, when these disciplines are taught, there is a tendency to focus only on a few specific issues, such as informed consent to therapy and questions of the beginning and end of life (21, 22).

Examination of the preliminary data also reveals that only a small proportion of physicians are aware of the different perspective of critical analysis adopted by bioethics in comparison with the strictly directive orientation assumed by deontology and the law. These findings indicate the need to create areas in which a clinical case can be analysed from different standpoints – ethical, deontological and juridical – in order to highlight both the points of contact and the differences among these various disciplines with which the medical profession is called upon to deal (23, 24).

Within medical training, particular attention should therefore be devoted to the specificities of medical deontology, on the one hand, and to those of the law, on the other.

The scant knowledge of the deontological rules and ethical principles should constitute a major critical point, given that half of the respondents stated that they had had to decide on ethical grounds whether or not to pursue a treatment and that they had encountered difficulty in solving the related ethical problem.

These data, even if obtained from a small sample, prompt us to stress the importance of implementing

initiatives to improve the training and ethical competence of doctors; this would involve developing, right from the outset, the individual's ability to recognise the moral dimension of medical practice and to identify the critical aspects of the various cases encountered in daily practice (25). Indeed, it is this very lack of synergy between technical-scientific skills and ethics that can give rise to deleterious effects on the proper functioning of healthcare personnel, thereby undermining, at least in part, their professional qualification. A thorough review of traditional curricula, together with the introduction of innovative teaching methods that prompt methodological reflection through systematic discussion of ethical problems, could help students to develop the necessary attitudes and skills for their future profession (26).

The validation study has some limitations. First, the relatively small and possibly homogeneous sample. The generalizability of this study should be somewhat limited in that it was conducted in only one geographic area (Genova province). Testing of the general knowledge of the deontological Code in other settings will increase confidence in the general applicability of the results. Second, the sample size was not calculated beforehand.

Conclusions

In summary this study showed that, the questionnaire has excellent internal consistency making it useful to study physicians' knowledge of deontological rules and ethical principles. Based on the confirmatory factor analyses of the data no subscales were identified. However, a few potential issues were also identified.

The preliminary data reveal that physicians have scant knowledge of deontological rules and ethical principles. This shortcoming, whereas it will be confirmed, could be particularly worrisome in the light of the frequency of the ethical problems encountered in medical practice. Our next investigation is to be conducted at the provincial level and should provide indications that can be used to check this interpretation and to focus on the implementation of ongoing training that is appropriate to physicians' requirements. The second phase of the study will involve distributing the questionnaire to a broader and more representative sample.

Conflict of interest: None to declare

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Appendix 1

The original survey with cover letter sent to Italian participants

Dear Colleague,

We need your help in order to validate a questionnaire on doctors' knowledge of deontological rules and ethical principles. We would therefore be grateful if you could connect to the link below and fill in the questionnaire.

It will only take you a few minutes to fill in the questionnaire, but this will enable us to collect important information that can be used to design training schemes that are better suited to the complexity of the field of medicine.

We thank you in advance for your precious cooperation.

ORIGINAL SURVEY

Survey of knowledge of the ethical principles of the 2014 Code of medical deontology

To fill it in, please access the following page:
https://docs.google.com/forms/d/1bi5gakrSDBgqG2NVRs0A2o911XJ9RZZD7U_ypeH5Zmg/viewform?c=0&w=1&usp=mail_form_link]

Age _____

Sex ☐ male ☐ female

Number of children (0, 1, 2, 3 etc.) _____

Nationality ☐ Italian ☐ Other:

Religious faith

☐ Christian Catholic ☐ Christian Orthodox ☐ Muslim
☐ Jewish ☐ None ☐ Other:

Year of graduation_____

Qualifications held
a) Research Doctorate N _____
b) Training course N _____
c) Specialty degree in _____
d) Other qualification (specify) _____

Activity carried out in
a) Public sector
b) Private sector
c) Both

Q1: Do you know the CMD (2014)?
a) No
b) Very little
c) Only some points
d) Quite
e) Yes

Q2: Do you think the current CMD (2014) fully covers the issues facing the medical profession?
a) Don't know
b) No
c) Very little
d) Quite
e) Yes

Q3: Which of the following bioethical principles do you know?
NB: You may tick more than one option
a) Non maleficence
b) Beneficence
c) Self-determination
d) Justice
e) None

Q4: In your opinion, is there any difference between bioethics, deontology and medical ethics?
a) No
b) Don't know
c) Yes

Q5: In your opinion, do bioethics, medical ethics and the CMD have the same area of interest?
a) Yes
b) Don't know
c) No

Q6: Regarding the patient's self-determination, do you think the current CMD is:
a) I don't know the position taken by the CMD
b) Excessively protective of the patient's rights
c) Excessively protective of the doctor's rights
d) Well-balanced

Q7: Regarding the critical cases you are sometimes faced with, do you think the ethical perspective offers:
a) No solution
b) A normative solution
c) A normative solution and a critical methodology
d) Don't know
e) A critical methodology for examining the case

Q8: From which sources did you obtain your current knowledge of bioethics?
NB: You may tick more than one option
a) University studies
b) Only during post-graduate training
c) Scientific journals
d) Conventions, seminars
e) The work environment
f) Newspapers, radio, TV
g) Other _____

Q9: Have you ever had to decide on ethical grounds whether or not to go on with a procedure?
a) Don't know
b) No
c) Yes

Q10: If you have answered "yes" to the previous question, have you ever had difficulty solving ethical problems?
a) Never
b) Rarely
c) Sometimes
d) Very often

Q11: When faced with an ethical problem, have you…?
NB: You may tick more than one option
a) Consulted other colleagues
b) Consulted your professional association
c) Consulted the ethics committee
d) Consulted the section/unit of bioethics and/or legal medicine
e) Taken a decision autonomously
f) I have never been faced with an ethical problem

Q12: In your professional activity, have you ever felt the need for an organism (ethics committee) to provide consultation or approval on questions of bioethics?
a) Never
b) Rarely
c) Sometimes
d) Very often

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Original article

Suicide in the elderly: a 37-years retrospective study

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Summary. *Background:* The rates of suicide increase with age and reach their highest levels in the oldest age groupings and are sufficiently large for them to constitute a public health concern. The number of deaths due to suicides after the age of 60 years in Italy is 1,775 (41.36%) in 2013; there is a constant increase of elder population over the last ten years and elderly are almost twice of young. It is in this context that suicide arises, a risk factor during old age. *Method*: This is a retrospective study of autopsy and police reports of suicide from January 1979 through December 2015. Data about suicides after the age of 60 years was collected from the Archives of the Legal Medicine of the University of Parma, a Northern Italian city. Trend and characteristics (age, sex, marital status, pathological factors and method of suicide) were assessed. *Results:* A total of 538 cases (394 males, 144 females) were identified. Male sex correlates to a higher suicidal risk, with a male-female ratio of 2.74:1. The highest risk of suicide is observed in the age between 70 and 79 years. Pathological factors were revealed in 427 cases (physical state for 194 cases, mental state for 233 cases); mental illness was related significantly to suicidal risk. Hanging is the most common suicide method (175 cases), followed by fall from height (130 cases), drowning (101 cases) and use of firearms (56 cases); differences regarding methods employed were detected between males and females. The choice of method sometimes is indicative of a clear decision, while other times it is strictly linked to the availability of the means. *Conclusions:* Suicidal behavior seems to be the product of the interaction of many factors, such as biological or psychological diseases or painful events. The presence of chronic and debilitating diseases, often accompanied by profound psychological suffering, is a powerful stimulus for suicide among men, whereas mental state is a significant risk factor for women, with the majority suffering from depression. The psychological and the biological changes, the cognitive deficits and the common diseases facilitate the structuring of depressive characteristics. (www.actabiomedica.it)

Key words: suicides, aged 60 and over, autopsy and police reports, suicide rates, risk factors

Introduction

The suicide death of an older subject is less impactful on the people than the loss of someone younger, particularly of adolescents and of young adults. For these reason, suicide in the elderly population is a phenomenon that is often ignored or neglected, drawing less attention than suicide in younger population.

This may be due to its lower economic impact on society, since most older suicide victims are not in the workforce, and the fact that fewer years of life are lost (1).

The World Health Organization (2) had defined suicide as an act deliberately initiated and performed by a person in the full knowledge or expectation of its fatal outcome. Much discussion took place with regard to definitions, with the ongoing evolution of terms in this field and the use of different terms for very good reasons elsewhere in this sector. Currently, suicide is the act of deliberately killing oneself (3). Every 40

seconds a person dies by suicide somewhere in the world. An estimated 804,000 suicide deaths occurred worldwide in 2012, representing an annual global age-standardized suicide rate of 11.4 per 100,000 population (15.0 for males and 8.0 for females) (3). Suicide is a significant cause of death in many European Union (EU) member states, with approximately 60,000 deaths in 2010-2011 (or nearest year). Suicide mortality rates per 100,000 population vary widely across European countries, with the lowest rates in southern European countries - Cyprus (3.6), Greece (3.0), Italy (5.4), Malta (7.4) and Spain (5.8) - as well as in the United Kingdom (6.4), at eight deaths or less per 100 000 population, and the highest rates in the Baltic States and Central Europe - Estonia (18.3), Hungary (21.7), Latvia (20.7), Lithuania (31.5) and Slovenia (17.2) - where suicide rates, more than 17 deaths per 100,000 population, are more than 50% higher than the EU average. There is more than a ten-fold difference between Lithuania (31.5) and Greece (3.0), the countries with the lowest and highest death rates. Low income, alcohol and drug abuse, unemployment and social isolation are all associated with higher rates of suicide. The number of suicides in certain countries may be under-reported because of the stigma associated with the act (for religious, cultural or other reasons). Comparability of suicide data between countries is affected by a number of reporting criteria, including how a person's intention of killing themselves is ascertained, who is responsible for completing the death certificate, whether a forensic investigation is carried out, and the provisions for confidentiality of the cause of death. Death rates from suicide are four-to-five times greater for men (average rate 20.7) than for women (average rate 4.7) across the EU, although in those countries with the highest rates, male deaths are up to seven times as common. Suicide is also related to age, with young people aged under 25 and elderly people especially at risk and suicide risk also generally increases with age (4). While suicide rates among the latter have generally declined over the past two decades, less progress has been observed among younger people (5).

In spite of mixed trends, suicide remains a significant public health problem worldwide. Potential explanations for cross-national variations in trends over time in elderly suicide rates include cross-national differences in trends over time in the prevalence of mental illness in the elderly, socioeconomic factors, cultural factors, the availability of appropriate healthcare services, and public health initiatives to improve the detection and treatment of mental illness, mental health and suicide prevention (6). Fundamentally, suicide rates in most industrialised nations increase with age, the highest rates of all occurring in elderly men. Risk factors for elderly suicide are: older age, male gender, living alone, bereavement (especially in men), psychiatric illness (depression, alcohol misuse, previous suicide attempt, vulnerable personality traits), physical illness (pain) (7).

The absolute number of deaths due to suicides in Italy - data based on a population of 60,782,668 residents - is 4291 (3323 for men and 968 for women) in 2013, with low death rate (6.6) per 100,000 population; amongst all cases, 1,775 are suicides after the age of 60 years (41.36%) (8). In the last 50 years we have witnessed a gradual increase in life expectancy and a simultaneous decrease in birth, which had led to population aging in a context of a capitalist and consumerist system that changed the imagine and role of the elderly, in society and in the family context as well. In our culture and social structure, productivity and work are fundamental elements in defining identity and social role. The onset of old age, often signaled by retirement (the transition from adulthood to old age, calls for time of rest), which implicitly coincides with a gradual placement in a marginal context. The world of relationships shrinks, interest in the outside world weakens, and the ritualization of everyday life and conservatism predominate (9). In this context, feelings of worthlessness, emptiness, lack of prospects or resources arise, and the elderly are not always to counter them with new objectives and interests. Rapid cultural changes, constant research and scientific success have made it possible to achieve results that a century ago were considered unreachable, with the increase of life expectancy because of better health care. Nevertheless, the extra years of life achieved do not necessarily provide a better quality of life; the increase of chronic diseases and the loss of physical strength often lead to feeling of worthlessness, anxiety for the future, lack of prospects or resources, until depression. To contribute

to the arising of these feelings there is also the changing of 'traditional' family, always ready to cure and care their elderly, with a 'new' one, in which, because of the importance of productivity and work, all the members are always busy with fewer and fewer time to dedicate to the weak part of the family. All these factors contribute to make the elderly feeling a burden for their own family and society.

It is in this context that suicide arises (10), a risk factor during old age. This retrospective study, conduced in a Northern Italian province where a high percentage of people reach the old age, sets out to analyze the characteristics of suicide and identify the variable that seem more specifically related to an increased risk of suicide (11).

Materials and methods

We retrospectively reviewed all cases referred to the archives of Legal Medicine of the University of Parma (Parma is a city in the Italian region of Emilia-Romagna, Northern Italy; it is home to the University of Parma, one of the oldest universities in the world, founded in the 12th century [1117 A.D.]; the schools of law and medicine were added in the 13th century). The study was conducted by examination of autopsy and police reports of all cases of suicides after the age of 60 years, a total of 538 cases (394 male cases and 144 female cases) during the 37-years period examined, between 1 January 1979 and 31 December 2015. These reports were often based on circumstantial information and personal testimony, especially the details provided by family members: for this reason, some of them are very accurate, while some others are approximate and incomplete, in particular the alleged motivation for suicide, subjected to the emotional conditioning and interpretations of people involved. Several autopsy records lack details since they only mention basic diagnostic findings. Information taken from each report were collected based on the following parameters: age, sex, marital status, pathological factors (physical state, mental state), method of suicide. The survey conducted and the analysis of such variables are purely statistical and intended to provide descriptive information about the phenomenon of suicide from which guidelines for interpretation may be drawn to further enhance the understanding and the possible prevention of suicide among the elderly.

Results

Analyzing the 538 cases during the 37-year period examined, the highest risk of suicide appears to be in men with 394 cases (73.23%) with respect to 144 cases (26.77%) of female suicides, showing a male-female ratio of 2.74:1. The figure of suicides annually occurring indicate that a higher number of female suicides was recorded only in 1983 and in 1986, 10 cases (50.00%) respectively; before and after such years, the distribution is constant over time, except for zero cases in 2015. Rates of male suicide have a much higher percentage of cases and records show two peaks: one in 1987 (23 cases) and another one in 2002 (20 cases); the years 1979 and 2015 show the lowest rates (3 cases, respectively). Of all the cases, three peaks were observed in 1987 (30 cases), 1988 and 2002 (24 cases, respectively), while 2015 (3 cases) show the lowest rate**.** However, it must be noted that there is a declining suicide trend in the last years.

By age, the most affected group appears to be between 60 and 69 years until 1990; from that moment on, the highest risk of suicide is observed in the age between 70 and 79.

The marital status is known only for 218 individuals (40.51% of the sample), married individuals (129 cases, 23.97%) and widows/widowers (89 cases, 16.53%). Dividing the data by gender, it is interesting to note that the state of being married is not a deterrent for male suicidal behavior (110 cases, 20.44%).

Review of medical and psychiatric histories revealed a pathological factor in 427 cases, physical state for 194 cases (45.43%) and mental state for 233 cases (54.57%). In reconstructing the motive of suicide, physical state is predominant in men (123 cases, 63.41%), whereas the mental state proves to be more significant for women (150 cases, 64.37%).

Hanging is the most common suicide method (175 cases, 32.52%), followed by fall from height (130 cases, 24.16%), drowning (101 cases, 18.77%) and use of firearms (56 cases, 10.40%). Other methods con-

sist of poisoning (30 cases, 5.57%), edge weapon (21 cases, 3.90%), train impact (15 cases, 2.78%), immolation (5 cases, 0.92%), asphyxia by confinement (4 cases, 0.74%) and self strangulation (1 cases, 0.24%). Hanging is the method most frequently used by men (150 cases, 27.88%), followed by drowning (85 cases, 15.79%). Fall from height is the leading method of suicide in women (61 cases, 11.34%), followed by hanging (25 cases, 4.64%). Firearm is a method mostly chosen by men (50 cases, 9.29%, against 6 female cases, 1.11%).

The characteristics of the specific variables are illustrated in table 1, 2, 3 and 4.

Table 1. Suicide mortality rates from January 1979 through December 2015

Year	Nr. of cases	M:F ratio	Male nr. (%)	Female nr. (%)
1979	9	1:2	3 (33.33%)	6 (66.67%)
1980	9	2:1	6 (66.67%)	3 (33.33%)
1981	8	2:1	5 (62.5%)	3 (37.5%)
1982	9	2:1	6 (66.67%)	3 (33.33%)
1983	20	1:1	10 (50%)	10 (50%)
1984	13	1:1	7 (53.85%)	6 (46.15%)
1985	15	4:1	12 (80%)	3 (20%)
1986	20	1:1	10 (50%)	10 (50%)
1987	30	3,3:1	23 (76.67%)	7 (23.33%)
1988	24	2:1	16 (66.67%)	8 (33.33%)
1989	17	3:1	13 (76.47%)	4 (23.53%)
1990	9	2:1	6 (66.67%)	3 (33.33%)
1991	20	3:1	15 (75%)	5 (25%)
1992	21	3:1	16 (76.19%)	5 (23.81%)
1993	15	3:2	9 (60%)	6 (40%)
1994	17	4,6:1	14 (82.35%)	3 (17.65%)
1995	21	6:1	18 (85.71%)	3 (14.29%)
1996	17	1,5:1	10 (58.82%)	7 (41.18%)
1997	10	2:1	7 (70%)	3 (30%)
1998	16	3:1	12 (75%)	4 (25%)
1999	14	6:1	12 (85.71%)	2 (14.29%)
2000	16	2:1	11 (68.75%)	5 (31.25%)
2001	15	4:1	12 (80%)	3 (20%)
2002	24	5:1	20 (83.33%)	4 (16.67%)
2003	18	5:1	15 (83.33%)	3 (16.67%)
2004	8	2:1	5 (62.5%)	3 (37.5%)
2005	20	6:1	17 (85%)	3 (15%)
2006	15	4:1	12 (80%)	3 (20%)
2007	10	9:1	9 (90%)	1 (10%)
2008	14	6:1	12 (85.71%)	2 (14.29%)
2009	13	5:1	11 (84,61%)	2 (15.39%)
2010	11	10:1	10 (90.90%)	1 (9.10%)
2011	11	3:1	8 (72.73%)	3 (27.27%)
2012	8	2.1	5 (62.5%)	3 (37.5%)
2013	10	4:1	8 (80%)	2 (20%)
2014	8	3:1	6 (75%)	2 (25%)
2015	3	3:0	3 (100%)	0 (0%)
Total cases	538	2,74:1	394 (73.23%)	144 (26.77%)

Discussion

The analysis of the 538 cases during the 37-year period examined, with reference to a limited territory - being only indicative results not generalizable to other districts - provides us with a uniform basis without variables that could complicate understanding the phenomenon of suicide.

Sex

There is a highest risk of suicide in men during the considered period, except for 1979, with a male-female ratio of 2.74:1. It should be noted that this is not as surprising as it might appear at first, since the rate of suicide for women has long been known to decline after age 60. One explanation of higher suicide among men than women - also among the elderly - could be that women have acquired a greater ability to adapt, the presence of a longer lasting social network and the ability of being able to look after themselves (managing a household) in small everyday matters. These stimuli may act as an emotional reinforcement against feelings of worthlessness and for self-esteem.

Age

Suicide rates increase with age and reach their highest levels in the oldest age groupings. There is a shift in the age group affected, between the age of 60 and 69 until 1990 and between 70 and 79 in the 1991-2015 period. The reason for the increase of suicide in that specific age group could simply reflect the increase of life expectancy and hence the presence of an ongoing rise in the elderly population size. Parma is a city with a high quality of life, therefore a high percentage of people reach the old age. There was a constant increase of elder population over the last ten years, simi-

Table 2. Socio-demographic characteristics

	Total number	% of total nr.	M:F ratio	Male nr. (%)	Female nr. (%)
Age (years)					
60-69	191	35.50%	2.29:1	133 (24.72%)	58 (10.78%)
70-79	215	39.96%	3.21:1	164 (30.1%)	51 (9.5%)
80-89	99	18.41%	5.18;1	83 (15.42%)	16 (2.96%)
90 and over	33	6.13%	0.74:1	14 (2.60%)	19 (3.53%)
Total cases	538	100.00%	2.73:1	394 (73.23%)	144 (26.77%)
Marital status					
Married	129	23.97%	5.78:1	110 (20.44%)	19 (3.53%)
Widow/er	89	16.54%	1.28:1	50 (9.29%)	39 (7.24%)
Total cases	218	40.51%	2.75:1	160 (29.73%)	58 (10.77%)

Table 3. Pathological factors

	Physical factors	Mental factors
Pathological factors: total cases		
427	194 (45.43%)	233 (54.57%)
	Male number (%)	Female number (%)
Physical state: total cases		
194	123 (63.41%)	1 (36.59%)
	Male number (%)	Female number (%)
Mental state: total cases		
233	83 (35.63%)	150 (64.37%)

Table 4. Methods

Methods	Total cases (%)	Male number (%)	Female number (%)
Hanging	175 (32.52%)	150 (27.88%)	25 (4.64%)
Fall from height	130 (24.16%)	69 (12.82%)	61 (11.34%)
Drowning	101 (18.77%)	85 (15.79%)	16 (2.98%)
Firearm	56 (10.40%)	50 (9.29%)	6 (1.11%)
Poisoning	30 (5.57%)	10 (1.86%)	20 (3.71%)
Edge Weapon	21 (3.90%)	15 (2.77%)	6 (1.13%)
Train Impact	15 (2.78%)	7 (1.30%)	8 (1.48%)
Immolation	5 (0.92%)	4 (0.72%)	1 (0.20%)
Asphyxia by confinement	4 (0.74%)	3 (0.56%)	1 (0.18%)
Self strangulation	1 (0.24%)	1 (0.24%)	0 (0,00%)
Total cases	538 (100%)	394 (73.23%)	144 (26.77%)

larly than in the whole Italy. Elderly are almost twice of young and represent the 23% of the entire population, while under 18 years old are just 14%; median age is 46 years. There were 172,8 elderly every 100 young people in 2015 (12), and this trend is expected to continue, accelerating even more in the future. With the increase of life expectancy the retirement age rises, with people working longer; nowadays, retirement is possible at 70 years old, while previously at 60. Retirement age, nonetheless, often overlaps the beginning

of the decrease of psychophysical abilities and loss of independence (13).

Another explanation could be that emotions tend to change both in terms of quantity and quality in old age. Subjective intensity decreases towards content that in the past provoked intense reactions; emotions concentrate around specific issues, especially physical and psychological wellbeing and socio-economic status. The examination of the data shows that the age of 70 is when aging proves to be the most difficult. Psychophysical abilities decrease, the elderly individual becomes more vulnerable and in need of more support and assistance. It therefore becomes harder to find one's own place and give new meaning to the concept of life; the increase of suicide in this age group demonstrates this fragility.

Marital status

The marital status (married individuals, widows/widowers) is known only for 218 individuals (40.51% of the sample) and could not be representative of the sample in our study model. State of being married does not appear to be a protective factor, but its impact on suicide differs by sex and men are at a higher risk of suicide while still married. It appears that when faced with feelings of worthlessness, loss, cognitive decline and gradual loss of independence (14) men slip into social isolation, which makes it difficult for them to ask for assistance. In these circumstances, a depressive-aggressive mechanism (15) is enacted: each loss is experienced with pain, but also anger; death in this circumstance removes the individual from a difficult condition while also being a cleansing, remedial catharsis. On the other hand, widowhood proves to be a decisive factor for women(16) because the disintegration of the marital unit initially causes admitting pain and intense support of family and friends. With time passing by, this support network weakens, and the individual finds herself in a decidedly solitary state. Women turn in on themselves, and this state of isolation gives rise to feelings of emotional emptiness and uselessness. The deep-seated rift or suffering finds no other answer but in death.

Between social factors implicated in suicide risk for older adults, living alone also appears to increase risk of attempt and completion (17, 18).

Physical state

Physical status, intended here as the presence of chronic and debilitating diseases, often accompanied by diversity in social relations and social participation (19) and by serious psychological suffering, proved to be a powerful motive for suicide, especially among men. In this case, death may be interpreted as liberation from an unbearable state (20). In this context, the idea of death seems almost "rational" when faced with a future of unbearable suffering and humiliating forms of dependence. This issue was addressed in a study by the University of Parma's Department of Psychiatry, which analyzed the method of psychological autopsies for 99 suicide cases, 77 men and 22 women, between 1994 and 2004. The study confirmed the correlation between elderly suicidal behavior and somatic diseases, especially cancer and cardiovascular diseases, diagnosis that accounted over 45% of the cases studied. Although more than 50% of older suicides were diagnosed as DSM-IV-TR depressed, only 20%-30% of them had been treated with medications (21). This result is confirmed by our study that show physical disease as predominant motive for suicidal behavior in men (63.41%), death as liberation from physical suffering.

The presence of physical illness should not detract from a close examination of the mental state, with particular regard to a coexistent depressive illness and associated suicidal feelings. Hypochondriacal and somatic symptoms may mask the underlying depression. This form of presentation of depression may be of particular importance in elderly men, who may be less likely to verbalise depressed mood or admit to have suicidal thoughts. Suicidal ideation and pessimistic thoughts are not uncommon among severely medically ill and continuing-care geriatric in-patients, necessitating staff training in these facilities in the recognition and treatment of underlying disorders (22, 23).

Mental state

While reconstructing in our study the motive of suicide, the review of psychiatric histories revealed a mental state predominant in women (64.37%), with the majority of them suffering from depression. De-

pression and many other psychiatric disorders are a significant risk factor for suicide in the elderly. But depression rarely leads to suicide by itself. Physicians must be aware that the concomitant presence of depressive symptoms and several life events (especially loss and loneliness in women and physical illness in men) should be considered warning signs for suicidal behavior (21). Among depressed suicide cases aged 60 and over years with a primary diagnosis of depression, a comorbid anxiety disorder was associated with a higher prevalence of several suicide risk factors (24).

Aside from documented cases of psychiatric diagnosis, informational reports attached to autopsy records frequently refer, and superficially so, to "depression", a term often used inappropriately. In fact, depressive disorder is rarely recognized in old age because psychological changes, inevitable age-related biological changes, cognitive deficits and frequent overlapping of neurological or internal diseases give rise to a different expression of depressive symptoms. In addition to traditional symptoms (25), the psychological symptoms of depression seem to be less common among the elderly, that are sadness, sense of guilt and sense of failure. Depressive distress may be dominated by symptoms of general anxiety, palpitations, lump in throat feeling, complaints of nervousness or irritability, psychomotor agitation, restlessness, obsessive ideation and akathisia. In other cases, cognitive symptoms, such as poor attention and concentration, memory loss and other orientation problems, dominate the clinical picture. A series of somatic symptoms are often part of elderly depression and are often accentuated by the patient. The most reported ones are fatigue, vague gastrointestinal discomfort, headaches, insomnia, weight loss, constipation and hypochondriacal worries. These characteristics make it difficult to diagnose depression as well as to make a diagnosis that differentiates between dementia and depression (26). If aging is viewed as a process of change, then investigating the sphere of emotions is important because alterations in psychophysical functions connected to a state of uncertainty and frustration are indicators of actual suffering. On one hand, they may prove to be signs of decathexis and loss that correspond with actual events of loss (health, status, profession, friendships); on the other hand, they may be indicators of marginalization and anxiety that put the elderly on the road towards death. In fact, the elderly individual reacts not only to mostly inevitable external conditions, but also to internal changes that indicate a new mental core (27).

Method of suicide

The act of suicide among the elderly is premeditated; it is a rather slow progression from suicidal thoughts to committing suicide and is not an impulsive act. The choice of the method of self-destruction is conditioned by different kinds of factors: the availability and accessibility of the method, the impact of imitative factors, and society's collective image of each method. This age group uses more violent and lethal means of committing suicide than those used by other groups, especially younger persons, which confirms the high level of determination that underlies the gesture.

The elderly individual is much more fragile and therefore less likely to survive physical injury. For this reason, less lethal methods should not be underestimated and, indeed, may result as equally effective. In this study, 85.85% of the suicides are hanging (32.52%), fall from height (24.16%), drowning (18.77%) and use of firearms (10.40%). Poisoning, edge weapon, train impact, immolation, asphyxia by confinement and self strangulation accounts for only 14.15% of the cases. Hanging is the most common suicide method in men (27.88%) followed by drowning (15.79%); fall from height is the leading method in women (11.34%) followed by hanging (4.64%). Hanging is a fast, certain and relatively painless method: since it requires a certain amount of organization, it demonstrates the high level of premeditation involved in this kind of suicide. On the opposite, fall from height is a choice that requires no organization, rather effective and easily accessible. Firearm is a method mostly chosen by men (9.29%) in comparison with women cases (1.11%), due to the greater knowledge needed of how the method works and the dramatic disfigurement caused by a firearm; culturally, it appears that women refuse this type of disfigurement. The number of men that used firearms shows a progressive increase after 1990, becoming the first method after 2010.

Conclusions

For the risk factors identified in this study we confirm that suicidal behavior after the age of 60 years is the product of an interaction of many antecedents factors, such as physical or psychological chronic diseases or painful events and social factors at a crucial moment in the life of a vulnerable individual. The elderly individual's inability to cope with suffering and a deteriorating mental and physical state often leads him or her to the belief that there is no other solution but suicide.

Elderly people reporting suicidal feelings presented markedly higher levels of physical and psychological distress, such as depression, anxiety, and hostility. Results implicitly confirm that depressive symptomatology is not adequately treated. Greater attention is warranted in psychological evaluation of the elderly to take into account those risk factors that, if properly identified and managed, could reduce the frequency of suicidal thoughts and, probably, associated actions (28).

Suicide in the elderly is associated with multiple risk factors, most of which can be identified, and are preventable with specific preventive strategies and research. Treatment of depression is an important measure of suicide prevention among the elderly and the European Pact for Mental Health and Well-being, launched in 2008, recognized the prevention of depression and suicide as one of five priority areas. It called for action through improved training of mental health professionals, restricted access to potential means for suicide, measures to raise mental health awareness, measures to reduce risk factors for suicide such as excessive drinking, drug abuse and social exclusion, and provision of support mechanisms after suicide attempts and for those bereaved by suicide, such as emotional support helplines (29). Suicide rates can play an important role in signaling weaknesses of mental health systems, in particular unmet needs for care (30).

Conflict of interest: None to declare

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Original article

Single center evidence for the treatment of basal cell carcinoma of the head and neck

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Summary. *Aim:* Basal Cell Carcinoma (BCC) alone accounts for 80% of cases of non-melanoma skin cancer (NMSC), which characteristically develops on sun-exposed skin. Indeed the most common site of BCC is the head and neck region (80%). The purpose of this study to review the experience of our center with BCC in the head and neck region to report the sites of occurrence and treatment. *Materials and method:* We retrospectively reviewed 77 patients with BCC of the head and neck, who revived surgical treatment within our plastic surgery division. Basic demographic data, cancer site and size, surgical treatment and histological data were collected. The mean follow-up period was 12 months. *Results:* The study population included 37 males and 40 females, with a mean age of 74.12 years. The nasal unit was the main site of BCC (31.82%), followed by the periorbital (13.64%) and cervical (12.5%) units. Primary closure was the main surgical procedure performed (72.5%), followed by local flap (26.1%) and full-thickness skin grafts (1.4%). The safety resection margin ranged from 4.5 to 9 mm, with a 98.7% complete removal rate. Neither recurrence nor any newly-developed lesions were reported during follow-up in any patient. *Discussion:* Our work reflects the shift in the incidence of BCC, which now seems to be more frequent in females. Furthermore, our data strengthens the association between UVR exposure and BCC, confirms its predilection to occur on the nasal unit and validates surgical excision as the gold standard treatment for skin cancer. (www.actabiomedica.it)

Key words: non-melanoma skin cancer, basal cell carcinoma, head and neck cancer, operative surgical procedure; epidemiology

Introduction

Non-melanoma skin cancer (NMSC) is the most common cancer in Caucasian populations worldwide (1). NMSC refers to all cutaneous cancers that do not develop from melanocytes, and is often incorrectly used to refer to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), which together account for more than 95% of cases of NMSC (2). Each year 2-3 million patients are diagnosed with NMSC worldwide, with average yearly increases of 3-8% since 1960 (2-6). Since 80% of cases of NMSC occur in individuals > 60 years-old, its incidence will soon be equal to that of all other cancers taken together (8-10). BCC alone accounts for 80% of cases of NMSC (1). The incidence of BCC is rising by 10% per year and it is increasingly diagnosed in younger individuals (<40 years) (7). Death due to BCC is extremely rare as the incidence of metastasis is estimated to be 0.0028-0.55%; however, BCC can result in severe morbidity since the lesions tend to be located on the skin of the head and neck (11). Moreover, NMSC places a considerable economic burden on healthcare systems: the total annual cost of skin cancer care in the United States

increased from $3.6 billion in 2002-2006 to $8.1 billion in 2007-2011 (12). Indeed NMSC is essentially an age-related disease and as populations grow older, its incidence and related costs will rise (2).

BCC develops from either the bulge region of the hair follicle, which is rich in keratinocyte stem cells, or from stem/progenitor cells in the basal cell layer of the epidermis (13). BCC grows slowly over a period of months to years, has a *de novo* onset with no visible pre-malignant phase, and may present as the nodular, superficial, sclerodermiform, pigmented or *ulcus rodens* subtypes (13). Metastasis are extremely rare; however, the tumor may be highly invasive and locally destructive. Since UV radiation (UVR) is one of the most important risk factors for skin cancer, which characteristically develops on sun-exposed skin, the most common site of BCC is the head and neck region (80%) followed by the trunk (15%) (13). BCC is usually associated with intermittent sun exposure and episodes of sunburn during childhood (13-17). Treatment varies depending on the clinical features, histological type, pattern of growth, size, location and comorbidities. Surgical excision with a 0.5 cm safety margin is the gold standard treatment. Wider excision margins are recommended for infiltrative, recurrent or multicentric-superficial BCC, and Mohs surgery has become established for these subtypes of BCC or when aesthetically relevant areas are involved (1,8). The reconstructive options are direct suture, skin grafts and local flaps, and vary from case to case. Radiation therapy and topical medicines are valuable alternatives treatment for patients who are not eligible for surgery (1).

The purpose of this study was to review the experience of our center over BCC if head and neck district to report the sites of occurrence and treatment.

Materials and methods

For this study, we retrospectively reviewed 77 patients with BCC of the head and neck, who revived surgical treatment within the Cutaneous, Mininvasive, Regenerative and Plastic Surgery Unit of Parma University-Hospital, Italy, between January 2014 and February 2016. For all patients, basic demographic data (sex, age), cancer site and size, method of surgical treatment and histological data were collected. The sites of occurrence of BCC were classified based on the principal facial aesthetic regions: scalp, frontal, supraorbital, periorbital, temporal, zygomatyc, infraorbital, nasal, auricular, mandibular, perioral, mental and cervical (19, 20). The nasal, periorbital and labial regions were subdivided into aesthetic units. The nasal region included the dorsum, tip and alar lobe, while the periorbital region was subdivided into the upper and lower eyelid; and the perioral region, the upper and lower lip.

Patients provided signed informed consent prior to surgery and were educated about surgical and cosmetic risks. Depending on the size and site of BCC, patients underwent surgical excision by primary closure, local flap or skin graft. All patients were followed-up as outpatients on a weekly basis in the first month, and then at three, six and 12 months postoperatively. Patients were instructed to return to their normal level of activity 2 weeks after surgery. The minimum follow-up period was 3 months; early and late complications were recorded.

Results

At our plastic and reconstructive surgery department, 77 patients underwent surgical treatment for BCC of the head and neck region between January 2014 and February 2016. This retrospectively-assessed population included 37 males and 40 females, with a mean age of 74.12 years (range, 35 to 98 years). The age at diagnosis was younger for males than females (71.7 vs. 76.32 years). The age-frequency distribution peaked in the seventh decade. Eleven patients (14.29%) presented with two BCC tumors, seven (63.6%) of whom were female and four (36.4%) were male.

The average size of tissue excised was 1.8 x 1.17 cm (width x length; range, 7-0.6 cm and 4.5-0.3 cm, respectively) with a mean area of 2.77 cm^2 (range, 31.5-0.18 cm^2). The average size of the BCC tumors was 0.9x0.72 cm (width x length; range, 2.5-0.3 and 2.3-0.2 cm, respectively) with a mean area of 0.83 cm^2 (range, 6.2-0.06 cm^2). Nodular BCC accounted for 65.9% (58) of cases, while the superficial, sclerodermiform, and pigmented subtypes accounted for 12 (13.6%), 14 (15.9%), and 4 (4.5%) of cases. At the time of surgical excision, 64 (72.7%) of all tumors were ulcerated.

The sites of occurrence of BCC by facial aesthetic regions and units are summarized in Table 1. The nasal unit was the main site of BCC (31.82%), followed by the periorbital (13.64%) and cervical (12.5%) units. The alar lobes were the most common location within the nasal unit (50%), followed by the nasal dorsum (35.7%) and nasal tip (14.3%). There was no lateral predilection for BCC site: 32 (36.4%) tumors were on the right side, 31 (35.2%) on the left side and the side could not be classified for 25 cases (28.4%).

Table 1. Anatomical sites of basal cell carcinoma in the head and neck region classified by aesthetic regions and units.

Region Unit	Total	Left-sided	Right-sided	Not Classified
Scalp (*n*, %)				4, 4.54%
Frontal (*n*, %)				4, 4.54%
Supraorbital (*n*, %)		0	1, 1.14%	
Periorbital (*n*, %)	12, 13.64%			
Upper eyelid (*n*, %)		0	0	
Lower eyelid (*n*, %)		7, 7.95%	5, 5.68%	
Temporal (*n*, %)	8, 9.09%	5, 5.68%	3, 3.41%	
Zygomatic (*n*, %)	5, 5.68%	2, 2.27%	3, 3.41%	
Infraorbital (*n*, %)	5, 5.68%	4, 4.54%	1, 1.14%	
Nasal (*n*, %)	28, 31.82%			
Alar lobe (*n*, %)	14, 15.9%	7, 7.95%	7, 7.95%	
Dorsum (*n*, %)				0, 11.38%
Tip (*n*, %)				4, 4.54%
Auricular (*n*, %)	5, 5.68%	2, 2.27%	3, 3.41%	
Mandibular (*n*, %)	3, 3.41%	1, 1.14%	2, 2.27%	
Perioral (*n*, %)	1, 1.14%			
Upper lip (*n*, %)				1, 1.14%
Lower lip (*n*, %)				0
Mental (*n*, %)				1, 1.14%
Neck (*n*, %)	11, 12.5%	5, 5.68%		6, 6.82%

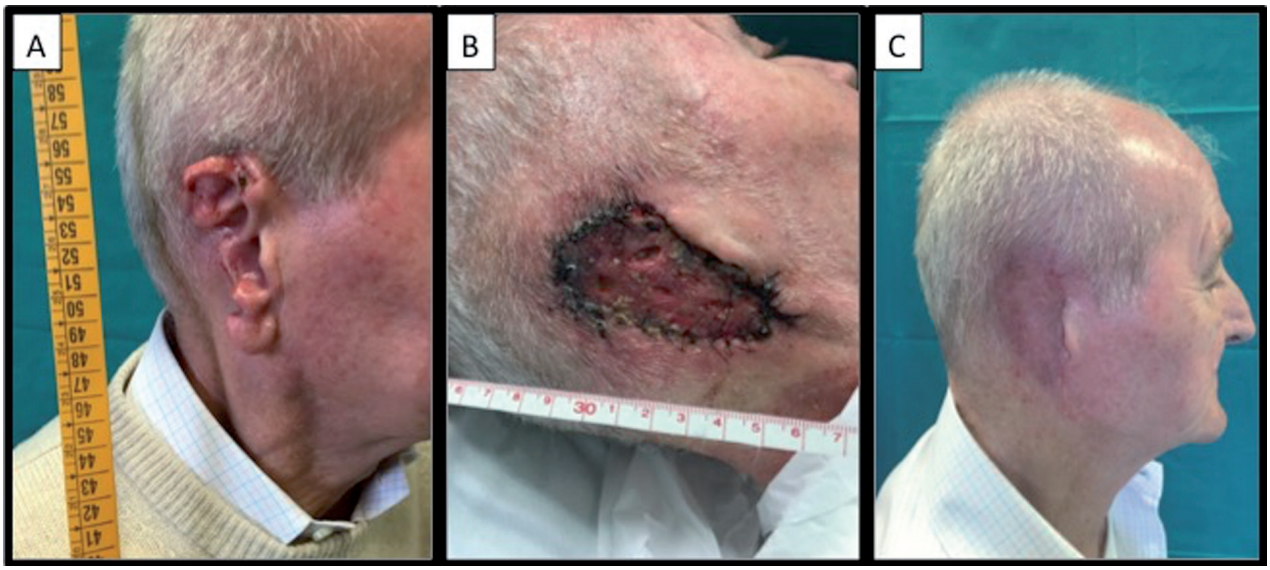

Figure 1. Images of a 73 year-old male patient who presented with ulcerated basal cell cancer of the right ear lobe. The patient had previously received incomplete surgery at another institution and requested complete auricular amputation at our unit. The patient refused any reconstructive surgery; therefore, we covered the resulting defect with a full-thickness skin graft harvested from the subclavicular area of the right chest. Images are shown before surgery (A), seven days after surgery (B), and three months after surgery (C)

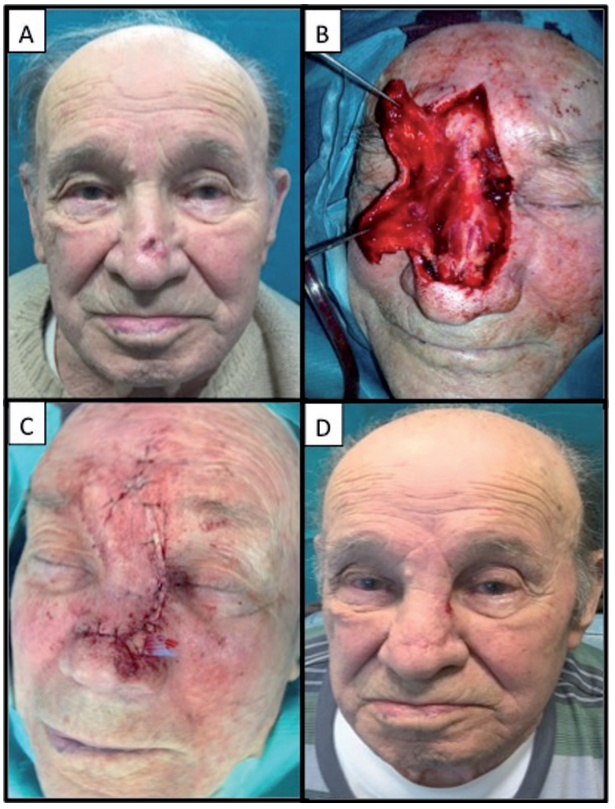

Figure 2. Images of an 82 year-old male patient who presented with nodular ulcerated basal cell cancer of the nasal dorsum. A dorsal nasal rotational flap was performed as the patient had adequate laxity of the glabbellar region. Laminar drainage was positioned in order to prevent hematoma formation and was removed on postoperative day 1. Images are shown before surgery (A), once the lesion had been excised and the flap elevated (B), immediately after the end of surgery (C), and three weeks after surgery (D)

Primary closure was the main surgical procedure performed (72.5%), followed by local flap (26.1%) and full-thickness skin grafts (1.4%). Partial wound dehiscence occurred in five (6.5%) patients, all of whom were receiving either oral anticoagulant therapy or aspirin that led to the formation of localized hematoma. Local cellulitis occurred in three (3.4%) cases, and was conservatively resolved by administration of topical antibiotics. In two (2.6%) patients, the scar developed into keloids, and one (1.3%) patient underwent revision surgery, as primary excision was incomplete. Neither recurrence nor any newly-developed lesions were reported during follow-up in any patient.

Discussion

The incidence of NMSC has dramatically increased worldwide over the last 30 years, mainly due to aging populations, as well as social and medical changes (2-6, 21, 22). BCC accounts for over 80% of cases of NMSC, and is the most frequently diagnosed cancer in Caucasian populations worldwide (23). Although death due to BCC is extremely rare, BCC is responsible for a significant economic burden and can lead to significant morbidity since most cases of BCC originate in key aesthetic and functional areas (24). UVR has been classified as a Class 1 'definite' human carcinogen by the International Agency for Research on Cancer (IARC); therefore, the carcinogenic role of solar radiation is well established (25). The head and neck are commonly exposed to sunlight during an individual's entire life, indeed numerous epidemiological studies have reported that approximately 80% of cases of BCC arise in the head and neck region (4, 18-26). In this cohort, the nasal region was the most commonly affected area of the head and neck; the nose is the most projected portion of the face and hence is more exposed to solar radiation. Moreover the fact that BCC developed on the lower eyelids, but not the upper eyelids, strengthens the evidence for UVR as an initiator of skin cancer. Similar findings have been reported in the literature. Choi et al. observed the highest occurrence of BCC on the nose (48.7%), followed by the orbital region; Kim et al. and Jung and Kim also noted the nose was the most common site for BCC (47.3% and 38.4%) (27-29).

BCC is traditionally considered to occur more commonly in older patients, usually males, due to their more extensive exposure to sunlight (2,4,17). However, recent studies have reported a higher incidence of BCC among females than males (27, 30-34). In this work, we observed a male to female ratio of 0.925:1. These changes may be due to the extended life expectancy of women (35). Furthermore, de Vrjes *et al.* also suggested that the 'typical' patient with BCC in northwestern Europe is more often female as young females, and even females with higher education, report stronger sun-seeking behavior than their male counterparts (36). Surveys of the general Italian population also revealed what has been defined as the sunscreen paradox,

which is described as a feeling of excessive protection when using sunscreen that disproportionately extends the sun exposure time and increases sun-seeking behaviors (37,38).

A study by Butler et al. observed skin cancers occurred more frequently on the left side of the body, which is supported by previous research that showed an increase in photo-damage and precancerous lesions on the left-side of the face due to exposure to sunlight through windows when driving and working (39-41). However, we observed a slightly higher incidence of BCC on the right side of the head and neck than the left side.

The primary aim of surgical treatment is complete removal of the lesion, while achieving the best aesthetic result as a main secondary goal. A 0.3 to 1 cm safety margin usually ensures a complete removal rate of 95%; unfortunately, radical surgical techniques may result in poor cosmetic outcomes depending on the site of BCC (17). In this cohort, the safety resection margin ranged from 4.5 to 9 mm, with a 98.7% complete removal rate, indicting the commonly-accepted surgical margin was adequate to ensure peripheral clearance in our experience. In this cohort, 72.5% of cases received primary closure while 26.1% required local flap surgery and 1.4% received a full-thickness skin graft. The high rate of direct closure may be explained by increased early diagnosis. As previously reported, BCC mostly occurs on the upper portion of the body and has a slow rate of growth, thus early diagnosis is usually relatively achievable. Indeed early diagnosis is mandatory in order to achieve the optimal surgical outcome, since smaller tumors generally require less invasive surgical procedures. Moreover, none of the patients in this cohort required topical medical therapy thanks to the high rate of early diagnosis.

Patients presenting with an NMSC are at a high risk of subsequent NMSC within the first year (42). Frankel et al. reported that 52% of patients developed subsequent NMSC within five years of therapy for the first skin cancer (43). Nevertheless we did not observe either recurrence or any newly-onset lesions within the first year of follow-up in this cohort.

This was a single center analysis of a small number of patients and therefore has several limitations. This data may not represent the most common sites of occurrence of BCC nor provide a general consensus for the treatment of BCC; multi-center studies of larger populations may help to precisely define the characteristics and optimal treatment for BCC. However, our work reflects the previously described shift in the incidence of BCC, which now seems to be more frequent in females. Furthermore, our data strengthens the association between UVR exposure and BCC and validates surgical excision as the gold standard treatment for skin cancer. Finally, this analysis highlights the key role of early diagnosis in achieving the optimal aesthetic outcome and - within the head and neck region - confirms the predilection of BCC to occur on the nasal unit.

Conflict of interest: None to declare

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Original article

European university students of pharmacy: survey on the use of pharmaceutical drugs

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Summary. *Background and aim:* In recent years, self-medication is an increasing public health issue, also among the European young people. Only 48% of people throughout the world use prescribed medications, while the remainder admits that they self-medicate with over the counter drugs or leftover prescribed drugs. Also, the risk of antibiotic resistance, throughout the world, has doubled, due to the recourse to these drugs when they are not called for, or to failure to follow their instructions for use. *Methods:* A five-part questionnaire, translated into the national languages and validated, was given to Pharmacy students in Italy, Spain, the Czech Republic and Romania obtain anonymous information about their pharmaceutical drugs use. *Results:* Regarding the use of pharmaceutical drugs, students in Spain and Romania indicated the highest percentages of use. In Italy and Romania, the pharmacist is rarely consulted, while the advice of family members or friends is more frequently requested. In all four countries the problem of taking antibiotics without a medical prescription is significant, and 50% of Romanian students use antibiotics to treat the flu. Another important result is that, in Spain, 38.4% of the respondents admitted to using medicines with alcohol. *Conclusions:* Considering that the drug information leaflet is not read by 50% of young people interviewed, it would be important for public health entities to instruct the population, especially younger age groups such as secondary school students, about the importance of reading this information carefully. The use of mass media in such a preventive medicine campaign could be effective. (www.actabiomedica.it)

Key words: students of pharmacy**,** pharmaceutical drugs, self-medication

Introduction

The World Health Organization states that "over half of all medicines are incorrectly prescribed, distributed or sold, and half of all patients fail to take medicines correctly." The problem is that over 50% of nations fail to implement policies to promote the rational use of medicines (1). In the European Union, on average, only 48% of people use prescribed medications in a two week period (2-5).

Self-medication is defined as the purchase of medicines without a prescription to treat self-diagnosed illnesses or symptoms, the extension of pharmaceutical drugs use beyond the period indicated by the physician, the re-use of old prescriptions to purchase medicines, or the sharing of medicines among relatives and friends. Political, economic and cultural factors have contributed to the steady increase in self-medication over the years, such that it is becoming one of the main problems of public health (6).

Self-medication mainly serves to deal with health problems that are not particularly serious or important, such as light discomfort or pain, colds or headaches, while it is not associated with the treatment of more severe illnesses such as hypertension. Thus self-medication is commonly indicated as treatment of transi-

tory illnesses or health problems that are not serious or significant (7). The most common and dangerous example of this behavior is the inappropriate use of antibiotics to cure infective diseases that are not serious, because this contributes to the spread of antibiotic resistant pathogens (8-10). Many studies regarding drugs use by young people point to a significant increase in the use of physician prescribed drugs but also in the use and abuse of drugs that have not been prescribed (11).

In the last ten years, the self-medication with antibiotics in young people has doubled, due to the recourse to antibiotics when they are not called for, or failure to follow the instructions for their use (1, 2). In fact, even among university students preparing for healthcare professions, there are high levels of self-medication with antibiotics to treat illnesses that would resolve spontaneously, and also of storing up supplies of antibiotics (12).

Another worrisome trend among people of this age group is the rise in the use of antidepressants (13). In the last five years in the United States (U.S.), antidepressant use has increased 100% in the entire population, while in recent years Holland has seen a 150% increase of the use of antidepressants by adults and young people. Many take them simply because they feel a bit down or because they are experiencing disappointments at school, with friends or with love interests.

There have been rare cases of increases in suicidal thoughts among adolescents who take antidepressants. Antidepressants have many other negative side effects, such as weight gain, altered blood lipid levels, and risk of diabetes (14, 15). Self-medication with antidepressants is thus a serious cause of concern. Another category of drugs misused by young people is amphetamines. American studies have shown that at universities, undergraduate use of amphetamines without a prescription every month ranges between 2% and 8%, while over the course of a year it can reach 16%. Even more worrisome is the habit of taking stimulants together with alcohol or other drugs (16, 17).

While the development of new drugs has permitted the treatment of many diseases, this does not mean that drugs should be considered a cure-all for every problem and consequently used inappropriately. In fact, the incorrect use of drugs and the medication errors (MEs) are cause of adverse drug reactions (ADR), the frequency of which is on the rise (18).

Therefore, in the light of these considerations, and given that many studies on the spread of self-medication have focused on university student populations, but without specifying their program of studies, or focusing on medical school students, we felt it would be particularly interesting and novel to explore.

Materials and Methods

A questionnaire was formulated to obtain anonymous information from Pharmacy students in Italy, Spain, Czech Republic and Romania about their use of medicines, their knowledge about them and their attitudes to them. The four nations were chosen on the basis of different social and cultural criteria. Romania and the Czech Republic were selected because they had only recently joined the European Union and have traditions and cultural backgrounds related to a national Communist system. Italy and Spain, founding nations of the European Union, have for some time now experienced an economic boom that has promoted a more consumerist lifestyle. The questionnaire was translated into the national languages and initially administered to a selected sample of university students in the four nations, in order to validate its design. Later, trained operators were sent to the four nations to conduct interviews in which they asked participants the questions in the questionnaire, and then noted the answers on the questionnaire forms. The interviews were conducted from 2015 until 2017 in the context of a broader two-part study, the first part concerned with lifestyles of high school students (19-21), and the second regarding the use and abuse of medicines among university students of Pharmacy. This paper analyzes the second part. Before the questionnaires were filled out, the operators informed the students about the purpose of the study, stressing the importance and usefulness of the data that would be acquired. Each student was asked to fill in and sign an informed consent form in accordance with the latest version of the Declaration of Helsinki. The questionnaire had five sections: questions to characterize the sample of Pharmacy students, questions to

understand how students take certain classes of drugs, questions to identify the people from whom students receive advice about medicine, and questions to learn about use, abuse and correct habits regarding preliminary reading of the information leaflet contained with the drug package. The data collected was input and processed using Access and Microsoft Excel. Statistical analysis was performed with X-Lstat software (22). Descriptive statistics were used to analyze the distribution of variables. Qualitative data were described using frequencies and percentages. The Chi-square analysis and the Odds Ratio (OR) to evaluate the association between pharmaceutical products use, doctor advice and self-administration has been applied. The level of statistical significance was set at $p<0.01$ with a confidence interval of 99%.

Results

A total of 4275 questionnaire across the universities of four countries were distributed, and 4099 pharmacy students completed all items of the questionnaire with a response rate of 95.8%, and a rate of refuse of 4.1%. The sample was composed principally by females, and the average age is 21.9±2.2 (Table 1).

Czech Republic

As can be seen in Figure 1, in response to the question "*Have you used pharmaceutical products in the last 12 months*?" 69.6% of Pharmacy students responded affirmatively, indicating mainly analgesics and antipyretics (80%) for headache (76.5%), toothache (5.8%) and other sources of pain (16.2%) (Figure 2).

Antibiotics were taken by 41.3% to treat infective diseases, and 2.1% of respondents indicated that they had taken drugs to alleviate anxiety. None, instead, had taken stimulants. In response to the question "*Who gives you advice on pharmaceutical products*?", 67.9% indicated physicians or pharmacists, and 32.1% indicated family members, friends, or self-medication. Specifically, regarding antibiotics, in response to the question "*Do you use medicines only on advice of a doctor or a pharmacist*?", the Czech Republic students gave one of the highest percentages of those who admitted using them without a prescription (32.2%). Regarding the correct use of antibiotics, a good percentage of students in the Czech Republic (81%) knew that antibiotics are used to treat bacterial infections, while the others thought erroneously that they are useful against viral infections and the flu. In response to the question "*When do you stop taking antibiotics*?" 80.7% gave the correct option, "*at the point indicated by the doctor*" while the others responded incorrectly (4.6%). In addition, if the same symptoms recur after some time, before taking the drugs used previously, 71.4% consult their doctor, 18.4% ask the pharmacist, and the rest consult a family member or friend, look up the information on internet, or do not seek any information at all.

Regarding the lack of awareness that drugs can cause poisoning if taken in incorrect ways or quantities, when asked: "*Do you think that using medicines is: mostly beneficial, doesn't harm health much, mostly harmful and little beneficial, and sometimes beneficial but sometimes harmful*", 69.4% declared that the medicines could be harmful and cause poisoning; 6.2% answered no, and 24.4% declared they did not know. Furthermore, to the question "*Have you ever taken medicine to-*

Table 1. Characteristics of the sample

	Italy		Romania		Czech Republic		Spain	
	n°	%	n°	%	n°	%	n°	%
Gender								
Males	843	49.6	498	28.8	149	38.7	210	45.4
Females	723	42.5	1202	69.6	236	61.3	238	51.4
No answer	134	7.9	27	1.6	/	/	15	3.2
Tot.	1700	100	1727	100	385	100	463	100
Age (mean±SD)	22.0±2.4		22.7±2.5		21.5±2.4		22.7±1.5	

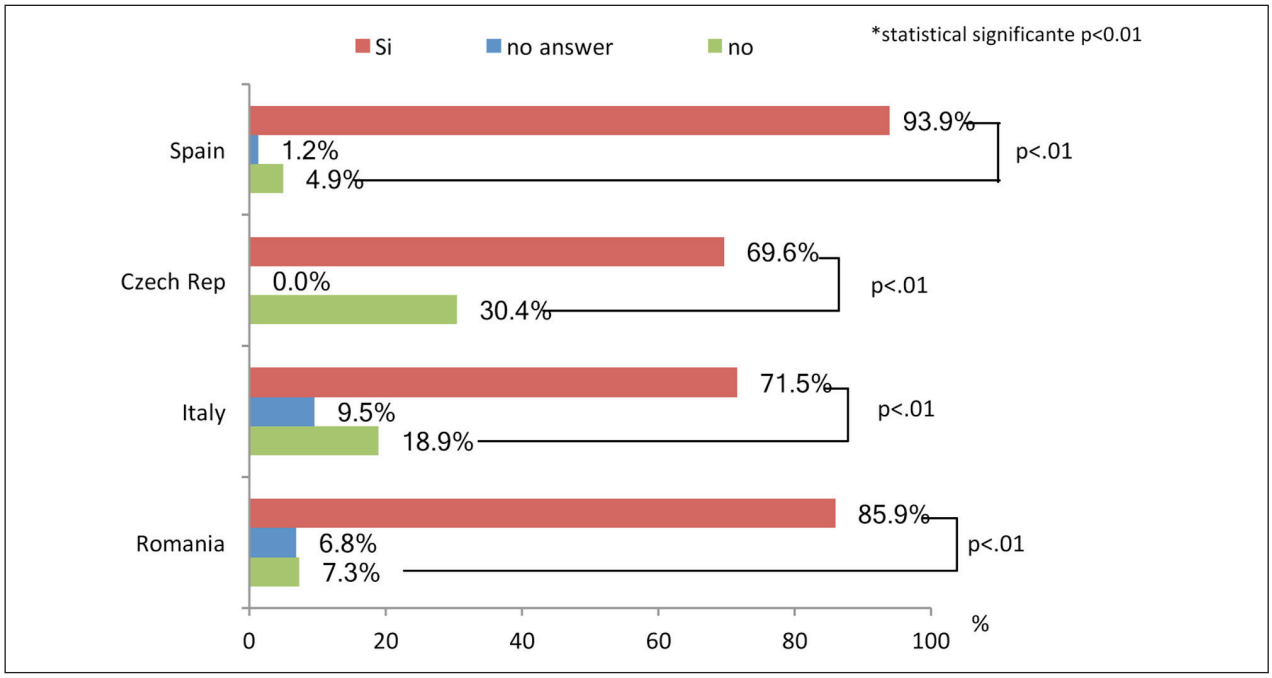

Figure 1. Have you used pharmaceutical products in the last 12 months?

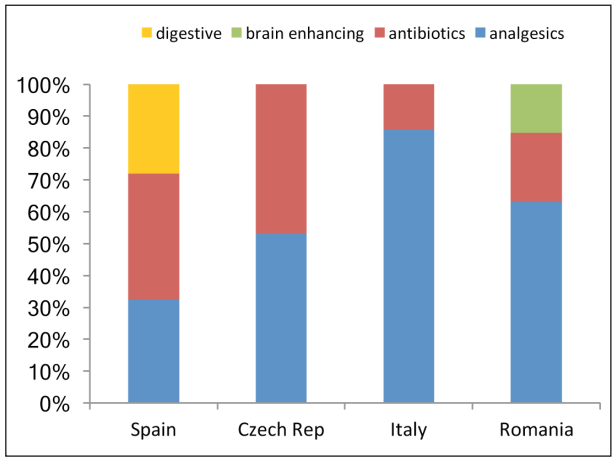

Figure 2. The pharmaceutical products most widely used by students

gether with alcohol?" 38.2% admitted taking medicine and drinking alcohol together (Figure 3). The instructions reported on the leaflet are clear only for 65.9% of students.

Romania

Romania gave the highest percentage (85.9%) of pharmacy student respondents with affirmative answers to the question about the use of pharmaceutical products in the last 12 months (Figure 1). Fully 68.6% of these Romanians answered the question "*Who gives you advice on pharmaceutical products*?", by indicating their doctor, specialists or pharmacists, and 31.4% reported family member, friends and self-administration, while only 36.4% of these students declared that the instructions in the leaflets are clear. Regarding the kind of medicines used, the greatest frequency was for analgesics (77.4% reported having taken these drugs occasionally), followed by those used for infections (26.5%), memory enhancers (18.6%) and for problems of anxiety (Figure 2). Regarding the consumption of prescribed antibiotics, 71.6% answered yes, whereas 28.3% responded no or not always. Over half of Romanian students, in response to the question "*For what purposes are antibiotics taken*?" indicated treatment of flu, while the remainder stated treatment of colds, viral and bacterial infections. Regarding the number of days antibiotics should be taken, 52.8% of the Romanian students follow their physician's indications, while 34.3% take them until symptoms disappear, and about 6.4% stop treatment when the fever passes; only 5.4% follow the instructions that come with the package, while 0.9% did not respond. Considering the answers to the ques-

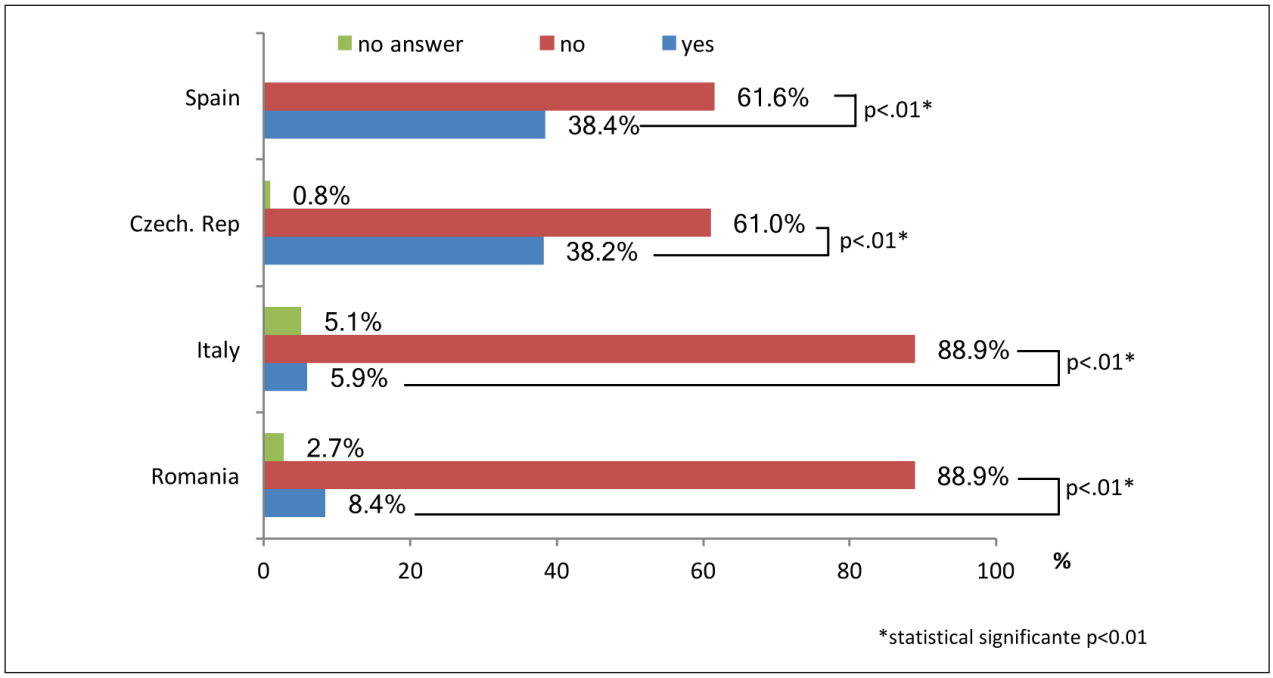

Figure 3. "Have you ever taken medicine together with alcohol?"

tion: "*Have you ever taken medicine together with alcohol*?" (Figure 3), one sees that the students in Romania were quite aware of the dangers of this behavior (88.9% indicated no as their answer). To the choice: "*Do you think that using medicines is: mostly beneficial, doesn't harm health much, mostly harmful and little beneficial, and sometimes beneficial but sometimes harmful*" 65.3% choose yes whereas 30% responded "I do not know".

Italy

64.5% of Italian pharmacy students declared they had used pharmaceutical products in the last 12 months (Figure 1). In Italy, the use of analgesics is occasional (46.2%) and the main pathologies for which medicines were taken were infections (39.1%), asthma, often associated with allergies, (4.6%), bronchitis (9.7%), headache (61.3%), anxiety (7.7%), associated with sleep disturbances, irritability (5.1%) and memory problems (4.9%) (Figure 2). In Italy, 26.6% admitted using antibiotics for viral infections in general, 10.3% for colds, 40.1% for the flu, while the rest did not respond. Among those who do not avail themselves of the advice of a physician, 29.1% believed that antibiotics cure viral infections, 13.4% deemed them useful for colds, 40.1% thought they cure flu, and the rest did not respond. Fully 74.3% end the treatment according to the doctor's instructions, 25.7% end the treatment when the symptoms disappear, and 85.1% trust themselves to their doctor's opinion even when the same symptoms recur. In Italy, pharmacists are consulted rarely (8.9%) about instructions for drugs use. In fact, a higher percentage (33.2%) of respondents treat themselves without any advice. 60.35% of Italian students responded that drugs can cause poisoning, while 23.5% did not know this fact. In response to the question "*Have you ever taken medicine together with alcohol*?" the students in Italy were quite aware of the dangers of this behavior, because only 5.9% admitted they had taken medicine and consumed alcohol contemporaneously (Figure 3). Regarding the clarity of the information provided in the instructions leaflet, 67.23% of the students reported that they found the instructions unclear, and only 11.5% said they were able to understand them.

Spain

Among the Spanish students, 54.8% indicated that they had used drugs in the previous 12 months,

with very limited use of sedatives or medications for hypertension, diabetes, or asthma, but greater use, albeit for short periods, of anti-flu medications, antibiotics, antivirals and analgesics. Drugs for problems of anxiety were taken by 30.7%, and memory enhancers were used by 27.4% (Figure 1). In response to the question: "*Who gives you advice on pharmaceutical products*?", the percentages showed that a specialist physician (42.3%) is consulted as often as the family doctor (47.1%), but a significant percentage of respondents (32.4%) admitted using drugs on the advice of family members. Spain had the greatest percentages of subjects who admitted to taking antibiotics without a prescription: 35.7% of the students admitted to this dangerous habit, while only 30.9% reported that they use antibiotics prescribed by their physician. Regarding the potential of drugs to cause poisoning, 58.1% of the Spanish students said they did not know whether this was true. Similar lack of knowledge emerged in the 34.7% of students who believed that antibiotics are useful for treating gastrointestinal disturbances, and the 32.4 % who believed they are effective in combatting the flu, while the rest of the students indicated that they are to be used for viral infections and colds. This confirms that the Spanish students, like the Italians, frequently use antibiotics for a simple cold or flu. In this way, antibiotics become ineffective for more important illnesses. Among Spanish students, 57% thought it is useful to stop taking antibiotics at the point indicated by the doctor, 21.2% at the disappearance of symptoms, 11.8% at the point indicated on the packaging, 8.7% when the fever passes, and 1.3% a few days after the first dose. Most students knew how to use antibiotics for the correct number of days, and similarly, 70.6% felt it is indispensable to consult the doctor should the medicine fail to have effect. To the choice: "*Do you think that using medicines is: mostly beneficial, doesn't harm health much, mostly harmful and little beneficial, and sometimes beneficial but sometimes harmful*", the data for Spain was the most worrisome, as almost 60% of students did not know how to answer the question, and 20% even said no. Looking at figure 2, one sees that in response to the question "*Have you ever taken medicine together with alcohol*?" 4 out of 10 students in Spain admitted taking medicine and drinking alcohol together (Figure 3).

Statistical Analysis

Looking at the results country by country provides some interesting comparisons. Among the Spanish respondents who indicated that they had taken drugs in the last 12 months, there was a significantly higher percentage who self-medicate or take medicines on the advice of friends or family (45.3%) than for those who consult a pharmacist before taking a drug (24%) (χ^2=7.92, p<0.01, OR=3.75), while there was not a significant difference between those who confer with a family physician or specialist and those who take advice from family or friends, or self-medicate.

In comparison, among the Italian respondents there was not a statistically significant difference between the percentage of those who confer with a family physician and the percentage of those who seek no advice from healthcare professionals. In contrast, the Italians showed a statistically significant higher percentage of young people who get advice from family and friends rather than a specialist (χ^2=7.77, p<0.01, OR=2.63), and this difference is even higher compared to those who consult a pharmacist (χ^2=15.84, p<0.01, OR=4.60).

Also for the Czech Republic, there was a statistically significant higher percentage of students who do not seek advice from a pharmacist, but prefer to ask advice from other figures (χ^2=10.56, p<0.01, OR=3.44), while there was not a statistically significant difference in the percentages of those who ask advice from family physicians/specialists and those who consult with other figures.

Regarding Romania, the percentages of students who self-mediate compared to those who consult a family physician or specialist did not differ significantly. Once again, the figure of the pharmacist emerges less frequently as a source of advice than do family members, friends, or simple self-medication (χ^2=10.22, p<0.01, OR=3.12).

Considering all four countries, the drugs most often taken as self-medication were antibiotics; this was particularly evident in Spain (Table 2).

As can be seen in Table 2, for Spain there is a significant Odds Ratio, while for the other countries, even though there is statistical significance (except for the Czech Republic), the Odds Ratio values do not

Table 2. Association between the prescription or nonprescription antibiotic use by the pharmacy students surveyed

Variables	Prescription %	Non prescription %	OR (99%)	P-value
Czech republic Antibiotic use	67.8	32.1	0.65 (0.325-1.29)	0.288
Italy Antibiotic use	74.3	23.6	0.38 (0.21-0.69)	0.002
Romania Antibiotic use	71.6	26.5	0.40 (0.22-0.72)	0.004
Spain Antibiotic use	30.9	68	4.40* (2.36-8.19)	<0.001

*Statistical significance: p<0.01 and 99% confidence interval

express a significant association between taking antibiotics and absence of a prescription. Statistical analysis of antibiotic use without prescription shows a greater risk of inappropriate exposure, and thus a possible future interaction between this type of behavior and the emergence of antibiotic resistance.

Discussion and Conclusions

Inappropriate use of drugs and the habit of self-medication, in particular that of antibiotics, are increasingly widespread practices even among university students, as noted before (6, 8-10). This study focused on a well-defined sample, pharmacy students, whom one would think would be especially attentive and sensitive to this issue. However, the percentage of students who take antibiotics without consulting a physician to verify the real need for them is truly striking. This dangerous habit is quite common among the Spanish and Czech students, but also present among the Italian and Romanian ones, though in lower percentages. This may not be inherently dangerous, but may become so when the person does not know how the drug should be used, for example, when antibiotics are used to treat viral infections or the flu (23-26).

Fully 45% of the students reported that they themselves choose when to stop taking antibiotics, which often makes the treatment ineffective, or worse, enables certain pathogenic microorganisms to develop resistance to these drugs.

Our findings highlighted that in the four countries the pharmaceutical products most widely used by the students are analgesics and antibiotics. Of concern is the percentage of subjects who get advice on medicine use from family members rather than from healthcare professionals, and in particular from pharmacist. These results are in accordance with the literature (27). In Italy and Romania, students indicated that they are more likely to treat themselves without any advice than to consult a pharmacist. These findings confirm the WHO statements about the health risks of the incorrect use of medicines, especially resistance to antibiotics that can result from wrongheaded use of these drugs, and are in accordance with other researches (1-3, 28, 29).

The same superficiality is seen concerning mind-acting drugs. Most students indicated that they knew the dangers of these products, but the answers of students in Spain and Romania in particular to the question about the dangers of tranquillizers and soporifics indicated that they were ill-informed, perhaps not perceiving them as part of this class of drugs. This result is in line with the WHO statement about the risks related to the abuse of mind-acting drugs (1), and with the results showed about the surfing internet to search medical information (29).

Another incorrect behaviour that emerged from this study was the consumption of alcohol together with the use of medicines, above all in the Czech Republic and Spain (30, 31). Very real dangers can ensue, including nausea and vomiting, headache, somnolence,

fainting, or loss of coordination, even cardiac problems and difficulty breathing. Alcohol can make a drug less effective or useless, or even dangerous or toxic (32, 33).

To our mind, one of the most important preventive actions that should be taken is to inform young people about the proper use of pharmaceutical products, in the hope that they will then use these drugs correctly (34). Simply educating them to read the drug information in the packaging would be an important measure, as our data indicate that almost half the students interviewed do not do so (35-39).

In addition, in order to avoid the use of medicines leftovers from a previous illness or of drugs passed on by family or friends, physicians should write prescriptions for exactly the quantity of drug needed for the patient. Similarly, pharmaceutical firms should produce packages of drugs such that proper doses would not be exceeded or pharmacists should be required to prepare personalized packages with precisely the number of doses prescribed for the patient.

Conflict of interest: None to declare

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Original article

Sleep disturbance and response to surgical decompression in patients with carpal tunnel syndrome: a prospective randomized pilot comparison of open versus endoscopic release

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Summary. *Background:* Sleep disturbance is a common complaint of patients with carpal tunnel syndrome (CTS). While carpal tunnel release (CTR) surgery has been shown to relieve subjective sleep-related complaints, data is lacking on the global effect on sleep using validated sleep measures. Additionally, it is not known if open (OCTR) or endoscopic release (ECTR) produce differing degrees of sleep-symptom relief. *Methods:* Sixty patients were randomly allocated to undergo either OCTR (n=30) or ECTR (n=30) surgery. Forty-three (71.7%) of the patients were female, and mean age of all patients was 49.4 years (range, 35-78). Prior to surgery, patients were administered three baseline self-reported outcome measures: the Pittsburgh Sleep Quality Index (PQSI), the Insomnia Severity Scale (ISI) and the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) survey, which were subsequently administered at three postoperative time points: 1-2 weeks, 4-6 weeks and 6-12 months. *Results:* All 60 patients experienced significant improvements in the three outcome scores by their first postoperative visit compared to preoperatively. ECTR provided superior improvement to OCTR at the first postoperative visit for ISI (P=0.006) and PSQI (P=0.016), and at the second visit for PSQI (P=0.0038). There were no significant differences between the two groups for the QuickDASH at any time points, or for the ISI/PSQI at the final follow-up. *Conclusion:* Endoscopic and open CTR both improve sleep symptoms postoperatively in the short-term which is sustained for 6-12 months, although endoscopic CTR does so more rapidly. (www.actabiomedica.it)

Key words: insomnia, carpal tunnel syndrome, PQSI, Insomnia Severity Index, open surgical release, endoscopic surgery, sleep disturbance

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremity, and often necessitates decompression via carpal tunnel release (CTR) when conservative management fails (1-3). CTS typically manifests with characteristic symptoms of numbness, tingling and pain in the median nerve distribution, which often hinder patients' ability to sleep, and in turn may profoundly affect their quality of life (4, 5). While CTR surgery is thought to result in subjective improvement in sleep symptoms, there is little data to quantify this improvement using validated sleep-quality or insomnia measures (5).

Both open (OCTR) and endoscopic carpal tunnel release (ECTR) effectively relieve nerve symptoms in the majority of CTS patients, although the superiority of one option over the other is debated (6, 7). Furthermore, it is not known if either surgical method is superior in treating secondary sleep symptoms. This is

potentially valuable information, as sleep disturbance is often the primary motivating factor towards seeking medical care for CTS. The purpose of this pilot trial was to test the null hypotheses that OCTR and ECTR would result in similar postoperative improvements in patients with CTS, as measured using validated patient-reported sleep-quality and insomnia outcome measures.

Methods

Patients

This study was approved by our Institutional Review (Ethics) Board. Patients were eligible for study enrollment if they were confirmed to have CTS warranting CTR surgery on the basis of clinical history, physical exam findings and electrodiagnostic (EDX) testing. Patients younger than 18 years of age, those with existing preoperative diagnoses of sleep disorders and/or taking sleep aid medications preoperatively, patients with prior history of surgery or trauma at the operative wrist, and patients with bilateral disease were excluded from participation. After obtaining study consent, patients were randomized either to the OCTR or ECTR groups using a custom random-number generator created with the Minitab statistical software package (Version 17.3.1 for Windows; State College, PA, USA).

Electrodiagnostic testing

All preoperative EDX testing was performed at our institution by one of two licensed clinical neuroelectrophysiologists using standardized techniques. For study of median nerve distal motor latency, the median nerve was stimulated at a position 3 cm proximal to the level the distal wrist crease between the flexor carpi radialis (FCR) and palmaris longus (PL) tendons. Recording was done from the abductor pollicis brevis muscle as the median nerve was stimulated, maintaining a 5 cm distance between the stimulating and the recording electrodes. To study median nerve sensory latency, a recording ring electrode was placed on the second digit and the median nerve was stimulated near the proximal crease with the cathode placed at a distance of 14 cm proximal to the ring electrode (8). Per our institutional standards, median nerve motor and sensory onset latencies greater than 4.2 and 3.5 msec, respectively are considered abnormal.

Surgical technique and postoperative course

OCTR was performed using a standard mini-open technique using a 2-cm longitudinal incision created in line with the fourth ray, with care taken to avoid extending the incision proximally past the distal wrist crease (9). ECTR was performed with the two-incision technique as described by Agee (10). Postoperatively, patients were seen for their first visit at 1-2 weeks for standard follow-up examination including wound inspection and suture removal. A second and final in-person evaluation was performed at 4-6 weeks.

Data collection and statistical analysis

Standard demographic information including age, gender and handedness, and EDX testing values were recorded for each study patient. To establish a baseline prior to surgery, patients were administered three validated self-reported outcome measures: the Pittsburgh Sleep Quality Index (PQSI) (11), the Insomnia Severity Scale (ISI) (12) and the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) (13) functional survey. The three outcome measures were re-administered at both follow-up visits and again during a final follow-up telephone call made at 6-12 months postoperatively. Statistical analysis was performed using Minitab software. Paired t-testing was used to compare the preoperative and postoperative scores for consecutive visits, while independent t-testing was used to compare the two treatment groups at each visit.

Results

Baseline demographics

A total of 60 patients who underwent open (n=30) or endoscopic (n=30) CTR satisfied study inclusion. The mean patient age was 49.4±8.0 years, and 43 pa-

tients (71.7%) were female. There were no significant differences in age, sex, hand dominance, preoperative nerve testing values and baseline preoperative QuickDASH, ISI and PSQI scores between the OCTR and ECTR treatment groups (Table 1). Distal sensory latencies were absent in 6 patients (2 OCTR, 4 ECTR).

Patient-reported outcome measures

At the first postoperative visit (12.4±2.4 days from surgery), all three outcomes were significantly improved compared to preoperatively, although there was no significant difference between the OCTR and ECTR groups for the QuickDASH (P=0.539). Contrarily, the ISI and PSQI had both improved to a significantly greater degree in the endoscopic group as compared to the open CTR group. At the second postoperative visit (31.4±12.4 days), all three outcomes were again significantly improved compared to the previous visit. At this visit however, only the PSQI was significantly different between the two treatment groups. By the final telephone follow-up (234±51 days), all three outcomes again demonstrated statistically significant improvements compared to their most recent prior visit. There were no significant differences between the open and endoscopic CTR groups for the any of the three outcome measures at this final telephone follow-up. These values are presented in Table 2, and depicted graphically in Figure 1.

Discussion

Although sleep disturbance due to nighttime symptoms is a highly prevalent component of CTS, the response or improvement of these symptoms to CTR surgery has not been adequately explored, as outcome measures specific to CTS or upper extremity conditions tend to address secondary sleep disturbance in a single item related to nocturnal pain (4, 14). In addition, while the relative efficacy of OCTR versus ECTR in alleviating general CTS-related symptoma-

Table 1. Comparison of baseline data between the open and endoscopic carpal tunnel release groups

Variable	Open (n=30)	Endoscopic (n=30)	P-value
Age, mean ± SD, years	49.1±7.1	49.7±9.0	0.78
Final follow-up duration, mean ± SD, months	7.5±1.5	8.1±1.9	0.17
Female sex, n (%)	21 (70%)	22 (73%)	0.77
Dominant side, n (%)	18 (60%)	18 (60%)	1.0
Type II Diabetic, n (%)	9 (30%)	8 (27%)	0.77
Motor nerve onset latency, mean ± SD, ms	6.0±1.7	6.2±2.0	0.74
*Sensory nerve onset latency, mean ± SD, ms	5.0±1.2	4.8±1.0	0.51
QuickDASH score	43±19	43±18	0.70
ISI score	12.8±7.1	14.1±6.7	0.46
PSQI score	10.9±3.1	11.3±2.7	0.51

*Note: sensory latency values were non-recordable in 2 and 4 patients who in the open and endoscopic groups, respectively

Table 2. Mean values of outcome measures for entire patient cohort compared over treatment course

	Postoperative Visit 1			Postoperative Visit 2			Final Phone Follow-Up		
Measure	Open	Endoscopic	P-value	Open	Endoscopic	P-value	Open	Endoscopic	P-value
Time interval (days)	12.3±2.0	12.5±2.1	0.708	31.6±12.0	31.0±13.2	0.863	225±44.2	243±56.1	0.172
QuickDASH	26±12	24±12	0.539	13±8	13±8	0.918	12±7	11±7	0.491
ISI	7.5±4.9	4.4±3.7	0.006*	4.3±3.1	3.8±3.4	0.567	3.5±3.4	3.4±3.4	0.941
PSQI	6.1±2.8	4.4±2.7	0.016*	4.6±2.6	3.3±2.2	0.038*	3.3±2.4	3.2±2.2	0.904

Note that values are Mean ± SD.
* denotes statistical significance

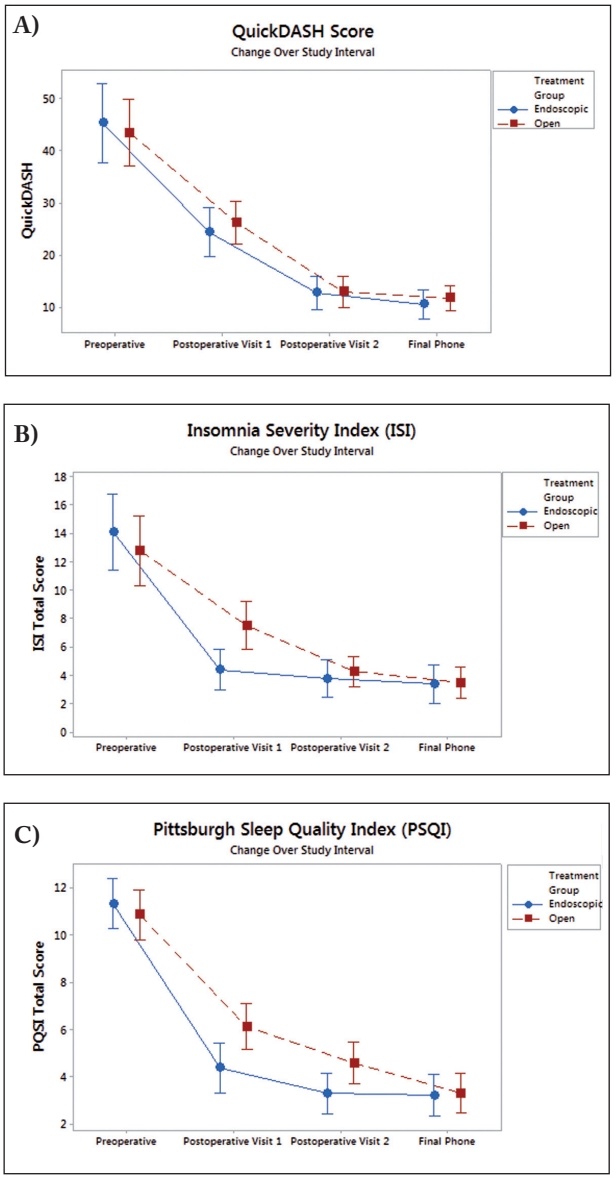

Figure 1. Interval plot of mean values of (A) the Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH), (B) Insomnia Severity Scale (ISI), and (C) Pittsburgh Sleep Quality Index (PQSI) outcome measures plotted over the duration of study enrollment. Interval bars represent 95% confidence intervals

tology has been studied extensively, secondary sleep symptoms have not been evaluated using patient-reported measures specific to sleep (6, 7). For example, although Aslani et al. reported no difference in nocturnal pain between open and endoscopic techniques at similar postoperative intervals as our current study, nocturnal pain is only one component of sleep-disturbance that is addressed in validated outcome measures (11, 12, 15).

In the presented study, both ECTR and OCTR resulted in significant improvements in sleep symptoms as assessed by the ISI and PSQI, although ECTR resulted in a more rapid improvement in symptoms. Contrarily, while the QuickDASH scores improved for both groups through the second postoperative visit, the two groups remained similar. These findings suggest that the more-rapid resolution in sleep disturbance seen in patients undergoing ECTR would not necessarily be recognized without using sleep-specific instruments to assess global sleep symptomatology.

This study has several limitations. The relatively small sample size makes it difficult to use this data to draw conclusions to the general population of patients with CTS. Another limitation was that we used the QuickDASH as our outcome measure to account for symptoms not specific to sleep. We elected to use this measure as it relatively short and is given to all new patients at our center per institution standards. Although it is not specific to CTS, its longer version has been validated for CTS (16).

Despite these shortcomings, we feel the results of this study provide important information for both the clinician and the patient. For those patients who are notably burdened by their sleep symptoms, it may be in their best interest to perform an endoscopic CTR due to the quicker resolution of symptoms compared to open techniques. Surgeons may want to consider employing the PSQI or ISI to screen for these patients, and also to monitor relief of sleep symptoms postoperatively.

Ethics Approval: Thomas Jefferson University Institutional Review Board

Conflict of interest: None to declare

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Original article

Prevalence and correlations of hepatorenal functions in diabetes and cardiovascular disease among stratified adults

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Summary. *Background:* The vulnerability of older adults to diabetes and cardiovascular complications is a global concern. Hepatorenal pathophysiology is implicated in these complications, but has yet to be clearly established, especially from rural low-mid income countries. This study investigates differences in prevalence of diabetes in aging groups and correlations of age with hepatorenal variables. *Methods:* 203 participants of both sexes above the age of 18 years underwent anthropometric measurements at Catholic Hospital, Abbi, Nigeria. Questionnaires collected demographic information and medical history. Urinalysis as well as routine liver and renal function tests were performed. Data analysis included determination of levels of hepatorenal abnormalities and prevalence of diseases in age groups. Percentage of disease subpopulations made up by each age-group was also determined as well as Pearson's correlation coefficient between age and hepatorenal variables, and comparison of average age and hepatorenal variables in disease subgroups. *Results:* Percentage hepatorenal abnormalities are not significantly different between age-groups. There is no significant difference in percentage level of disease between groups, but in age-groups constituting disease sub-populations ($p<0.00001$). The apparently healthy subpopulation comprises of younger adults compared to older adults constituting diabetes and hypertension ($p < 0\ldots$). Age shows moderate correlation with renal function parameters, especially urea and chloride ($r = 0.42$), but relatively insignificant with liver function variables. *Conclusion:* This report affirms that diabetes cardiovascular co-morbidity comes with aging. It also indicates that renal pathophysiology may be more associated, than liver, functions in the vulnerability of adults. (www.actabiomedica.it)

Key words: age, cardiovascular complications, diabetes, liver function test, renal function test

Introduction

The liver is important in carbohydrate metabolism since it is responsible for balancing blood glucose levels by homeostasis involving processes such as gluconeogenesis, glycogenesis and glycogenolysis (1). Diabetes can develop as a complication of hepatic disease (cirrhosis) and is known as hepatogenous diabetes (2). It has been observed that fatty liver, obesity and insulin resistance are factors that cause liver damage resulting in hepatic disease. In the presence of hepatic disease, the metabolic homeostasis of glucose is impaired as a result of insulin resistance, glucose intolerance and diabetes (3). The diabetes manifests as liver function deteriorates, thus hepatogenous diabetes can be considered as an indicator of advanced liver disease (4).

It is estimated that prevalence of diabetes and prediabetes in chronic liver diseases are high (5, 6), and that liver transplant is capable of lessening insulin resistance en-route restoring endogenous glucose production and insulin sensitivity in cirrhotic-diabetic patients (7). However, the prevalence of abnormal liver function markers in diabetes relative to non-diabetes

and in young adults compared to older subpopulations are yet to be clearly established, especially in the rural and sub-urban communities of low-mid income countries (LMIC).

Renal complication of diabetes is a significant public health issue and possibly related to the chronic liver disease in hepatorenal syndrome (8, 9). That is, renal disease may also occur in the context of liver cirrhosis, either as glomerular injury or as hepatorenal syndrome (10), beside the fact that patients with diabetes mellitus can also develop renal disease, especially after years of disease progression (11).

Aging is a major risk factor for most chronic diseases such as diabetes and cardiovascular complications. Hence it is a factor in common models of diabetes cardiovascular risk assessment (12, 13). Aging is also a risk factor in vulnerability to acute liver injuries (14). Further, renal diabetes progression and the association of kidney disease with other comorbidities in older people are understudied and therefore poorly understood (15). It is important to study these associations especially in vulnerable groups such as the elderly. What is unknown, especially in rural communities of Nigeria such as Ndokwa local government areas is the level of hepatorenal abnormalities among older adults hence this study evaluates aging-related liver and renal status.

Study objective

This study evaluates the association of hepatorenal function with diabetes and its cardiovascular complication in older adults. Specifically, this study investigates the prevalence of diabetes in stratified age-groups and whether there exists a correlation with hepatorenal variables. Biomarkers of liver and renal functions are also investigated in the study populations with a view to establish associations.

Methods

Ethics and selection criteria

Ethical approval was obtained from various authorities including Charles Sturt University Australia and Novena University Nigeria, as well as a priori approval from Ndokwa West Local Government councils. The study was part of the prediabetes and cardiovascular complications screening (PACCS), an international research collaboration involving the department of Public and Community Health of Novena University and Charles Sturt University (16). This was a descriptive cross sectional study as defined in health research methodology (17) confined to the catchment zone of Catholic Hospital Abbi, and Friends Diagnostic Laboratories Obiaruku, both in Ndokwa communities of Delta State, Nigeria. Participants included males and females above the age of 18 years.

Data collection

Two hundred and three participants comprising 141 females and 62 males of ages ranging from 18-90 years underwent vital signs measurements, which included height, blood pressure, pulse, temperature, and weight. A questionnaire was used to collect other relevant data including anthropometry, family history, lifestyle and social economic status. Provisions were also made on the questionnaire for participants to indicate 'other health conditions' such as arthritis, back pain, stomach ulcer, etc., that may be confounding factors. Blood and urine samples were collected for clinical biochemistry. The haematology tests and urinalysis were performed at the Catholic Hospital Laboratory. The clinical biochemical investigations comprised of routine liver and renal function tests were performed at Friend's Laboratory, Obiaruku.

Statistics

Analyses were performed using MicroSoft Excel Data Analysis ToolPak 2010. The focus of analyses included determination of comparative (1) levels of abnormalities in stratified age groups, (2) percentage distribution of age groups in disease subpopulations, (3) differences in hepatorenal variables between 'healthy vs. diabetes' groups, (4) Pearson's correlation coefficient between age and hepatorenal variables, and (5) comparison of average age and hepatorenal variables in disease subpopulations.

Results

Descriptive statistics of abnormalities in parameters of liver and renal function tests are presented in absolute numbers per stratified age group. When analyzed in terms of percentage (i.e. prevalence) of hepatorenal abnormalities in each age-group and compared, there is no statistical difference between age groups (Table 1). Analysis of variance of the percentage hepatorenal abnormalities does show lowest average prevalence in group 1 (16%), followed by 18% in group 3, and relatively equal level (20%) in other groups.

There is also no significant difference in prevalent levels of disease between groups (Fig. 1). In corrobora-

Table 1. Absolute number of hepatorenal abnormalities in age groups

	Group 1	Groups 2	Group 3	Group 4	Group 5
Age range (years)	18-39	40-59	60-69	70-79	80+
N	40	53	46	35	29
Urine protein	6	6	8	7	9
Urine glucose	0	2	3	0	0
Blood urea nitrogen	17	30	28	29	23
Serum creatinine (high)	11	31	14	16	7
Plasma sodium	9	9	9	8	8
Plasma potassium	13	24	22	15	16
Plasma bicarbonate	26	32	18	24	11
Plasma chloride	6	16	7	4	11
Serum amino aspartate transferase	4	3	4	3	2
Serum amino alanine transferase	0	0	0	0	0
Serum alkaline phosphatase	1	1	1	0	0
Serum total protein (low)	13	16	20	10	9
Serum total protein (high)	13	12	10	9	9
Serum albumin	1	2	1	0	0
Serum total bilirubin	5	3	2	2	1
Serum direct (conjugated) bilirubin	0	1	0	0	0

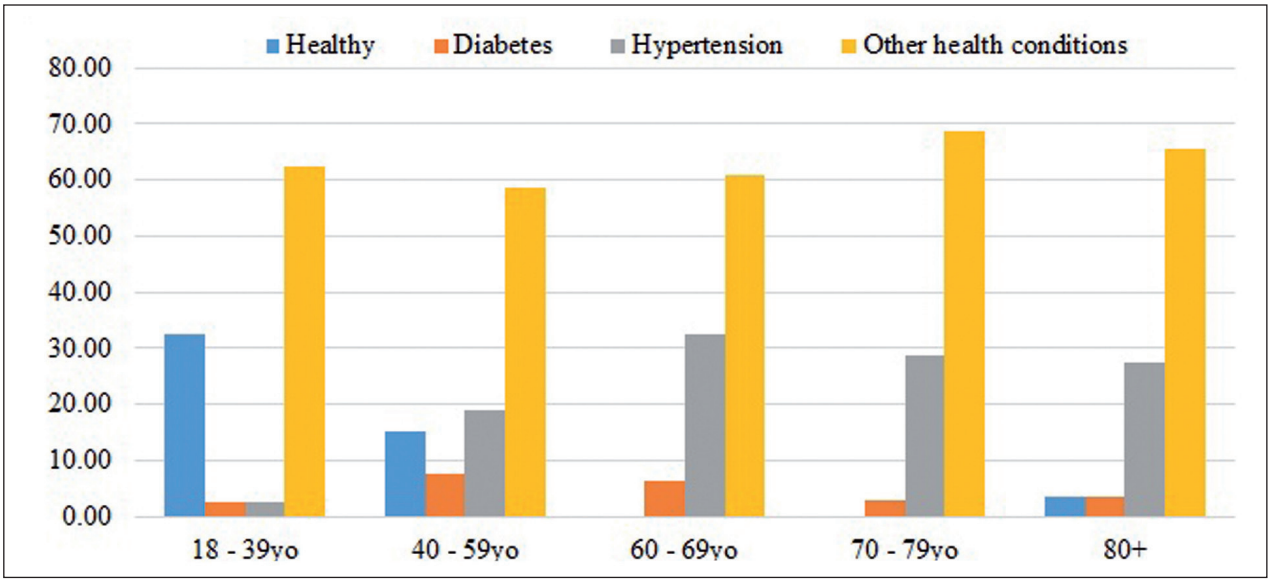

Figure 1. Prevalence of health and diseases in different age groups (p>0.99)

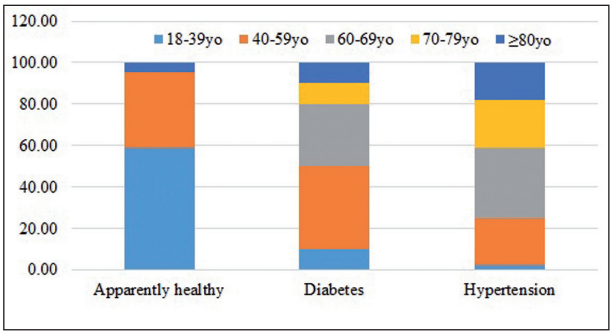

Figure 2. % age-groups that make up disease sub-populations (P<0.00001)

tion with table 1, there highest prevalence apparently healthy individuals in group 1 (33%), followed by 15% in group 2, and 3% in group 4, but none groups 3. Further, the result show that prevalence of other health condition, which includes dyslipidaemia and obesity amongst others, is neither lowest in the youngest group 1, nor highest in oldest group 5. However, a more critical review of the figure show that as from the 60years upward, there is apparent difference in prevalence with good health being little or non-existent, sequentially followed by lower number of diabetes, higher prevalence hypertension and highest proportion being other illnesses (Fig 1).

On the reverse when percentage of the separated apparently healthy, diabetes and hypertension subpopulations made up by each age-group was analyzed, result show significant different (Fig 2; p<0.00001). A critical review of the figure will show that the apparently health subpopulation is 60% made of the youngest age group 1 and 36% age-group 2. That is, 96% of the research participants who indicated to be apparently healthy are below 60years old. On the corollary, only 2% of the subpopulation with hypertension are below 40 years old (Fig. 2).

A further evaluation of average age among people with diabetes and hypertension relative to apparently health participants indicate significant difference (Fig 3; p<0.00001)). In this study, result show that the apparently healthy subpopulation averaged 38 years old followed by diabetes 58 years compared to those with hypertension averaging 63 years old. This affirms what can only be gleaned by critical review of result presented in Fig 1 – i.e. that as from the 60years upward, there is apparent difference in prevalence with good health being little or non-existent, sequentially followed by lower number of diabetes, higher prevalence hypertension and highest proportion being other illnesses (Fig. 1). Evaluation of average levels of liver and renal function test parameters among people with diabetes and hypertension relative to apparently health participants indicate no significant difference (p>0.50), though blood urea nitrogen show unidirectional change (Fig 3).

Lastly, comparing average age and hepatorenal variables in disease subpopulations: ANOVA shows no

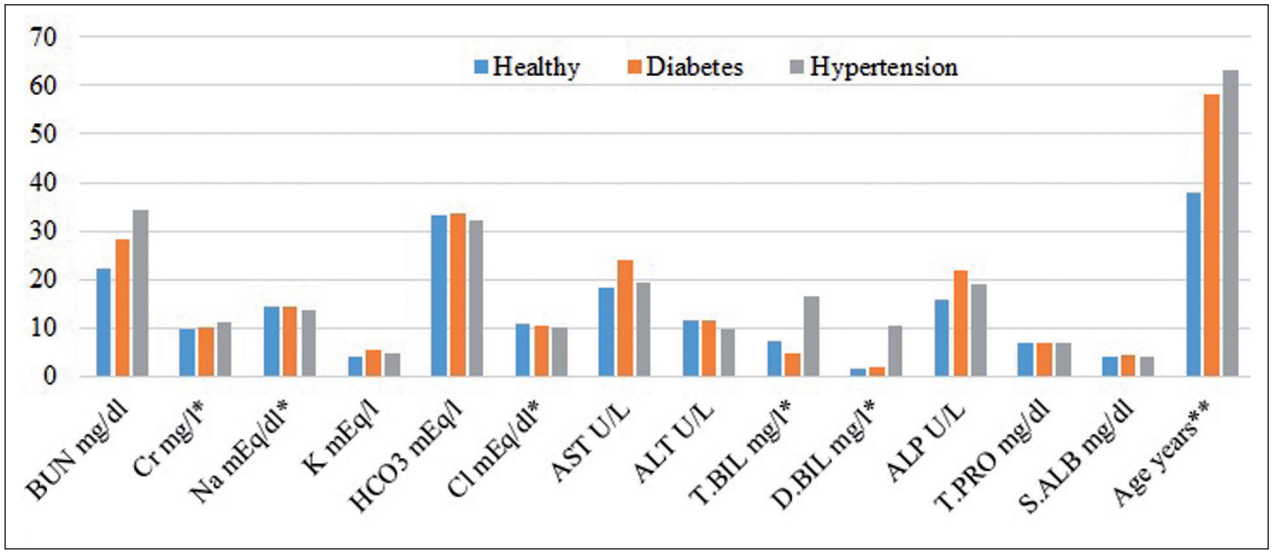

Figure 3. Average age (p<0.0.0001) and hepatorenal levels (p>0.05) in health sub-populations
*Note: Unit of measurement modified for graph purpose only

Table 2. Pearson correlation between age and hepatorenal function in apparently healthy cohort

Measurement	Correlation
Age	1
Blood urea nitrogen/urea	0.42
Creatinine	-0.15
Sodium	0.36
Potassium	0.39
Bicarbonate	0.02
Chloride	0.42
Amino aspartate transaminase	-0.10
Amino alanine transaminase	0.11
Total bilirubin	-0.15
Direct (conjugated) bilirubin	0.21
Alkaline phosphatase	0.09
Total protein	0.08
Albumin	0.16

unidirectional change or significant difference in the liver function tests, but there is indication that the 'apparently' healthy subpopulation are of lowest age compared to the cohort with hypertension, being of oldest adults. There is also unidirectional change in urea levels that seems to tally with age (Fig. 2; $p<0.001$), and corroborates with the correlation result (Table 2).

Discussion

Studies report that diabetes cases will increase from 2.8% in 2000 to 4.4% in 2030 or from 171 million in 2000 to 366 million in 2030, and especially among adults aged 65 years and older (18). This depicts a global public health problem, which is acknowledged as 'vulnerability of older adults to diabetes and its cardiovascular complications'. Diabetes causes serious complications and World Health Organization's estimates showed that in 2012, diabetes caused about 1.5 million deaths (19). It is further estimated that by 2025 there may be up to 380 million people who will suffer type 2 diabetes and another 418 million with impaired glucose tolerance (20). Further, liver and renal abnormalities (hepatorenal patho-physiology) are implicated in diabetes and its cardiovascular complications (21-24). Our observations show that in study population, approximately 23% and 5% indicated to have diagnosis of cardiovascular disease and diabetes, respectively. Obesity was approximately 9%, while existing diagnosis of dyslipidemia among the study population appeared to be <0.5% (Table 1), and these comprised clients who attended a previous screening exercise in the ongoing research activities. Since lipid profile testing is relatively inaccessible and unaffordable in the rural low-mid income communities, therefore this observation may not be a true representation of dyslipidaemia prevalence. Hence in the analysis, obesity and dyslipidaemia have been discretionally included among the 'other health condition'.

With emphasis on prevalence of diabetes and cardiovascular disease (indicated by hypertension) and in the context of vulnerability of older adults; the young adults age-group 18-39 years has the highest percentage of healthy people (about 33%), lowest percentage of diabetes and hypertension (less than 5%), but 62% have other health conditions such as arthritis and back pain, amongst others (Fig. 1). Indeed, studies report of increasing prevalence of adults with back pain in LMICs (25). Age-group 40-59 years had the lowest percentage of healthy people (about 15%), higher percentage of diabetes (7%), hypertension (19%) and 58% have other health conditions. The two age-groups 60-69 and 70-79 years have the least percentage of healthy people (<1%), 60-69 years has highest percentage of hypertension (32%) and 61% have other health conditions; while 70-79 years has highest 68 prevalence of other health condition (Fig. 1).

Thus, the non-significant difference in health status between age-groups can be attributed to existence of 'other health conditions' being present in >58% in every age-group. That is, 'other health conditions' being present in most individuals regardless of age-group may be a confounding factor. This conclusion is further supported by the observation of statistical non-significance in percentage of hepatorenal abnormalities being 16% in 18-39 years, 18% in age-group 60-69 years and 20% in other three age-groups (Table 1). Further, the observation corroborates with findings that neither outcome of diabetes treatment, nor consequent improvement in health status varies with stratified age groups (26).

The non-significant difference in health status between age-groups needs to be differentiated from how the age groups constitute disease sub-populations, or

average age of members constituting disease-groups. Results show that age-group 18-39 years constitutes the highest percentage of healthy population (60%), 10% of diabetes subgroup and only 2% of those with hypertension. This is followed by age-group 40-59 years constituting 37% of healthy sub-population but also the highest percentage of diabetes sup-population (40%) and 23% of those with high blood pressure. In contrast, age-group 80+ years constitutes only about 5% of healthy sub-population, 10% of diabetes and approximately 20% of the hypertension sub-population. Age-groups 60-69 and 70-79 years constitute the lowest percentage of healthy subpopulation (<1%) and highest percentage (>35%) of sub-population suffering hypertension (Fig 2; $P<0.00001$). Such observations are consistent with reports from other studies that show the risk factors for non-communicable diseases to be higher in older persons than the young (27). The result also affirm the concern on vulnerability of older adults to diabetes and cardiovascular diseases, which to our knowledge is the first from a rural low-mid income country setting.

Further, statistical non-significance in percentage of hepatorenal abnormalities between age-groups must be differentiated from correlation of individual biomarkers with age. Although, ANOVA showed no unidirectional change or significant difference in the liver function tests with aging, there is moderate correlation between age and renal function test parameters, especially BUN and some electrolytes (Table 2), which is corroborate with unidirectional change in BUN with age (Fig. 3).

Conclusion

The implication of hepatorenal functions in vulnerability of adults to diabetes and its cardiovascular complications has been investigated. It has been observed that 'other health conditions' existing in most individuals regardless of age-group may confound observation of significant difference between young versus older adults. However, there is observation that while prevalence of diabetes with cardiovascular co-morbidity increases with age, there is also renal abnormality indicated by BUN being unidirectional with increasing age. This study looked at age distribution and future studies need to consider sex distribution as well as studying the subtypes of diabetes and liver disease separately in regards to liver function association with diabetes.

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Conflict of interest: None to declare

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Case report

Charcot-Marie-Tooth disease with pyramidal features due to a new mutation of *EGR2* gene

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Summary. *Background and aim of the work:* Childhood-onset peripheral neuropathies are often of genetic origin. Charcot-Marie-Tooth (CMT), is considered the commonest neuromuscular disorder. Due to its high clinical heterogeneity, especially in the pediatric age, the co-existence of central and peripheral symptoms and signs does not necessarily rule out a diagnosis of hereditary peripheral neuropathy. *Methods:* We describe the clinical, neurophysiological and genetic findings in a teen-age patient evaluated for acquired toe-walking and progressive difficulties in walking since the age of 5. Genetic testing was carried out with a targeted NGS panel. Identified variants are analyzed using Variant Studio program (Illumina). Rare variants and variants considered as pathogenic were analyzed by Sanger direct sequencing. *Results:* The coexistence of peripheral and pyramidal signs in the lower limbs, the absence of a significant pre/perinatal history, the unremarkable brain and spine MRI, together with the presence of a sensory-motor polyneuropathy in all four limbs, prompted the execution of genetic investigations with an NGS panel covering hereditary spastic paraplegias, motor neuron disease and Charcot-Marie-Tooth. We identified a previously undescribed variant (c.1142G>T, p.Arg381Leu) in the *EGR2* gene. *Conclusions: ERG2* gene has been described as a cause of various phenotypes, including a rare autosomal dominant form of CMT (CMT type 1D) representing approximately 1% of all CMT subgroups. We describe a novel pathogenic variant in *EGR2* gene leading to the development of a complex association of peripheral and central neurological signs, underscoring the genetic and clinical heterogeneity of hereditary neuropathies of pediatric onset. (www.actabiomedica.it)

Key words: *EGR2*, Charcot-Marie-Tooth, CMT-1D, hereditary polyneuropathy, pediatric, sensory-motor neuropathy

Introduction

Childhood-onset peripheral neuropathies are frequently genetically determined. Charcot-Marie-Tooth (CMT), is considered as the commonest neuromuscular disorder, typically presenting with distal wasting and weakness, decreased deep tendon reflexes, contractures and skeletal deformities (1). Exceptionally, pes cavus has been described as an isolated finding in congenital CMT1A (2). The presence of additional clinical signs, such as marked sensory or upper limbs involvement, visual/hearing impairment, pyramidal signs or intellectual disability results in a need to extend the differential diagnoses to complicated forms of hereditary spastic paraplegia, inborn errors of metabolism or neurodegenerative disorders (3-5). Conversely,

the coexistence of central and peripheral nervous system involvement does not exclude a diagnosis of hereditary peripheral neuropathy (6).

Case report

Our patient is a 16-years-old boy born at term after uneventful pregnancy and delivery, from non-consanguineous, healthy parents. Following a normal early psychomotor development, since 5 years of age he has started to toe walk, with constant, progressive difficulties in walking.

His last neurological examination shows distal lower limbs hypertonus, bilaterally brisk tendon reflexes in his lower limbs and extensor plantar reflexes, no clonus, cavovarus supinated feet, postural/intention tremor in his upper limbs, hypotrophy of the intrinsic hand muscles and of the peroneal and extensor digitorum brevis (EDB) muscles. MRC muscle strength is mildly reduced (4/5) in the peroneal/extensor, thumb abductor/adductor, intrinsic and orbicularis oculi muscles. EMG/ENG shows a sensori-motor polyneuropathy in all four limbs.

The patient has undergone serial, non-contributory diagnostic investigations, including brain and spine MRI, full ocular examination, audiometric evaluation, array-CGH, vitamin E dosage, urinary organic acids profile, molecular testing for *SPG3A*. Somatosensory evoked potentials (SSEP) in the lower limbs are in keeping with bilateral central conduction delay.

Methods

Based on the coexistence of peripheral and central neurological sings, a targeted next generation sequencing (NGS) panel evaluating 185 genes associated with hereditary spastic paraplegias, motor neuron and the most common forms of Charcot-Marie-Tooth diseases was performed. Identified variants were analyzed using Variant Studio (Illumina), enabling verification of the frequency of occurrence of each variant in dedicated databases (dsSNP and ExAC), their association with known diseases (OMIM, HGMD) and their impact on protein structure and function (SIFT and Polyphen2 software). All potentially pathogenic variants (based on the scientific literature or databases) and rare variants resulting in either an aminoacidic substitution, the creation of a stop codon or a change in a splicing site were verified by Sanger sequencing.

Results

Three variants were identified. Two involved the *EGR2* (Early Growth Response 2) gene. The first variant (NM_000399.3 c.1142G>T, leading to the protein variant NP_000390.2 p.Arg381Leu), is not reported in ExAC database and is predicted to be potentially damaging, while the second variant (NM_000399.3 c.736C>T, leading to the protein variation NP_000390.2 p.Arg246Cys) is reported with a frequency of 0.001% by the ExAC database (dbSNP ID rs774391305). An additional heterozygous variant in the BSCL2 (seipin lipid droplet biogenesis associated) gene was identified: c.116A>G (NM_001122955.3) which leads to the protein variation p.Gln39Arg (NP_001116427.1. This variant is reported in the ExAC database (dbSNP ID rs 531137749) with a frequency of 0.03% and is predicted to be potentially damaging. Segregation analysis in the parents indicated that only the *EGR2*-p.Arg381Leu is a likely *de novo* variant, while *EGR2*- p.Arg246Cys and *BSCL2*- p.Gln39Arg are inherited from one of the parents.

Discussion

EGR2 mutations have been associated with the development of different inherited neuropathic phenotypes, including dominant and recessive forms of Dejerine-Sottas disease (severe early-onset hereditary neuropathy with motor delay, very low nerve conduction velocities, nerve hypertrophy, severe dysmyelination (1, 7)), congenital neuropathy with hypomyelination (7) and an autosomal dominant form of severe CMT (CMT type 1D), representing less than 1% of all CMT subgroups, in which cranial nerve involvement has also been described (1). This characteristic involvement in peripheral demyelinating and dysmyelinating disorders can be explained by the high expression of the EGR2 gene product (a zinc-finger transcription factor) in Schwann cells, where it activates the transcription of several myelin-associated genes. It is also implicated in myelin development and maintenance (1). How-

ever, cases of adult-onset axonal Charcot-Marie-Tooth disease with variable disease severity have also been exceptionally reported, and have been related to specific mutations leading to mild conformational protein changes disrupting axon-myelin interactions (8).

In this wide range of clinical features, genotype-phenotype correlations have started to be recognized. An association between a different pathogenic variant affecting the same Arg381 residue (p.Arg381His) and CMT1 with sensorineural hearing loss, third cranial nerve palsy and vocal cord palsy has been published (9). Cranial nerve involvement has also been described in association with respiratory compromise and multiple disabilities in a case with the p.Arg359Trp pathogenic variant (10), while the p.Asp383Tyr pathogenic variant has been reported in severe (Dejerine-Sottas syndrome) phenotype (11). Finally, an association with scoliosis has been noted in individuals with the p.Arg359Gln pathogenic variant (12).

Although the presence of pyramidal signs, to the best of our knowledge, has never been reported in association with pathogenic variants in the *EGR2* gene, it has been reported in the context of various genetic mutations causing Charcot-Marie-Tooth disease (6, 13).

The *BSCL2* variant, p.Gln39Arg, may likely contribute to some extent, to our patient's clinical picture, as this gene has been associated with SPG 17 (Sylver syndrome) and with a hereditary distal motor neuropathy (14).

We described a novel heterozygous mutation in the *EGR2* gene in a patient with a complex clinical picture of peripheral and central neurological signs, further underscoring the genetic and clinical heterogeneity of hereditary neuropathies, especially of pediatric onset.

Conflict of interest: None to declare

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Case report

Spontaneous iliopsoas hematoma in a trasfusion dependent β-thalassemia patient with hypersplenism: a case report

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Summary. A 27-year-old married man with transfusion dependent β-thalassemia (TDT) complaining low back pain due to a spontaneous iliopsoas hematoma is reported. A magnetic resonance imaging (MRI) confirmed the diagnosis.The patient was managed conservatively. The mechanism of spontaneous iliopsoas hematoma was unclear, although tearing of muscle fibers, unrecognized minor trauma, low platelet count, secondary to hypersplenism, and severe liver iron overload, associated to abnormalities of clotting factors synthesis, were the suspected etiologies. He showed a good response to treatment and was discharged home 11 days later. A new MRI, performed 7 months later, showed a complete resolution of hematoma. Although iliopsoas haematoma is an uncommon complication in patients with TDT, it should be considered in the differential diagnosis of a patient with back pain. (www.actabiomedica.it)

Key words: iliopsoas hematoma, trasfusion dependent β-thalassemia, diagnosis, treatment. hypersplenism

Introduction

β-thalassemia is an inherited hemoglobinopathy caused by β-globin gene mutations that impair the production of one or both β-globin chains. Distinction between the various phenotypes of β-thalassemia relies primarily on the clinical severity of the disease, which should be assessed both at initial presentation and over a period of close follow-up (1). Transfusion-dependent β-thalassemia (TDT) patients commonly present to our clinics in early childhood with severe anemia that requires life-long regular transfusion therapy for survival. On the other hand, non-transfusion-dependent β-thalassemia (NTDT) patients, usually present later in childhood or even in adulthood with mild/moderate anemia which only requires occasional or short-course regular transfusions in certain clinical settings (2).

The physical findings of TDT are related to severe anemia, ineffective erythropoiesis, extramedullary hematopoiesis, and iron overload resulting from transfusion and increased iron absorption. Manifestations generally include anemia, jaundice, pigment stones due to lifelong hemolytic state, skeletal changes secondary to erythroid hyperplasia with intramedullary expansion and cortical bone thinning, hepatosplenomegaly, heart failure and arrhythmia related to either severe anemia or iron overload. Iron overload causes clinical problems like those observed with primary hemochromatosis (eg, endocrine dysfunction, liver dysfunction, cardiac dysfunction) (3).

The iliopsoas muscle compartment can be involved by many different disease processes, including infection, tumor, and hemorrhage. Patients may present with a wide variety of symptoms that are often nonspecific, resulting in a delay in diagnosis. Spontaneous haematomas of the iliac psoas muscle are rare lesions that occur, most often, in patients receiving anticoagulant agents or in patients with either inherited or acquired clotting disorders (4). Furthermore, the iliopsoas compartment may become injured during trauma, percutaneous instrumentation, laparoscopic or open surgical procedures and extension from adjacent bleeding organs and vessels (5). Liver cirrhosis as a cause of spontaneous iliopsoas haematoma has also been reported (6). There is one case report of a haematoma of the iliopsoas muscle from thrombocytopenia resulting from the administration of a third generation cephalosporin (7).

We report a rare case of spontaneous iliopsoas haematoma in a male patient with TDT, diagnosed by magnetic resonance imaging (MRI). The patient responded well to a conservative treatment.

Case report

A 27-year-old married man with TDT, while travelling abroad complained low back pain requiring a hospital treatment with subcutaneous morphine and blood transfusions (2 units of packed red blood cells) because of a severe anemia. After hospital discharge, the patient came back immediately home, but due to the back pain recurrence he was referred to our hospital. He did not have a history of a similar complaint in the past and no personal or family history of bleeding disorders. There was no history of fall or trauma, fever or abdominal pain, motor or sensory complaints. He referred an intact bowel and bladder functions.

The clinical examination, two days after the symptoms appearance, was remarkable only for positive straight leg raising test on right side and hepatosplenomegaly. He was discharged after pain management with a plan to do MRI of spine in our outpatient department. Due to worsening of his back pain, which radiated to right groin, and the "aspect" of right thigh, he returned to the hospital after a few hours. On admission, his weight was 56 kg, height 161 cm, vital signs were stable, but he was in severe pain, lying in bed with the right leg flexed. Physical examination revealed that he had tender fullness over the right iliac crest region compared to the left side. Tenderness was also noted on right upper gluteal area. Passive motion of the hip aggravated his pain, but there were no focal neurological deficits.

Initial laboratory tests showed were significant for white blood cells (WBC) count: 2.4x10^3/uL (reference range: 4-10^3/μL), platelets count (Plt): 110x10^3/uL (reference range: 150-400x10^3/μL), hemoglonin (Hb): 6.5 g/dL (reference range: 13-17 g/dL), International Normalised Ratio (INR): 1.5 (normal range for a healthy person 0.8-1.2), activated partial thromboplastin time (aPTT): 41 seconds (reference range: 9.4-12.5 sec), D Dimer: 0.98 mg/L fibrinogen-equivalent units (FEU) (reference range: 0-0.49 mg/L), fibrinogen: 5.3 g/L (reference range: 2-4.1g/L). Clotting factor assay showed a reduced level of factor VII: 25% (reference range: 50 to 150), and biochemistry was significant for indirect hyperbilirubinemia and mildly increase of aspartate aminotransferase (AST): 45 U/L (reference range: 0-34 U/L). No endocrine complications were documented.

He was regularly transfused with red blood cell concentrate and on treatment with deferasirox (35 mg/kg per day). His last serum ferritin level was 3.247 ng/mL (normal levels: 23-175 ng/mL) An extremely high liver iron content (LIC) measured, five months before, by FerriScan® (8) was found: 39.9 mg/g dry liver. Four classes of LIC have been reported in thalassemic patients: Class 1=normal LIC <3 mg Fe/g dry liver, Class 2=mild overload LIC 3-7 mg Fe/g dry liver, Class 3=moderate LIC overload 7-15 mg Fe/g dry liver, and Class 4=severe LIC overload ≥15 mg Fe/g dry liver (3).

Magnetic resonance imaging (MRI) showed a hematoma in the right iliopsoas muscle extending to the upper thigh. The calculated size of the lesion in all imaging modalities was approximately 12x5x2.5 cm (Figure 1).

He was managed conservatively with transfusion of red blood cell concentrate, analgesics, vitamin K, steroids, bed rest and physiotherapy. He showed a good response to treatment and was discharged home 11 days later. A new MRI, performed 7 months later, showed a complete resolution of the iliopsoas hematoma (Figure 2).

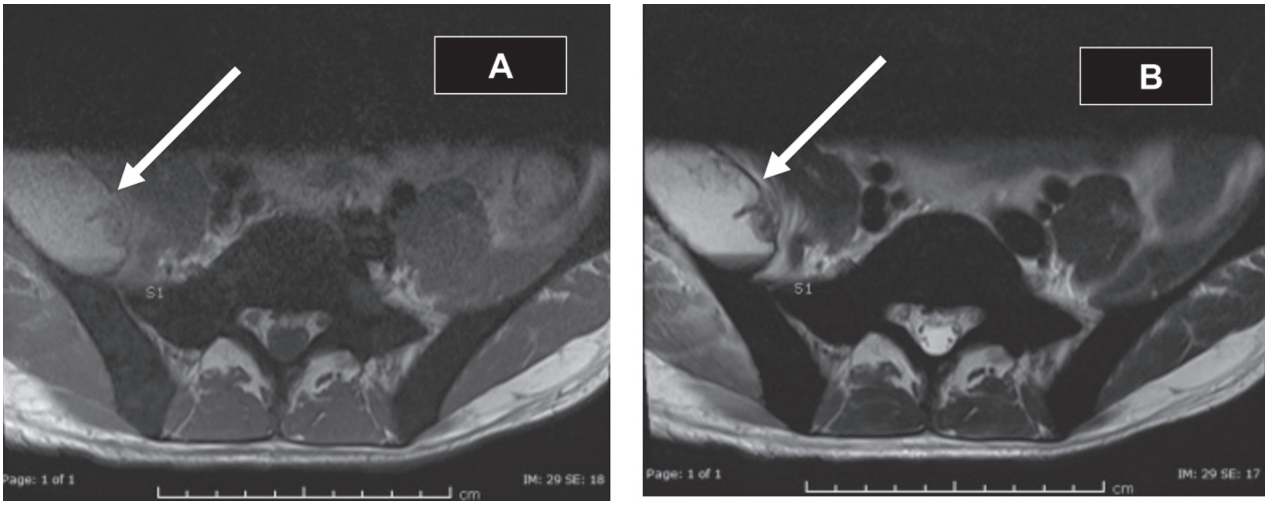

Figure 1 A-B. Axial T1 and T2 WI of the spine at S1 level. Images show a large diffuse hematoma in the right iliopsoas muscle (white arrows)

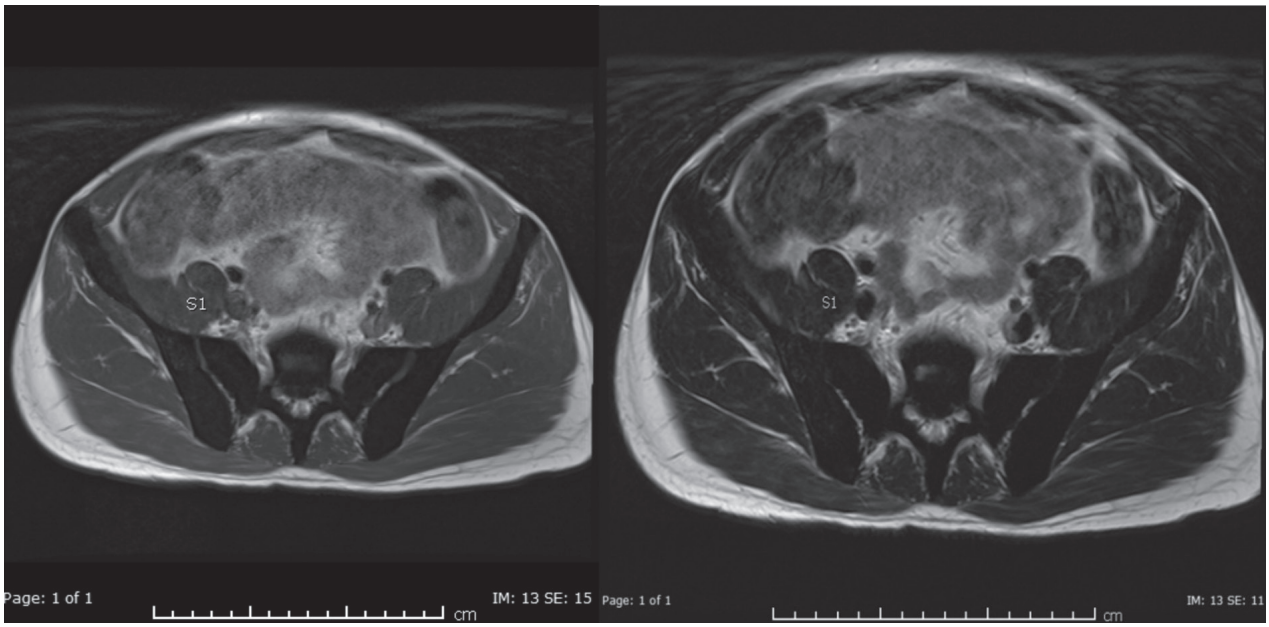

Figure 2. Axial T1 and T2 WI of the spine at S1 level, after 7 months, showing complete resolution of the previous right iliopsoas hematoma

Discussion

Even though iliopsoas hematomas are well-described in the literature, their incidence remains uncommon. Iliopsoas hematomas are typically caused by trauma in patients on anticoagulation/ antiplatelet therapy or in those with hemophilia.

To the best of our knowledge, this is the first reported case of spontaneous iliopsoas hematoma occurring in a patient with TDT. The mechanism of spontaneous iliopsoas hematoma was unclear, although tearing of muscle fibers, unrecognized minor trauma, low platelet count, secondary to hypersplenism, and severe liver iron overload, associated to abnormalities of clotting factors synthesis, were the suspected etiologies.

A review of literature for spontaneous bleeding in patients with TDT revealed three cases of intracranial hemorrhage. Svahn et al. (9) reported a case of

subarachnoid hemorrhage observed during the postpartum period in a 27-year-old woman suffering from TDT. Brain MRI revealed a complex vascular abnormality. Lee (10) reported two cases of fatal intracranial hemorrhage in children with TDT, aged 7and 12 years. According to the author, the bleeding was likely multifactorial due to recent blood transfusion, prolonged prothrombin time, partial thromboplastin time and reduced platelet count.

The iliopsoas muscle is formed by 2 sections (the psoas and the iliacus) and runs from the retroperitoneum through the pelvis into the thigh (11). When a hematoma of the iliopsoas occurs, the main symptoms are pain and functional impairment. However, owing to the anatomical proximity of these muscles to the lumbar plexus and the femoral nerve, this can be a source of neurological dysfunction, through the compression of the former or, more frequently, the latter (12,13). The clinical presentation of iliopsoas hematomas is often that of sudden-onset low back pain or severe persistent pain in the lower abdominal quadrants, as well as inguinal region, and radiate to the anterior, medial, or lateral aspects of the lower extremities. Patients also describe using leg flexion to try to relieve pain on the involved side (psoas sign). The differential diagnosis for back pain is extensive and includes pancreatitis, ureteric colic, lumbar spondylosis, aortic dissection, and musculoskeletal pain (14). A careful physical examination is important but often not specific. Besides clinical examination, there are several imaging modalities that can aid in establishing the diagnosis. Ultrasonography has been used to diagnose iliopsoas hematoma but its sensitivity and specificity are user-dependent, rendering the results potentially less reliable. Computed tomography (CT) has a high degree of sensitivity and is the most commonly utilized test for the diagnosis. However, MRI remains the investigation modality of choice due to its high sensitivity and specificity to identify the site and the extent of bleed (14).

The optimal treatment of iliopsoas haematomas remains controversial, as current evidence favours neither the conservative management nor surgical or percutaneous drainage. All these therapeutic measures had good outcomes in previously published case reports. Generally, a conservative approach is chosen in smaller haematomas in haemodynamically stable patients with slight-to-moderate neurological impairment, and a drainage procedure is the option in larger haematomas with severe neurological impairment and/or haemodynamic instability (15).

Conclusions

Iliopsoas hematoma has a variety of clinical manifestations. The most common symptom is sudden onset of lower back and flank pain. Besides clinical examination, there are several imaging modalities that can aid in establishing the diagnosis. Delay in diagnosis can lead to inappropriate initial treatment and, in some cases, serious complications. There is no clear strategy for treatment of iliopsoas hematoma yet, and a variable treatment plan may be used according to the patient's condition. Physicians should be aware of such potential complication. A high clinical suspicion should be designated to a patients with a sudden onset of back pain. Close monitoring of patient is important for an early diagnosis and for avoiding an inappropriate treatment.

Conflict of interest: None to declare

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Case report

Megarectosigmoid in anorectal malformations: the role of laparoscopic resection

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Summary. Surgical treatment for anorectal malformations may lead to chronic constipation or stool incontinence. The first condition is mostly linked to an abnormal dilation of rectum and sigma and it is primarily managed with medical therapy (laxatives, diet and enemas). When medical therapy fails to improve the symptoms, a surgical resection of the dilated colon is advocated. When performing the procedure it is mandatory to consider all the previous operations the patient undergone. We present a laparoscopic left emicolectomy for an extremely dilated megarectosimoid after posterior sagittal anorectoplasty in childhood for a recto-urethral fistula. (www.actabiomedica.it)

Key words: anorectal malformation, megarectosigmoid, laparoscopy, emicolectomy, megacolon

Introduction

Severe constipation associated with occasional soiling is among the principal complications ollowing posterior sagittal anorectoplasty (PSARP) for anorectal malformations (ARM) in children (1). A megarectosigmoid (MRS) is often the leading cause for this condition (2). For cases refractory to medical bowel management (BM) (laxatives, diet and enemas) a resection of the dilated bowel is needed (1-3). For this kind of interventions the laparoscopic approach is gaining consensus in young patients like it did in adults in the last decades (4-6).

Case report

A 19 year old boy of North African origins came complaining of severe constipation associated with encopresis. He was born by spontaneous delivery at 37 weeks with a recto-urethral fistula associated with anterior ipospadia. No renal anomalies or vertebral defects had been shown. A colostomy had been performed the very same day of birth and after 5 months the baby underwent a posterior sagittal anorectoplasty. Four months after that an anoplasty had to be performed for rectal prolapse. At the age of 11 months colon recanalization was done but 20 months later the baby needed a new operation for rectal prolapse which necessitated an anoplasty. At the same time a right orchidopexy for cryptorchidism was done. Sixty days later the hypospadias was repaired performing an urethroplasty following the Thiersc-Duplay's technique. At the age of 7 year old a second PSARP, combined with colostomy, was needed due to rectal mucosal prolapse. Three months later the colostomy was closed by termino-terminal manual anastomosis.

From the age of 16 the boy, who had been following the BM program discontinously, started complaining about difficult hard stools evacuation and fecal incontinence; a barium enema showed a really dilated distal colon. After bowel disimpaction, the condition was treated with daily BM with Peristeen® transanal irrigation. After 3 years, for lack of symptoms im-

provement, a new barium enema was done (Fig. 1) which demonstrated the persistence of dilation of the rectum and the distal colon, hence we decided to submit the patient to surgical therapy.

The patient underwent a laparoscopic left emicolectomy with primary reanastomosis and temporary loop colostomy.

In modified lithotomy position we carried out a laparoscopic approach. Revision of the abdomen showed extremely dilated sigmoid colon and rectum and a descending colon with a normal caliber. The inferior mesenteric vein was transected at its termination close to the Treitz ligament. For all the previous surgical operations, to guarantee a satisfactory blood inflow to the rectal stump, we divided the left colic artery and the sigmoid arteries sparing the superior rectal artery.

The splenic flexure was lowered and the left colon was released from its parietal attachment.

The rectal dissection was performed till the medium rectum which was transected with a linear stapler. Through a mini Pfannenstiel incision the descendent colon was extracted and transected where his caliber was normal. With a circular stapler a Knight and Griffen colo-rectal mechanic anastomosis was performed after reinduction of pneumoperitoneum.

The surgical operation was concluded performing a loop colostomy. The recovery was uneventful and the patient was discharged after 8 days.

The pathological examination of the specimen showed a normal colon without any ganglion abnormality.

One month later a barium enema (Fig. 2) displayed no anastomosis leakage or stenosis. A dilated residual rectum with change of caliber at the anastomosis was still present. The loop colostomy was reversed 3 month after the colectomy.

At one year follow-up no more soiling was reported and evacuations were constant. Only occasionally an enema was needed to clean the bowel.

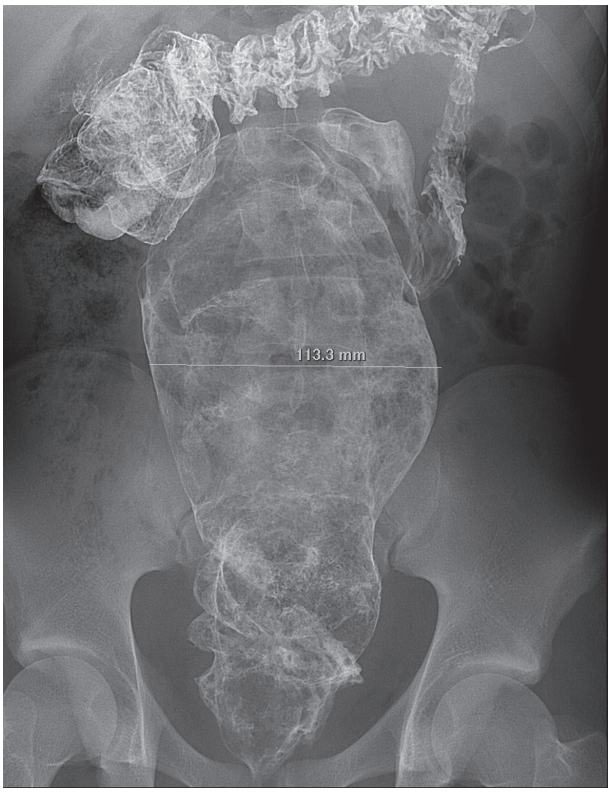

Figure 1. Preoperative barium enema showing a really dilated colon and rectum (maximum caliber 11 cm)

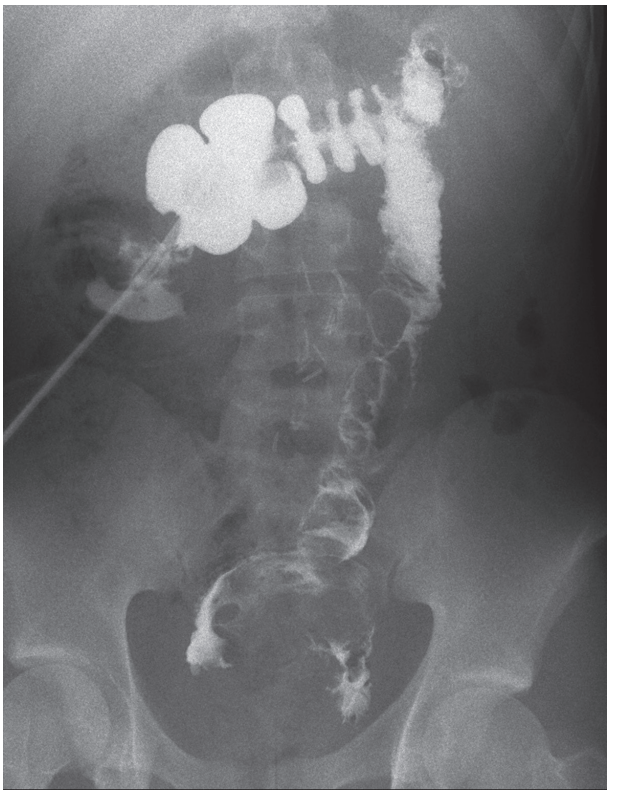

Figure 2. Postoperative barium enema: a change of caliber at the anastomosis is present, but no stenosis or anastomosis leakage are shown

Discussion

The worldwide incidence of ARM is 2-6 per 10,000 liveborn infants, nevertheless a slight variability exists between countries (7). A rectourethral fistula is the most common anorectal malformations in males, who are also lightly more affected by these kind of anomalies. Rectovestibular fistula is the most frequent defect in females (8).

Treatment options for surgical management of anorectal malformations include a colostomy followed by delayed repair of the defect or, in selected cases, a single stage procedure (9). Posterior Sagittal Anorectoplasty, introduced by DeVries and Pena, became the standard of care for dealing with ARM (10, 11). Recently, laparoscopically assisted anorectal pull-through (LAARP) has gained consensus for high-type ARMs (8, 12). No statistical difference in incidence of rectal prolapse is demonstrated between PSARP and LAARP (13).

To evaluate surgical outcome, voluntary bowel movement, soiling and constipation are considered as main parameters. After PSARP the principal complications are represented by chronic constipation, with overflow incontinence, or stool incontinence. The former due to impaired rectal motility, the latter to incompetence of anorectal sphincters (1).

The first step to manage these symptoms is represented by BM which had been shown to be able to significantly improve this weary condition (14, 15).

Moreover Borg et al found an improvement in bowel functional outcome with age, probably related to delayed maturation of enteric neurons (16); nevertheless these children do not achieve the level of healthy children: dilation of rectum and sigma is among the factors which weaken such improvements (2, 11, 17). The average prevalence of MRS is 33% (2). In addition, multiple operations are associated with a worse level of continence (17).

When the constipation is unmanageable with BM a partial rectal resection or even a sigmoidectomy may be needed (1-3), even if recent studies showed a similar functional outcome in children treated either with surgery or BM, thanks to improvement with age of MRS (2). The dilation degree determines the extent of colon resection needed. Furthermore Borg et al demonstrated no new dilatation after surgery but some grade of BM was still needed (2).

In our case, in performing the left emicolectomy, the blood supply of the rectum was uncertain due to the multiple operations the patient had undergone. We were thus forced to save the superior mesenteric artery and to divide the left colic artery and all the sigmoid branches in order to maintain a reliable arterial flow to the rectum through the superior rectal artery.

Although Lambrecht et al showed the presence of normal superior and inferior rectal arteries in almost all ARM animal models (18) in performing surgery for constipation it is advised to check the arterial supply of the pulled-through colon (2, 3).

As shown in other studies (2) the histological finding of our specimen shows a normal colonic wall.

Although bowel functional outcome, and MRS, seem to improve with age, nevertheless in some cases such a progress may not be satisfactory. Surgical resection of the dilated bowel is therefore unavoidable in these cases to grant resolution of symptoms and a good quality of life. It is our believe that a left emicolectomy, instead of a limited sigmoidectomy, guarantees a better functional long-term result, keeping in mind that a great carefulness must be taken in account performing this operation to avoid accidental damages to inferior mesenteric nerve plexus.

By now the laparoscopic approach has gained consensus in treatment of severe constipation thanks to a reduction of postoperative pain and a shortening of recovery (5), what's more it allows a better cosmetic results which, standing the same functional outcome, may have a great value in a young patient like the one we treated. However, standing the technical difficulties linked to the enormous MRS filling the abdomen and the multiple surgical operations the patient previously underwent, advanced laparoscopic skills are obviously needed to safely perform such an intervention.

Conclusions

Standing the advantages brought by laparoscopy in abdominal surgery, this approach should always be taken into account in choosing the suited therapy for MRS. Considering both previous surgical operations

and the skill level of the surgeon, the intervention and the extent of resection should be tailored on each specific case. Furthermore a great care must be taken regarding the residual blood supply of the rectum.

Conflict of interest: None to declare

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Case report

Triradiate cartilage fracture of the acetabulum treated surgically

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Summary. Fractures of the acetabulum are rare in the pediatric age and may be complicated by the premature closure of the triradiate cartilage. We report a case of triradiate cartilage displaced fracture treated surgically. A 14 years old boy, following a high-energy road trauma, presented an hematoma in the right gluteal region with severe pain. According to radiographic Judet's projections was highlighted a diastasis of the right acetabular triradiate cartilage. CT scan study with 2D-3D reconstructions confirmed as type 1 Salter-Harris epiphyseal fracture. Due to the huge diastasis of the triradiate cartilage, the patient was operated after 72 hours through a plating osteosynthesis. We decided during the preoperative study that the plates should not be removed. Two years after surgery, the patient is clinically asymptomatic; the radiographic evaluation shows a complete cartilage's fusion and the right acetabulum is perfectly symmetrical to the contralateral. For the treatment of acetabular fractures in pediatric age should be carefully evaluated fracture's pattern, patient's age, skeletal maturity's grade, acetabulum's volume and diameter. (www.actabiomedica.it)

Key words: acetabulum, triradiate cartilage, fracture, pediatric, surgery

Background

Fractures of the acetabulum are rare in the pediatric age and may be complicated by the premature closure of the triradiate cartilage hesitating in secondary acetabular dysplasia.

These injuries are mainly caused by high-energy trauma despite the energy required to fracture the strong and elastic pelvis in children is significant (1).

Among pediatric patients with pelvic trauma, the 1-15% have an acetabular fracture. Even fewer patients has a specific damage to the triradiate cartilage and the incidence of premature closure is less than 5% (0-11%) (2).

Due to the low frequency of these injuries, at this time, specified protocols of treatment were still not defined.

In literature both treatments, surgical and conservative, are supported with the common aim of restoring the anatomy without causing further damage to the triradiate cartilage's blood supply, hoping to avoid symptomatic and dysplastic hip (3).

For these reasons, in the pediatric age, the early diagnosis and the choice of treatment of an acetabular fracture may be difficult.

We report a case of fracture of the triradiate cartilage we treated surgically.

Case presentation

A 14 years old boy, following a high-energy road trauma, arrived in the Emergency Room with pain in the right gluteal and inguinal region hightened by hip

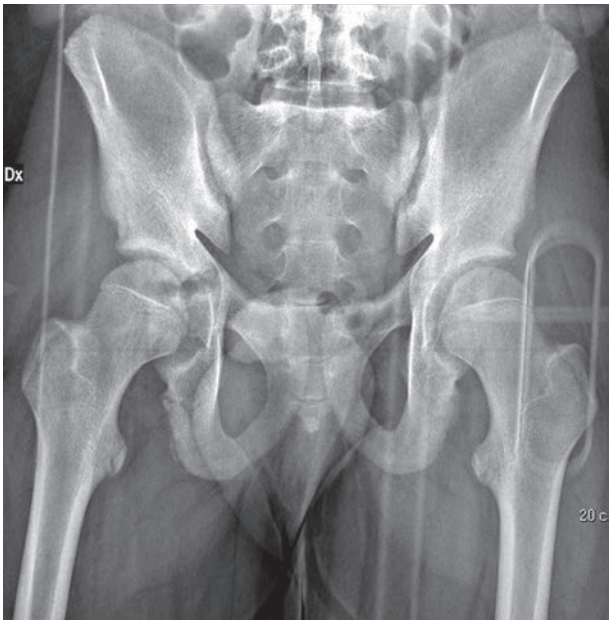

Figure 1. Outlet view: fracture-diastasis of the triradiate cartilage

joint mobilization's maneuvers. An evident hematoma was associated in the gluteal region. No other anatomic region was involved.

The radiographic study, according to Judet's views, showed a right triradiate cartilage's diastasis (Figure 1), later confirmed by CT scan performed in emergency.

The lesion was evaluated with 2D-3D reconstructions and confirmed as Salter-Harris epiphyseal fracture-separation of ileum-ischium and ischium-pubis flanges of the triradiate cartilage (Figures 2a-b; 3a-b).

Furthermore radiographic study of the pelvis showed us an advanced ossification valuable as Risser sign of a grade III (4).

Due to the huge diastasis of the triradiate cartilage and skeletal age , the patient was operated after 72 hours through ORIF with plate and screws.

The patient was positioned prone on the operating table with flexed knee 90°.

A Kocher-Langenbeck approach (5) was performed and the posterior column was exposed after aspiration of the fracture's hematoma.

Fracture was reduced using dedicated retractors and levers avoiding further damage to ileo-ischiatic and ischio-pubic cartilage's flanges.

Using C-arm with AP, Obturator and Iliac view the osteosynthesis with annealed steel Matta Plate (8 holes) and 4 screws, was performed.

Piriformis and external rotators tendons were reinserted, a drainage was placed suturing soft tissues. Postop X-ray control in Judet's view was carried out (Figure 4a-b-c).

The patient remained in bed-rest 45 days postop. Two weeks after surgery, he began hip passive mobilization and chair sitting; ten days later he got the active mobilization of the lower limbs.

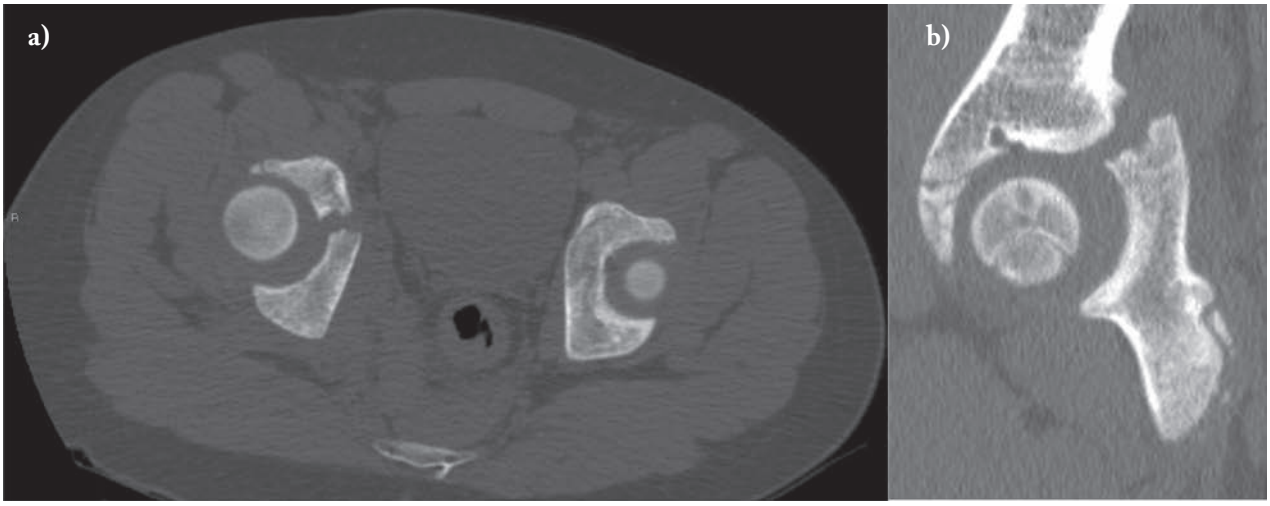

Figure 2a, b. 2 D CT reconstructions of the femoral head and quadrilateral surface

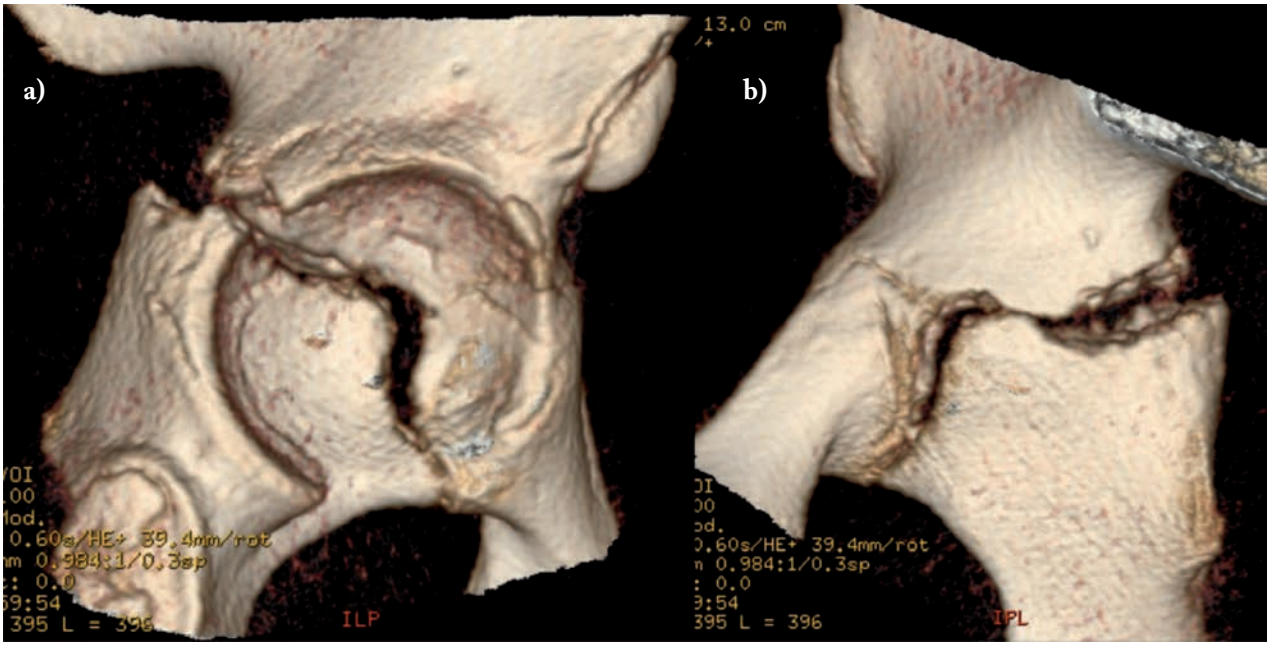

Figure 3a, b. 3 D CT reconstructions of the quadrilateral surface removing femoral head

45 days after surgery radiographic controls showed an epiphysiodesis bridge between ileum, ischium and pubis while respecting the coxofemoral anatomical relationship.

Therefore the patient started deambulation with 2 antibrachial crutches.

One month later he was walking freely without limping and pain.

He could come back to sport's activity six months after surgery.

2 years later, the complete closure of the triradiate cartilage was displayed by a radiographic control (Figure 5a-b). The growth of the right acetabulum appeared well proportioned. The measurements of both acetabulum demonstrated a symmetrical development (Figure 5c-d).

No radiographic signs of hip dysplasia was appreciated (shallow acetabulum, hip joint lateralization, femoral neck antiversion) as well as no signs of femoral head's osteonecrosis.

The patient recovered a total hip range of motion (Figure 6) and came back to normal daily activities.

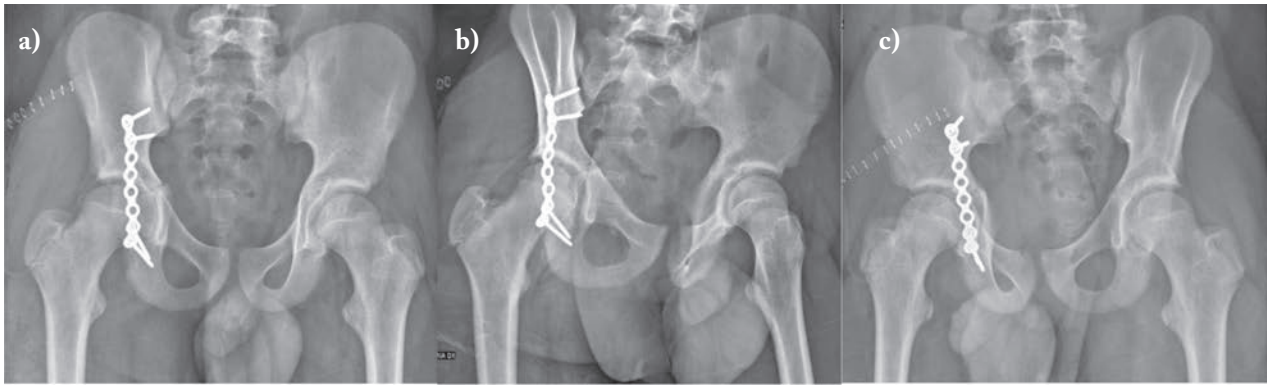

Figure 4. Osteosynthesis with Matta Plates: antero-posterior (a), obturator (b) and iliac (c) view

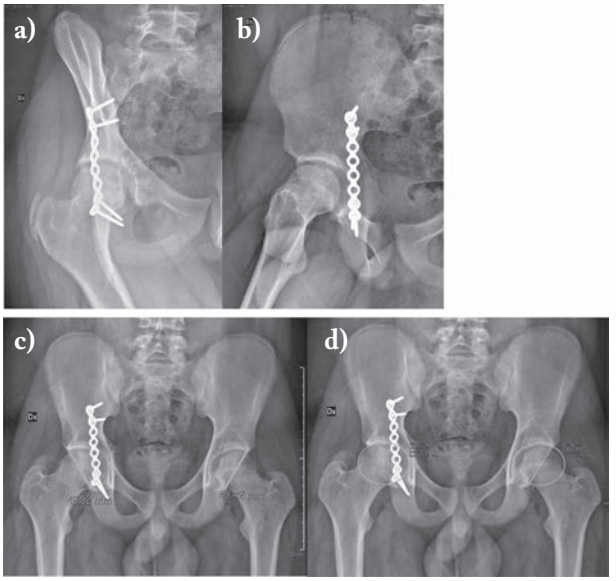

Figure 5. At 2 years complete healing of the right acetabulum in oblique views: obturator (a) and iliac (b). Symmetrical growth measuring the diameter (c) and the circumference (d) of both acetabulum

Figure 6. At 2 years complete active range of motion: flexion and abduction

Discussion

The damage of the triradiate cartilage, caused by high-energy trauma, can lead to premature fusion with the formation of a bony bridge. If the acetabular cartilage remains entire and the triradiate closed, the growth will be not proportionate and will lead to a thickened medial wall with secondary lateralization of the hip joint.

The acetabulum becomes shallow deep whereby the femoral head will tend to subluxation.

The femoral neck antiversion will increase to avoid/reduce this dislocation.

Multiple events of subluxation could lead during the time to the cephalic osteonecrosis (2-6-7-8).

Clinically, patients may be asymptomatic even for a maximum of two following decades after trauma. As initial clinical signs may occur reduced range of motion, Trendelenburg positive sign and pain mobilization (8).

Radiographs can show the lateralization of the hip joint, an excessive femoral antiversion, a high acetabular index, up to joint degeneration's signs (osteophytes, geodes, reducing joint space), osteonecrosis of the femoral head and other anomalies (2-8-9).

Treatment options are surgical and non-surgical. A lot of authors agree that the age at the time of the trauma, the breakdown of the fracture and the congruence of the articular surface are elements that influence the functional result of the patient. Few other authors stressed specific guidelines for surgical or nonsurgical treatment (3).

The majority of authors propose conservative treatment with bed rest and skeletal traction for 4-8 weeks (8).

Recently, the ORIF of unstable fractures of the pelvis and acetabulum was advocated even in childhood to restore symmetry, periarticular pelvic anatomy and function. This type of treatment has been shown to be associated with favorable clinical results with a low incidence of perioperative complications (10-11).

Bucholz et al. (7) suggested as an indication for surgical treatment, displaced fracture's fragments (entity not well defined), patient's age and fracture's pattern.

Heeg et al. (12) recommended the surgical treatment in case of central fracture-dislocation, irreducible

medial subluxation, intra-articular fragments, dislocated and exposed fractures and/or with posterior instability (12-13).

Brooks and Rosman (9) suggested ORIF when the central dislocation fracture is associated with central fragments.

The case presented in this study is one of the few cases in literature of epiphyseal acetabular fracture treated surgically.

The choice of surgical treatment was due after a careful radiographic study of the pelvis in AP obturator and iliac view and CT-scan 2D-3D reconstructions.

The main injury's features were:

- a type I epiphyseal Salter-Harris fracture occurred trough the ischial-ileum flange and the ilium-pubic triradiate cartilage with a diastasis more than 2 mm enlarged
- an obvious deformity of the acetabular articular surface
- joint incongruence higher than 50% in a patient in teenage period (Risser III).

Then we decided for the surgical treatment.

In our case, considering patient's age, acetabulum's volume and diameter, skeletal maturity's grade, we evaluated the expectation of acetabulum's remaining growth during adolescence until adulthood (Table 1).

This study shows that the volumetric enhancement of the acetabulum is expected to be small.

The aspect that we considered most important was to prevent the acetabulum become shallow deep avoiding a development of excessive femoral neck antiversion.

Table 1. Measurement (arithmetic mean) of the acetabular's diameters and circumferences (100 cases for each age group)

Age	Acetabular diameter (in mm)	Acetabular circumference (in mm)
10	43,7	137,1
12	48,9	153,5
14	49,3	154,9
16	50,1	157,2
20	53	166,4
CM (16yo)	49,9	156,7

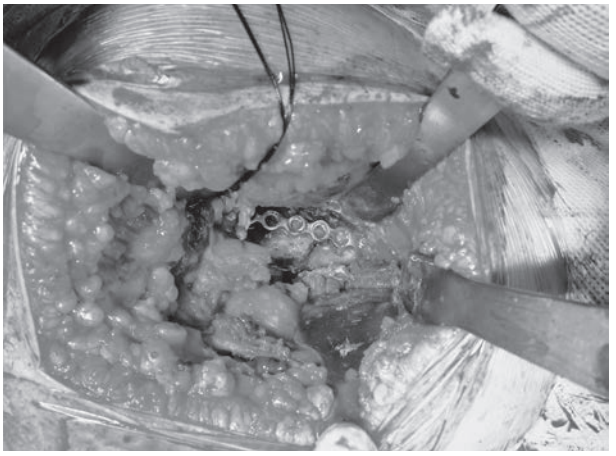

Figure 7. Reduction with a little diastasis between the growing flanges of the triradiate cartilage and osteosynthesis with annealed steel Matta Plate (8 holes)

After the acetabulum enhancement's estimation (Table 1), we calculated that the deepening expected since the trauma to adulthood, would be less than 2 mm.

For this reason, surgical reduction was conducted creating an epiphysiodesis that could facilitate the achievement of size and volume of an adult acetabulum.

Accepting a reduction with a little diastasis between the growing flanges of the triradiate cartilage, any compression causing an early closure of the cartilage was avoided (Figure 7).

Two years after surgery the growth of the right acetabulum seems to be regular.

The measurements on both acetabulums allow to appreciate a perfectly symmetrical eumorphisms (volumes and diameters) (Figure 5c-d).

At this time, the patient 16 years old is asymptomatic without radiographic signs of hip dysplasia.

Because estimated acetabulum enhancement from now to adulthood is minimal (Table 1), because of Risser IV sign, because of triradiate cartilage of both hip appeared fused (Figure 5c-d) don't bring out indications that justify the removal of plate and screws by an additional surgical approach that would be invasive and not without risks.

Nevertheless it would be essential to follow the patient over time until the adulthood.

Conclusion

During the pediatric age the choice of epiphyseal hip fracture's treatment is still controversial.

Fracture's pattern, patient's age, skeletal maturity's grade, acetabulum's volume and diameter should be carefully evaluated.

When the surgical treatment is chosen, an additional surgical time to remove fixation devices in adolescence may not be strictly necessary.

Conflict of interest: None to declare

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Case report

Endovascular repair of an abdominal aortic aneurysm using bifurcated stent-graft in a patient with bilateral external iliac artery occlusion

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Summary. Abdominal aortic aneurysm (AAA) in association with external iliac artery (EIA) occlusion is a rare entity which may limit endovascular aortic aneurysm repair (EVAR) feasibility. We describe the case of an 84-year-old man affected by a 64mm infrarenal inflammatory abdominal aortic aneurysm with complete bilateral occlusion of EIA and patency of both common and internal iliac arteries. The common femoral arteries (CFA) were patent, and the patient was asymptomatic for lower limb claudication. The treatment was performed by EVAR using a bifurcated stent-graft after the recanalization of the left EIA, achieving technical success. (www.actabiomedica.it)

Key words: aortic aneurysm, abdominal [MeSH], endovascular procedures [MeSH], iliac occlusion

Introduction

Concurrent external iliac artery (EIA) occlusion and abdominal aortic aneurysm (AAA) is rare and limits usage of endovascular aortic aneurysm repair (EVAR) (1). Traditionally open abdominal surgery is the first approach in these patients. Compared with open surgery, EVAR has been found to have lower rates of early mortality and morbidity (2). However, endovascular treatment strategy differs with severity of iliofemoral occlusive disease.

We present a case report illustrating an infrarenal AAA with bilateral EIA occlusion treated through EVAR using a bifurcated stent-graft after recanalization of the left EIA.

Case Report

An 84-year-old man, affected by chronic obstructive pulmonary disease, hypertension and an infrarenal AAA (diagnosed two years earlier), was admitted for fever of unknown origin. A computed tomography angiography (CTA) showed that the diameter of AAA has enlarged since its initial detection and was now approaching 64 mm with signs of perianeurismal inflammation (figure 1a). Moreover, this CTA revealed the patency of both common (CIA) and internal iliac arteries (IIA), and a complete bilateral occlusion of the EIA (figure 1b). The common femoral arteries (CFA) were patent, and the patient was asymptomatic for lower limb claudication.

The need for urgent intervention for his 64mm AAA was discussed with the patient. Informed consent was obtained.

Considering the high risk of complications of major open abdominal surgery due to his multiple comorbidities (ASA score 4), we agreed to attempt EVAR after recanalization of the chronic occlusion of the left EIA. We planned to perform EVAR using a bifurcated stent graft in order to preserve the patency of both IIA.

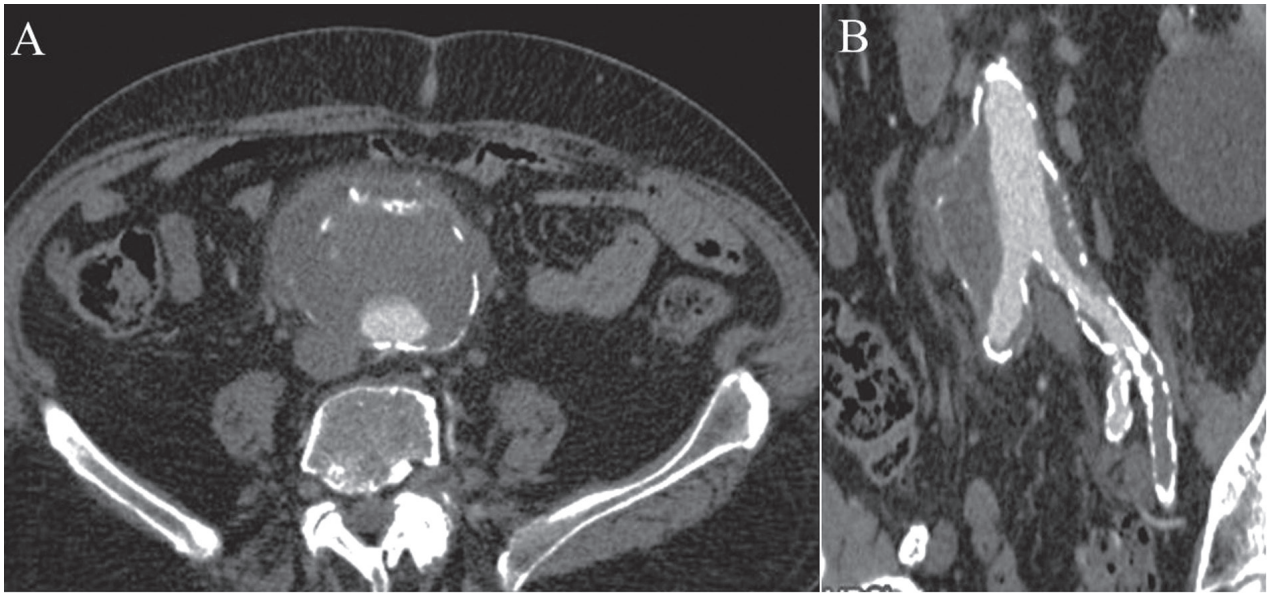

Figure 1. Preoperative computed tomography angiography (CTA). A: Infrarenal inflammatory aneurysm. B: Multiplanar reconstruction showing the patency of both common iliac and hypogastric artery and the occlusion of external iliac artery

The procedure was performed in the operating room with the patient under general anesthesia. Both CFA and the left axillary artery were surgically exposed.

Then, the left axillary artery was then punctured for insertion of a 12Fr sheath introducer, 90cm in length (Flexor KCFW, Cook medical Inc.) and abdominal aortography was obtained (figure 2a).

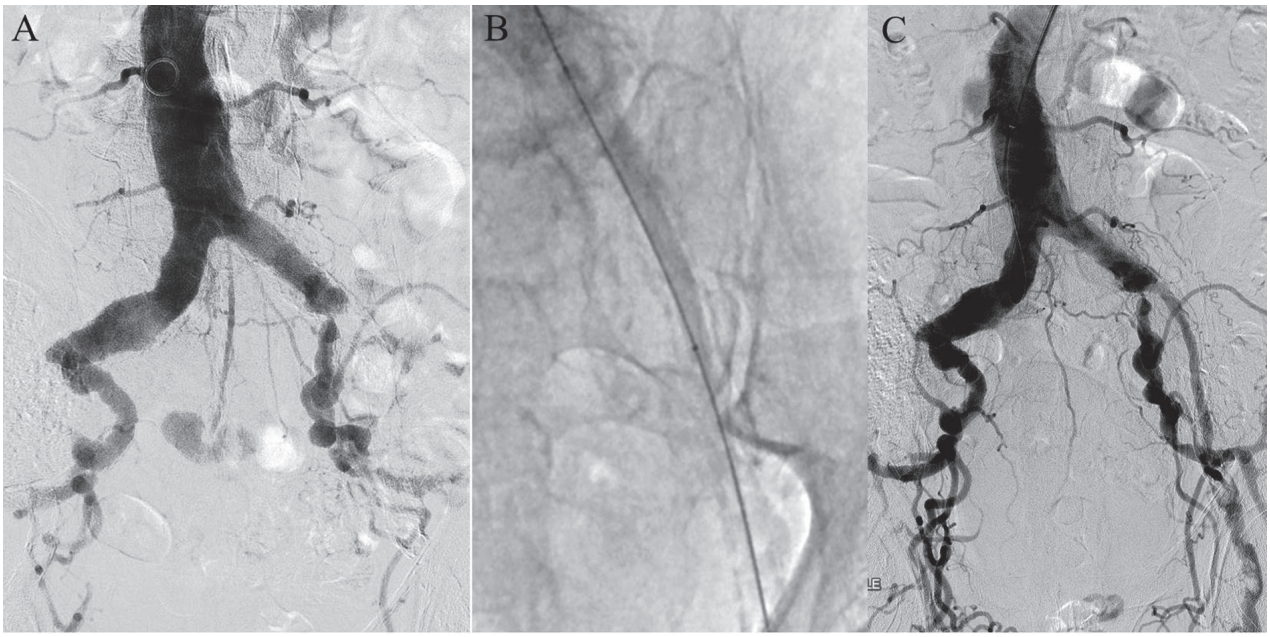

Figure 2. Recanalization of left external iliac artery. A: Diagnostic angiography. B: Predilation of the left external iliac artery with 4x120mm;7x40mm balloon C: Completion angiography

Anterograde recanalization of the left EIA through the left axillary access was attempted by using a 0.035 inch angled glidewire (Terumo Medical) supported by a 4Fr Vertebral Glidecath catheter (Terumo Medical). This guidewire crossed easily the occlusion of the left CFA. Multiple predilatations of the EIA were performed with balloon catheters Powerflex 4x120 mm-7x40 mm (Cordis) (figure 2b) getting the recovery of the left femoral pulse (figure 2c).

The same procedure was attempted without success for the recanalization of the contralateral EIA.

A 9Fr sheath introducer was placed into the left CFA from the groin.

Numerous dilations of the left external iliac artery using 16Fr then 18Fr dilators (Cook Medical Inc) (figure 3) were performed with success. The main body of a Zenith Alpha (Cook Medical, Inc) abdominal endovascular bifurcated stent-graft (ZIMB-26-84) was introduced through the left CFA and deployed below the renal arteries. Then we implanted the ipsilateral limb extender (ZISL-16-42) just proximal to the left IIA origin ensuring continued patency.

Through the left axillary access, the contralateral gate of the bifurcated aortic stent-graft was engaged and a stiff guidewire was placed in the right IIA. Two Viabahn stent grafts 13x100 mm-13x50 mm (W.L. Gore, Flagstaff, AZ, USA) were advanced and released as a bridging stent-graft from the right gate of the aortic main body to the origin of right IIA to both achieve distal sealing and maintain the patency of the right IIA.

The main body and the contralateral limb (two Viabahn stent-grafts) were dilated with a Coda balloon catheter (Cook Medical Inch). The kissing balloon was performed inside the stent-graft limbs with an 18 mm non compliant balloon Esophageal XXL (Boston SC) into the left limb and an 12 mm balloon Powerflex (Cordis) into the Viabahn (right limb).

The completion angiography was satisfactory. It showed the patency of the endograft and both hypogastric iliac arteries (figure 4) and revealed a low-flow type II endoleak from lumbar arteries.

Endarterectomy of the left CFA was required before arterial reconstruction. The patient had no intraoperative or postoperative complications.

A CTA performed 7 days after the operation, demonstrated the patency of the both CIIA, IIA and left EIA (figure 5a) and a type II EL (figure 5b). The patient was discharged on 8th postoperative day.

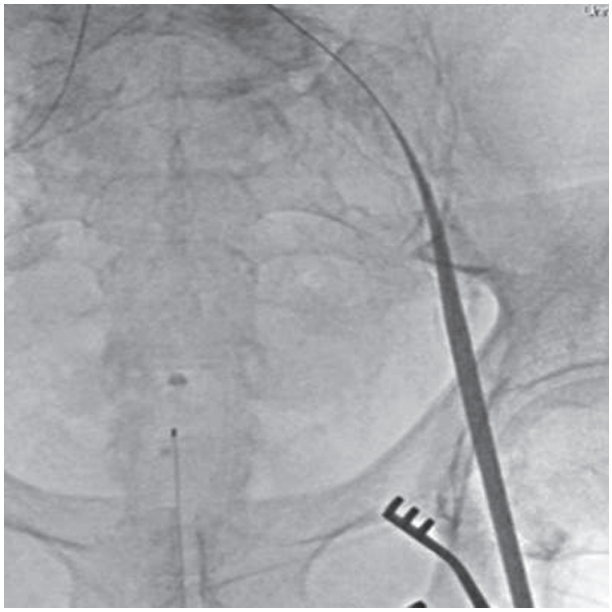

Figure 3. Dilation the left external iliac artery using 16Fr sheath introducer dilators (Cook Medical Inc)

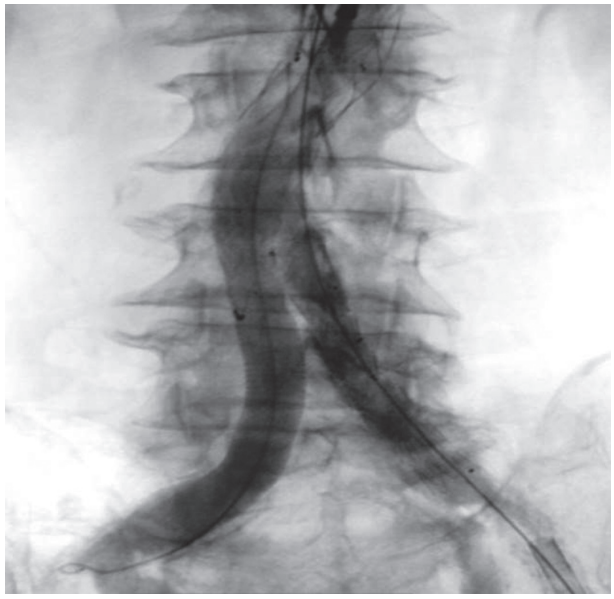

Figure 4. Completion angiography shows patency of the endograft and both hypogastric iliac arteries

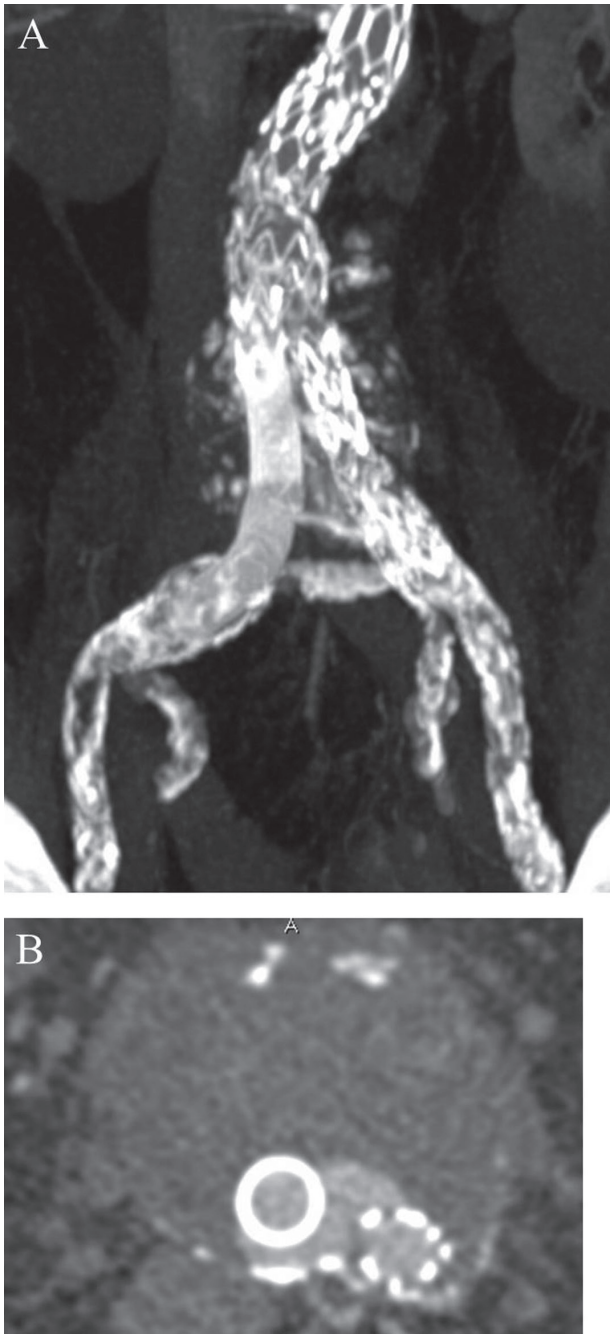

Figure 5. Computed tomography angiography performed 7 days after the operation. A: Maximum intensity projection reconstruction showing stent-grafts and extensive calcification of iliac axes. B: Axial image showing type II endoleak from lumbar arteries.

Discussion

Open surgical repair is the traditional therapy in patients with concurrent iliac occlusion and AAA. However, open surgical repair is associated with higher rates of perioperative morbidity and mortality compared with EVAR (2).

Given the current state of endovascular technology, challenging aortoiliac anatomy represents one of the more frequent limiting factors in EVAR applicability (3). Iliofemoral occlusive disease is a possible contraindication for EVAR, and the treatment strategy differs depending on severity of the lesion (4). Small size, severe calcified stenoses, and severe angulation of the iliac anatomy represent some of the most frequently cited reasons for non-navigability of the stent-graft delivery systems.

Multiple innovative techniques are described in the literature to modify the iliac anatomy to facilitate the advancement of the EVAR delivery system. These include simple dilation of the iliofemoral segment using over-the-wire dilators, balloon angioplasty, stenting or surgical conduit (5-7).

Although good results are reported using an aorto-uni-iliac configuration, bifurcated stent-grafts seem to have better hemodynamic results from direct flow (8) and to increase primary and secondary patency rates compared to AUI device and femoro-femoral crossover bypass. A prosthetic femoro-femoral bypass graft is also associated with possible postoperative complications (infection of the prosthesis in the groin area, steal phenomenon caused by the bypass) (8, 9). Furthermore, the presence of the anastomosis at the CFA limits possible secondary interventions, especially with percutaneous access.

Our case shows that the use of a bifurcated EVAR to treat patients with concomitant infrarenal AAA and bilateral chronic total occlusion of the EIA is feasible, effective and essential in patient asymptomatic for lower limb claudication and with patency of both IIA. On the other hand, our case showed the lack of available material necessary to achieve EVAR with bifurcated stent-graft. In this specific case Viabahn stent-graft has congruous diameter (13 mm), sheath length (120 cm) and delivery system diameter (12F) to be deployed from axillary access and to achieve a good sealing in the contralateral gate of Zenith Alpha main body (11 mm).

The thorough knowledge of endovascular techniques and devices is an essential condition to a suc-

cessful treatment . With the left CFA access after recanalization of the left EIA and the axillary access, we are able to insert and deploy an aortic abdominal bifurcated stent-graft to treat infrarenal AAA with bilateral complete occlusion EIA.

Conflict of interest: None to declare

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Quarant'anni (1978-2018) di politiche vaccinali in Italia

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Forty years (1978-2018) of vaccination policies in Italy
Summary. The paper traces the evolution of vaccination policies in Italy in the first 40 years of the National Health Service. Four phases have been identified: the first (1978-98) characterized by the eradication of smallpox, the hopes of further eradications and the introduction of hepatitis B and acellular antipertussis vaccines; the second (1999-2008) coincided with the first national vaccination plans and with the hypothesis of a progressive transition from mandatory vaccinations to nudging initiatives with the relevant experimentation in the Veneto Region; the third phase (2009-14) was characterized by the spread of health information on the web and social networks, by anti-scientific judgments and by an increasingly vaccines hesitancy that led to incorrect perceptions, falls in coverage rates and re-ignition of some epidemics; in the last phase (2015-18) there was a strong political committment that led to the approval of the National Plan (PNPV) 2017-19, to the extension of the mandatory vaccinations and to the sanctions against the anti-vaxxers doctors. This has led to a rapid rise in coverage, but also to a heated political and media debate on the ethical and social aspects linked to the admission bans and sancions of unvaccinated children in schools. (www.actabiomedica.it)

Riassunto. Il lavoro ripercorre l'evoluzione delle politiche vaccinali in Italia nei primi 40 anni del Servizio Sanitario Nazionale. Sono state identificate quattro fasi: la prima (1978-98) caratterizzata dall'eradicazione del vaiolo, dalle speranze di ulteriori eradicazioni e dall'introduzione dei vaccini antiepatite B e antipertosse acellulare; la seconda (1999-2008) è coincisa con i primi piani vaccinali nazionali e con l'ipotesi di un progressivo passaggio dall'obbligo all'adesione consapevole, segnata dall'importante sperimentazione della Regione Veneto; la terza fase (2009-14) è stata caratterizzata dalla diffusione dell'informazione sanitaria su web e social, da sentenze giudiziarie antiscientifiche e da una sempre più diffusa *vaccine hesitancy* che hanno portato a errate percezioni, cali generalizzati delle coperture e riaccensione di focolai epidemici; nell'ultima fase (2015-18) c'è stata una reazione delle istituzioni che ha portato all'approvazione del PNPV 2017-19, all'estensione degli obblighi vaccinali e a sanzioni contro i medici antivaccinisti. Ciò ha portato ad un rapido rialzo delle coperture ma anche ad un acceso dibattito politico e mediatico sugli aspetti etici e sociali legati alle sanzioni e ai divieti di ammissione dei bambini non vaccinati nelle scuole.

Nella sanità moderna l'Italia ha sempre rivestito un ruolo di Paese leader nelle vaccinazioni per gli eccellenti contributi scientifici, la lungimiranza delle sue politiche vaccinali, l'esperienza dei suoi ricercatori e operatori di sanità pubblica e anche alcune produzioni industriali di vaccini. L'occasione del 40° anniversario del SSN è anche quella per ripercorrere la storia più recente delle politiche vaccinali italiane che ha segnato, negli anni più recenti, un dibattito, talvolta anche acceso, con il coinvolgimento di parti tecniche e istituzioni politiche nazionali e regionali. Sono state così identificate quattro principali fasi delle politiche vaccinali italiane che vengono così riassunte:

1. 1978-1998: L'era delle eradicazioni

Nel 1978 l'aspettativa di vita della popolazione italiana superava di poco i 70 anni, le malattie infetti-

ve erano ancora molto temute ed i vaccini obbligatori dell'infanzia erano quattro (vaiolo, tetano, difterite e poliomielite). Il primo periodo della riforma sanitaria universalistica del 1978 è stato caratterizzato dall'offerta di un numero relativamente ridotto di vaccini, con obiettivi sanitari tendenti più all'efficacia protettiva che alla sicurezza e dalla convinzione che, dopo l'ormai imminente eradicazione del vaiolo (dichiarazione dell'OMS del 1980) (1), si stesse imboccando la strada per ulteriori eradicazioni, poliomielite e morbillo in primis. Il ventennio 1978-98 fu caratterizzato dalla sospensione dell'obbligo per il vaccino antivaioloso e dall'introduzione dell'obbligo per la vaccinazione antiepatite B (1991) per tutti i nuovi nati e per gli adolescenti al compimento del 12° anno di vita, schedula che permise un rapido e drastico calo non solo delle nuove infezioni da virus HBV ma anche dei tumori primitivi del fegato (Figura 1) (2). Il coinvolgimento importante dell'Italia nella sperimentazione del vaccino antipertosse acellulare (3) è una testimonianza dell'interesse e del coinvolgimento scientifico del nostro sistema sanitario nel progresso della vaccinologia. La sperimentazione coinvolse l'ISS e le ASL di quattro Regioni (Piemonte, Veneto, Friuli-Venezia Giulia e Puglia) a testimonianza di ottime capacità tecniche e organizzative dei servizi vaccinali collocati nei Dipartimenti di prevenzione delle ASL.

In questo periodo si discusse anche della possibilità di inserire tra le vaccinazioni obbligatorie quelle contro morbillo e rosolia e, a riguardo, furono diverse le proposte di legge che, nonostante i pareri tecnici favorevoli anche del Consiglio Superiore di Sanità, non furono mai approvate. Citiamo ad esempio la proposta di legge n. 265 del 1996 della Regione autonoma della Sardegna (4).

2. 1999-2008: La via dell'adesione consapevole

Facciamo risalire al 1999 l'inizio della fase di superamento della divisione tra vaccinazioni obbligatorie e raccomandate, nel frattempo aumentate per l'introduzione di nuovi ed efficaci vaccini tra cui quello polisaccaridico contro lo pneumococco (2001), quello contro il papillomavirus (2006) nonché il vaccino antimeningococcico tetravalente coniugato (2008). Si era nel frattempo entrati in un contesto etico-sanitario caratterizzato da una riconosciuta maggior autodetermi-

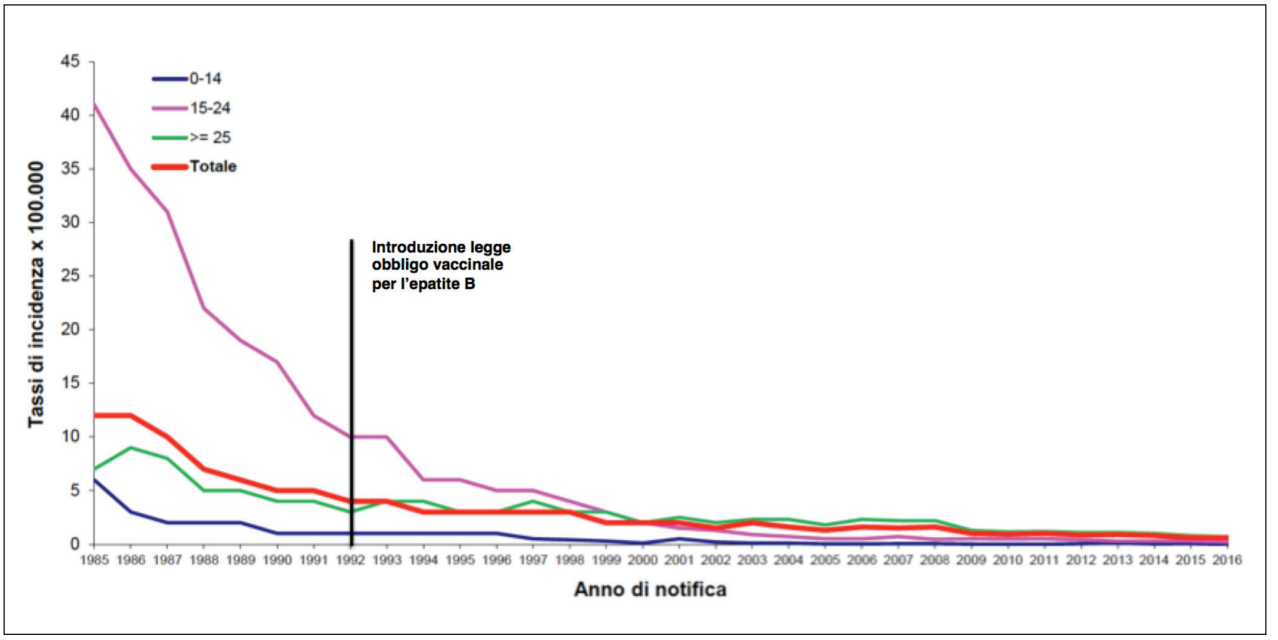

Figura 1. Tassi di incidenza (x 100.000) dell'epatite B per età ed anno di notifica. (modificata da: SEIEVA, 2016)

nazione nelle scelte del paziente-utente, che ha riguardato anche la prevenzione e i vaccini; parallelamente si è assistito a una notevole diminuzione di incidenza delle malattie infettive e quindi una minore propensione alla protezione individuale. Nel 1999 inizia anche la fase dei Piani Nazionali Vaccini che contengono, oltre ai calendari, anche obiettivi legati alle coperture, alle anagrafi ed alla sorveglianza degli effetti avversi (5).

E' di questo periodo uno dei più significativi atti normativi in tema di vaccinazioni e cioè la Legge della Regione Veneto n° 7 del 23 marzo 2007 di sospensione amministrativa dell'obbligo vaccinale per l'età evolutiva. La nuova norma, inizialmente osteggiata dal Ministero della Salute, è stata voluta fortemente dall'allora assessore alla sanità Flavio Tosi e supportata da una larga parte del mondo scientifico sia nell'ambito della sanità pubblica che della pediatria (6). Con la sua entrata in vigore, il 1 gennaio 2018, iniziava in Veneto una fase di rinforzo delle iniziative comunicative e informative senza più l'obbligo di legge, che ha destato l'interesse della comunità scientifica. E, secondo i dati di copertura a 24 mesi per la poliomielite, la sperimentazione sembrava inizialmente fornire risultati incoraggianti (Figura 2).

Nel 2006 accade un altro evento rilevante nella vaccinologia, non solo italiana, cioè l'immissione sul mercato, a distanza di pochi mesi l'uno dall'altro, di due vaccini contro le infezioni da HPV, ossia i primi vaccini progettati per la prevenzione del cancro ed in particolare per il tumore della cervice uterina (7). L'Italia è stato uno dei primi Paesi ad introdurre la vaccinazione universale nelle dodicenni, grazie all'impegno del Ministro Livia Turco e al coinvolgimento dell'intero Parlamento che dovette inserire un emendamento specifico nella Legge finanziaria del 2008 per finanziare la prima campagna vaccinale a causa dell'iniziale alto costo del vaccino (circa 500 euro per la schedula di tre dosi).

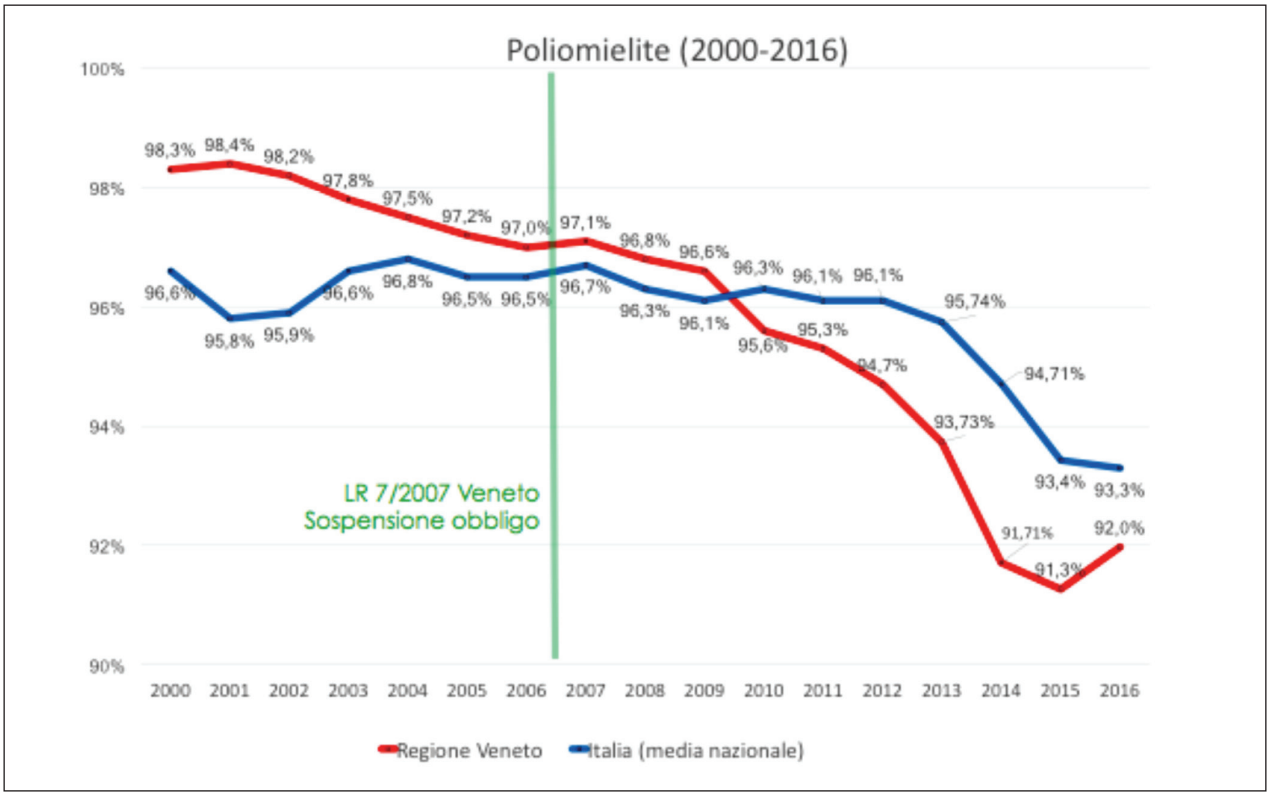

Figura 2. Andamento delle coperture vaccinali per poliomielite (a 24 mesi) in Italia e nella Regione Veneto dal 2000 al 2016 (fonte: Ministero della Salute)

3. 2009-2014: Esplode la *vaccine hesitancy* …. sotto effetto del web

Nel 1999 era stato pubblicato su *The Lancet* (8) uno studio inglese - ritirato 12 anni dopo dalla prestigiosa rivista (9) - che associava la somministrazione del vaccino MPR all'autismo. Gli effetti negativi sulla percezione delle vaccinazioni da parte delle popolazioni (non solo inglesi) si osservarono solo alcuni anni più tardi ma, con l'amplificazione dei media (e soprattutto dei sempre più usati social media) (10) e di alcune sentenze giudiziarie, furono dirompenti sul sistema. L'onda lunga del caso Wakefield si ritiene essere stato uno dei principali fattori ad aver scatenato quella che, alcuni anni più tardi, fu definita la "*vaccine hesitancy*" (11). Nella dinamica delle politiche vaccinali la sicurezza veniva ritenuta sempre più un elemento imprescindibile, mentre parallelamente venivano immessi sul mercato nuovi ed efficaci vaccini (meningococco B, rotavirus, herpex simplex e pneumococco coniugato polivalente). Si giungeva al paradosso di avere più vaccini sempre più efficaci ma una minore copertura complessiva della popolazione.

Aumentando le vaccinazioni per adulti e anziani il mondo scientifico si orienta sempre più a considerare un'offerta vaccinale estesa, che trova nel primo calendario vaccinale per la vita, elaborato da quattro società scientifiche (SItI, SIP, FIMP, FIMG), un importante momento di convergenza e sinergia (12). Non è forse un caso che, in concomitanza con la presentazione del primo Calendario vaccinale per la vita (2012) sia stato approvato anche il Piano 2012-14, con l'importante inclusione delle offerte universali per pneumococco e meningococco C.

Questa fase storica è stata anche caratterizzata dalla modifica costituzionale del 2001 (13) che, introducendo la legislazione concorrente in materia sanitaria, ha reso più praticabili scelte regionali che hanno avuto l'effetto di favorire offerte difformi nelle regioni, non giustificate da differenze nell'andamento epidemiologico delle malattie.

Sta di fatto che, tra il 2010 e il 2014, si osservano cali generalizzati per tutte le vaccinazioni obbligatorie e raccomandate, nei bambini quanto negli adulti (Figura 3).

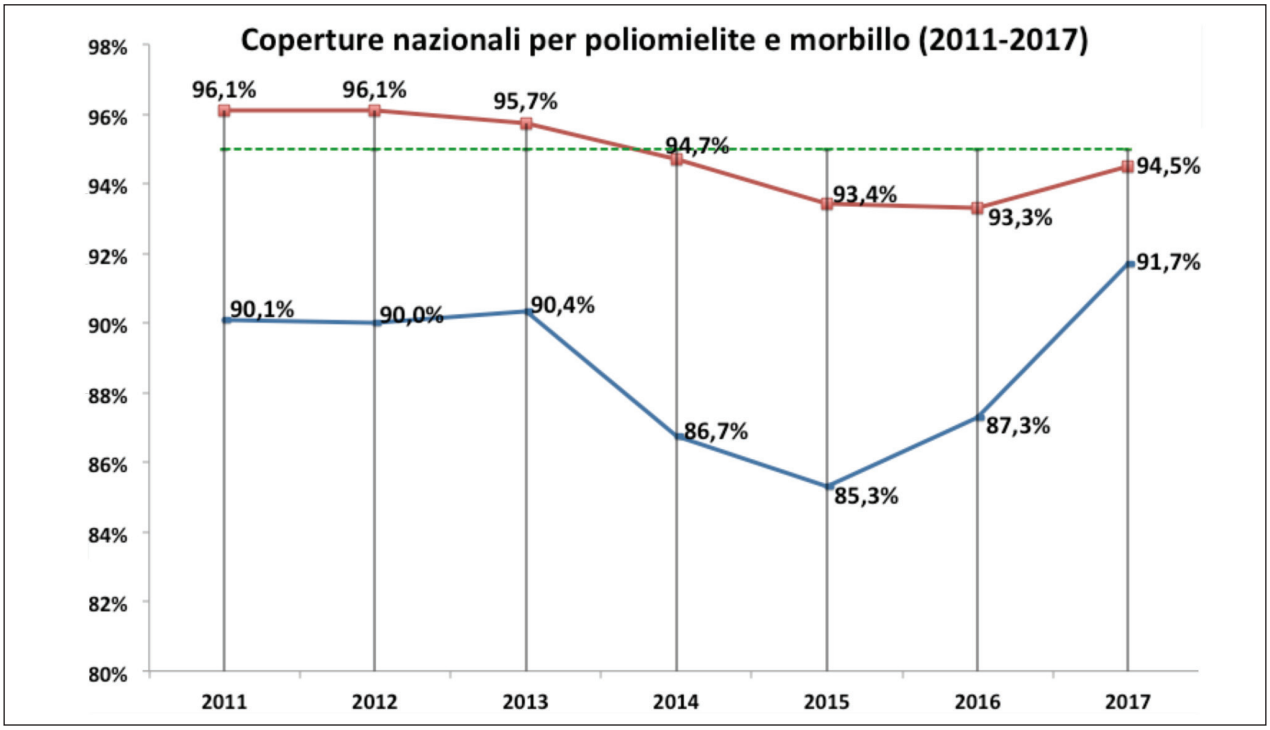

Figura 3. Andamento delle coperture vaccinali per poliomielite e morbillo (a 24 mesi) in Italia dal 2011 al 2017 (fonte: Ministero della Salute)

4. 2014-2018: la politica in campo e il rinforzo degli obblighi

Ci pare significativo identificare nel 24 novembre 2014 il punto più critico per la propaganda antivaccinale in Italia. Infatti, nel giro di pochi giorni, ci fu la pubblicazione di una sentenza del Tribunale di Milano che associava impropriamente un caso di autismo al vaccino esavalente e si verificò il noto "caso Fluad", con alcune morti sospette dopo somministrazione del vaccino antinfluenzale (14). Questo "minimo storico" avveniva nell'anno in cui il Ministero della Salute, anche sollecitato dal mondo scientifico (15), inseriva tra le priorità di Governo l'implementazione delle politiche vaccinali.

Il Ministro della Salute Lorenzin ha proposto l'Italia per il coordinamento della Global Health Security Agenda per l'implementazione delle politiche vaccinali nel mondo (16), ha portato all'approvazione, nel semestre di Presidenza Italiana, una risoluzione del Consiglio della UE sulle vaccinazioni (17) e ha dato l'avvio all'elaborazione del nuovo Piano di Prevenzione Vaccinale (PNPV) con il coinvolgimento attivo dell'ISS, del CSS e delle società scientifiche, in particolare le quattro (SItI, SIP, FIMP, FIMMG) che avevano spontaneamente proposto il Calendario vaccinale per la vita basato sulle più recenti evidenze scientifiche (18).

L'iter del nuovo PNPV è stato lungo e travagliato, per le difficoltà economiche (coperture finanziarie per i nuovi vaccini) e politiche (accordo con tutte le regioni) ma ha portato, all'inizio dell'anno 2017, all'approvazione definitiva di un documento programmatico innovativo e completo che è stato formalmente inserito tra i Livelli Essenziali di Assistenza (LEA) (19). Il nuovo Piano abbandona l'idea di superare gli obblighi vaccinali, aprendo invece a misure coercitive in riferimento alle ammissioni scolastiche, alle vaccinazioni del personale sanitario e a sanzioni disciplinari per i medici antivaccinisti. Durante il dibattito, alcune regioni (Emilia Romagna e Friuli Venezia Giulia) avevano già approvato norme regionali per l'esibizione obbligatoria dei certificati vaccinali negli asili e nelle Scuole dell'infanzia.

Ma un impulso più forte è venuto nel maggio del 2017, quando il Governo ha approvato il Decreto Legge n° 73/2017 (poi convertito con la legge 119/2017) che ha previsto l'estensione delle vaccinazioni obbligatorie (da 4 a 12, poi ridotte a 10 nella conversione in legge) e l'esibizione dei certificati vaccinali all'ammissione scolastica. La Legge 119/2017 ha rappresentato il punto di partenza di un nuovo scenario per le politiche vaccinali italiane, guardate con grande interesse anche da altri paesi (20).

Il dibattito etico e scientifico sul punto si era aperto già nel 2015 quando la California, dopo il drastico calo delle coperture e la riaccensione di focolai epidemici tra cui uno di morbillo a Disneyland, ha approvato una norma che ha bandito i convincimenti personali tra i motivi di esonero dalle vaccinazioni e ha di fatto rinforzato l'obbligo vaccinale per l'ammissione scolastica (21). Nonostante negli USA e in California in particolare il tema delle libertà individuali sia molto sentito, la Corte Suprema ha chiarito che la libertà di religione «*non include la libertà di esporre la comunità o singoli bambini alle malattie infettive*» (22). Concetti simili sono stati espressi dalla Corte Costituzionale italiana quando ha rigettato un articolato ricorso della Regione Veneto contro la legge 119/2017 (23).

La valutazione epidemiologica dell'introduzione dei nuovi obblighi vaccinali in California ha evidenziato un aumento delle coperture di circa il 5% nei due anni scolastici successivi all'introduzione dei nuovi obblighi (24). Di contro la valutazione dei dati della Regione Veneto non ha mostrato, sulla distanza, alcun effetto positivo legato alla sospensione dell'obbligo (Figura 2) (25).

Molti degli esperti del settore hanno sempre ritenuto che l'adesione alle vaccinazioni dovrebbe essere basata sulla consapevolezza della popolazione, sostenuta e supportata dalle evidenze scientifiche che provano l'efficacia e la sicurezza dei vaccini (26). Tuttavia, di fronte all'evidenza che la *Vaccine Hesitancy* sia attualmente basata soprattutto su opinioni personali non suffragate da prove scientifiche, le opinioni degli esperti si sono diversamente orientate, come emerge anche da sondaggi tra esperti di sanità pubblica, uno dei quali effettuato all'indomani dell'approvazione, a larga maggioranza, della legge 119/2017. Le risposte dei 149 intervistati hanno mostrato come il 68,5% si dichiarasse favorevole al provvedimento, il 24,8% favorevole con riserva e solo il 6,7% contrario (27).

I più recenti dati sulle coperture vaccinali in Italia mostrano riprese a partire dall'anno 2015 con un significativo "rimbalzo" nel 2017 (Figura 3) a seguito dell'entrata in vigore dei nuovi obblighi (28-32).

A tali confortanti risultati hanno probabilmente contribuito diversi fattori, tra cui una miglior informazione e sensibilizzazione del personale sanitario, il forte consenso politico a favore delle vaccinazioni, la pubblicazione di sentenze che hanno categoricamente smentito il rapporto tra vaccini e autismo e il cosiddetto "effetto Burioni", che ha consentito una rapida e netta inversione, sui circuiti web e social, da una netta predominanza di contatti su siti non scientifici o di antivaccinisti a un ribilanciamento a favore della corretta informazione scientifica. Il microbiologo Burioni ha guadagnato consensi come *"influencer"*, affrontando apertamente gli antivaccinisti con gergo e modalità fino ad allora poco praticati (definendoli ignoranti, somari, indegni di partecipare a dibattiti scientifici ecc.), che non hanno sicuramente fatto cambiare idea a quei gruppi ma potrebbero aver inciso positivamente sugli esitanti (33).

Conclusioni

I dati incoraggianti, a partire dal 2015, su diverse coperture vaccinali hanno forse segnato l'inizio di una fase di *"Vaccine Recovery"*, che richiederà tuttavia pazienza, impegno e attenzione da parte di tutti gli *stakeholder* al fine di raggiungere gli ambiziosi obiettivi di copertura previsti dal PNPV 2017-19.

Tuttavia, dopo le elezioni politiche del 2018, che hanno visto prevalere i partiti tradizionalmente contrari alle coercizioni vaccinali, è iniziata un'ulteriore fase di dibattito che potrebbe anche portare, nei prossimi mesi, a una revisione della normativa nazionale vigente e a una nuova differenziazione delle politiche vaccinali regionali.

Saranno il tempo e le accurate valutazioni epidemiologiche sulle coperture per tutte le vaccinazioni - obbligatorie e raccomandate - e sull'andamento delle malattie infettive a fornire ulteriori elementi tecnici ai decisori sanitari. Ma è certo che anche in questa recente fase l'Italia ha continuato la tradizione di innovazione e di sperimentazione di nuove politiche vaccinali, supportata dalle offerte attive e gratuite di vaccini da parte del Servizio Sanitario Nazionale, che fanno del PNPV vigente uno dei più avanzati, più equi e più sofisticati dell'intera Regione Europea.

Conflict of interest: None to declare

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The juvenile fibromyalgia syndrome (JFMS): a poorly defined disorder

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Summary. Juvenile fibromyalgia syndrome (JFMS) is a chronic condition characterized by symptoms of chronic diffuse musculoskeletal pain and multiple painful tender points on palpation. It is often accompanied by fatigue, disorders of sleep, chronic headaches, irritable bowel syndrome, and subjective soft tissue swelling. The complexity of the presenting clinical picture in JPFS has not been sufficiently defined in the literature. Similarities to adult fibromyalgia syndrome in JFMS are often difficult to compare, because many of the symptoms are "medically unexplained" and often overlap frequently with other medical conditions. However, a valid diagnosis of JFMS often decreases parents' anxiety, reduces unnecessary further investigations, and provides a rational framework for a management plan. The diagnostic criteria proposed by Yunus and Masi in 1985 to define JFMS were never validated or critically analyzed. In most cases, the clinical diagnosis is based on the history, the physical examination that demonstrates general tenderness (muscle, joints, tendons), the absence of other pathological conditions that could explain pain and fatigue, and the normal basic laboratory tests. Research and clinical observations defined that JFMS may have a chronic course that impacts the functional status and the psychosocial development of children and adolescents. This paper briefly reviews the existing knowledge on JFMS focusing on the diagnosis, clinical and the epidemiological characteristics in children and adolescents for better understanding of this disorder. (www.actabiomedica.it)

Key words: juvenile fibromyalgia syndrome, epidemiology, clinical characteristics, diagnosis

Introduction

Chronic pain (defined as persistent and recurrent pain) is a significant problem in the pediatric population, conservatively estimated to affect from 20% to 35% of children, especially adolescents, around the world (1). In general, pain can be categorized into 3 types that sometimes overlap: *nociceptive or peripheral pain* (related to damage of tissue by trauma or inflammation); *neuropathic pain* (associated with damage of peripheral or central nerves); and *centralized pain* **(**has no identifiable nerve or tissue damage and is thought to result from persistent neuronal dysregulation, overactive ascending pain pathways, and a deficiency of descending inhibitory pain pathways) (2).

Fibromyalgia syndrome (FM) is an idiopathic condition, of a yet unidentified aetiology, characterized by chronic widespread musculoskeletal pain, fatigue and sleep disorders. The pain is not caused by local inflammation but may be due to abnormal function of pain receptors in the brain (3, 4)

Patients with FM commonly experience symptoms for several years prior to diagnosis. Repeated and often expensive laboratory investigations, frequent

healthcare visits, and referral to a wide range of specialists contribute to considerable discomfort and cost to patients.

Recent guidelines are in agreement that the diagnosis remains clinical, and the purpose of a precise physical examination and limited laboratory investigations is to exclude other somatic diseases that have similar symptoms (3, 4).This has fostered a sense of insecurity in health care professionals leading to unnecessary investigations, excessive medicalization of patients (5, 6), and referral to numerous pediatric specialists (e.g., neurologists, rheumatologists, pain medicine) before the identification of the syndrome.

Although children and adolescents can meet the criteria of FM for adults (3), no general consensus has been achieved for the diagnosis and management of children and adolescents with chronic widespread pain (7).

This paper reviews briefly the existing knowledge regarding the diagnosis as well as the clinical and epidemiological characteristics of FM for better understanding of the juvenile fibromyalgia syndrome (JFMS).

Brief history of fibromyalgia

In 1592, in the book "Liber de rheumatismo", Guillaume deBaillou described some of muscular pains similar to FM. This is probably the very first medical description of FM. An important step was made by William Balfour (8), a surgeon in Edinburgh who was the first, in 1815, to describe "A special pain, usually driven by an inflammatory action, involving fibrous and white tissues, belonging to muscles and joints, like tendons, aponevroses". He called this widespread pain "fibrosistitis."

In 1880, an U.S. psychologist named Beard wrote about a collection of symptoms consisting of fatigue, widespread pain, and psychological disturbances. He called it 'neurasthenia' and attributed the problems to the stress of modern life (9). For many years, lack of a unifying aetiology and a universal terminology hindered the understanding and recognition of FM.

In 1904, a pathologist, Ralph Stockman, reported evidence of inflammatory changes occurring in the fibrous, intramuscular septa of biopsies from afflicted patients (10). That finding led Gowers W. (11) to introduce the term "fibrositis" to describe the inflammation of fibrous tissue in his description of low back pain. In subsequent years, the terms fibrositis, fibromyositis, psychogenic, psychosomatic, or muscular rheumatism have all been used as descriptors for this syndrome.

The term "fibromyalgia" was first used by the Nobel Prize winner, Hench in 1976 (12). Smythe and Moldofsky (13), and Yunus et al. (14) formulated diagnostic criteria for FM, while Müller and Lautenschläger (1990) formulated diagnostic criteria for generalized tenomyopathy (15). The main manifestations were defined as pain in multiple parts of the body, in addition to constitutional and vegetative manifestations, and local hyperalgesia at muscle and tendon insertions ("tender points").

Between the 1970s and the 90s, the recognition of the disease was an important step both for patients and physicians. The disease received a name, diagnostic criteria, and assessment tools.

In 1990 the American College of Rheumatology (ACR) first established criteria for the classification and diagnosis of the disease (16). New ACR classifications came into effect in 2010 (17), 2011(18) and 2016 (19) to validate the clinical diagnosis of FM.

Prevalence of fibromyalgia in children and adolescents

The prevalence of FM in adults is about 2% (95% CI, 1.4-2.7). It is higher among women (3.4%) than men (0.5%). The average age of diagnosis in adults is around 40-50 years, and 13-15 years for children and adolescents (3, 6, 20).

The reported prevalence of JFMS varies widely probably reflecting differences in ethnicity, socio-cultural background, psychological traits of the population and diverse methodologies that have been used in the published studies (21, 22).

The prevalence of JFMS reported in the literature in different countries is summarized in Table 1.

JFMS has a prevalence around 1-6%, more common in girls, and can be seen in children of all ages.

Table 1. Prevalence of juvenile fibromyalgia syndrome in children and adolescents: review of the literature

References	Diagnostic criteria	Cohort variables	Country/ prevalence
Buskila et al. J Rheumatol 1993; 20(2): 368-70.	1990 ACR criteria	338 healthy school children, 179 boys and 159 girls, aged 9 to 15 yrs.	Israel Prevalence 6.2%.
Clark et al. J Rheumatol 1998; 25(10): 2009-14.	1990 ACR criteria.	548 children, 264 boys and 284 girls, aged 9-15.	Mexico Prevalence 1.2%.
Mikkelsson et al. Pain 1997; 73(1): 29-35 and J Rheumatol 1999; 26(3): 674-82.	Structured pain questionnaire to assess the prevalence and persistence of self-reported musculo-skeletal pain symptoms and disability caused by pain.	1626 third and fifth grade schoolchildren	Finland Prevalence 1.3% at baseline.
Weir et al. J Clin Rheumatol 2006; 12(3): 124-8.	ICD-9 criteria (*)	2595 incident cases of adult and juvenile FMS	U.S.A The estimated prevalence per age group was: 0.5 to1% for 0-4 yrs; 1 to 1.4% for 5-9 yrs; 2 to 2.6% for 10-14 yrs; and 3.5 to 6.2% for 15-19 yrs.
Fuda A et al. Egypt Rheumatol Rehabil 2014; 41: 135-138	A questionnaire was completed by students. A clinical diagnosis of FM was established in only 25 cases.	2000 students: 960 boys (48%) and 1040 girls (52%). Ages: 9-15 yrs, mean 11.9 yrs	Egypt Prevalence 1.2%.

Legend: JFMS: Juvenile fibromyalgia syndrome; FM: fibromyalgia; (*) International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to identify fibromyalgia cases (ICD code 729.1).

Pathophysiology

Current evidence indicates that FM is the result of the combination of a genetic predisposition and various extrinsic stressors that result in a process called *central sensitization* of the central nervous system (CNS) (23-26). Central sensitization is a complex phenomenon in which there is hyperexcitability of central nociceptive circuits brought on by activity dependent changes in synaptic transmission. This increased sensitization involves changes in receptors, neurotransmitters, ion channels and signalling pathways in the central nervous system to such an extent that even innocuous non-nociceptive stimuli are perceived as painful and the perception of noxious stimuli is exaggerated, prolonged and widespread.

Adolescents with FM were found to be more sensitive to pressure pain than their healthy peers; this suggests a tendency for sensitization of peripheral and/or central nociceptive information often reported in adults with FM (27). In addition, abnormalities associated with FM include an inability to sustain deep stage 4 sleep, neurotransmitter abnormalities (especially serotonin, dopamine, and norepinephrine), hypothalamic-pituitary-adrenal axis dysfunction, and peripheral sensitization.

Recent studies in patients with FM looked at functional activity in the brain. They have proposed that, in these patients, acute pain seems to activate somatosensory, insular and cingulate cortical areas, whereas chronic pain preferentially activates prefrontal and limbic cortical areas. In addition, anatomical changes such as regional decrease in grey matter density, volume or thickness in various regions of the brain, not limited to nociceptive areas, are described in patients with different chronic pain conditions. These

anatomical and functional connectivity changes are likely to be secondary to chronic pain (28-31). In support of this view, treating chronic pain effectively can reverse these structural and functional abnormalities and restore normal brain function in humans (32).

Familial studies identified the possibility of genetic predisposition, with up to one-quarter of relatives of FM patients reporting chronic widespread pain (33). A genetic predisposition to fibromyalgia has been demonstrated linking certain genes to fibromyalgia, such as the SS genotype polymorphism in the promoter region of the serotonin transporter gene (5-HTT) (34), and the LL and LH genotype polymorphisms in the gene encoding the COMT (catechol-O-methyltransferase) enzyme (35).

Moreover, inflammatory processes may also play a significant role in the pathogenesis of FM (36).

There is a subset of people with FM who test positive for antinuclear antibody (ANA) and have constitutional symptoms that resemble those of patients with early lupus (37).Therefore, in individual cases, FM may be an early sign of an autoimmune disease (38).

Some studies have sought to demonstrate the occurrence of hormonal abnormalities in individuals with FM, but not specifically in young patients.

In summary, the pathophysiology of FM remains unclear, although some data indicate that a significant central sensitization component is at the root of the syndrome. It appears that the musculoskeletal system, neuroendocrine system, and central nervous system play a significant role in the pathogenesis of this disorder (39,40).

Clinical symptoms of fibromyalgia syndrome

Chronic widespread pain, the pivotal and most important symptom, is not localized to any specific body tissue and tends to move from site to site. Symptoms of fatigue, sleep disturbances, cognitive changes, mood disturbances and various somatic symptoms may occur to a greater or lesser extent.

Pain is described as being diffuse, deep, and continuous often with periods of exacerbation, and symptoms may be modulated by various factors including psychological stress, excessive physical activity, viral infections and fatigue. Therefore, the clinical presentation of FM can be quite diverse with some areas of the body more painful than others, fluctuations in intensity of pain and variable intensity of other associated symptoms. Patients also differ considerably in terms of severity of functional impairment (7, 25, 41).

Although JFMS has been less well studied than adult fibromyalgia, it is evident that the clinical features are basically similar, with minor differences (41), e.g., joint hypermobility is more common in JFMS (42), while psychological comorbidities are common but less severe; altered sleep pattern seems to be a common among patients with JFMS (21,43, 44).

Patients with JFMS may be particularly vulnerable to school absenteeism because of their unremitting widespread pain, disrupted sleep, and chronic fatigue (45).

Table 2 reviews the literature on the commonest clinical features in 277 patients with JFMS below or above 10 years of age.

Physical examination

Many musculoskeletal diseases seem capable of triggering the process of central sensitization with an associated increase in sleep disturbance, fatigue, widespread pain, and other symptoms common in FM (46-49). Therefore, physical examination (regardless of whether tender points are counted) remains the key in the evaluation of patients to assess the tenderness (allodynia and hyperalgesia) associated with FM as well as to aid in the differential diagnosis (50).

The clinical characteristics of FM among men are similar to those in women, except that men have fewer symptoms, pain sites and tender points, and less frequent fatigue and irritable bowel syndrome, (51).

The challenge of criteria for the diagnosis of fibromyalgia

There are no instrumental tests to confirm the diagnosis of JFMS, and thus differential diagnosis is by exclusion by means of an extensive clinical examination and patient's history.

Table 2. Most common clinical findings in 277 patients below or above 10 years of age with juvenile fibromyalgia syndrome (From: Eraso RM et al. Clin Exp Rheumatol.2007;25:639-644; Gedalia et al. Clin Exp Rheumatol. 2000;18:415-419; Fuda A et al. Egypt Rheumatol Rehabil.2014:41:135–138; Siegel DM et al. Pediatrics. 1998;101:377-382, modified)

Clinical feature	Eraso RM et al. Onset age 10 or under N: 46 (%)	Eraso RM et al. Onset > age 10 N: 102 (%)	Gedalia A et al. N: 59 children (%) *	Fuda A et al. N: 25 children (%) **	Siegel DM et al. N: 45 children (%) ***
Generalized aches & pain	(100)	(100)	(97)	(100)	(>90)
Headache	(78)	(80)	(76)	(52)	(71)
Sleep disturbances	(65)	(74)	(69)	(40)	(>90)
Morning muscle stiffness	(39)	(21) (§)	(29)	(56)	(53)
Fatigue / tiredness	(28)	(23)	(20)	(100)	(62)
Abdominal pain	(39)	(19) (§)	(17)	-	-
GI symptoms				(29)	-
Irritable bowel				(20)	-
Subjective joint swelling	(39)	(14) (§)	(24)	-	-
Joint hypermobility	(17)	(23)	(14)	-	-
Depression	(9)	(9)	(7)	(60)	

Legend = §: P value <age 10 vs, >age 10 - statistcally significant; GI: Gastrointestinal; * 47 F and 12 M diagnosed with primary JFMS. The mean age at onset was 13.7 years, and the mean age at diagnosis was 15.5 years; ** 7 M (28%) and 18 F (72%). Their ages ranged between 9 and 15 years, with a mean age of 11.9 years; *** 45 subjects (mean age, 13.3 years; 91% females), of whom 33 were available for telephone interview at a mean of 2.6 years from initial diagnosis (0.1 to 7.6 years).

Several different classification schema have been proposed for adults. The most frequently used diagnostic criteria were published by the American College of Rheumatology (ACR) in 1990, with revised criteria proposed in 2010, 2011 and 2016 (16-19).

The first ACR criteria for FM in 1990 (16), based on 293 patients (mean age 44.7 years), emphasized chronic widespread musculo-skeletal pain (including pain in the axial skeleton), and the presence of pain on at least 11 of 18 specified tender point sites (pain is at the site of pressure, without radiation or referral) with digital palpation of 4 kg/cm^2 (Figure 1).

In practical terms, the pressure to assess tenderness with digital examination is the pressure needed to see the examiner's own nail bed blanch. Tender points are located at soft tissue sites and reflect a reduction in pain threshold without any underlying tissue pathology. Although these criteria were widely accepted within the medical community, many primary care physicians were either not performing tender point examinations at all or performing them inaccurately (52).

The criteria proposed by Yunus for JFMS in 1985 (14) required fewer tender points for the diagnosis of FM in children than in adults (5 instead of 11). They also incorporate additional symptoms representing the broader spectrum of FM, as opposed to the ACR 1990 criteria that were based solely on the presence of pain and tenderness. These symptoms include anxiety, fatigue, poor sleep, headache, irritable bowel syndrome, subjective soft tissue swelling, numbness, pain modulation by physical activity, pain modulation by weather, and pain modulation by anxiety and distress; diagnosis of FM in a child depends on presentation of 3 of 10 symptoms (Table 3).

Debate considerations

Tender points have elicited considerable debate and their true value has been questioned because of many reasons. The criteria were originally designed to standardize patient classification in clinical trials rather than to diagnose FM in routine clinical practice and did not consider any other concomitant symptoms or severity of symptoms. They may be present in normal individuals and can increase with age. Their reliability

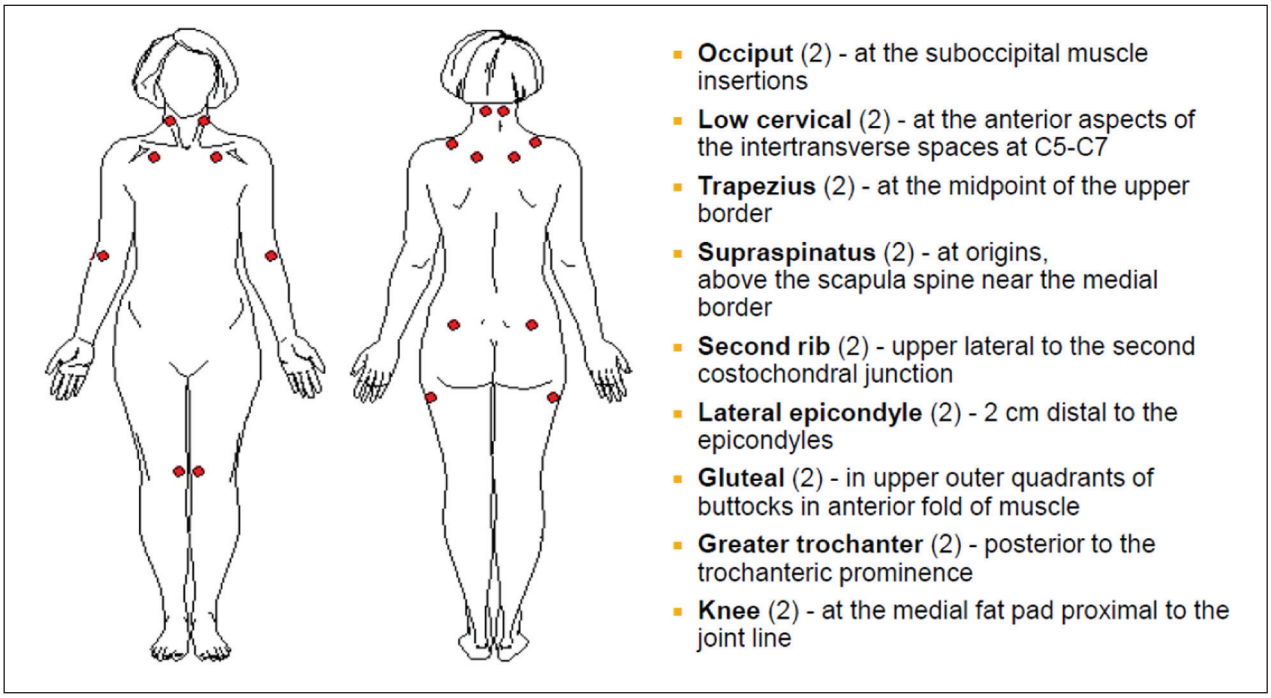

Figure 1. American College of Rheumatology 1990 criteria for the loci of tender point examination of fibromyalgia (Adapted from: Wolfe F et al. Arthritis Rheum 1990; 33: 160-172)

Table 3. Yunus and Masi diagnostic criteria for juvenile primary fibromyalgia syndrome (Adapted from: Arthritis Rheum 1985; 28: 138-145)

Major Criteria
1. Generalized musculoskeletal pain at three or more sites for three or more months
2. No underlying medical condition
3. Normal laboratory tests
4. Five or more typical tender points
Minor Criteria
Presence of three of the following features:
1. Chronic anxiety or tension
2. Fatigue
3. Poor sleep
4. Chronic headache
5. Irritable bowel syndrome
6. Subjective soft tissue swelling
7. Numbness
8. Pain modulation by physical activities
9. Pain modulation by weather factors
10. Pain modulation by anxiety or stress

is variable, ranging from good to poor (53, 54). Tender point examination remains a subjective test, open to individual interpretation and reflects an overall reduction in pain threshold, rather than a pathological process at the soft tissue site (55). Moreover, the association of pain report and tender point count is poorly correlated, suggesting that these measurements represent different parameters of pain experience in FM syndrome (56). There is a poor concurrent validity when tender points were examined digitally or by dolorimetry (57). The patient psychological state influences the measurement of tender points, suggesting an association with distress rather than an accurate indicator of pain (58).

In summary, although the tender point examination has been used in hundreds of studies and is recognized by the ACR for the diagnosis of FM, it had never been validated in the pediatric population. Furthermore, there is some evidence that application of the 4 kg cut off when assessing tenderness by dolorimetry is not applicable in children, and that a 3 kg cut off is more appropriate (58, 59).

Consequently, the 2010 ACR Diagnostic Criteria (17) eliminated the tender point examination and made diagnosis more difficult by requiring evaluation of symptoms and imposed a special burden on the ex-

aminer: the necessity to interview the patient in order to identify the extent and severity of the symptoms. The new criteria indicate two distinct but combined diagnostic pathways: a widespread pain index (WPI) and a symptom severity scale (SS). Furthermore, they have also included other domains, using a checklist of 41 associated symptoms, for exclusion of other conditions causing pain.

Thus, unlike the 1990 ACR criteria, the new 2010 criteria require exclusion of other conditions causing pain. Additionally, symptoms must have been present at a similar level for at least 3 months.

The WPI is calculated by summing up patient reports of pain in 19 separate regions of the body (Figure 2).

The SS scale score is calculated by grading several symptoms (e.g., pain, fatigue, awaking unrefreshed) on a severity scale from 0 ("no problem") to 3 ("severe, pervasive, continuous, life-disturbing problems"). Fatigue, waking unrefreshed, and cognitive symptoms are rated on the basis of the level of severity during the previous week. Additionally, in adults a list of 41 potential comorbid symptoms or signs is provided to represent an FM-related review of symptoms. The magnitude of their contributions to the patient's behavior was categorically quantified from 0=none, 1=few (1-10), 2=many (11-30), to 3=very many (31-40).

A patient satisfies the proposed diagnostic criteria if the following 3 conditions are met:

- The patient has a widespread pain index (WPI) of 7 or more and symptom severity score (SS) of 5 or more. Alternatively, a patient could meet criteria with a WPI of 3 to 6 and SS scale score of 9 or greater.
- Symptoms have been present at a similar level for at least 3 months and must not be explained by another disease process.
- The patient does not have a disorder that would otherwise explain the pain.

The use of WPI combined with SS enabled a 90.8% diagnostic accuracy (90.9% sensitivity and 85.9% specificity) when compared with the 1990 ACR criteria (17). Based on analysis of criteria studies and clinician and researchers' comments, Wolfe et al. iden-

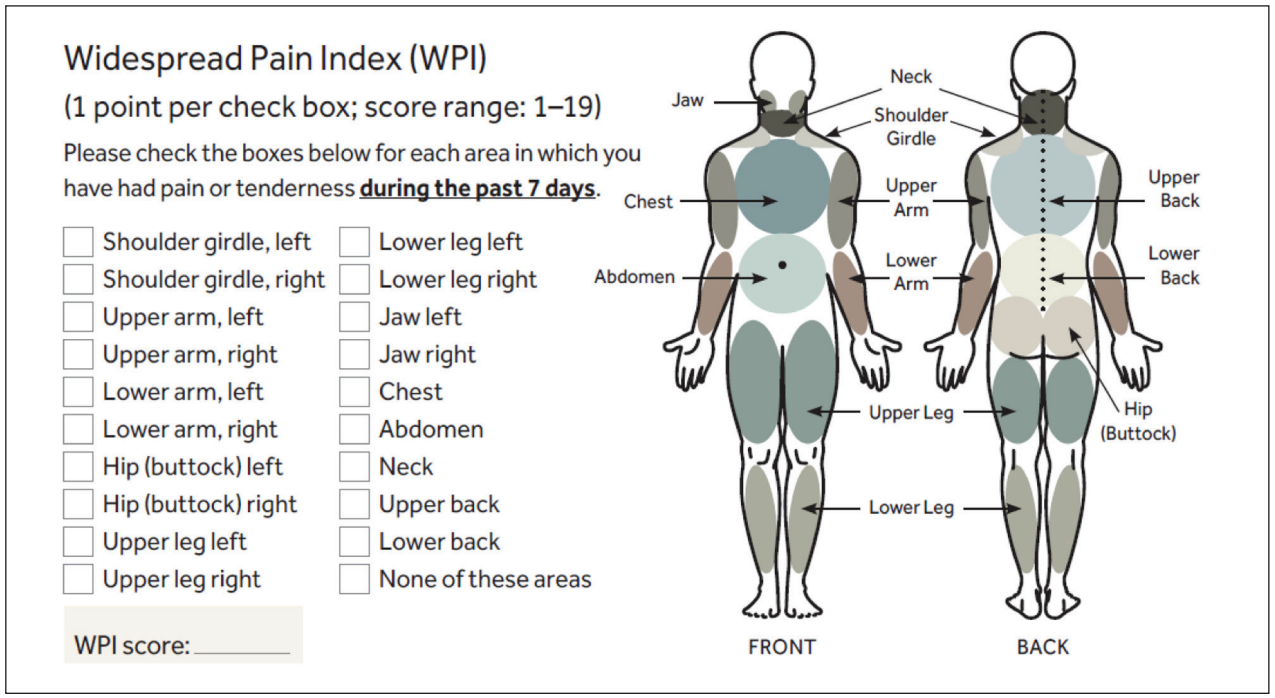

Figure 2. Diagnostic and Severity Criteria for Fibromyalgia: Widespread Pain Index (WPI). (Adapted from: Wolfe F. et al. Arthritis Care Res (Hoboken) 2010; 62: 600-610).

tified problematic areas, including: a) misclassification in asymmetric pain disorders, b) inconsistent and unclear instructions in the presence of other medical conditions, c) different clinician and self-report criteria, d) unclearly defined pain assessment regions. Therefore, they developed in 2016 a revision of the 2010/2011 fibromyalgia criteria (19). The revision makes the following changes:

1) Changes Criterion 1 to WPI ≥7 and SS score ≥5 or WPI 4-6 and SS score ≥9 (WPI minimum must be ≥4 instead of previous ≥3).

2) Adds a generalized pain criterion (Criterion 2) that is defined as pain in at least 4 of 5 regions (left upper, right upper, left lower, right lower, axial). In this definition, jaw, chest and abdominal pain are not evaluated as part of the generalized pain definition.

3) Standardizes and makes 2010 and 2011 criterion (Criterion 3) wording the same: "Symptoms have been generally present for at least 3 months."

4) Removes the exclusion regarding disorders that could (sufficiently) explain the pain (Criterion 4) and adds the following text: "A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses."

5) Adds the Fibromyalgia Symptom (FS) or polysymptomatic distress (PSD) scale as a full component of the fibromyalgia criteria.

6) Creates one set of criteria (2016) instead of having separate physician (2010) and patient (2011) criteria by replacing the physician estimate of somatic symptom burden with ascertainment of the presence of headaches, pain or cramps in lower abdomen, and depression during the previous 6 months.

Practical considerations

The 2016 revision combines physician and questionnaire criteria, minimizes misclassification of regional pain disorders, and eliminates the previously confusing recommendation regarding diagnostic exclusions. The physician-based criteria are valid for individual patient diagnosis. The self report version of the criteria is not valid for clinical diagnosis in individual patients but are valid for research studies.

The diagnosis of fibromyalgia in children and adolescents

The diagnosis of JFMS remains the subject of debate about which criteria to use: those of the ACR (2010) or those proposed by Yunus and Masi (14); the measurement of the force to be applied in the evaluation of tender points; the definition of headache and the most adequate assessment tools for the determination of anxiety and depression.

The 2010 criteria were validated in adolescent girls (aged 11-17 years) by Ting et al. (60). The authors suggested minor modifications to suit the developmental level of the patients, without compromising the integrity of the test.

They recommend extending the time frame of the WPI to "in the past 3 months" and to specify that the pain was persistent ("every day or almost every day") to enhance the understanding of the nature of chronic or recurrent pain. For the somatic symptoms, several items rarely were endorsed by the youth (<10%), and some were not understood and/or were redundant. Therefore, they recommend removing these items (muscle pain, fatigue/tiredness, chest pain, fever, diarrhea, wheezing, Raynaud phenomenon, hives/welts, vomiting, oral ulcers, loss of/ change in taste, seizures, rash, sun sensitivity, hearing difficulties, hair loss, painful urination, and bladder spasms) from the list of somatic symptoms and to utilize only the most useful 22 remaining items.

They also emphasized that a standard detailed physical examination and history should be conducted as part of clinical practice to ensure other conditions (e.g. thyroid dysfunction, systemic lupus erythematosus, juvenile idiopathic arthritis, sleep disorders) are ruled out.

Practical considerations in children and adolescents

The use of the ACR 2010 diagnostic criteria, which do not require tender point examination, is recommended for clinical diagnosis, but should not preclude a thorough physical examination. However, these criteria do not precisely define how symptom severity is to be ascertained, leaving this to the clini-

cian. Therefore, the concept of JFMS remains a work in progress with many current unanswered clinical and pathophysiologic issues. For example, the developmental changes which occur during childhood and adolescence make the measurement of paediatric pain particularly challenging (61), and the cognitive and metacognitive skills required for a child to give reliable self-reports of pain (such as the ability to rank-order objects, consider numerous options simultaneously, and retain and manipulate information) change significantly during childhood and adolescence (62).

Each symptom plays a variable role in the presentation of the individual patient and all contribute to a greater or lesser degree towards the overall effect of impaired quality of life and reduced functional activity. Therefore, such patients may be referred to numerous pediatric specialties (e.g., neurology, rheumatology, pain medicine) before symptoms of JFMS are finally identified.

Differential diagnosis of fibromyalgia in children and adolescents

Because the most prominent complaint of patients with FM is body pain, the differential diagnosis should consider a wide variety of other painful conditions. Similar to FM in adults, JFMS is often difficult to classify, because many of the symptoms are scientifically "medically unexplained" and often overlap with other medical conditions such as chronic fatigue syndrome (63), irritable bowel syndrome, and migraine headache.

Practically, the differential diagnosis of FM includes disorders that have symptoms of widespread pain and fatigue. These disorders include hypothyroidism, inflammatory and other myopathies, polymyalgia rheumatica, other rheumatic diseases, viral infections, and severe vitamin D deficiency (5-7, 41).

Laboratory testing

There are no specific tests to confirm the diagnosis, but many of the differential diagnoses diseases can be excluded by an extensive clinical examination and specific laboratory testing. Although not required to establish the diagnosis of FM, routine laboratory testing (if not already performed within the past 6-12 months) is frequently obtained. These tests include measurements: of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, complete blood cell count, comprehensive metabolic panel, and thyroid function tests.

Depending on symptoms (e.g., duration of pain and acute vs. chronic), medical history, and physical examination findings, other tests may be indicated (e.g. antinuclear antibodies, rheumatoid factor, viral infections, vitamin D levels, imaging, electroencephalography, electrocardiography, genetic studies, biopsy) if there is a clinical suspicion for an alternative cause of the pain (3-5, 64-66).

Psychological problems/disorders should be considered since they are even more common, e.g., depression (subtypes according to DSM-V), anxiety disorders (subtypes according to DSM-V), posttraumatic stress disorders and dissociative disorders with or without self-injurious behaviour. There is also the possibility of mental illness of parents, as seen in Munchhausen by proxy syndrome (64).

Debated is the possible role of hyperparathyroidism in FM, reported only in adults. A high frequency of hyperparathyroidism, in women with FM versus the general population, was reported by Costa et al. (65). By contrast, Ferrari and Russell found that the incidence of primary hyperparathyroidism in FM patients was not different than that seen in other patients with widespread or localized pain (66).

Ciregia et al. (67) investigated the presence of potential diagnostic and/or prognostic biomarkers in saliva which could be useful for the management of FM patients. Specifically, the salivary profile of FM patients was compared with those of healthy subjects, subjects suffering migraine (model of non-inflammatory chronic pain), and patients affected by rheumatoid arthritis (model of inflammatory chronic pain). Two-dimensional gel electrophoresis (2-DE) 2-DE serotransferrin and alpha-enolase were found differentially expressed in FM patients. The authors concluded that the identification of disease salivary biomarkers could be helpful in detecting FM clusters and targeted treatment.

Practical considerations

There are currently no instrumental tests or specific diagnostic markers for FM.and JFM. It is hoped that, in the near future, some tests such as salivary indicators can offer a clue for shedding light upon complex diseases like FM. The difficulty in diagnosing this condition, particularly in children and adolescents, can cause a great deal of frustration among patients and parents, when no definitive medical cause and/or explanation for the child's symptoms is provided. Therefore, parents may look for multiple consultations in the conviction that a serious underlying disease is going to be missed.

Prognosis of fibromyalgia in children and adolescents

Initial studies indicated a positive long-term prognosis for JFMS (44, 68). By contrast, studies in subjects with JFMS recruited from hospital settings have shown a chronic and fluctuating course, with symptoms persisting in ~70% of young people (43, 69, 70).

One controlled study published in 2010 of patients with JFMS and matched healthy controls (mean age, 15 years) showed that about 50% of patients with JFM met the full ACR criteria for fibromyalgia at ~4 years follow-up (mean age, 19 years), and >70% had continuing symptoms of pain, fatigue or sleep difficulty (70).

Several authors report different prognoses between adults and youths with FM. (43, 45, 71). They suggested that the early detection of JFMS is an indication of a better prognosis (69), with significant gains in quality of life (73), and functionality for individuals who receive adequate treatment, whereas those with widespread pain that are not treated adequately have a greater chance of developing fibromyalgia (74). On the other hand, in a large prospective longitudinal study of JFMS patients, Kashikar-Zuck et al. (75) found that the majority of adolescent patients (~80%) with JFMS seen in a pediatric specialty care setting continued to report persistent pain and other FM symptoms as they transitioned into young adulthood (Table 4).

In conclusion, most of youth with JFMS continue to experience symptoms into adulthood, which highlights the importance of early diagnosis and intervention. However, more research into the variability of outcomes within the JPFS group, with closer examination of risk and protective factors associated with future outcomes is essential to designing focused interventions.

General principles of treatment in children and adolescents

Goals of treatment should be pain relief, restoration of functioning, reduction of school absenteeism, dissolving social isolation, strengthening self-awareness, mobilizing domestic resources and the development of strategies for coping with pain. The inclusion of the family, the training of strategies in everyday life and the treatment of mental co-morbidities are also important (64).

Evidence-based treatment guidelines in FM include those developed by the American Pain Society (APS) in 2005 (76, 77) and the European League Against Rheumatism (EULAR) in 2008 (78).

However, they were developed before FDA approved any medications for treating fibromyalgia and substantial heterogeneity exists between the recommendations. Furthermore, the studies evaluated during the development of these guidelines were not directly comparable as a result of variations in study design and short duration that limit their general applicability in clinical practice (79).

Little is known regarding treatment choices of youth diagnosed with JFMS as they move into young adulthood.The management of JFMS is centered on the issues of education, behavioral and cognitive change (cognitive-behavioral therapy (CBT)) with a strong emphasis on physical exercise), and a relatively minor role for pharmacological treatment with medications such as muscle relaxants, analgesics and tricyclic agents (80-84). Any patient being treated with a medication should be carefully evaluated for both efficacy as well as side effects, and medications should be discontinued unless there is evidence for definite benefit. More controlled studies are needed to investigate

Table 4. Long-term outcomes of juvenile fibromyalgia syndrome and review of the literature

Reference	Results
Malleson PN et al. Idiopathic musculoskeletal pain syndromes in children. J Rheumatol 1992: 19: 1786-1789	After a variable observation period between 1 and 48 months, 17 of 28 patients with so-called JFMS had persistent symptoms after an average of 27 months.
Buskila D et al. Fibromyalgia syndrome in children - an outcome study. J Rheumatol 1995; 22: 525-8.	A spontaneous remission of symptoms was observed in 73% of patients evaluated after a 30-month follow up.
Siegel DM et al. Fibromyalgia syndrome in children and adolescents: clinical features at presentation and status at follow-up. Pediatrics 1998; 101: 377-82.	In the present study, 46% of the patients improved, 43% remained unchanged, and in 11% symptoms became worse. There was no statistically significant difference between the younger and older patients.
Mikkelsson M. One year outcome of preadolescents with fibromyalgia. J Rheumatol 1999; 26: 674-82.	The JFMS persisted in only 26% of the patients evaluated at a one-year follow up.
Calvo I et al. Pediatric fibromyalgia patients: A follow-up study. Ann Rheum Dis. XIV European League Against Rheumatism Congress Abstracts, Glasgow, Scotland, 1999, p 353.	At 48-month follow-up, 15/22 (68.2%) had no longer fulfilled the FM criteria.
Gedalia A et al. Fibro¬myalgia syndrome: experience in a pediatric rheu¬matology clinic. Clin Exp Rheumatol 2000; 18: 415-419	Conducted a retrospective study over a period of 4 years. At an average follow-up of 18 months (range 3-65 months), 60% of the children improved, 36% experienced no change and 4% experienced a worsening of pain symptoms.
Kashikar-Zuck S et al. Controlled follow-up study of physical and psycho¬social functioning of adolescents with juvenile primary fibromyalgia syndrome. Rheumatology (Oxford) 2010; 49: 2204-2209	Of 48 U.S. American children and adolescents diagnosed with JFMS, after an average of 3.7 years, 62.5% suffered from widespread musculoskeletal pain, and 60.4% fulfilled criteria for so-called JFMS.
Libby CJ et al. Protective and exacerbating factors in children and adolescents with fibromyalgia. Rehabil Psychol 2010; 55: 151-158	Exacerbating factors for widespread musculoskeletal pain included the following: daily hassles, pain-related catastrophizing, lack of self-efficacy and lack of positive family support.
Kashikar-Zuck S et al. Long-Term Outcomes of Adolescents With Juvenile-Onset Fibromyalgia in Early Adulthood. Pediatrics 2014; 133: e592-600.	This prospective study demonstrated that pain and other symptoms persisted into adulthood for 80% of JFMS patients, with associated impairments in physical functioning and mood. At follow-up, one-half of the sample met full criteria for adult FM.

the effectiveness of these complementary methods to assist treatment providers in giving evidence-based treatment recommendations.

A recent Cochrane review has concluded that psychological treatments may improve pain control for children with a variety of pain conditions, including muscle pain, abdominal pain, headaches and FMS (85). Therefore, it appears that CBT should be offered as a preferred modality of non-pharmacological treatment for JFMS.

If disease development is assumed to be linked to the family background, hospitalization aimed to temporarily isolate the patient from his or her home environment should be taken into consideration (86).

Prompt recognition of JFMS may decrease problems for pediatric patients with chronic pain, while

pediatric primary care providers' lack of familiarity with JFMS can cause a delay in diagnosis and management (87, 88).

Conclusions

JFMS is characterized by persistent widespread musculoskeletal pain, sleep disturbances, fatigue, and the presence of multiple discrete tender points on physical examination. Its pathogenesis is not entirely understood, although it is currently believed to be the result of a central nervous system (CNS) malfunction that increases pain transmission and perception. To date, there is no "gold standard" for diagnosing FM because symptoms may be part of or overlap with other diseases or syndromes. Therefore, until a better clinical definition is achieved, all diagnostic criteria should be interpreted with caution and subject to modification. Recent guidelines agree that the diagnosis remains clinical, and the purpose of the physical examination and limited laboratory investigations is to rule out some other somatic disease that can sufficiently explain the symptoms.

Emerging evidence suggests that JFMS is a condition that frequently continues into adulthood with chronic physical and psychological symptoms, making it important to correctly identify and treat this condition in adolescence. A multidisciplinary approach, combining pharmacological, behavioral and exercise-based modalities is currently the standard of care for JFMS.

Conflict of interest: None to declare

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Clinical manifestations, evaluation and management of hyperprolactinemia in adolescent and young girls: a brief review

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Summary. Hyperprolactinemia (HPrl) is considered as a rare endocrinopathy in childhood. In children and adolescent girls, there are three major categories of HPrl causes; physiological, pathological and iatrogenic. Through hypogonadotropic hypogonadism, prolactin hypersecretion and production leads to the typical functional syndrome which is observed in female children and adolescents; delayed puberty, primary or secondary amenorrhea and/or galactorrhea. Regarding prolactinomas, clinical signs manifest with mass compression of the optic chiasm and anterior pituitary gland or prolactin hypersecretion. Targeted identification of HPrl is of significant importance for proper management and follow-up. The aim of this review is to focus on the evaluation of HPrl in adolescent and young girls. In addition, we aimed to summarize the current knowledge regarding the proper management of such cases. (www.actabiomedica.it)

Key words: hyperprolactinemia; adolescent girls; visual field defects; dopamine agonists

Introduction

Hyperprolactinemia (HPrl) with a prevalence of 0.4% to 5% is considered a frequent endocrinopathy, although rare in childhood. Prolactin is one of the major pituitary hormones that is secreted from the pituitary gland and plays an important role in reproductive functions. The normal serum prolactin concentration level in female children and adolescents is between 5 and 20 ng/ml (1, 2).

Prolactin is produced from the lactotropic cells of the anterior pituitary lobe in response to a singular and unique tonic inhibitory (dopamine) signal that is prevalent on the stimulatory TRH (thyrotropin-releasing hormone) hormonal signals (3).

The elevated prolactin levels in interruption of peduncle or in obstruction of portal venous system is due to loss of inhibitory action of dopamine.

Several agents such as stress, suckling, estrogens, TRH, vasoactive intestinal polypeptide (VIP) and oxytocin, among others, act as stimulants of prolactin release directly to anterior lobe or by reducing the inhibitory action of dopamine (3, 4).

The primary activity of prolactin is its lactotrophic effect on the epithelium of the mammary gland as well as regulating gonadal function by inhibiting GnRH excretion and secretion of Follicle stimulation hormone (FSH) and Luteinizing hormone(LH) (5, 6). Interestingly, prolactin also demonstrates regulatory effects in the immune system, lactation, adipose tissue and insulin secretion (7-9).

The clinical manifestations of HPrl are various but usually specific and easy to recognize only in adolescence, while in childhood onset symptomatology is neurologic with headache and visual deficit. Once the presence of prolactin hypersecretion is identified,

further evaluation to establish the underlying cause is necessary in order to preserve and restore normal growth potential early in childhood (1, 2). In general, there are three major categories of HPrl causes in childhood: physiological, pathological and iatrogenic.

The aim of this review is to focus on the evaluation of HPrl in adolescent and young girls. In addition, we aimed to summarize the current knowledge regarding the proper management of such cases.

Etiology and risk factors

There are several different conditions that are linked to prolactin over production and secretion.

Natural causes include the circadian rhythm, where an acrophase shift is observed during morning hours (2.00 am to 5.00 am). Prolactin concentration elevates in several conditions such as during Rapid eye movement (REM) sleep, physical activity, high-protein diet, hypoglycaemia, stress (before and during venipuncture procedure) and pregnancy. Pathological conditions of HPrl can be divided into three groups; tumors, systemic diseases and miscellaneous (1, 2).

Although rare, pediatric prolactinoma represents one of the most frequent forms of pituitary adenoma (10). Pituitary adenomas in children and adolescents are benign disorders with an estimated incidence of 0.1/1,000,000 (11). These tumors may be hormone-secreting (e.g. prolactinoma) or non-hormone-secreting (e.g.incidentalomas) (12).

Pediatric prolactinoma predominantly is detected in early puberty. The exact etiology remains enigmatic although in most of the cases they are sporadic forms. Girls are affected more frequently with microadenomas (<10 mm in diameter) where prolactinomas tend to be smaller and less aggressive compared with boys.

Clinical symptoms, prolactin hypersecretion and typical brain magnetic resonance imaging (MRI) findings confirm the diagnosis. Pediatric prolactinoma may also coexist with hormonal deficiencies in thyroid stimulating hormone (TSH) and growth hormone (GH) which is more common in macroadenomas (10-40 mm) (13).

Notably, incidentalomas are asymptomatic pituitary lesions that are more prominent in children than prolactinomas and they should also be taken into consideration (14).

Other lesions, like congenital colloid cyst, may also cause HPrl due to obstruction of portal venous system termed as "pseudoprolactinomas" (5). Systemic diseases include a variety of conditions causing HPrl. Chronic renal failure can cause HPrl due to reduction of prolactin clearance. Polycystic ovarian syndrome (PCOS) induces HPrl as a result of stress, obesity and hypoglycaemia (6). Additionally, endocrine disorders like Cushing's disease and Addison's disease may also result in increased lactotropin secretion (10). Recently, Sharma LK et al. (15) detected in a cohort study that HPrl accompanies a third of children with subclinical hypothyroidism and >50% of children with overt hypothyroidism.

Miscellaneous conditions include genetic syndromes such as multiple endocrine neoplasia type 1 (MEN 1) and McCune-Albright syndrome (MAS), inflammatory diseases (lymphocytic hypophysitis, meningitis), injury of pituitary infundibulum and seizures (epilepsy, febrile seizures) (3, 6, 10).

Iatrogenic HPrl may be induced due to various medications such as dopaminergic receptor antagonists (e.g. metoclopramide), estrogens, antidepressants (e.g. tricyclic agents), antihypertensive drugs (e.g. verapamil), opiates, antipsychotics (e.g. risperidone, haloperidol), oral contraceptives, antiepileptics and gonadotropin-releasing hormone (GnRH) agonists (triptorelin) (10).

From all of these risk factors mentioned above, pharmacological treatments (antiepileptics, antipsychotics) and pituitary adenomas are considered to be the most frequent HPrl causes in childhood and adolescence (2, 16).

Clinical manifestations and complications

The clinical manifestations of prolactinoma vary mainly according to gender, age of onset, tumor size and PRL levels (4).

Regarding prolactinomas, clinical signs manifest with mass compression of the optic chiasm and anterior pituitary gland or prolactin hypersecretion. According to the literature, headache is the commonest com-

plaint followed by vision impairment in cases where the tumor is enlarged, although it remains unknown if hormonal hypersecretion represents the primary cause of the headache.

Interestingly, Thomas Breil et al. (12) in a retrospective study confirmed 3 macroadenomas (>1 cm) reached to the suprasellar area accompanied by hemianopia, optic atrophy and anterior pituitary hormone imbalances.

According to current knowledge, pituitary adenomas may lead to unilateral or bilateral visual symptoms when their sizes go beyond 1cm in diameter. In the early stages, diplopia or visual field defects are mostly observed. Bitemporal hemianopsia and superior temporal visual field impairment are detected in the majority of children. Rarely, sudden visual loss, papilledema and complete opthalmoplegia are diagnosed (17).

Surgery is required if visual disturbance is detected at the time of diagnosis of pediatric prolactinoma, in order to decompress the optic chiasm and further to preserve the visual function (12).

Elevated PRL causes alterations of the gonadotropic axis, inhibiting pulsatile Gn-RH secretion. Such alterations appear in adolescent females as delayed puberty (48%), primary amenorrhea (14-41%), secondary amenorrhea (29-45%) and oligomenorrhea (up to 29%) (4, 18).

In the past, Dong-Yun Lee et al. (19) retrospectively studied 1704 young women with menstruation related problems. They observed that secondary amenorrhea and abnormal uterine bleeding are mainly due to idiopathic causes of HPrl other than prolactinomas or medications.

In PCOS hyperinsulinaemia causes hyperandrogenaemia by inhibiting androgen catabolism. Subsequently, aromatase conversion of androgens leads to estrogen hyperproduction which stimulates prolactin secretion either directly in lactotropic cells or by inhibiting dopamine tone (6). Primary hypothyroidism in children stimulates TRH release, which shows an endogenous trophic effect in lactotropic cells leading to elevated prolactin levels in blood.

Overt hypothyroidism in adolescent and young girls has been associated with pituitary hyperplasia, enlargement and rarely with various pituitary hormonal imbalances (20-22).

Medications and other conditions cause HPrl by reducing dopaminergic inhibition signals or by lack of prolactin clearance (23).

Complications related to chronic untreated HPrl are apparent in female adults and mainly include three groups; functional (menstrual issues, ovulatory abnormalities, infertility), skeletal (stature defects, osteoporosis, osteopenia, osteomalacia) and psychometric irregularities (24, 25).

Colao et al. (26) described an impaired bone health with decreased bone mineral density in relation to sex and age in adolescent patients with hyperprolactinemia.

Diagnosis and screening

Clinical diagnosis and assessment of HPrl in adolescence is determined by the symptoms of the functional syndrome (primary or secondary amenorrhea, galactorrhea) and the presence of any pre-existing medical condition that could lead to HPrl.

It is widely accepted that HPrl in the absence of clinical symptoms is not diagnostic (27). An adequate physical examination (including gynecological examination) should be conducted, in order to assess patient's mammary glands (galactorrhea), skin (acne, hair growth indicative for PCOS) and any clinical sign which could be linked to a certain medical disorder (10).

For the diagnosis of HPrl, blood sample through venipuncture should be obtained without excessive venipuncture stress, in the morning hours (2 hours post-awakening) in order to avoid any false positive HPrl due to circadian acrophase shift (10).

Screening through evaluation of prolactin levels is suggested in children and adolescent girls with short stature and/or obesity because they are in a higher risk (28).

Due to the pulsatile secretion of prolactin, a single measurement of prolactin concentration > 20 ng/ml is not reliable for the diagnosis of HPrl in childhood (27).At least two abnormal prolactin values in samples obtained on different days with a pre-test 20-min free interval are suggested to confirm HPrl.

In cases where prolactin concentration is extremely high (>100 ng/ml) and or associated with clinical symptoms, a single measurement is adequate (27).

As far as the prolactinoma is concerned, prolactin levels >100 ng/ml demonstrates a high predictive and diagnostic value (29). A prolactin level higher than 500 ng/ml is diagnostic for macroprolactinoma.

In adolescent girls with prolactinoma, serum prolactin levels are 10 times greater in macroadenoma compared to microadenoma.

Moderate elevation of prolactin cannot exclude the possibility of tumorous etiology other than various organic or functional causes, and may be due to prolactinoma (1st measurement), incidentaloma or other masses that can compress the pituitary stalk (6). Particularly, it should also be noted that prolactin level <200 ng/ml with compatible history of medication indicates drug-induced (iatrogenic) HPrl (30).

In the presence of HPrl, several systemic conditions should be excluded.

Detection of renal failure by measuring blood urea nitrogen and creatinine levels is mandatory for all cases. Moreover, evaluation of thyroid function tests is recommended in all children and adolescents with HPrl, with a TSH ≥4.00 mIU/L having high sensitivity and specificity in identifying HPrl related to hypothyroidism (15). Furthermore, exclusion of PCOS and a pregnancy is essential for the adolescent girls (6).

During diagnosis of HPrl there are two major pitfalls that should be taken into consideration; the presence of macroprolactinemia, and the "hook effect".

Prolactin circulates in three distinct molecular isoforms; monomeric 23 kDa (biological active), dimeric 50 kDa, and macroprolactin 150 kDa (biological inactive) (3).

The current knowledge have indicated that macroprolactinaemia accounts for up to 26% of biochemical HPrl and, thus it is important to exclude macroprolactinaemia in young patients with HPrl, which is described as the formation of aggregates of monomeric prolactin and IgG with size of 150-170 kDa (6). As far as the macroprolactin molecule is concerned, it does not bypass the endothelial barrier, thus resulting in poor bioactivity and false positive increased levels of prolactin (6).

Macroprolactinemia represents a frequent benign cause of misdiagnosis and mismanagement in children and adolescents with HPrl, due to the high rate of analytical errors during biochemical analysis, resulting in false-high/low levels of serum prolactin, especially in asymptomatic patients (12).

The recommended laboratory method used in prolactin interpretation for macroprolactinemia screening is polyethylene glycol precipitation (PEG) , which provides a better estimation of monomeric bioactive form of prolactin since there is a possible form of a combined HPrl (monomeric + macro) (31-33).

In a young asymptomatic girl, with slightly elevated prolactin and negative MRI findings, prolactin isoforms should be suspected (4). "Hook effect" occurs when artificially low concentrations of prolactin detected by immune radiometric assay (IRMA) test, coincide with a macroprolactinoma. Large amount of serum prolactin saturates the antibodies used in IRMA test, resulting in this artifact, thus falsely suggesting the presence of a non-secreting macroadenoma (34). This phenomenon creates the need for multi-evaluation of prolactin levels with clinical symptoms and MRI before making a definite diagnosis (12).

In the previous decades, dynamic tests for prolactin secretion (metoclopramide, TRH) had been used to facilitate the differential diagnosis of prolactinomas since prolactin response in TRH stimulation is distinctively blunted in prolactinoma cases (35). However these tests demonstrate low specificity.

In a large retrospective study Famini P et al. observed 47 % of patients suffering from hyperprolactinemia or hypogonadism with a normal pituitary gland on MRI. Parallel, MRI detected prolactinoma in 40% and incidentaloma in 37 % of cases. Thus, when secondary causes of HPrl have been excluded, imaging studies such as computed tomography (CT) and/or MRI should be performed (36). However, enlargement of pituitary gland does not always suggest an adenoma, but it may be due to physiological conditions (puberty, lactation, pregnancy) as a result of lactotroph hyperplasia (37).

In cases of severe or persisting HPrl of any degree in addition to circadian rhythm disturbances, with a concurrent detection of a pituitary mass in MRI or CT scan, prolactinoma should be suspected (27). Definite diagnosis of prolactinoma can be made rarely through biopsy and preferably through adequate size reduction of tumor or total remission after proper medical management of HPrl (4). However, well noted, neuro-

ophthalmologic findings still maintains its importance in diagnosis and management of such conditions (17).

Other investigations include detection of pituitary auto-antibodies for lymphocytic hypophysitis (38), and determination of MEN 1 mutation gene (in prolactinomas) and/or chromogranin A for investigation of possible genetic diseases associated with HPrl (39-43).

Therapeutic approach

The main targets of management are the resolution of HPrl symptoms, the normalization of pubertal development, the sufficient restoration of gonadal function, the shrinkage of the pituitary tumor, maintenance of bone mass and the preservation of future fertility (4).

Symptomatic HPrl is indicative for medical treatment, whereas asymptomatic girls, due to idiopathic HPrl or pituitary adenomas (incidentalomas, microprolactinomas) should be monitored without initial treatment.

In children with hypothyroidism, pituitary function is often restored after proper thyroid hormone replacement therapy. Adequate medical therapy of PCOS returns prolactin levels to normal range in these patients (6).

Rarely, kidney transplantation is curative in cases of renal failure (44).

As far as drug-induced HPrl is concerned, withdrawal of the responsible medication is necessary, since elevation of prolactin is a dose-dependent phenomenon (45, 46).

Careful estimation of risk-benefit profile of the incriminated drug is essential especially in children and adolescents receiving antipsychotic therapy, where a withdrawal might result in exacerbation of psychotic symptoms. Thus additional medical treatment for the alleviation of HPrl should also be considered (28).

The gold standard primary therapy in accordance with formal guidelines, are dopamine agonists (DA) due to their efficacy in regularizing prolactin levels in any case with HPrl (including micro- and macroadenomas) (47-51). These include semisynthetic ergot alkaloid derivatives, mainly bromocriptine or cabergoline, and hardly pergolide or quinagolide (12).

Through the tuberoinfundibular pathway, they directly act via a strong stimulation of postsynaptic G-protein-coupled D2 dopamine receptors and/or partial stimulation of D1 dopamine receptors. The restriction of the signaling cascades of adenylatecyclase, phospholipase C and inositol phosphate results in repression of prolactin by inhibiting the transcription of prolactin gene in lactotropic cells (4, 28).

As in adults, bromocriptine is administered in children and adolescents in the dose range of 2.5-15 mg/day, standardized with split doses of 5 and 7.5 mg/day, twice a day (4). In addition to the aforementioned mechanism of action, bromocriptine prevents mitosis and growth of lactotropic cells, initiates cell death and promotes perivascular fibrosis, thus resulting in reduction of tumor mass (52).

Saranac L et al. (3) observed that bromocriptine treatment in 11 young individuals (including 6 female patients) with HPrl, either due to microprolactinoma or fuctional HPrl, achieved full restoration of gonadal function, normalization of prolactin levels and reduction in tumor mass within half year of therapy in all cases.

However, several case studies of children and adolescents with prolactinoma indicate that the mean efficacy of bromocriptine in normalizing prolactin levels and restoring gonadal function is lower than that reported in adult studies (52).

Well of note, it was previously observed that bromocriptine monotherapy in children with prolactinoma and short stature due to GH deficiency is able to improve growth and GH secretion without additional GH therapy (53). Furthermore, combined therapy with bromocriptine and GH replacement was efficient in children with macroprolactinoma and coexisting GH deficiency (49).

Although great in tolerance and efficacy, bromocriptine is well-known for its various adverse effects such as nausea, vomiting, orthostatic hypotension and mood disturbances, which represent the primary reasons for treatment discontinuity (54). Initially, a single dose of 1.25 mg/day and wise titration is beneficial in order to reduce such symptoms (4).

Parallel, cabergoline should be offered in children and adolescents with an initial dosage of 0.25-0.5 mg once weekly and gradually increase by 0.5 mg every 4

weeks, in order to reach a medium dose ranging from 0.5 mg up to 3.5 mg twice and once weekly respectively, preferably administered in the night for more tolerant results (55). A monthly re evaluation of prolactin levels is necessary for the adjustment of ideal carbegoline dose (12). The advantage of the low frequency of administration of cabergoline unlike other DAs is due to its long half-life, owing to its low pituitary clearance, prolonged enterohepatic cycling, and strong binding with D2 dopamine receptors (4, 18).

Apart from that, cabergoline has been reported by numerous studies to demonstrate a better efficacy and tolerance contrary to bromocriptine (56,57). A recent retrospective study by Breil et al. (12) reported that cabergoline therapy in children and adolescents with prolactinomas demonstrated a great efficacy and tolerance in normalizing prolactin levels, reducing symptoms and diminishing tumor size. It was also observed that microprolactinomas required lower dosage of cabergoline than macroprolactinomas.

Similar results have been reported by previous authors regarding carbegoline therapy in pediatric patients with prolactinomas (4, 18), where adequate restoration of growth in cases of concurrent prolactinomas and GH deficiency was achieved through monotherapy with cabergoline (12, 58).

Concerning the use of quinagolide and pergolide in children and adolescents with HPrl the available information is limited (52). Adverse effects of DAs can be divided into four main groups; gastrointestinal, cardiovascular, neurological, and psychiatric.

Gastrointestinal effects include nausea, vomiting, and abdominal pain and they are often responsible for treatment discontinuity in 3-5% of cases. Cardiovascular effects include orthostatic hypotension basically at the initial stage of therapy. Other rare effects are mild tricuspid regurgitation and aortic valve calcification, which have been reported in high-dose and long-term therapy in prolactinoma cases. Neurological effects include fatigue, drowsiness, headache, dizziness, and vertigo. Deterioration of psychotic episodes and mood alternations represent the prominent psychiatric effects (4).

Regarding treatment of prolactinomas in the pediatric population, dopamine agonists seem to be safe and effective in the reduction of the tumor size and normalization of the circulating prolactin. Surgery is offered in children who do not respond to medical treatment or in cases where visual preservation is crucial, because operative innervations are associated with a higher risk of morbidity due to iatrogenic hypopituitarism.

Transsphenoidal approach is the gold standard surgical method in pediatric patients, apart from children < 10 years old where sphenoid sinus is still hypoplastic. However, surgery is not fully curative and an additional post-operative maintenance with a low-dose of DA agonist is essential in all pediatric patients with macroprolactinomas (28). Rarely, radiation is suggested in malignant prolactinomas (12).

Moreover, all children presenting with pituitary apoplexy should be closed monitored and treated with corticosteroids. In cases where sudden loss of vision is confirmed, urgent craniotomy and decompression of the optic nerve and chiasm is performed (3).

In general, follow-up includes prolactin measurements and MRI control. Prolactin serum levels should be estimated every 2-4 weeks initially, and every 6-12 months after normalization. MRI scan is suggested after 1 year of therapy in microadenomas and after 3-4 months in macroadenomas in addition to proper visual field evaluation in the latter situation. According to current formal guidelines, discontinuation of DA therapy is indicated after ≥2 years of treatment, normal prolactin levels, and no MRI image of pituitary adenoma (14). A recurrence rate up to 64% has been observed within first year of DA treatment withdrawal (59-61). In cases of drug intolerance or resistance with a persistent HPrl and no tumor suppression, clinicians should shift to another medical agent (51, 62).

Conclusion

Targeted identification of HPrl is of significant importance for proper management and follow-up. Although the level of prolactin provides major clues in making a decision, the clinicians should take into consideration the pitfalls that incorrectly mask a physiologic state such as macroprolactinemia or the "hook effect."

Further studies should be conducted considering the efficacy, tolerance, dosage and follow-up of medi-

cal treatment especially with DAs in children and adolescents, in order to establish specific guidelines.-

Future issues

Although there is a broad literature regarding HPrl, there are no large epidemiologic studies on hyperprolactinemia among children and adolescent girls. The available publication is limited about the clinical manifestations, efficacy of medical therapy, and long-term outcome.

The newly advanced field of genetic medicine will have a major impact in studying prolactin receptor gene alterations in different anatomical brain areas and their relations with stress and aging (3). Moreover, a better understanding of several molecular and genetic variations will help unraveling the pathogenesis of prolactinomas, thus aiding the development of a causal management (12). The role of various isoforms of prolactin in children and adolescents is yet to be investigated, as well as the impact of asymptomatic HPrl (4).

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The experience of a tertiary unit on the clinical phenotype and management of hypogonadism in female adolescents and young adults with transfusion dependent thalassemia

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Summary. *Background:* Transfusion-dependent β-thalassemia (TDT) is associated with several complications necessitating a multidisciplinary approach for diagnosis, treatment and follow-up. Hypogonadism in female TDT patients is one of the most common endocrine complications, requiring hormone replacement therapy (HRT) throughout reproductive life. Little is known about the balance of benefits versus risks of treatment with sex steroids. *Aim:* The aim of this manuscript is to review the action and the associated adverse effects of HRT in hypogonadal TDT females. *Design:* Retrospective medical database records from a single centre, over a period of 38 years (January 1980 to June 2018), were reviewed. *Study population:* Forty-two cases of hypogonadism in TDT females followed in a pediatric and adolescent outpatient clinics, were in included in the study. *Methods:* Auxological, clinical, laboratory, hormonal and imaging investigations were reviewed, as well as all adverse events registered during HRT. *Main results:* In general, HRT was safe for most patients. There were few minor side effects and a couple of rare but serious adverse events. *Conclusions:* The study provides a representative clinical profile of long-term effects of HRT in hypogonadal adolescents and young adult TDT women. Our results highlight also the need for further research in other areas for which HRT may have a role. We hope this will contribute to a wider understanding, and potential improvement, of patient safety and quality of life. (www.actabiomedica.it)

Key words: transfusion-dependent β-thalassemia, hypogonadism, primary and secondary amenorrhea, hormone replacement therapy, stroke, thin endometrium, adverse events, ICET-A

Introduction

Hypogonadism is one of the most common endocrine complications in transfusion dependent β-thalassemia patients (TDT). It is mainly caused by iron overload of the pituitary gland; in females it is clinically characterized by the absence of pubertal development or by menstrual cycle disturbances. Careful history, physical examination and selected laboratory testing can often detect the site of the defect. Hypogonadotropic hypogonadism (HH) is biochemically characterized by low serum concentrations of lutein-

izing hormone (LH) and follicle-stimulating hormone (FSH), and of sex steroids (1, 2).

Hormone replacement therapy (HRT) in patients with hypogonadism aims to alleviate symptoms of estrogen deficiency and prevent long-term complications, such as osteoporosis. Hormones are also important in female sexual functioning; low serum estrogen causes vaginal atrophy and higher vaginal pH, which predispose to infections, incontinence, and sexual dysfunction (3). Multiple formulations of estrogens are available for treatment: oral, micronized, vaginal, transdermal patches, and gel. Progesterone therapy is needed to avoid an unopposed estrogen effect and maintain endometrial health (3).

The dosage and route of administration of HRT is extremely complex because of the prolonged period of treatment which can run for decades and the changes in physical and psychological status of the individual over this period. Furthermore, HRT treatment is extremely complex in TDT patients because of associated co-morbidities, such as iron overload, thrombophilic status, chronic liver disease, impaired glucose tolerance or diabetes, and cardiomyopathy (4).

Despite the large numbers of TDT patients for whom HRT is prescribed, few data exist to aid clinicians in making decisions on optimal treatment regimes. Furthermore, no reliable experiences or clinical studies about the potential risk factors and side effects of continuous hormonal therapy in adolescents and young adult TDT women with hypogonadism have been reported in the literature. Therefore the co-ordinator (VDS) of the International network of Clinicians for Endocrinopathies in Thalassemia and Adolescent Medicine (ICET-A) promoted a retrospective study on the effects of HRT in hypogonadal women with TDT.

In this report the findings of the study are presented and discussed. We hope that our findings will promote further understanding of hypogonadism and will facilitate the management of young female TDT patients with HH.

Patients and Methods

Forthy-two TDT patients were selected for the study: 26/42 (61.9%) patients regularly followed in Ferrara and 16/42 (38.1%) patients referred to the tertiary Ferrara clinic for endocrine investigations or second opinion. All patients were following the national (www.site-italia.org) and international guidelines of Thalassemia International Federation (TIF) (5).

In TDT patients regularly followed in Ferrara, transfusional management was changed over time. Before 1972, blood transfusions were given when anemia was severe enough to cause symptoms. Thereafter, patients were regularly transfused every 2-3 weeks to maintain the mean hemoglobin (Hb) level around 9.5 g/dl. Treatment with intramuscular desferrioxamine mesylate (DFO) at a dose of 20 mg/kg body weight (BW) was available for most patients since 1969. Regular subcutaneous (SC) DFO infusion was started in 1978 in patients older than 2 years. Initially, the recommended DFO dose was 20 mg/kg body weight administered daily at night, by infusion pump over 10 hours. Based on transfusional iron input the dose increased to 40 mg/kg BW in 1982 and up to 60 mg/kg BW in 1984. Ascorbic acid was added orally at a dose of 2-5 mg/kg (maximum dose 200 mg) in a selected group of patients. Since 1995, the oral chelator deferiprone (DFP) has been available; it was given at a dose of 75 mg/kg BW to some patients over the age of 11 years, as monotherapy or combined with DFO. In 2007, the new oral chelating agent deferasirox (DFX) was introduced at a dose of 25-30 mg/kg BW for patients in whom treatment with DFO was contraindicated or inadequate.

A basic examination and a re-examination at 3-6-12 month intervals were carried out. Patients' information were abstracted from medical database records, including: country of origin, demographic, clinical and pubertal characteristics, chelation therapy, diagnosis and treatment of hypogonadism, associated endocrine complications, bone metabolism and mineral density (BMD), pelvic ultrasonography, and associated adverse events (AE) registered during HRT.

Inclusion study criteria were: 1) diagnosis of TDT, based on universally accepted hematological criteria and 2) duration of follow-up not less than 4 years. Exclusion criteria were: 1) TDT patients with delayed puberty; 2) non-transfusion-dependent thalassemia patients (NTDT); 3) eating disorders; 4) renal insufficiency; 5) bone marrow transplanted patients; 6)

patients positive for HIV and 7) TDT patients with incomplete data.

Heights were routinely measured on a wall mounted stadiometer. Short stature was defined as height below the third percentile using the Italian growth charts of Cacciari et al. (6). Height velocity was calculated as the difference in height, divided by the difference in age between consecutive annual study visits. Body mass index (BMI) was assessed using the formula: kg/height in m^2 (7). A subject was considered overweight when the BMI was between 25 and 30 and obese above 30 (8).

Sexual maturation was determined by physical examination. Tanner stage 2 breast (B2) development was used to define pubertal onset. Delayed puberty (DP) was diagnosed clinically as the absence of the first signs of pubertal development beyond the normal range for the population. In Italy, this means the absence of breast development (B2) by age of 13 years. Pubertal arrest was defined as the lack of pubertal progression for >2 years after spontaneous breast bud onset. Primary amenorrhoea (PA) was defined as the absence of menarche at the age of 16 years, and secondary amenorrhea (SA) as the cessation of menses for at least 6 months in an already cycling woman. HH was diagnosed in the presence of low serum concentrations of gonadotropins, in the setting of normal serum prolactin and low concentrations of 17 β-estradiol (E_2 <20 pg/ml), in combination with signs and symptoms of estrogen deficiency.

The presence of associated endocrine complications was defined according to the I-CET guidelines, published in 2013 (8).

Serum FSH, LH, prolactin, 17 β- estradiol, FT4, TSH, insulin, cortisol and ferritin were measured by radioimmunoassay, immunoradiometric assay or chemiluminescent assay.

To evaluate liver function, serum concentrations of alanine aminotransferase (ALT), gamma glutamyl transferase (γ GT), total and direct bilirubin, total proteins, and albumin were measured at 1-3 months intervals.Urea, creatinine, electrolytes, lipids [cholesterol, HDL, low-density lipoprotein (LDL), triglycerides], and coagulation tests (platelets count, prothrombin activity, activated thromboplastin time, fibrinogen, antithrombin III, protein C and S) were also assessed at 3-6 month intervals using routine laboratory methods.

Uterine development was evaluated by transabdominal ultrasound (US); size (uterine length and uterine volume), shape (by calculation of the fundus-to-cervix ratio) and maximum endometrial thickness (the highest value of endometrial thickness in the plane through the central longitudinal axis of the uterine body) were recorded. To characterize uterine maturity the following parameters were used: mature uterus: a length of ≥6.5 cm; transitional uterus: length 5.0-6.4 cm, and immature uterus: length <5.0 cm (9). The ovarian volume was calculated using the approximate formula for an ellipsoid: length × breath × width × 0.523.

Bone mineral densitometry (BMD) was measured at lumbar spine, from L2 to L4, and at the femoral neck using a DXA-scan (dual energy x-ray absorptiometry) device (Hologic). The diagnosis of osteopenia/osteoporosis was based on the definitions of the National Bone Health Alliance Working Group (10).

Iron overload was classified at the time of first examination, as mild (serum ferritin <1,000 ng/ml), moderate (serum ferritin >1,000 ng/ml to <2,000 ng/ml) or severe (serum ferritin >2,000 ng/ml). In females the manufacturer's normal reference serum ferritin range values was 15-150 μg/l (11).

HRT adverse event was defined as an unfavourable medical event that in coincidence may present during treatment with a pharmaceutical product, which does not necessarily have a causal relationship with the product. Attribution was also made if a major side effect resulted in discontinuation of the drug, even without re-challenge.

All procedures were carried out with the adequate understanding and consent of parents or patients. As the survey was a retrospective collection of data, research ethics committee approval was not required.

Statistical analysis was carried by Student's "t test"; a p value less than 0.05 was considered as the limit of significance. Linear regression analysis was employed for evaluating correlations between parameters.

Results

Forty-two cases of hypogonadism in TM females of Italian ethnic origin were registered over a period

of 38 years (January 1980 to June 2018). Sixteen out of 42 patients (38%) were examined for absence or arrested puberty, and 26 out of 42 patients (61.9%) for secondary amenorrhea which started from 6 months to 17.5 years (mean: 6.2±5.2 years) after menarche. Three patients (7.1%) reported a single menstrual cycle followed by a prolonged period of amenorrhea (6-9 months). At the first evaluation their median age was 21 years (range: 15-32 years), and their mean serum ferritin level was 2,470 ng/ml (range: 760-6,260 ng/ml).

At the last observation 32 patients were on treatment with subcutaneous DFO (76.1%), 8 with DFP (19%), and 2 with DFX (4.7%).

The diagnosis of HH was made based on the available medical records (Basal E_2: 11.6±4.1 pg/mL - controls: 31.6±4.1 pg/mL, range: 28.0–40.0 pg/mL, p<0.01; basal FSH: 3.3±0.5 IU/L- controls: 10.2±3.8 IU/L, range: 7.3-13.2 IU/L, p<0.001; and basal LH: 3.6±1.0 IU/L- controls: 6.2±1.4 IU/L; range: 5.3-9.5 IU/L, p<0.001). After an acute Gn-RH stimulation test, a poor or lack of gonadotropins response was observed in all patients followed in Ferrara. Twenty-two healthy young adult women served as controls.

Four patients were on treatment with L-thyroxine, (3 for primary and 1 for central hypothyroidism), 4 had insulin dependent diabetes, 5 an impaired glucose tolerance, and 4 were on treatment with calcitriol for hypoparathyroidism. Hypocortisolism (basal cortisol: 3.5 μg/dl=98 nmol/L or less) was not reported in the records of patients. None of them was on treatment with recombinant growth hormone.

All TDT patients received 6 different HRT regimes (Table 1). The majority (29/42, 69.0%) were taking either oral conjugated estrogens (CE) or oral contraceptive pills (CO). Relatively few were using transdermal or vaginal ring (Table 1). The latter treatment was mainly recommended by gynecologists. The patients were followed, regularly or occasionally, by the same clinician for a period of 4-24 years (median: 15 years).

In patients with PA, estrogen replacement was initiated at a low dose (ethinyl estradiol, 5 μg/d) and gradually increased, every 4-6 months, to a maximum dose of 20-30 μg/d. Medroxyprogesterone acetate (MPA 5 mg/d) was added when breakthrough bleeding occurred or after 24-28 months, on days 12-21 of each month, to induce menstrual flow. At this stage, HRT with oral conjugated equine estrogen (0.625 mg/d) combined with MPA, CO, 17 β-estradiol or by transdermal patch combined with MPA or ethinyl estradiol/ norelgestromin transdermal patch were advised and discussed (pros and cons) with the patient. CO was the most accepted method (49.9%) of HRT by the patients.

The compliance to HRT treatment was, in general, fair. Ten out of 42 TDT patients (23.8%) stopped HRT, after 6 months to 2 years, because of experience of discomfort, appearance of adverse events, or financial constraints.

Imaging of the uterus by transabdominal high-resolution US documented that only 50% of TM patients with PA had a mature, heart-shaped uterine configuration and endometrial thickness after 2-3 years of treatment; 19/42 patients (45.2%) presented a smaller sized uterus (transitional) with normal endometrial thickness and 2/42 patients (4.7%) a transitional uterus associated with thin endometrial lining (2-3 mm) with failure of endometrium to respond to long-term treatment with cyclic transdermal estrogen (TE: 37.5 μg and 50 μg, respectively; three weeks on and one week off) and MPA (5 mg in the last 12 days of TE). The same US finding was found in a patient with SA with failure of endometrium to respond to oral HRT with ethinyl estradiol 30 μg + gestodene 0.075 mg. In two patients with PA and transitional uterus, associated with thin endometrial lining, the serum ferritin levels were 3,420 ng/ml and 2,210 ng/ml, respectively, and 910 ng/ml in the patients with SA and failure of endometrium to respond to oral HRT. In spite of intensive iron chelation therapy, amenorrhea persisted. In general, ovarian US showed ovaries with a reduced volume, containing few small follicles.

A reduction of BMD (osteopenia: Z score ≥-1.0 to -2.5 and osteoporosis: Z score ≤-2.5) at spine and/or femoral neck sites occurred in 81% of patients with PA and SA. The degree of low BMD was less evident in patients with a greater BMI and with recent development of SA [r (s)=0.239; p< and 0.172, respectively; p<0.01]. The BMD values increased during the first 2-3 years of treatment by an average of 7.7% at lumbar spine and of 8.9% at left femoral neck. Two patients

Table 1. Adverse events (AE) registered during hormone replacement therapy (HRT) in hypogonadal female TDT patients

HRT treatments	Number of patients treated- (percentage)
Cyclic oral conjugated estrogen (**CE**: 0.3-0.625 mg daily, administered cyclically - e.g. three weeks on and one week off) combined with **medroxyprogesterone acetate** (**MPA** 5 mg in the last 12 days of CE)	8/42 (19%)
Ethinyl estradiol (30 **µ**g) **+ gestodene** (0,075 mg) **(EE+GSD)**	13/42 (30.9%)
Ethinyl estradiol (20 **µ**g) **+ desogestrel** (0,15 mg) **(EE+DSG)**	8/42 (19%)
Transdermal estrogen (**TE**) patch (25-50 **µ**g, administered cyclically - e.g. three weeks on and one week off) combined with **medroxyprogesterone acetate** (5 mg in the last 12 days of TE)	9/42 (21.4%)
Vaginal ring (ethinyl estradiol/ etonogestrel)	4/42 (9.5%)
AE and HRT	
Skin irritation at the application site or discomfort on patch removal (TE)	4/9 (44.4%)
Partial patch detachment under conditions of heat, humidity, and exercise or partial peeling of the patch corner (TE)	3/9 (33.3%)
Mild breast tenderness (EE+GSD)	4/42 (9.5%)
Shorter duration of bleeding in patients with secondary amenorrhea (CE+ MPA and EE+DSG)	5/42 (11.9%)
Failure of endometrium to respond to estrogen (see results)	3/42 (7.1%)
Deterioration of glucose tolerance from normal to impaired (3 patients) from impaired to diabetes (1 patient) (EE+DSG and EE+DSG)	4/42 (9.5%)
Melasma of face (EE+DSG and EE+DSG)	3/42 (7.1%)
Acne (EE+DSG and EE+DSG)	3/42 (7.1%)
Fluid retention (EE+GSD)	2/42 (4.6%)
Mild elevation of liver enzymes (EE+DSG and EE+DSG)	3/42 (7.1%)
Mild elevation of total bilirubin (EE+DSG and EE+DSG)	3/42 (7.1%)
Mild elevation of lipids (EE+DSG and EE+DSG)	3/42 (7.1%)
Headache (EE+GSD)	2/42 (4.6%)
Unusual weight gain (>3 kg) (EE+GSD)	1/42 (2.3%)
Stroke (HRT: see results)	1/42 (2.3%)
Retinal artery spasm (HRT: see results)	1/42 (2.3%)

with SA, during the HRT, presented fractures of ribs, secondary to a mild trauma.

Two severe adverse events (AE) were observed during the long-term HRT treatment: a stroke with right hemiparesis in a 31-year-old splenectomized TDT patient who had been taking sequential ethinyl estradiol (20 µg/d) combined with MPA for the last 3 years, and an episode of transient monocular visual loss in a 29-year-old splenectomised patient treated for the last 4 years, with a CO (ethinyl estradiol: 30 µg/d combined with a third-generation progestin). In both patients a family history of thromboembolism was negative. An immediate discontinuation of HRT was recommended in both patients.

In the first patient with stroke a systematic clinical and laboratory evaluation revealed normal blood

pressure and BMI, negative history of migraine, severe iron overload (serum ferritin 3,215 ng/ml), diabetic curve after oral glucose tolerance test, and a hypercoagulable state condition (deficit protein C and S, and platelets count of 570×10^9). In the second patient, the vascular accident was due to central retinal artery spasm. It was not associated with migraine, smoking, obesity, hypertension, abnormal lipids or impaired glucose metabolism. Her serum ferritin level was 1,755 g/ml. Thrombocytosis post-splenectomy (platelets count: 480 $x10^9$), and a reduction of plasminogen <60% were documented. Both patients were on treatment with low dosage of acetylsalicylic acid (ASA:100 mg/d), as a thromboprophylaxis, but the compliance to treatment was inconsistent.

Seven out of 9 patients (77.7%) complained of skin irritation at the patch application site, or patch detachment under conditions of heat, humidity, and exercise.

Short stature (<2 SD below the mean height for age and sex) was reported in 10/16 patients (62.5%) with PA and in 6/26 patients (23.6%) with SA. A BMI between 25 and 30 kg/m^2 was reported in 3 patients (32.1, 25.7 and 27.4 kg/m^2, respectively). Reduced pubertal height gain (peak height velocity 5.8±2.0 cm, and pubertal growth gain to final height 13.7±3.0 cm) was observed in TDT patients with PA, while in European and British female population the average peak height velocity is 8.0±1.4 cm (12) and the contribution of pubertal growth to final height is ~25 cm, accounting for 17% of the final height.

A deterioration of glucose tolerance was observed in 4 patients (2 with moderate and 2 with severe iron overload); in 3 patients from normal tolerance to impaired glucose tolerance (IGT) and 1 (with HCV related liver disease) from IGT to diabetes. The impact of HRT on blood pressure was negligible. The other AE registered in the database are reported in table 1.

Discussion

Thalassemic disorders have a spectrum of severity with different clinical phenotypes, complications, and strategies for treatment. The grade of this severity depends on the β-globin gene mutation and coinheritance of other genetic determinants. The degree of transfusion dependence is one of the elements considered in a recent classification of thalassemic disorders into TDT and NTDT. In TDT patients, iron accumulation in organ tissues is highly evident and leads to organ toxicity and dysfunction (1, 2).

Patients with TDT have a variety of medical needs throughout their lives. Absent pubertal development and secondary amenorrhea due to HH are the most common complications in TDT patients. For the management of these patients no evidence-based guidelines exist, and recommendations are based on the theoretical knowledge of physiology and endocrinology, and extrapolated from the evidences of HRT in patients with estrogen deficiency, such as premature ovarian insufficiency.

The goals of therapy for hypogonadal adolescents or young adult females are the induction and maintenance of normal puberty, induction of fertility when the patient desires, psychosocial support, annual screening to assess metabolic and endocrine functions, and routine preventive health care. Young women with HH are also at risk for bone loss and fractures.

Multiple formulations of estrogen are available and include oral estradiol, oral conjugated estrogens, transdermal estrogen patches, and gel. Transdermal estradiol may provide a more physiological mechanism for estrogen replacement than oral administration because of delivering estrogen into the systemic circulation and avoiding exposure of the liver to supraphysiological estrogen concentrations (13, 14).

At present, patients who have not yet started pubertal development, induction of puberty is initiated and carried out in a manner that simulates the normal growth and development of secondary sex characteristics as closely as possible. The inability to make an accurate differential diagnosis between delayed puberty and HH at initial presentation presents difficulties in providing appropriate counselling for prognosis; this may generate anxiety among adolescents and families, and can affect treatment decisions. Our policy is to treat these patients with a short low dose course of estrogens (3-4 months after the age of 13-14 years), and to monitor the following at regular intervals (3-4 months): sexual maturation (by Tanner staging on physical examination), gonadotropins and sex hor-

mone levels, and bone age. In patients presenting with lack of spontaneous pubertal progression, estrogen therapy is restarted at low dose increased gradually (at intervals of 3-6 months).

Transdermal E2 application avoids liver exposure to increased estrogen concentrations and provides a more physiologic mechanism for hormone delivery. Doses are adjusted to the response (Tanner stage, bone age or uterine growth), with the aim of completing feminization gradually over a period of 2-3 years, after which time cyclic progesterone is added (or after the first menstrual bleed) to maximize breast development.

In post-menarcheal TDT women who ceased menstruating due to acquired HH secondary to iron overload, estradiol is given orally (at a dose of 1-2 mg) or transdermally (50 μg daily by patch) as a maintenance dose with a cyclic progestin regimen (5 mg of MPA for 12-14 days of the month) to avoid endometrial hyperplasia. Oral contraceptives provide a variety of estrogen and progesterone forms and dosing options. Although there is no clinical trial to support an optimal length of time, HRT should continue at least until the average age of natural menopause (5).

If a risk of unwanted pregnancy cannot be ruled out, there is a need to consider contraception. Although no case of pregnancy was reported in our retrospective study, two patients (not included in the present study) complained of "irregular menstrual bleeding" during HRT; in both patients pregnancy test was positive. The first TDT patient had a spontaneous abortion after 3 weeks. The second patient, with successful bone-marrow transplantation, had a normal pregnancy and delivered a healthy boy (De Sanctis V, personal observations).

Due to the long-term of treatment and the many physical and psychological changes that occur during this period, the treatment options should be carefully discussed with patient, considering the pros and cons of therapy, the patients' age, the duration of hypogonadism, the medical history, and personal preferences (5).

CO, containing ethinyl estradiol, or transdermal HRT are usually recommended by doctors and preferred by the patients. We assessed the attitudes and practices of doctors taking care of 2,326 females and males with TDT. Twelve different formulations and three routes of administration for HRT were used. In 33.3% of cases CO pill: ethinyl estradiol 30 μg/drospirenone 3 mg as first-line treatment choice followed by ethinyl estradiol 20 μg/drospirenone 3 (25%). Ethinyl estradiol 35 μg/cyproterone acetate 2 mg and ethinyl estradiol 20 μg/drospirenone 3 mg were reported, as second-line treatment choice, in 41.6% and 29.1%, respectively. Transdermal estrogen patch, ethinyl estradiol/ norelgestromin transdermal patch, and etonogestrel/ethinyl estradiol vaginal ring were used and recommended by 16.6%, 4.1%, and 4.1%, respectively (15).

Similar results emerged from an international survey conducted online, in July 2016. Oral HRT with different progestin contents were the first treatment choice in 11 centers (68.7%) (5).

Oral HRT has an increased risk for venous thromboembolic events (pulmonary embolism or deep vein thrombosis), and arterial thrombotic events (acute myocardial infarction, ischemic stroke), cardio metabolic changes (increase in blood pressure, unfavourable lipid profiles), and adverse liver dysfunction (16-18). In our patients, two severe AE have been observed during long-term HRT.

In a retrospective multicentre study, Taher et al. (19) reported that thromboembolic events (TE) occurred in a clinically relevant proportion (1.65%) of 8,860 thalassemia patients (75.3% with TDT). A survey, done in 9 Italian thalassemia Centres, disclosed that 32 patients out of a total of 735 (683 with TDT and 52 with NTDT), had venous thromboembolic events (VTEs) corresponding to an incidence of 3.95% and 9.61%, respectively. Localization of TE varied; the main one (16/32) involved central nervous system (20).

Several factors have been implicated in the pathogenesis of the hypercoagulable state in patients with thalassemia, such as the specific changes in the lipid membrane composition of the abnormal red blood cells with increased expression of negatively charged phosphatidylserine at the outer surface, post splenectomy thrombocytosis, cardiac dysfunction, and liver dysfunction leading to protein C and protein S reduction. Furthermore, it has been suggested that absence of the spleen in a variety of hemolytic diseases may contribute to an increased propensity to thromboembolic complications, related to extreme thrombocytosis (21).

This potential risk was confirmed by Haghpanah and Karimi (22), The authors conducted an electronic search on PUBMED (MEDLINE), SCOPUS, and Google Scholar databases up to January 2011. Out of 152 thalassemic patients with cerebral thromboembolic events; 48% were splenectomised, Nine TDT patients had diabetes and activated protein C resistance, decreased protein C or protein S or plasminogen level were detected in 8 patients. In brief, cerebral involvement was associated with age (older patients), inadequate transfusion, splenectomy, thrombocytosis, and decreased protein C level (22).

Before prescribing any kind of HRT, physicians should be aware of the potential associated side effects of therapy and how best way to address them. Attention should be made before administration of HRT in TDT patients with splenectomy, impaired glucose tolerance/diabetes, hypercoagulable state (5), migraine with aura (23), and family history of thrombophilic defect. In TDT patients with a known hypercoagulable state (such as deficiency of antithrombin, protein C or protein S), that has been identified through screening, the pros and cons of HRT treatment should be discussed with a specialist. Patients should be informed that there is an increase in the risk of blood clots with HRT use and that there are symptoms that would prompt immediate medical attention, such as warning signs of VTEs (leg swelling or pain), visual disturbances, sensory or motor impairment, chest pain, and new headache.

In such patients, the application of transdermal estrogen can be considered after careful individual evaluation (24). Splenectomised TDT patients with hypogonadism on HRT should receive anti-platelet therapy with aspirin. Young women should be counselled as to alcohol and tobacco avoidance, daily exercise for obesity prevention, and an appropriate diet to achieve optimal cardiovascular health (5).

Patients with a personal history of deep vein thrombosis, or pulmonary embolism are assigned to risk category 4, according to the World Health Organization Medical Eligibility Criteria (WHO MEC), "a condition which represents an unacceptable health risk if the contraceptive method is used" (25).

If HRT is contraindicated or declined, weight-bearing exercises, increased calcium and vitamin D intake, and avoidance of tobacco and alcohol should be recommended. It must be emphasized that these latter strategies have been shown to be inadequate at maintaining bone density in the reproductive-aged population (26). Clinicians should maintain serum 25-hydroxy-vitamin D levels in the normal range (30-80 ng/mL). Women with HH should take 1,000 to 2,000 IU of vitamin D3 (cholecalciferol) daily, along with 1200 mg of elemental calcium, either through dietary sources or supplements to optimize bone health. Bone density should be monitored every 12-24 months and follow-up visits should be scheduled at 6-12-month intervals with periodic laboratory testing.

Failure of the endometrium to respond to oral or transdermal HRT was reported in 3 patients. A thin endometrium is mostly defined as an endometrial thickness of <7 mm and can result from various factors. The most common are inflammatory (acute or chronic infection can lead to the destruction of the basal layer of the endometrium) and iatrogenic (surgical, due to repeated or vigorous curettage damaging the basal layer of endometrium or indiscriminate use of drugs such as clomiphene citrate) (27). Thin endometrium may not necessarily be secondary to a disease process, because it can result from individual uterine architecture (28), intrinsic properties of endometrium that affect its growth (29), and inadequate estrogen stimulation for endometrial proliferation (30). In the general population, numerous treatments have been tried to improve refractory endometrium, but success has been limited (27).

An additional factor could be the increased iron content (hemosiderosis) of endometrium as documented by Birkenfeld et al. in 3 patients with TDT (31). Iron deposition was mainly evident in the apical part of endometrial glandular epithelium cells above the nuclei, and should be taken into consideration as a contributing factor to the infertility in these patients by altering endometrial receptivity for implantation (26). Iron chelating treatment with desferrioxamine induced a fully or significant regression of the endometrial hemosiderin (31).

A deterioration of glucose tolerance was observed in 4 patients, from normal tolerance to impaired in 3 and from impaired to diabetes in 1 (with chronic HCV liver disease). Available data in a healthy population do not support a significant influence of OC on glucose and insulin homeostasis (32). It is highly likely

that the risk of diabetes development depends on individual patient characteristics, such as family history of diabetes, age, ethnicity, BMI, severity of iron overload and presence of a chronic liver disease. Therefore, in patients with TDT a cardio- metabolic risk assessment needs to be performed, including a 75-g standard 2-hour OGTT and lipid profile at baseline and during follow-up at regular intervals. An annual visit is required to control for further compliance, side effects, and evaluation of glucose tolerance and lipids. Future studies evaluating the long-term effects and safety of oral HRT in the treatment of TDT patients with hypogonadism are needed.

Despite an adequate HRT and general measures including control of anemia, adequate chelation therapy, healthy nutrition and lifestyle, two insufficiency fractures of ribs were registered in our patients with SA. Therefore, since the origin of bone disease in TDT is multifactorial and some of the underlying pathogenic mechanisms are still unclear, further research in this field is needed, to design the optimal therapeutic measures (33).

Melasma of face was reported in 3 patients. It is a common dermatosis that involves changes in normal skin pigmentation, resulting from the hyperactivity of epidermal melanocytes, predominantly affecting women of childbearing age. The pathogenesis is not yet fully understood, but there is relation with a genetic component, sun exposure, OC, HRT, cosmetics, photosensitising medication, pregnancy, and psychological stress (34, 35).

In summary, TDT is a chronic disease associated with a number of complications and conditions which need the attention of specialised multidisciplinary teams for diagnosis, treatment and follow-up. TDT patients with complications need optimum surveillance strategies. Despite the wide agreement that hormonal substitution remains the most effective option for treating the signs and symptoms of hypogonadism, a careful evaluation of the benefit-risk balance is essential prior to prescribing a HRT regimen. Our results highlight also the need for further research in other areas for which HRT may have a role. These areas include: growth, skeletal development and mineralization, glucose tolerance, safety, social interactions, and sexuality. Therefore, research consortia should be established to allow investigation of these important questions, and to allow clinicians to make judicious analysis for the best possible health care decisions.

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Pros and Cons in General Medicine and Geriatrics - 2018

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A perspective on some research in the field of general medicine and geriatrics from the past year could give argument of discussion and should be used in common practice.

Many clinicians and family doctors were greatly pleased with a study discouraging use of digital rectal exams for routine prostate cancer screening, while others were greatly displeased by bacteria becoming tolerant to hospitals' alcohol handwashes.

The growth of the aging population leads to the increase of chronic diseases, of the burden of multimorbidity, and of the complexity polypharmacy. The prevalence of medication errors rises in patients with polypharmacy in primary care, and into residencies and hospitals too, and this is a major concern to healthcare systems.

The inappropriate use of medicines was pointed out in order to articulate recommendations on how to reduce it in chronic patients, particularly in the oldest, polymedicated and multipathological that take five or more medications a day.

Many papers demontrated the importance of nutrition in general, and of physical activity, and their effects in aging process, and a lot of researchers discussed on the efficacy of calcium, vitamin D supplements,statins, and aspirin, focusing on prevention strategies, side effects and efficacy.

A prevention study demonstrated the value of 24-hour ambulatory **blood pressure monitoring** (ABPM). The clinical community has tended to use ABPM sparingly, but it predicted mortality more accurately than clinic measurement. Masked hypertension predicted mortality as strongly as sustained hypertension. In another meta-analysis, automated office blood pressure readings were more accurate than typical office readings among patients with hypertension *(JAMA Internal Medicine*). Researchers examined 31 studies of 9300 people that compared fully automated office BP readings, in which a clinician was not present and the patient was resting quietly, to other methods of BP measurement. Among patients with automated systolic BP of 130 mm Hg or higher, systolic BP readings taken at routine office visits were significantly higher than automated readings (mean difference, 14.5 mm Hg). Meanwhile, automated BP readings and awake ambulatory BP readings were statistically similar. The usefulness of light technology should strongly influence incoming epidemiological studies in hypertension.

Liquid biopsy (LB) is a blood test that can spot early-stage cancers by identifying circulating tumor cells (CTC) or cell-free DNA from tumors that has been shed into the blood. This technology could accurately detect the methylation pattern of very small amounts of circulating tumor DNA. Seven different malignancies (lung, breast etc) were tested, and each had a characteristic methylation pattern. The accuracy of the test was very high (very few false negatives or false positives), even in patients with early-stage cancers. The performance of this inexpensive blood test to detect early-stage cancers is encouraging, also if whether the test has value in patients with cancer who are presymptomatic remains to be determined. LB could help diagnose and monitor cancer, and tracking circulating tumor cells in metastatic patients could prove effective in this application and treatment planning. Identifying and characterising CTC in cancer

patients shoul provide a unique insight into metastatic disease, which is responsible for over 90% of cancer deaths.CTC detection could also help unravel new therapeutic targets for cancer treatment. *(Shen SY et al. Sensitive tumour detection and classification using plasma cell-free DNA methylomes. Nature 2018 Nov 22; 563:579).*

Personalised Physical Exercise for in-hospital prevention. An individualised, multicomponent exercise program proved safe and effective to reverse the functional decline associated with acute hospitalisation in oldest patients *(JAMA Internal Medicine).* The inhospital intervention included individualised moderate-intensity resistance, balance, and walking exercises (2 daily sessions).The primary endpoint was change in functional capacity from baseline to hospital discharge, assessed with the Barthel Index of independence and the Short Physical Performance Battery (SPPB). Secondary endpoints were changes in cognitive and mood status, quality of life, handgrip strength, incident delirium, length of stay, falls, transfer after discharge, readmission rate, and mortality at 3 months after discharge.The exercise intervention program provided significant benefits over usual care, and also improved the SPPB score and benefits were also found at the cognitive level. Intervention involving innovative, personalised multicomponent physical exercise that includes moderate intensity endurance training over a very short period of time has a significant benefit on routine care, and may help to reverse the functional and cognitive deterioration associated with the hospitalisation of old patients,fighting the risk of bedrest and immobility.

Exercise training is associated with lower risk for falls and possibly for fall-related injuries. In a meta-analysis of 40 randomized, controlled trials (mean duration, 17 months) that involved almost 22.000 community-dwelling or institutionalized old persons (mean age 73 yrs), researchers explored the value of exercise in lowering risk for falls, fractures, hospitalizations, and death. Researchers found no beneficial effects on hospitalization or death among participants in exercise programs compared with those in control groups. In trials for which fracture rate was reported as an outcome, fewer fractures occurred among those who exercised, but the difference was not statistically significant. In trials for which fall and injurious fall rates were reported, 12% fewer falls and 26% fewer injurious falls occurred in exercise programs *(de Souto Barreto P et al. Association of long-term exercise training with risk of falls, fractures, hospitalizations, and mortality in older adults: A systematic review and meta-analysis. JAMA Intern Med 2018 Dec 28; [e-pub]).* Another important study demontrated that life expectancy increases as **aerobic fitness** improves with no upper limit of benefit at any age *(Mandsager K et al, association of cardiorepiratory fitness with long-term mortality among adiults undergoing exercise treadmill testing JAMA 2018).* Cleveland Clinic reasearchers are reassuring that, with regards to mortality, one can exercise safety at an elite level throughout life. But those who aren't interested in acheiving elite levels still will derive mortality benefits when they improve their cardiorespiratory fitness.

Moving More in Old Age May Be Linked to Sharper Memory: older adults who move more, either with daily exercise or simple routine physical activity like housework, may preserve more of their memory and thinking skills, even if they have brain lesions or biomarkers linked to dementia. Exercise is an inexpensive way to improve health, and perhaps it may have a protective effect on the brain. But it is important to note that this study does not show cause and effect. It may also be possible that as people lose memory and thinking skills, they reduce their physical activity. More studies are needed to determine if moving more is truly beneficial to the brain. *(American Academy of Neurology 2018).*

Frailty and sarcopenia have emerged as serious public health concerns worldwide and major reasons for the loss of functional independence among older people. An easier way to screen for sarcopenia risk using simple questionnaires, a systematic way to make the diagnosis, and suggestions for practical tools and tests at each step are needed. The consensus also underscores the importance of poor physical function as a "red flag" for severe sarcopenia. There are multiple types of sarcopenia, driven by different underlying risk factors or diseases, An important step is classify-

ing the syndrome into primary and secondary forms to make the pathophysiological diagnosis and care. Eating more protein could contribute to fighting sarcopenia and frailty, helping people maintain independence as they grow older *(Journal of the American Geriatrics Society)*. Protein is known to slow the loss of muscle mass and having enough muscle mass can help preserve the ability to perform daily activities and prevent disability. Older adults tend to have a lower protein intake than younger adults due to poorer health, reduced physical activity, and changes in the mouth and teeth. Older who ate more protein were less likely to become disabled when compared with those who ate less protein.

Vitamin D deficiency is common in older people, and it may lead to bone loss, impairment of muscle function, and frailty. The results from studies assessing the effect of vitamin D on bone mineral density have yielded conflicting results. Vitamin D supplementation doesn't seem to prevent fractures or falls, according to a large meta-analysis. Researchers analyzed 81 randomized trials that compared vitamin D supplementation (with or without calcium) to placebo, control, or lower-dose vitamin D among 54.000 adults. Vitamin D supplementation had no significant effect on fractures, hip fractures specifically, or falls. Supplementation's effects on bone mineral density were inconsistent and not clinically meaningful. The authors conclude: "There is little justification for the use of vitamin D supplements to maintain or improve musculoskeletal health, and clinical guidelines should reflect these findings. The clear exception to this is for the prevention or treatment of the rare conditions of rickets and osteomalacia" *(Lancet Diabetes & Endocrinology)*. Further analysis is underway on the effects of sun exposure on vitamin D levels in older people and the impact of vitamin D supplements on muscle strength. Experts are also looking at the impact of genes and kidney function on vitamin D levels and their function in the blood, but enthusiasm for recommending vitamin D supplementation to prevent a wide range of skeletal and extraskeletal disorders was diminished considerably.

Does Cardiovascular Health Influence Risk for Dementia? In a study in older adults (mean age, 74 yrs) without CV disease or dementia subjects were assessed at baseline for optimal measures of CV health, smoking status, physical activity, diet, body-mass index, cholesterol level, blood pressure, and fasting glucose level. After mean follow-up of 8.5 years, dementia incidence, as assessed by structured instruments and physician assessments, was associated inversely with number of optimal CV risk factors at baseline. For example, the incidence of dementia in people with less than 2 factors at optimal levels was 1.56/100 person-years, compared with 0.83 for people who had 5 to 7 optimal factors. Controlling for demographic, clinical, and socioeconomic variables yielded similar results. Also, studies in young adults support promoting CV health to lower dementia risk in older adults. (*Samieri C et al. Association of cardiovascular health level in older age with cognitive decline and incident dementia. JAMA 2018 Aug 21; 320:657; Williamson W et al. Association of cardiovascular risk factors with MRI indices of cerebrovascular structure and function and white matter hyperintensities in young adults. JAMA 2018 Aug 21; 320:665; Saver JL and Cushman M. Striving for ideal cardiovascular and brain health: It is never too early or too late. JAMA 2018 Aug 21; 320:645*).

Mild Hypertension treatment, in low-risk patients, might not reduce mortality and could induce side effects. The American College of Cardiology and American Heart Association currently recommend that all patients with systolic blood pressure at or above 140 mm Hg or diastolic BP at or above 90 mm Hg receive antihypertensive therapy.Using U.K. electronic medical records, researchers matched 19.000 adults with mild hypertension (140/90-159/99 mmHg) and low cardiovascular risk who received antihypertensive medication to another 19.000 who weren't treated. During a median 6 years' follow-up, rates of mortality and cardiovascular disease were similar between the groups. Antihypertensive treatment was, however, associated with higher risk for hypotension, syncope, electrolyte abnormalities, and acute kidney injury *(JAMA Internal Medicine*).

Aspirin for Primary Prevention of CV Disease? The role of aspirin in the primary prevention setting is continuously evolving. Recent randomized trials have challenged the role of aspirin in the primary preven-

tion setting. Electronic databases were searched for randomized trials that compared aspirin vs. placebo (or control) in subjects without established atherosclerotic disease. The primary efficacy outcome was all-cause mortality, while the primary safety outcome was major bleeding. At a mean follow-up of 6.6 years, aspirin was not associated with a lower incidence of all-cause mortality [risk ratio (RR) 0.98, 95% confidence interval (CI) 0.93-1.02; $P = 0.30$]; however, aspirin was associated with an increased incidence of major bleeding (RR 1.47, 95% CI 1.31-1.65; $P < 0.0001$) and intracranial haemorrhage (RR 1.33, 95% CI 1.13-1.58; $P = 0.001$). A similar effect on all-cause mortality and major bleeding was demonstrated in diabetic and high cardiovascular risk patients (10-year risk more than 7.5%). Aspirin was associated with a lower incidence of myocardial infarction (RR 0.82, 95% CI 0.71-0.94; $P = 0.006$); however, this outcome was characterized by considerable heterogeneity, and sequential analysis confirmed the lack of benefit of aspirin for all-cause mortality up to a relative risk reduction of 5%. In conclusion, among adults without established cardiovascular disease, aspirin was not associated with a reduction in the incidence of all-cause mortality; however, it was associated with an increased incidence of major bleeding. The routine use of aspirin for primary prevention needs to be reconsidered .*(European Heart Journal).*

Fluoroquinolone antibiotics are associated with increased risk for aortic dissection and aneurysm. The caution applies to all systemic fluoroquinolones. The FDA said that while there are limitations to the data, the evidence appears to be consistent across multiple epidemiological studies showing an approximately two-fold increased risk over the baseline risk of aortic aneurysm or dissection in each study. The FDA offers the following advice for clinicians: a) do not prescribe fluoroquinolones to patients with, or at risk for, an aortic aneurysm, unless there are no other options. Such patients include older adults and those with peripheral atherosclerotic vascular disease, hypertension, Marfan syndrome, and Ehlers-Danlos syndrome; b) tell all patients to seek immediate medical attention if they develop symptoms of aortic aneurysm, c) stop fluoroquinolones right away if patients have symptoms of aortic aneurysm or dissection.

Statins for primary prevention in olders? With few studies and objective data for prescribing statins in the very old, this remains today an important question. Guidance on appropriate use of statins for primary prevention of cardiovascular disease has become increasingly confusing. Some study suggests that we are overtreating. Guidelines on cardiovascular disease (CVD) prevention classify most olders as eligible for statin therapy, because CVD risk is highly associated with age. However, little evidence supports statins for primary prevention in these patients. In a recent retrospective study, statins did not lower risks for atherosclerotic CVD and all-cause death among participants without diabetes. The guideline-recommended risk thresholds for initiating statins for primary prevention of cardiovascular disease may be too low, and have to be balanced with potential harms, like myopathy, hepatic or renal dysfunction, cataracts, hemorrhagic stroke, type 2 diabetes, and cancer. Most current guidelines recommend statin initiation when a person's 10-year CVD risk is 7.5%-10%, but in recent studies the benefits only began to outweigh the risks when CVD risk was 21% for men of 70 to 75 years; for women, thresholds ranged from 17% to 22%. The lipid management of old patients is not an easy challenge. On the one hand, simply because of age the risk is high, and statins would be effective in reducing this risk, but we have to consider the potential harms related to drug-drug interactions, secondary disease/pathology, competing for risk of deaths, life expectancy and preference of patients as well. Weighing the pro's and con's, including the co-morbidities and co-medications is pivotal with a strong emphasis on well informed shared decision making, particularly in frail aged people *(Ramos R et al. BMJ 2018 Sep 5 ; Yandrapalli S, Gupta S, Andries G* et al. *Drug Therapy of Dyslipidemia in the Elderly. Drugs Aging 2019).*

Omega-3 Polyunsaturated Fatty Acid: are they associated with Healthy Aging? Although consuming long-chain ω-3 polyunsaturated fatty acids (PUFAs) has favorable physiological effects (on endothelial function), the relation between plasma PUFAs and healthy aging has not been established. In a prospective cohort study, researchers determined the longitudinal association between serial measures of summed

and individual plasma PUFAs and α-linolenic acid and healthy aging into 2622 persons (mean age 74 yrs) with healthy aging at baseline, defined as absence of cardiovascular disease, cancer, lung disease, severe chronic kidney disease, and cognitive and physical dysfunction. During the study, 89% of participants experienced unhealthy aging. In an analysis that was adjusted for multiple variables, risk for unhealthy aging was 18% lower in participants in the highest PUFA quintile compared with those in the lowest PUFA quintile. A significant dose-response trend was observed. Assessed individually, higher intake of eicosapentaenoic and docosapentaenoic acid was associated with lower risk for unhealthy aging. Higher plasma levels of PUFAs, especially seafood-derived eicosapentaenoic acid and endogenous and seafood-derived docosapentaenoic acid, were associated with higher likelihood of healthy aging. However, given the study design, causality could not be established, residual confounding was possible, and the results might not be generalizable to younger people. Nonetheless, the results support for increased consumption of fish *(Lai HTM et al. Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the Cardiovascular Health Study: Prospective cohort study. BMJ 2018 Oct 17;363:k4067; Zhu Y et al. Omega 3 polyunsaturated fatty acids and healthy ageing: Fresh evidence provides clues to healthier, not just longer lives. BMJ 2018 Oct 17; 363:k4263)*. Another meta-analysis of 10 randomized trials (78.000 total patients) showed no significant differences between ω-3 recipients and controls in risks for coronary heart disease-related death, nonfatal MI, any coronary heart disease event, or major adverse CV events overall. Subgroup analyses among participants with known coronary heart disease or diabetes yielded similar findings *(JAMA Cardiol 2018; 3:225).* Many trials do not support the use of ω-3 fatty acid supplements for preventing adverse CV events in patients with no history of CV disease. Work in progress!

Diabetes Guidelines Updated. The document *(Diabetes Care*) includes all of the group's current clinical practice recommendations related to diabetes treatment and care. Among the recommendations: a) for patients with type 2 diabetes who require an injectable drug, a glucagon-like peptide 1 receptor agonist is preferred over insulin, b) for patients with type 2 diabetes who aren't using insulin, routine glucose self-monitoring is of limited additional benefit, c) ten-year atherosclerotic cardiovascular disease risk should be part of a patient's overall risk assessment, d) water intake should be stressed, and consumption of sugar-sweetened and nonnutritive-sweetened beverages should be discouraged. The proliferation of pharmacologic agents available for glycemic control in diabetes has made the therapy of diabetes much more complicated, thus having evidence-based guidance is quite useful.

Is Glycemic Management Too Intensive in Older Diabetic Patients? Too many older diabetic patients are being managed intensively with medications that confer high risk for hypoglycemia. Many clinicians are unaware of guidelines that advise less-intensive glycemic targets in this population. More specific directives on de-escalating drug treatment and minimizing risk for hypoglycemia in older patients, in particular in frail or dependent subjects must be widespread. Tight glycemic control is unlikely to benefit older people with longstanding type 2 diabetes and is associated with excess risk for hypoglycemia *(Arnold SV et al. J Am Geriatr Soc 2018 Apr 10)*. SGLT2 Inhibitors Are Associated with Risks for Amputation and Diabetic Ketoacidosis. In randomized trials, patients with type 2 diabetes and elevated cardiovascular disease (CVD) risk who received canagliflozin experienced fewer adverse CV events but more lower-limb amputations than did placebo recipients *(NEJM JW Gen Med Aug 1 2017 and N Engl J Med 2018; 377:644).* In a new cohort study, SGLT2 inhibitors were associated with significantly higher risks for lower-limb amputation (hazard ratio, 2.3) and diabetic ketoacidosis (DKA; HR, 2.1) but not bone fracture, acute kidney injury, serious urinary tract infection, venous thromboembolism, or acute pancreatitis. Although canagliflozin already carries an FDA black-box warning about amputation risk, the American College of Cardiology recently recommended SGLT2 inhibitors (and GLP-1 receptor agonists) to lower CVD risk in patients with type 2 diabetes and established CVD *(J Am Coll Cardiol 2018 Nov 26; [e-pub]).* **What to do?** The authors speculate that volume depletion induced by SGLT2 inhibitors might be a mechanism by which they confer

risks for amputation and DKA. Clinicians might want to avoid prescribing SGLT2 inhibitors to patients who are prone to volume depletion and those with known lower-extremity peripheral vascular disease *(Ueda P et al. Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: Nationwide register based cohort study. BMJ 2018 Nov 14; 363:k4365).* **A hard commitment?**

A **good new**: middle aged adults with five low-risk lifestyle factors (healthy diet, never smoking, moderate to-vigourous physical activity, moderate alcohol consumption and healthy body mass index) could live more than a decade longer than their less healthy peers *(Circulation 2018).* The research found that each low-risk factor was associated with significantly reduced risk for all cause,and for cardiovascular mortality: 74% for those who met all five criteria average life expectancy at age 50 was extended of 14 years longer for women and 12 years longer for men with all five low-risk factors.

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