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EDITORIAL

Diabetic ketoacidosis as the onset of type 1 diabetes in children

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List of abbreviations:
Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) at the onset of type 1 diabetes is an emergency for the pediatrician.

The younger the child, the more difficult is the clinical management of DKA.

Epidemiological data show that the incidence frequencies of DKA range from 13% to 80% (1).

In Great Britain the incidence rate is 23% (2) and has remained unchanged over the last 20 years (3).

In Italy, the incidence is about 40.3% with a frate of 29.1% for mild and moderate forms and 11.2% for severe forms. The severe forms are those that are more frequent in children less than 5 years of age (4).

Precisely a smaller age at onset is more alarming; in fact younger children (<5 years) have a higher risk of mortality and long-term morbidity (5, 6).

For this reason, the main aim is to make a diagnosis as early as possible through targeted interventions, such as diabetes awareness campaigns in association with parents and health professionals in order to highlight the symptoms of the disease precociously and reduce the risk of acute and chronic complication.

To date, several scientific reports have focused the problem, trying to underline the correct strategies.

The report of Iovane et al (published in the present issue of Acta Biomedica) is very interesting and the principal aim was to evaluate the prevention of ketoacidosis in young children (<5 years) compared to an older group (6-10 years), with the identification of premonitory clinical symptoms.

Interestingly, in the group of younger children compared to the other group, parents were totally unaware of the presence of diabetes awareness campaigns, which resulted in a higher rate of mild/moderate (65%) and even severe ketoacidosis (22%) at the onset of diabetes.

Therefore, in the younger child the possibility of having additional symptoms such as weight loss, the continuous use of diapers and polyuria must be taken into account as warning signs of a possible onset of diabetes and preventing diabetic ketoacidosis.

A further scientific contribution was offered by Parma School with the paper of Cangelosi et al (7) who developed an information campaign on diabetic ketoacidosis (DKA) based on the realization of posters and flyers in the pharmacy and at the pediatricians office, of a telephone number directly connected to the pediatric diabetes and radio announcements after the debut of a couple of clinical case.

The campaign lasted about 4 years gave its results, a time useful to reduce the number of severe ketoacidosis.

The paper of Deylami et al (8) is very interesting, in fact the Authors reviewed all the awareness campaigns on diabetic ketoacidosis that have been carried out in Europe. Almost all studies evaluated the incidence rates of DKA before and after the awareness campaign over a long period (from 1 to 8 years); the campaignes were carried with creation of poster and campaign on television.

Ahmed et al (9), using posters, information leaflets and educational program with professional nurses and health workers, showed that in Saudi Arabia the awareness campaign, over a 4-year period, led to a decrease in the DKA frequency of 6 %.

Much more significant was the DKA decline in Turkey, in fact, Ucar et al (10) , always with the use of posters, demonstrated a decrease of 24.4%.

In Italy, Vanelli et al (11) showed a 65% decrease in the incidence of DKA in 8 years, with a campaign based not only on the use of posters but also on a educational program, with also glycemic control.

A similar situation was highlighted by King et al (12) in Australia where the risk of ketoacidosis after the campaign was reduced by 64%.

In contrast, Lansdown (13) and Fritsch (14) do not demonstratd in Wales and Austria, respectively, a decrease of the frequency of DKA after an awareness campaign based on the use of poster, TV and radio broadcasts, educational programs provided by school and doctors.

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Review

Smartphone APPlications in the clinical care and management of Rheumatic Diseases

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Summary. *Background:* Rheumatic diseases (RDs) are the most common cause of severe long-term pain and physical disability, affecting hundreds of millions of people around the world. Smartphones technology have the potential to become an important tool that rheumatologist can employ in the clinical care management of RD. *Methods:* Research of the published literature on the principle electronic databases available as Ovid MEDLINE, Health Technology Assessment Database, Embase, and PsycINFO was conducted, and the studies evaluated eligible were reviewed. *Results:* Our search produced 120 results from which 47 eligible articles were identified reporting studies of smartphone apps for patients with RD. All examined feasibility and five assessed the efficacy of a smartphone intervention for clinical care management. *Conclusions:* It has been demonstrated a strong evidence for the feasibility of using smartphone to enhance care of patients with RD. Based on the available literature and our personal experiences, we consider useful the development of some mobile phone apps, to simplify and assist the rheumatologist during his clinical practice. Still remains limited data on the efficacy of such interventions. (www.actabiomedica.it)

Key words: Rheumatic disease, mHealth, smartphone, patient-reported outcomes, clinical care management

Introduction

Rheumatic diseases (RDs) are the most common cause of severe long-term pain and physical disability, and they affect hundreds of millions of people around the world (1-4). The reported disease prevalence of RD complaints ranged broadly from 9.8% to 33.2% (5-8). Almost one third of people aged over 75 has a significant musculoskeletal problem, and the prevalence of locomotor disability rises from 3.1% in those aged less than 60 to almost 50% in those aged more than 75 (9, 10). In a survey carried in Italy, the point prevalence of chronic pain caused by a RD is estimated at 27% of the general adult population (11), the prevalence is higher among women and increases markedly with age.

In the 2010 World Health Organization (WHO) Global Burden of Disease Study, RD were reported to be the second leading cause of disability worldwide, as measured by years lived with disability (12). Results for specific diseases and impairments have been extensively reported (13-17): not only rheumatic disorders are progressive debilitating diseases, but they also have a devastating impact on health-related quality of life (HRQoL) (18, 19). HRQoL has become an important measure when studying health status and health outcome infact surveys from the industrialized world revealed a high prevalence of RDs and its negative effect on the perceived HRQoL, as compared with other common chronic conditions (20-25). Traditional methods of evaluation, with a focus on the locomotor system and measures of impairment, may fail to describe the extensive multi-dimensional issues associated with RDs. Patient-reported outcomes (PROs) are an attractive option in a busy medical practice, as the time burden is transferred from the clinician to the patient. PROs include physical function or HRQoL,

pain, general health status, side effects, medical costs and other factors, and instruments for measuring PROs are easier to administer and less expensive than physician-observed disease activity and process measures. Although, in Italy, the use of the instruments is still quite limited, the validity and usefulness of PRO data in evaluating and monitoring patients with RDs have been well documented (26-29). Electronic data collection improves data quality by providing software safeguard against entry omission and inconsistent response sets, and by eliminating data entry errors made by researcher's (30-32). The development and spread of smartphones offers several advantages, it is a device that combine the characteristics of a typical mobile phone with the capabilities of a personal computer, due to the presence of a full and autonomous operating system. The fields of application of mobile health are various and heterogeneous, without a special training automated health tracking and timely interventions are possible. In this paper, we aim to review the published studies of smartphone apps applied for the care of patients with rheumatic disorders and explore the current evidence base for their potential impact on clinical care.

Eligibility criteria and study selection

Only original English research articles were included in the review. We included any study that reported on any quantitative outcomes of a smartphone-based intervention among patients with RD. An electronic database search of Ovid MEDLINE, Health Technology Assessment Database, Embase and PsycINFO was conducted on March 20, 2017, using the following keyword search algorithm: ("smartphone*" or "mobile phone*" or "cell phone" or "iPhone" or "mobile app*" or "phone app*") AND ("rheumatic diseases", rheumatoid arthritis", "osteoarthritis", "fibromyalgia", "spondyloarthritis" and "chronic pain sindrome"). All eligible studies were systematically reviewed, and proportional meta-analyses were applied to pooled data on recruitment, retention, and adherence to examine the overall feasibility of smartphone interventions for RDs.

Search Findings

Our search produced 120 results from which 47 eligible articles were identified reporting studies of smartphone apps for patients with RDs. All examined feasibility and five assessed the efficacy of a smartphone intervention for clinical care management. However, there was substantial heterogeneity across studies, due to the fact that each app was unique. Table 1 provides summary information from apps presented in the context of different individual study, selected based on their content quality, user-friendliness, availability and time optimization.

Medical applications for the rheumatologist

The emergence and enhancement of electronic medical applications and web-internet based tools have been driven by private and public sector initiatives with the goals of improving individual patient care, reducing medical errors and health care costs, increasing physician access to information for medical decision making, and facilitating communication between providers (33-34). Medical apps are being used with increasing frequency in rheumatological practices to make relevant patient data more readily available at the time of the patient encounter. They were subdivided into 5 categories: medical calculators, risk assessment tools, eLiterature, classification prognosis & training and applications for medical and nursing students.

Medical calculators: A medical calculator or clinical calculator is a software program for calculating various clinical scores and indices such as Disease Activity Score - 28 joints (DAS-28), Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), for rheumatoid arthritis, Lequesne index for knee and hip osteoarthritis or Ankylosing Spondylitis Disease Activity Score (ASDAS) for ankylosing spondylitis. Usually, calculation of composite clinical scores or indices involves complex formulas using several input parameters. Medical calculators typically provide a user interface to enter parameters and calculate scores using a standard formula. Physicians and/or patients do not need to use or even know the actual formula for calculating a clinical

Table 1.

	Application	Characteristics	OS	Web link
Calculators	DAS28	Allows calculation of Disease Activity Score 28 for evaluation of disease activity and disease progress in rheumatoid arthritis.	iOS/ Android	https://itunes.apple.com/it/app/das28-calculator/id492236295?mt=8 https://play.google.com/store/apps/details?id=tantor.systems.das28&hl=it
	DAS 28/ACR EULAR criteria	Allow the calculation of Disease Activity Score 28 for evaluation of disease activity and progress	iOS	https://itunes.apple.com/it/app/das28-acr-eular-criteria/id443707029?mt=8
	ASAS/ASDAS	Offers a calculator for the Ankylosing Spondylitis Disease Activity Score (ASDAS) as well as information on classification, diagnosis, outcome assessment, and treatment of spondyloarthritis.	iOS/ Android	https://itunes.apple.com/it/app/asas-app/id650291528?l=en&mt=8 https://play.google.com/store/apps/details?id=org.asas_group.asdas_calculator&hl=it
	Radiation Calculator	It is developed to help you learn about the many types of imaging studies that use radiation and track the amount of your radiation exposure.	iOS/ Android	https://itunes.apple.com/it/app/radiation-calculator/id451907773?mt=8 https://play.google.com/store/apps/details?id=com.radcalc
	PSODisk	Visual and intuitive tool, dedicated to people affected by Psoriasis.	iOS/ Android	https://itunes.apple.com/it/app/psodisk/id966462945?mt=8 https://play.google.com/store/apps/details?id=com.abbvie.psodisk&hl=it
	PASI	Indicator of the sum of the results obtained separately for the upper and the lower limbs, head and torso, considering erythema, infiltration and degree of exfoliation of the skin.	iOS/ Android	https://itunes.apple.com/it/app/kalkulator-pasi/id691958412?mt=8 https://play.google.com/store/apps/details?id=org.dipler.psoriasiscalc.android&hl=it

(continued)

Table 1.

Pain Lab	Ability to directly access to the list of all the scales available or can define the patient profile by compiling a specific form and view the scales selected based on the information entered.	iOS/ Android	https://itunes.apple.com/it/app/painlab/id588987028?mt=8 https://play.google.com/store/apps/details?id=it.edizioniedra.painlab&hl=it
BMI calculator	Body Mass Index is a measurement of body fat based on height and weight that applies to both men and women between the ages of 18 and 65 years.	iOS/ Android	https://itunes.apple.com/us/app/bmi-calculator-app-free/id477745468?mt=8 https://play.google.com/store/apps/details?id=com.splendapps.bmicalc&hl=it
BSA	It is an application useful to calculate the body surface area expressed in m^2	iOS/ Android	https://itunes.apple.com/it/app/body-surface-area/id565129864?mt=8 https://play.google.com/store/apps/details?id=com.springer.bsa&hl=it
PSORIASIS 360	App designed to consider the severity and the impact of psoriasis	iOS/ Android	https://itunes.apple.com/it/app/psoriasis-360/id377366782?mt=8 https://play.google.com/store/apps/details?id=com.sapnagroup.p360&hl=it
Lequesne	The Lequesne Algofunctional Indexes of severity for OA of the hip (LAI-hip) and knee (LAI-knee) include three sections (which are not graded separately) and take a few minutes to complete.	iOS/ Android	https://itunes.apple.com/it/app/indice-algo-fonctionnel-lequesne/id518586214?mt=8 https://play.google.com/store/apps/details?id=com.arthrolink.app.android.iaflequesne

(continued)

Table 1.

Framingham CRP Score - Reynold's Risk	High-sensitivity C-reactive protein and family history are independently associated with future cardiovascular events and are incorporated into risk prediction models for both women and men.	iOS	https://itunes.apple.com/us/app/framingham-crp-score-reynolds/id344908878?mt=8
Corticonverter	A quick and easy-to-use utility application to perform corticosteroids unit convert. Includes the follow corticosteroids: betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone and triamci-nolone. Useful for physicians and healthcare professionals.	iOS/ Android	https://itunes.apple.com/us/app/corticonverter/id334564150?mt=8 https://play.google.com/store/apps/details?id=mindex.med&hl=it
Medicine Toolkit	It is a medical education app developed and used at Harvard's top teaching hospitals. Bayes at the Bedside enables you to apply Bayesian reasoning to patient care in real-time with a database of over 175 likelihood ratios. Pocket Evidence provides summaries of over 440 teaching articles with PubMed links at your fingertips in the classroom, the clinic, or the wards.	iOS	https://itunes.apple.com/us/app/medicine-toolkit-teaching/id468578403?mt=8
DocNomo	It is a graphical tool to enhance the bedside interpretation of a diagnostic test result. From the diagnostic sensitivity and specificity of the test and the probability of the patient having the target disorder before running the test (Pre-Test Probability), it calculates the probability of the patient having the target disorder after running the	iOS	https://itunes.apple.com/it/app/docnomo/id901279945?mt=8

(continued)

Table 1.

		test. Using the convenience of tactile sliders, each of these parameters may be changed to visually assess their impact on the Post-Test Probability.		
Risk assesment	ASCVD Risk calculator	Cardiac Risk Assist is an application that aids in calculating the 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD) based on the information provided by the user.	iOS/ Android	https://itunes.apple.com/it/app/ascvd-risk-calculator-pooled/id761924005?mt=8 https://play.google.com/store/apps/details?id=org.acc.cvrisk&hl=it
	QRISK 2	This app brings the QRISK®2-2014 cardiovascular disease risk calculator to the iPhone.	iOS	https://itunes.apple.com/it/app/qrisk2/id497745015?mt=8
	CV RISK calculator	Allows a cardiovascular risk calculation based on given set of parameters and the Framingham equation.	iOS/ Android	https://itunes.apple.com/it/app/cv-risk-calculator/id794922133?mt=8 https://play.google.com/store/apps/details?id=com.magna.microlabs.cvriskcalculator&hl=it
	Frax	The Fracture Risk Assessment Tool (FRAX®) offers the medical practitioner an easy-to-use tool to calculate an individual patient's 10-year probability of an osteoporotic fracture.	iOS/ Android	https://itunes.apple.com/it/app/frax/id847593214?mt=8 https://play.google.com/store/apps/details?id=com.inkrypt.clients.iof.frax
	HAQ	The Health Assessment Questionnaire (HAQ) is administered and validated in patients with a wide variety of rheumatic diseases including rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, lupus, scleroderma, ankylosing spondylitis, fibromyalgia, and psoriatic arthritis.	iOS	https://itunes.apple.com/it/app/haqdas/id464778196?mt=8

(continued)

Table 1.

eLiterature and Education	PubMed plus	PubMed Plus connects to abstracts, citations of biomedical literature from MEDLINE, life science journals and online books.	iOS	https://itunes.apple.com/it/app/pubmed-plus-biomedical-journal/id1008345571?mt=8
	Radiopaedia	This app is a way to explore high quality medical imaging material, designed for all health professionals, with emphasis on radiologist and radiology trainees	iOS	https://itunes.apple.com/it/app/radiopaedia/id473157176?mt=8
	PubMed4Hh	App for discovering relevant health information at the National Library of Medicine. Journal abstracts, TBLs and full text articles can be accessed.	iOS/ Android	https://itunes.apple.com/us/app/pubmed4hh/id544354407?mt=8 https://play.google.com/store/apps/details?id=gov.nih.nlm.lhc.pubmed4hh&hl=it
	iAnkylosing Spondylitis	Educational app about ankylosing spondylitis (AS). Contains voice and text videos that introduce the condition's symptoms, and refer to associated diseases, diagnostic criteria, genetics, incidence, morbidity/mortality, pharmacological manage-ment, and physical therapy. Includes medical imaging, showing sacroiliitis and syndesmophytes, treatment suggestions and exercise animations	iOS	https://itunes.apple.com/gb/app/iankylosingspondylitis/id414586259?mt=8

(continued)

Table 1.

	Biblioclick in Rheumatology	It builds and submits highly complex queries to Pubmed based on selected topics	iOS	https://itunes.apple.com/it/app/biblioclick-in-rheumatology/id659286200?mt=8 https://play.google.com/store/apps/details?id=com.servier.biblioclick_rheumatology&hl=it
	Netter Flashcard	This app is the complete set of the 531 Netter Plates from the 6th edition Atlas of Human Anatomy, illustrated by master medical illustrator Frank H. Netter, MD, enhanced with a suite of quizzing and customization features.	iOS	https://itunes.apple.com/us/app/netters-anatomy-atlas/id461841381?mt=8
	Rheumatology- the Animated Pocket Dictionary	Animated dictionaries that provide definitions of medical terms with the aid of realistic and narrated 3D animations, complimented with text definitions.	iOS/ Android	https://itunes.apple.com/it/app/rheumatology-animated-pocket/id508294508?mt=8 https://play.google.com/store/apps/details?id=com.focusmedica.md.rheumatology&hl=it
	American College of Rheumatology Pubblications	Dedicated to presenting articles of interest to who is involved in healing, preventing, and curing arthritis and related disorders of the joints, muscles, and bones.	iOS	https://itunes.apple.com/it/app/american-college-rheumatology/id438747092?mt=8
Classification Prognosis and Training	RheumaHelper	It provides a complete toolbox of disease activity calculators and classification criteria were rheumatologist can reference during day-to-day work	iOS/ Android	https://itunes.apple.com/it/app/rheumahelper/id581905758?mt=8 https://play.google.com/store/apps/details?id=si.modrajagoda.rheumahelper&hl=it
	Rheumatology Advisor	It provides daily healthcare news, the latest clinical cases, treatment review articles, opinions in medicine, CE/CME courses, and concise drug monographs	iOS	https://itunes.apple.com/it/app/rheumatology-advisor/id1078450533?mt=8 https://play.google.com/store/apps/details?id=com.usbmis.troposphere.rheumad&hl=it

(continued)

Table 1.

ArthritisID	Contains information on detecting, treating and managing arthritis. Information on the prevention of arthritis includes facts about exercise, diet and nutrition. Treatment strategies and details about medication are discussed. An interactive arthritis screening tool and questionnaire helps the user detect indications of arthritis. Personal information about arthritis screenings can be saved.	iOS	https://itunes.apple.com/gb/app/arthritisid/id457961189?mt=8
Lupus Companion	The Lupus Companion is a symptom, medication and appointment diary for people living with Systemic Lupus Erythematosus (SLE). The Lupus Companion makes it easy for you to record how you are feeling day-to-day and to present the information to your doctors in an easy to read format.	iOS	https://itunes.apple.com/it/app/lupus-companion/id727297856?mt=8
My Lupus Log	Allows the user to record how symptoms of lupus are affecting daily life, with the aim of tracking the progression of the condition, and being able to report detailed information on symptoms to the doctor at the next visit. Represents the severity and frequency of symptoms in chart form. Organises information on living with the symptoms of lupus. Offers alerts and reminders. Contains a dictionary of terms relevant to lupus.	Android	https://play.google.com/store/apps/details?id=com.gsk.lupus

(continued)

Table 1.

Prognosis Rheumatology	Providing easily accessible information and a fun problem solving approach, this app is designed to update busy physicians while being an educational tool for residents, medical students and other healthcare professionals studying for academic and licensure exams.	iOS/ Android	https://itunes.apple.com/it/app/prognosis-rheumatology/id759859892?mt=8 https://play.google.com/store/apps/details?id=com.medicaljoyworks.prognosis.rheumatology&hl=it
Pill Reminder	Pill Reminder is an easy-to-use and reliable app that helps you remember to take your medications at the right time. It allows you to create any type of recurring reminders. It tracks the remaining quantity of each medication and shows a refill alert when running low.	iOS/ Android	https://itunes.apple.com/it/app/promemoria-per-farmaci-con/id816347839?mt=8 https://play.google.com/store/apps/details?id=com.appfun.medicinealert
Osirix Training	It possible see videos that train the workstation OsiriX PRO software. The 35 videos are separated into 7 chapters, from the initial preferences configuration over basic and advanced image viewing and manipulation to anonymizing and exporting. Both beginners and advanced users can learn from several workflows of handling, viewing and manipulating medical image data.	iOS	https://itunes.apple.com/it/app/osirix-pro-video-tutorials/id391086332?mt=8

Abbreviations: *DAS28* (Disease Activity Score-28 joints), *ACR* (American College of Rheumatology); *EULAR* (European League Against Rheumatism), *PsoDisk* (Psoriatic Disk); *PASI* (Psoriasis Area Severity Index); *BMI* (body mass index); *BSA* (Body Surface Area); *ASCVD* (Atherosclerotic Cardiovascular Disease); *HAQ* (Health Assessment Questionnaire);

score or index. For example, body mass index (BMI) is the most commonly used measure of obesity in all over the world. Other applications available are, *Corticonverter,* that is a quickly and useful application to perform corticosteroids unit converter, *DocNomo,* a graphical tool to enhance the bedside interpretation of a diagnostic test result, a digital adaptation of Two-Step Fagan Nomogram which is the updated version of the original Fagan's nomogram developed by *Fagan* in 1975 (35).

Risk Assessment calculators: More and more frequently the rheumatologist is requested to assess the cardiovascular risk of each single patient suffering from an inflammatory disease: in this sense are available different tools. The *QRISK®2-2014* is a cardiovascular disease risk calculator for the iPhone, it uses traditional risk factors (age, systolic blood pressure, smoking status and ratio of total serum cholesterol to high-density lipoprotein cholesterol) together with body mass index, ethnicity, measures of deprivation, family history, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, diabetes mellitus, and antihypertensive treatment. The QRISK®2 algorithm has been developed by doctors and academics working in the UK National Health Service and is based on routinely collected data from many thousands of GPs across the country who have freely contributed data for medical research. It is updated annually refitted to the latest data to remain as accurate as possible. The *ASCVD Risk Estimator* is published jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA) to help health care providers and patients estimate 10-year and lifetime risks for atherosclerotic cardiovascular disease (ASCVD) using the Pooled Cohort Equations and lifetime risk prediction tools. This app is intended as a companion tool to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk and the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. The ASCVD Risk Estimator provides easy access to recommendations specific to calculate risk estimates. Additionally, the app includes readily accessible guideline reference information for both providers and patients related to therapy, monitoring, and lifestyle. Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Many risk assessment tools are available to predict fracture incidence over a period, and these may be used to aid decision making. These tools are limited in that they may not include all risk factors, or may lack details of some risk factors. The most used tool is the Fracture Risk Assessment Tool (FRAX), it was developed using baseline and follow up data from nine prospective population-based cohorts (including Europe, Australia, Canada and Japan) and validated in 11 prospective population-based cohorts (> 1 million patient years). The FRAX's app offers to the medical practitioner an easy-to-use tool to calculate an individual patient's 10-year probability of an osteoporotic fracture.

Literature search applications: Literature search applications for healthcare professionals facilitate searching biomedical literature databases to find and display medical reference information, thus providing a usefull resource both for physicians and students. Some apps that we consider are *PubMed plus*, that connects to abstracts, citations of literature from Medline, Netter flashcard, a complete set of all Netter Plates from the 6th edition Atlas of Human Anatomy. Other literature apps for rheumatologists are American College of Rheumatology Publications and the Animated Pocket Dictionary-Rheumatology, the first one is dedicated to presenting articles of interest to researchers, physicians and health professional regarding arthritis and related disorders of the joints, muscles and bones, the second one is animated dictionary that provides definitions of medical terms with the aid of realistic and narrated 3D animations with text definitions. There is also the possibility to analize various imaging material usind Radiopedia, exploring a collection of high quality medical imaging, for all health professionals. The app useful to learn about spine condition is iAnkylosing-spondylitis in fact it contains voice and text videos introducing the symptoms, associated diseases, incidence, morbidity/mortality, genetics, diagnostic criteria, physical therapy and pharmacological management of the ankylosing spondylitis.

Medical classification prognosis & training applications: Smartphones are also used for medical training and continuing medical education (CME). CME

provides training in the most current evidence-based medical practice. *OsiriX HD* (Di Pixmeo SARL) is a full DICOM image viewer for *iOS* (DICOM Files & DICOM Network protocol support) so that you can access to medical images, download and manipulate them using iPhone or iPad. It works with all imaging modalities: ultrasound, CT scanner, MRI, PET, etc. in their native standard DICOM format used by the medical/scientific industry. It's designed to work seamlessly with any DICOM compatible software, including PACS, medical workstations, acquisition modalities. It also supports communications through the *iOS* built-in VPN for secure and encrypted connections. *Rheuma-Helper* is a mobile rheumatology assistant. It provides a complete toolbox of disease classification criteria the informed rheumatologist can reference during day-to-day work. Easy to use and always with you on mobile phone, all the included classifications and disease activity calculators are based on referenced equations. *My lupus log* allows the user to record how symptoms of lupus are affecting daily life, tracking the progression of the condition, and report detailed information on symptoms to the physician. *Prognosis Rheumatology* it is an easy and reliable app to access information with a fun problem solving approach. It explores 16 varied clinical cases based on actual patients and update knowledge on the latest therapeutic guidelines. Providing easily accessible information and a fun problem solving approach, this app is designed to update busy physicians while being an educational tool for residents, medical students and other healthcare professionals studying for academic and licensure exams.

Applications for medical and nursing students: There are many smartphone-based applications containing primarily as educational material for medical or nursing students. They are Netter' s Atlas of Human Anatomy, Netter' s Anatomy Flash Cards, Rheumatology Advisor, PubMed4Hh, Oxford Handbook of Clinical Specialties, Medicine Toolkit and Radiation Calculator.

Our smartphone applications for rheumatic disease management

The health care of patients was improved associating the use of smartphone on the curative strategies, allowing more rapid decisions, a better quality on the managing of data, and a more effective way to reach outcomes. Based on the available literature and our personal experiences, we considered useful the development of some mobile phone apps, to simplify and assist the rheumatologist during his clinical practice. In the following section are described some examples of these Apps.

a) *Simple Psoriatic Arthritis Screening (SiPAS)*

Psoriatic arthritis (PsA) has an estimated prevalence in Italy of 0.5% in the general population (11) and the prevalence of PsA among patients with psoriasis is reported from 6% to 44% (36). To date, several screening tools have been realized to identify psoriasis patients with musculoskeletal manifestations of PsA. In this respect, recent guidelines for managing psoriatic recommend the usage of questionnaires to screen for the presence of PsA (37). Most of these screening tools have been validated in a variety of independent populations and in several clinical settings. However, the sensitivity and specificity of these instruments is well under 50% when the polyarticular forms of arthritis are excluded (38) and no Italian versions of these tools have yet been developed and validated in the dermatology and rheumatology settings. The Simple Psoriatic Arthritis Screening (SiPAS) questionnaire, is a valid and efficient, self-administered, user-friendly PsA screening tool, to screen psoriasis patients for signs and symptom of PsA, starting from the questions coming from the already existing questionnaires (39-40). The development of the SiPAS followed multiple major steps: identification of a specific patient population, item pool development, item reduction, internal consistency, *pre*-testing of the prototype instrument a validation study (Figure 1A).

b) *Detection of arthritis in inflammatory bowel diseases (DETAIL) calculator*

The presence of an inflammatory arthropathy is the commonest extra-intestinal manifestation in patient suffering from an inflammatory bowel disease (IBD), involving from the 4% to the 23% of the subjects, classified in the context of SpA (41-44). We de-

veloped a new self-administered screening tool, called DETection of Arthritis in Inflammatory boweL diseases (DETAIL) tool, in patients suffering from IBD not previously diagnosed as having a SpA (Figure 1B). One-hundred and twenty-eight patients were tested with the DETAIL questionnaire in the gastroenterology setting. After the rheumatologic assessment, in 21 (16.4%) subjects was diagnosed a SpA according to the ASAS classification criteria. Of the six items of the DETAIL questionnaire, the best positive likelihood ratio (LR+) has been found in item 2 (LR+ 3.82), exploring dactylitis, and in item 6 (LR+ 3.82) and item 5 (LR+ 3.40), two questions exploring inflammatory low back pain. Enthesitis (item 3 – LR+ 2.87) and peripheral synovitis (item 1 – LR+ 2.81) gave similar results, while item 4, exploring the duration of low back pain, resulted in the worst performance (LR+ 1.99). Three of the six items answered in affirmative way gave a post-test probability ≥75%.

c) ***Simplified Erosion and Narrowing Score (SENS)***

Rheumatoid Arthritis (RA) is a chronic systemic disease of unknown origin that, predominantly, involves synovial tissue. RA affects 0.5% of the global population, with a clear predilection for women. Conventional radiography (plain radiographs or X-rays) is the most widely used imaging technique for diagnosing and monitoring the progression of RA (45). Advanced imaging techniques (e.g. MRI, computed tomography, ultrasound, and nuclear scintigraphy), that are better suited for detecting soft-tissue inflammation are available, but they are costlier and some of them may expose the patient to higher doses of radiation. Plain film radiographs are inexpensive, easy to generate, can be compared with baseline and prospective films, and provide a permanent, reproducible record. The plain radiographs of the hands and feet can detect the features that are specific to RA such as

Figure 1. (A) Simple Psoriatic Arthritis Screening (SiPAS) and (B) Detection of arthritis in Inflammatory bowel diseases (DETAIL) calculators

joint space narrowing or erosions, and serial radiography can be used as a objective marker for monitoring treatment response in clinical trials, since assessing abnormalities radiologically is one of the most powerful means available to the clinical investigator for determining the effects of RA. Progression of structural damage to joints is commonly used as an outcome measure in RA and in observational studies (46, 47). Radiographic scores, such as the Sharp scores and their modifications, are the standard semiquantitative methods for determining joint damage and its progression. The scoring time is one drawback of both Sharp method and Sharp/van der Heijde method, related to their detailed evaluation. In order to overcome these limitations, it has been developed the Simplified Erosion and Narrowing Score (called SENS), that is entirely based on the van der Heijde modification of the Sharp score (48). It exploits the same joints of hands and feet, but as opposed to applying a semiquantitative scale of 0-4 for joint space narrowing and 0-5 for erosions, the SENS simply dichotomizes (bimodal answer modality) whether an erosion is absent (score of 0) or present (score of 1), and whether joint space narrowing is absent (score of 0) or present (score of 1). The hand score per joint can, therefore, range from 0 to 2. Joint erosions are scored in 32 joints in the hands and wrists and 12 joints in the feet. JSN is scored in 30 joints in the hands and wrists and in 12 joints in the feet. Consequently, the maximum total erosion score is 44, the maximum total JSN score is 42 and the maximum total score is 86. The SENS showed a good intra- and inter-reader reliability, and is sensitive to change. Its decisive advantage is its feasibility in clinical practice (49) (Figure 2).

d) ***Italian DElphi in psoriatic Arthritis (IDEA)***

To create a protocol for PsA diagnosis and global assessment of patients with an algorithm based on anamnestic, clinical, laboratory and imaging procedures, we established a Delphi study on a national scale, the Italian DElphi in Psoriatic Arthritis (IDEA). After a literature search, a Delphi pool, involving 52 rheumatologists, was performed. Based on the literature search 202 potential items were identified, the steering committee planned at least two Delphi rounds. A total of 43 recommended diagnosis and assessment procedures, recognized as items, were derived by combination of the Delphi survey and two National Expert Meetings, and grouped in different areas including medical (familial and personal) history, physical evaluation, imaging tool, second level laboratory tests, disease activity measurement and extrarticular manifestations. In the context of any area, a rank was assigned for each item, by Expert Committee members in order to create the logical sequence the algorithm. The final list of recommended diagnosis and assessment procedures, by the Delphi survey and the two National Expert Meetings, was reported also as algorithm. The IDEA algorithm might lead to a multidimensional approach and could represent a useful and practical tool for addressing the diagnosis and for assessing appropriately the disease (50) (Fig. 3).

e) ***The PsAID-12 questionnaire***

The overall assessment of PsA is challenging and include may domains. The European League Against Rheumatism (EULAR) developed two PsA Impact of Disease questionnaires (PsAID) including both physical and psychological domains: one for clinical practice (12 domains of health) and one for clinical trials (nine domains). The PsAID score is developed, translated and validated across several countries; it is free of charge and fast, making it feasible and widely applicable (35). The longer questionnaire, developed for clinical practice contains components to assess 12 domains, each with 0–10 NRS that are perceived by patients to be particularly important for their health. Each domain has different weight. The final score has a range from 0 to 10 (10 worst health). The PsAID scores had satisfactory psychometric properties in an international validation study (51, 52). The touchscreen mode of administration of PsAID-12 can be a feasible and suitable alternative to the paper-and-pencil mode for the assessment of patients with PsA (32, 52) (Figure 4). In our study 159 patients with PsA, as a part of clinical treatment, on the waiting room perfomed both the paper-and-pencil and touch screen version of PsAID-12 showing a high concordance between them (*32*).

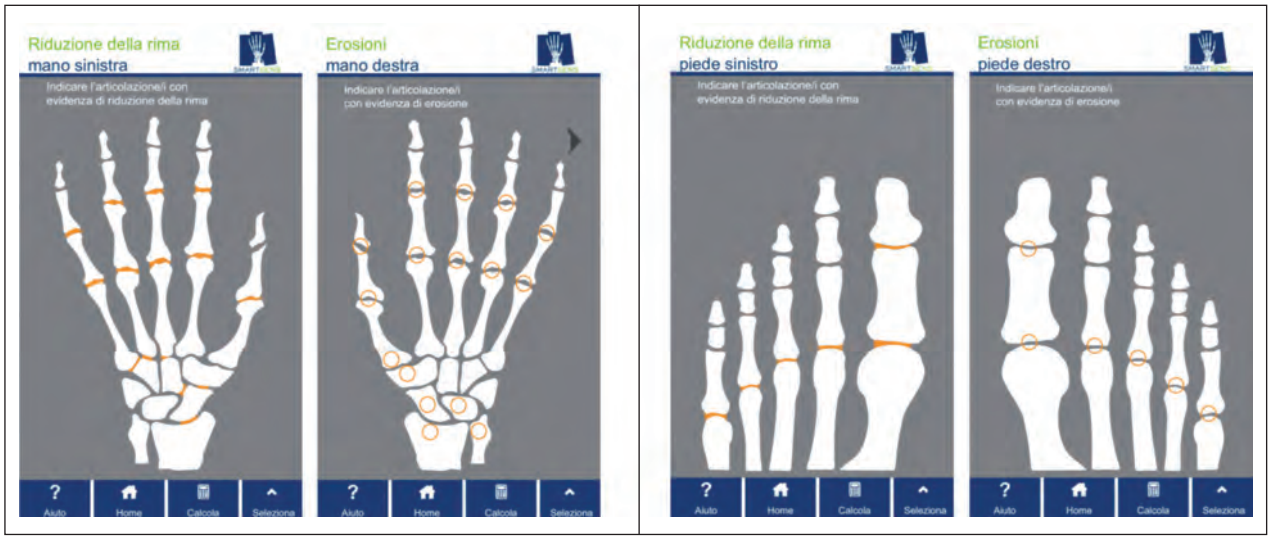

Figure 2. Simplified Erosion and Narrowing Score (SENS)

f) *Patient-Reported Outcome –Clinical Arthritis Activity (PRO-CLARA) index*

RA PRO-CLARA is a validated, short and easy to complete self-administered index to evaluate RA diseases activity, without formal joint counts, combining three items on patient's physical function (as measured by Recent-Onset Arthritis Disability – ROAD – questionnaire), self-administered tender joint count (TJC) and patient global assessment (PtGA) into a single measure of disease activity (26) (Figure 5). The total score is a sum of scores of the three individual

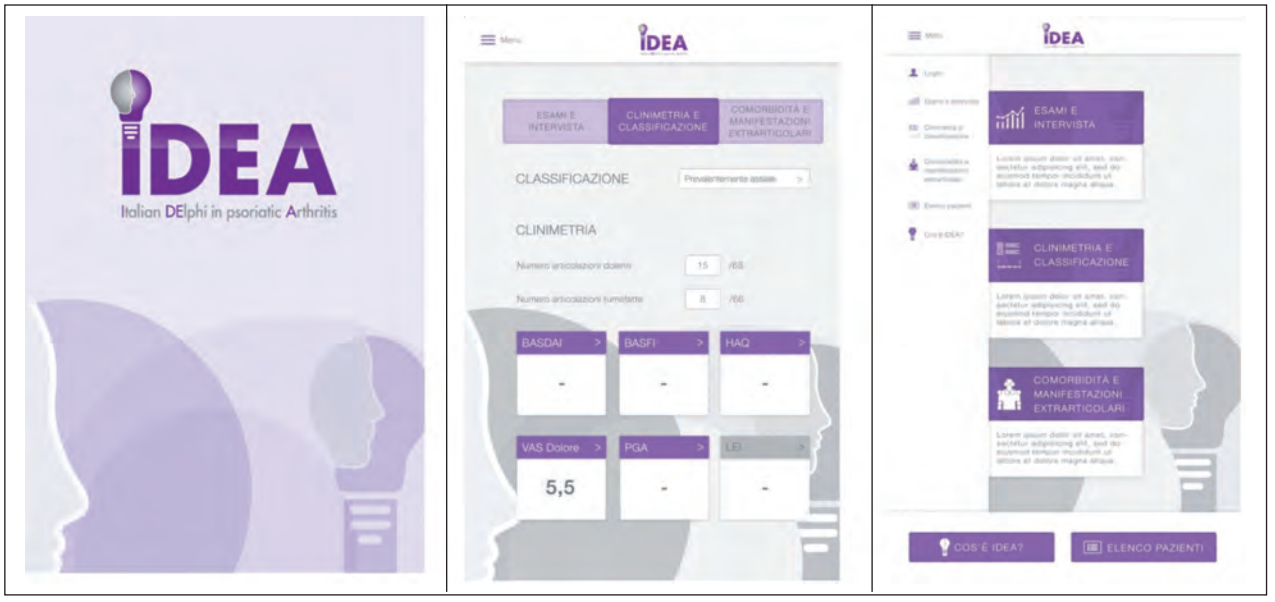

Figure 3. Italian Delphi in psoriatic Arthritis (IDEA) tool

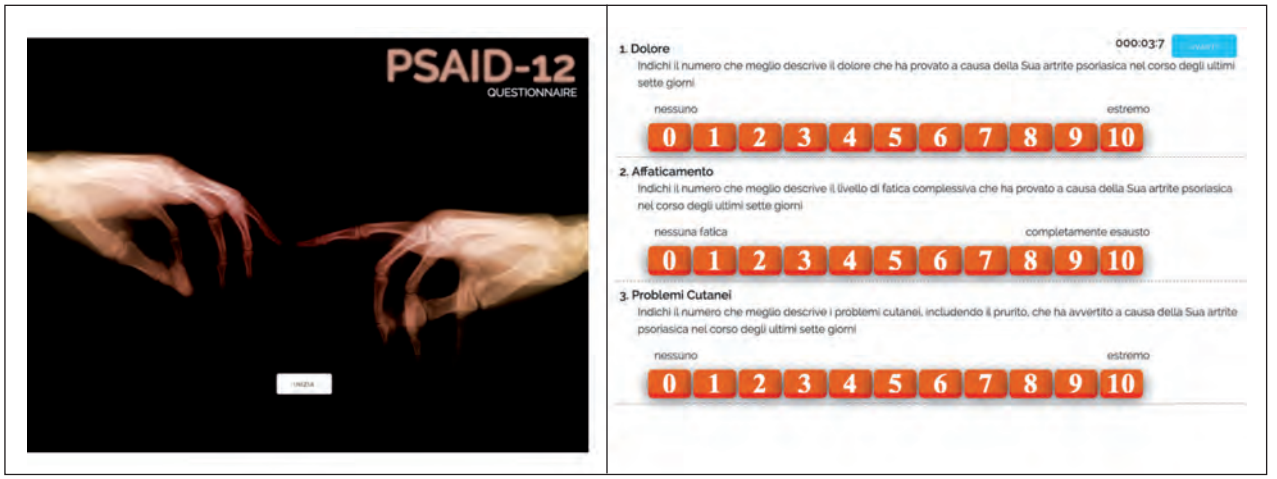

Figure 4. The PsA Impact of Disease questionnaires (PsaID)-12 questionnaire

measures divided by three, and ranges from 0 to 10. The ROAD questionnaire is a reliable, valid and responsive tool for measuring physical functioning in patients with RA, and it is suitable for use in clinical trials and daily clinical practice (53-55). The self-administered TJC is evaluated according to joint list of the Rheumatoid Arthritis Disease Activity Index (RADAI). The PtGA, is scored with the following question: "Considering all the ways in which illness and health conditions may affect you now, please make a mark below to show how you are doing" on a 0-10 numerical rating scale (NRS) with very well (0) and very poorly (10) as anchors. The three 0–10 scores are added together for a raw score of 0–30, and divided by 3 to give an adjusted 0–10 score.

g) *PROs Thermomer – 5 items scale: a brief assessment tool for rapid evaluation of rheumatic diseases in research and clinical practice*

Patients with RDs conditions have been shown to suffer deficits in HRQoL along several physical

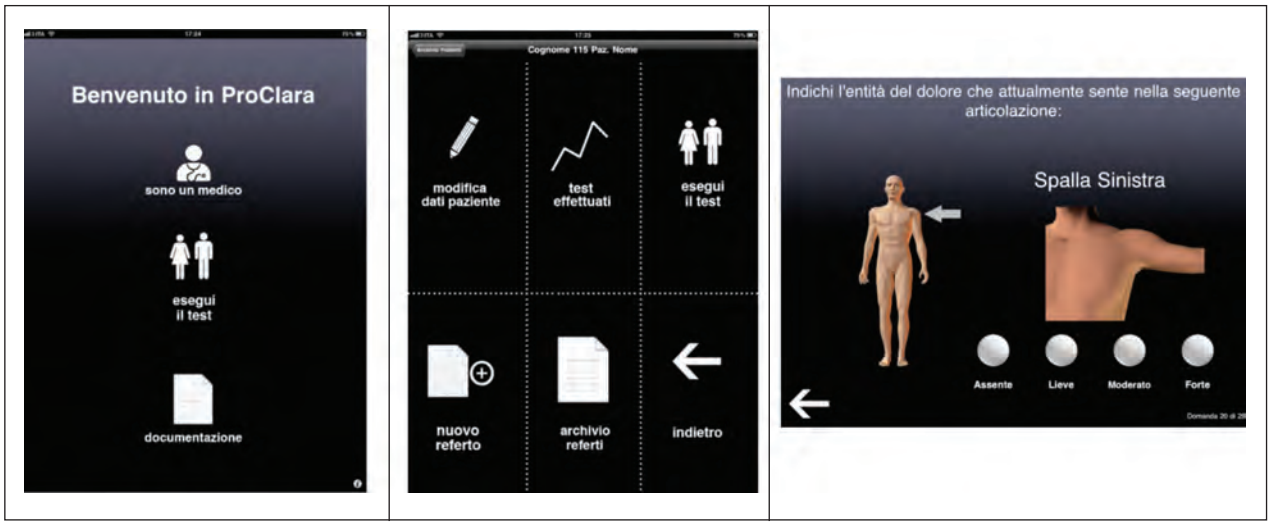

Figure 5. The Patient-Reported Outcome –Clinical Arthritis Activity (PRO-CLARA) index

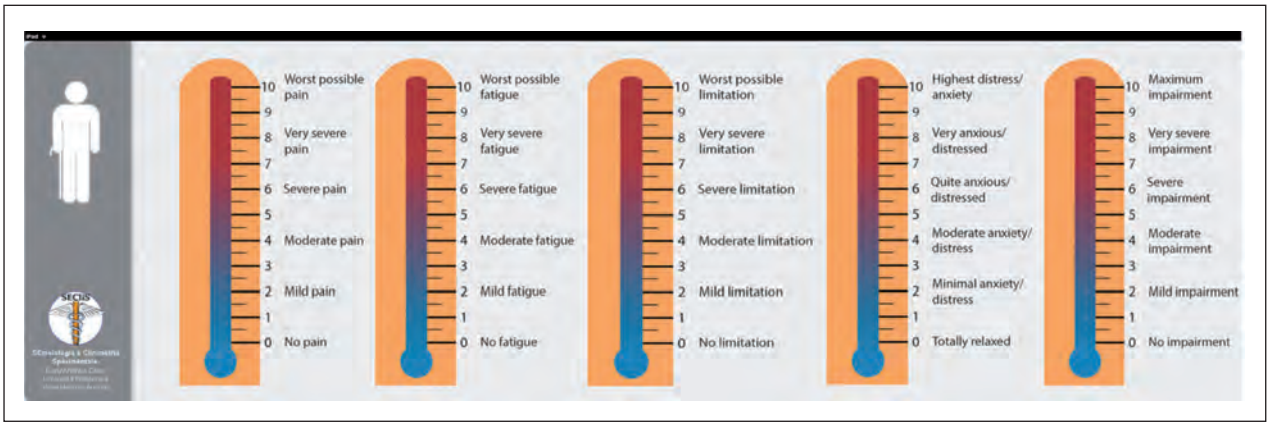

Figure 6. The PROs Thermomer – 5 item scale (5T-PROs)

functioning and mental health dimensions (5, 11, 19, 56-58). A comprehensive assessment of the multiple symptoms domains associated with RDs and their impact on multidimensional aspects of HRQoL should be a routine part of the care of patients. Clinical trials and long term clinical registries have used disparate outcome measures (59-60). We developed a PROs Thermomer – 5 items (5T-PROs) scales that measure overall health status in patients with a five-items domain (pain, fatigue, physical functioning, anxiety/depression, general health status). These five-items measures in which participants mark their subjective status on a graphic thermometer scale, afford simple and rapid administration, and increased comprehension and completion rates (Figure 6).

Conclusions

Over the past decade, smartphones have radically changed many aspects of our everyday lives, from banking to shopping to entertainment. With innovative digital technologies, cloud computing and machine learning, the medicalized smartphone is going to upend every aspect of health care. Although the current literature on the role of smartphones in RD is small, results suggest high feasibility and acceptability. However, there is currently limited data on the efficacy of smartphone apps. With further research and clinical innovation, smartphone may provide an effective means to improve access to rheumatology care. This would allow for both direct patient care by rheumatologists and support of primary care providers, who can be educated, mentored and given diagnostic and management advice.

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The ethics of organizational change in healthcare

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Summary. The article addresses the increasingly important issue of organizational ethics in healthcare. Assuming that the governance of organizational change consists of a seriousness of continuous choices and of objectives to be determined and achieved, a possible definition of this new discipline is then deepened, and its fields of application are identified. In the discussion therefore emerge the close link between ethical choice in organization and legality, passing through transparency and prevention of corruptive phenomena. After a focus on the strategic role played by the Medical Doctor of the healthcare management team, in conclusion, the need arises to support a strengthened supervisory and evaluation system and a culture of the ethical organizational choice of health managers, a rooting of the sense of identity and belonging to the healthcare organization and its mission by Professionals. Also governing this last aspect is the new challenge for the management of public healthcare enterprises. (www.actabiomedica.it)

Key words: ethics, clinical governance, healthcare organization, health product design

One of the key characteristics of a dynamic public healthcare enterprise is organizational change, understood in all its possible meanings: proactive or adaptive, spontaneous or induced. The change is a phenomenon universally present in the experience of the organizations and this is more relevant in those healthcare characterized by a continuous search for quality, excellence and innovation.

We speak of "organizational change" when organizations modify their systems and organizational sub-systems to survive in contexts characterized by uncertainty and by the need for change through the innovative capacity of successful experiences (1).

Governing change in healthcare consist in making continuous choices consistent with short, medium and long-term goals achievement.

Ethics is considered a very ancient discipline, a valid definition was provided by Aristotle in the 4th century BC.: "*Ethics is that branch of philosophy that studies the conduct of human beings and the criteria by which behavior and choices are evaluated*".

Therefore, as an organization (from the ancient Greek language: ὄργανον -organon- instrument) is *a group of people formally and deliberately united (social unit) to achieve one or more common objectives*, difficult to achieve individually, the health organization is characterized by the goal that it must achieve: an appropriate response to the health needs of the population it belongs to (art. 32 of Italian Constitution). The fields of application of organizational ethics are:

a) the ethics of financial management (to guarantee sustainability and equity of access),
b) transparency in management and in roles,
c) professional responsibility (both by health professionals and managers).

A practical and pragmatic definition was provided by the Ethics Committee for Clinical Practice of the Azienda ULSS 18 of Rovigo (2) in an official docu-

ment: "*Organizational Ethics consists of intentional use and discernment of values to guide managerial decisions that influence patient care and health practice, resulting from scientific and clinical changes in health care*".

What derives from this, for those who daily take care of the planning, management and administration of a complex health organization system, is that the organization is ethical as far as its mission consists in the creation of interfaces and models of patient-centered integration that guarantee the absolute continuity of assistance to the patient. However, it must also be ethical towards its Professionals by protecting them in two directions: creating organizational, structural, resources, procedural and relational conditions for working at the maximum level of safety and at the maximum of their abilities, and also in order to enhance their skills and vocations, being able in turn to derive their added value.

It is advisable for each Professional, in the face of an organizational choice or a formulation/revision of an organizational project, to verify step by step the compliance with these general principles. This is valid both because of the specific character of Profession aimed at protecting the most important single and collective good, and because every choice may result in an inappropriate use of public resources.

The difficulty in comparing, in the daily work, choices or organization polices with the respect of seemingly general principles is instead the effort that ensures the ethical behaviour and organizational choices in extremely complex systems in continuous change:

- change in demand (demographic evolution, epidemiological transition, migratory flows, ...);
- technological innovation;
- scientific progress;
- change in the availability of resources;
- important organizational innovations (interface with community resources, integrated assistance, proactive approach, patient centered medicine);
- increased citizen empowerment levels.

Today healthcare management team, integrated into the healthcare enterprise strategic administration, appears to be strongly involved in the respect of organizational ethics, precisely in relation to the roles it plays both institutionally and by delegation of the General Manager.

Traditionally the function of Health Directorate, precursor of the current health management team, originated with the Petragnani Law of 1938 (3) and oriented towards the "*good governance of the Hospital*", was mostly interpreted as a "*notarial*" activity aimed at certifying and guaranteeing the hygienic - organizational conditions suitable for carrying out the functions of the institute.

The 1992 health reform and its amendments and additions (4) has determined the overcoming of the historical notion of Health Directorate strongly adhering to a technical - operational decision-making power of a strictly hygienic order. Today the healthcare management team stands as a link between citizens/users and the services offered embodying modern health and managerial responsibilities.

From the emanation of the 1992 health reform the path has been long and tortuous, drawing new challenges and competences of the healthcare management team in the following application areas:

- the area of clinical governance;
- the area of epidemiology and evaluation;
- the area of internal operating reports;
- the area of relations with the public;
- the programming area;
- the area of management control;
- the area of Resource Management;
- the area of quality and accreditation
- supervision of compliance with the rules on clinical trials, by participating in the enterprise ethics committee.

These areas combine to design, as a whole, a new perspective in virtue of which health management team and the whole strategic administration have the dignity of existing, consisting in the exercise of the function of Health Product Design (5), which represents the element with the greatest ethical impacts and which implies, for the healthcare management team, an assumption of daily responsibility. The relationship between organizational ethics in health and legality passes through various regulatory provisions [the main ones date back to the years 2012 (6) and 2013 (7)] that concerned more generally the Public Administration, but also through an ever closer relationship between managerial choices, roles, management procedures and the transparency of acts and procedures. Areas must

to be guarded from the perspective of the prevention of corruption phenomena and behaviour are certainly institutional accreditation, private practice, research, human resource recruiting and public contracts management. Especially in these areas, the true cultural change should pass through the conscious responsibility of the manager of public resources.

Although law, repression of crimes, prevention of incorrect behaviours through internal and external monitoring systems, transparency and citizen empowerment could help to correct and prevent specific situations, health care organizational ethics and professional ethics are able guarantee the constant implementation of correct behaviour.

Precondition for the diffusion and the rooting of the organizational ethics is the achievement of a sense of belonging to a system and its objectives. Sharing objectives and mission in a general sense by professionals could be easier in healthcare organizations compared with other systems not involved with patient's needs. However, this is not enough to develop an ethical organization in which each practitioner feels part and protagonist of a complex patient-centered system whose purpose is to protect the most basic of rights.

Interpreting the ethical sphere of an organization and presiding over its functions and characteristics goes through the perspectives articulated by two substantial determinants:

1) development, management and continuous maintenance of clinical pathways, which transversely affect the quantity and quality of productivity of a health system incorporating the criteria of institutional accreditation recently marked in the Emilia Romagna Region by a special Resolution of the Regional Council (8) (implementation/development of a healthcare enterprise management system, guarantee of provision of services and services, adequacy and safety of structural aspects, development and maintenance of staff skills, correct communication, clinical appropriateness, improvement and innovation processes, humanization);
2) to oversee and support the values of an organization focused on clinical governance, safety, risk management and the care of the patient; starting from the daily expressions of health activities (eg hand hygiene, risk of falls, sentinel events management) (9) to the monitoring and surveillance of Information and Communications Technology (ICT) and evaluations of Health Technolgy Assessment (HTA).

In conclusion, ethics of organizational change is perhaps the most emergent issue in recent years, representing the main challenge for the management of public healthcare enterprises: not only to take charge of governing a system of highly trained professionals but also to increasingly involve them in self-identifying with the healthcare enterprise and its goals.

The health organizational discipline has made a great progress in recent years becoming able to perform the role of vigilance towards unethical behaviours creating appropriate organizational contexts and, at the same time, governing a process of identity matching between the individual Professional and the healthcare enterprise.

Therefore it is the authors' opinion that any daily professional choice of health management professionals, such as those involved in health management teams, should overcome individual and personal ethics to reach the level of organizational ethics and shared decision making by individual Professionals.

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Aspirin for thromboprophylaxis in major orthopedic surgery: old drug, new tricks?

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Summary. Major orthopedic surgery, mainly entailing hip fracture surgery, hip and knee arthroplasty, is associated with significant morbidity and mortality, which are especially attributable to the high risk of postoperative VTE. Such a considerable risk is mainly due to a procoagulant state sustained by several important mechanisms, including massive release of procoagulants from tissue and bone damage, blood vessel injury, reduced venous emptying, perioperative immobilization and cement polymerization, among others. The risk of VTE during and after major orthopedic surgery approximates 50-80% in patients with no thromboprophylaxis, and persists for up 3 to 6 months after surgery. The anticoagulant or antithrombotic armamentarium entails several anticoagulants such as heparin, coumarins, fondaparinux, and the recently developed DOACs inhibiting either activated factor Xa (i.e., rivaroxaban, apixaban, edoxaban) or thrombin (i.e., dabigatran), as well as aspirin, i.e., the oldest antiplatelet drug to be ever discovered and used in clinical practice. The current guidelines are not in complete agreement regarding the choice of the ideal thromboprophylaxis, since some consider aspirin, and some discourage it. Recent evidence seems to support the use of aspirin in selected situations and in selected protocols. Therefore, we believe that consideration should be made about increasing the use of this old but still effective drug for perioperative prophylaxis of VTE, especially in patients for whom the administration of DOACs may be challenging. (www.actabiomedica.it)

Key words: aspirin, venous thrombosis, deep vein thrombosis, pulmonary embolism, prophylaxis

In a recently published article, Kim et al (1) showed data about the trend of thromboprophylaxis and complications after major lower limb orthopedic surgeries in Korea. Although the findings of this study are somehow interesting from an epidemiological perspective, part of the conclusions seem misleading especially when the authors insinuated that the enhanced risk of both venous thromboembolism (VTE) and bleeding after hip surgery may be due to increased prescriptions of aspirin (and fondaparinux and low molecular weight heparin; LMWH) combined with fewer prescriptions of direct oral anticoagulants (DOACs).

Major orthopedic surgery, mainly entailing hip fracture surgery, hip and knee arthroplasty, is associated with significant morbidity and mortality, which are especially attributable to the high risk of postoperative VTE (2). Such a considerable risk is mainly due to a procoagulant state sustained by several important mechanisms participating to the pathogenesis of venous thrombosis, thus including massive release of procoagulants from tissue and bone damage, blood vessel injury, reduced venous emptying, perioperative immobilization and cement polymerization, among others (2). Interestingly, the risk of VTE during and after major orthopedic surgery approximates 50-80% in patients with no thromboprophylaxis, and persists for 3 to 6 months after surgery (3).

These alarming figures have encouraged many scientific organizations to publish recommendations that

primary thromboprophylaxis should be administered to all patients undergoing major orthopedic surgery. Specific guidance about the possible therapeutic options in this clinical setting has considerably evolved over time (4). Briefly, the anticoagulant or antithrombotic armamentarium entails "conventional" anticoagulants such as heparin (namely LMWH), coumarins (warfarin, acenocoumarol), fondaparinux, but also includes DOACs inhibiting either activated factor Xa (i.e., rivaroxaban, apixaban, edoxaban) or thrombin (i.e., dabigatran), as well as aspirin, i.e., the oldest antiplatelet drug to be ever discovered and used in clinical practice.

According to the current evidence-based guidelines of the American College of Chest Physicians (ACCP) (5), one of the following drugs is recommended for antithrombotic therapy and prevention of thrombosis in patients undergoing major orthopedic surgery: LMWH, fondaparinux, DOACs (dabigatran, rivaroxaban or apixaban), low-dose unfractionated heparin, vitamin K antagonist and aspirin (Grade 1B recommendation). Interestingly, the use of LMWH is preferred over other agents, including aspirin (Grade 2C/2B recommendation) (5). This straightforward recommendation is in apparent disagreement with that of the American Academy of Orthopaedic Surgeons (AAOS). Although the panel of AAOS experts concluded that it is advisable to use pharmacologic agents for preventing VTE in patients undergoing major orthopedic surgery, and that it is still unclear which prophylactic strategy may be optimal, perioperative use of antiplatelet agents such as aspirin or clopidogrel has been discouraged (6). The recommendations of both the ACCP and AAOS have been published more than 5 years ago (i.e., in 2012 and 2011, respectively) and, since then, a number of very recent studies have been published about the potential effectiveness and safety of aspirin in patients undergoing major orthopedic surgery.

Nielen et al carried out a retrospective study including 3261 patients undergoing total knee replacement and 4016 patients undergoing total hip replacement, aimed to compare efficacy and safety of DOACs, LMWH and aspirin (7). Compared with patients undergoing aspirin therapy, LMWH and DOACs were associated with a 2.0 (95% confidence interval [95% CI], 0.2-17.2) and 9.4 (95% CI, 1.1-82.0) enhanced risk of gastrointestinal bleeding after total hip replacement, respectively. The administration of LMWH was also found to be associated with a 20.9-fold (95% CI, 1.9-232.3) higher risk of gastrointestinal bleeding after total knee replacement compared with aspirin. As regards clinical efficacy, the risk of post-operative VTE after total hip replacement was found to be non-significantly higher with DOACs than with aspirin (hazard ratio [HR], 4.7; 95% CI, 0.6-37.9), but was clearly higher using LMWH than aspirin (HR, 39.5; 95% CI, 18.0-87.0). Similarly, the risk of post-operative VTE after total knee replacement was much higher with LMWH than with aspirin (HR, 17.2; 95% CI, 6.9-43.0).

Bala et al carried out a large analysis of Humana and Medicare database for identifying all primary total knee arthroplasty performed between the years 2007-2016 (8), for recognizing potential differences in incidence of VTE and bleeding in patients undergoing total knee arthroplasty and taking different antithrombotic drugs (i.e., warfarin, LMWH, DOACs and aspirin). The administration of DOACs was associated with the lowest overall incidence of deep vein thrombosis (i.e., 2.9%), closely followed by aspirin (3.0%), then by LMWH (3.5%) and warfarin (4.8%). Similarly, DOACs were also the most effective drugs for preventing pulmonary embolism (0.9%), closely followed by LMWH (1.1%), aspirin (1.2%) and then by warfarin (1.6%). Notably, aspirin administration was associated with the lowest incidence of postoperative anemia (19%), followed by warfarin (22%), LMWH (23%) and DOACs (23%).

Chu et al carried out another retrospective study including 342401 patients undergoing major orthopedic surgery (231,780 total knee arthroplasty and 110,621 total hip arthroplasty), who received chemoprophylaxis with aspirin or anticoagulant drugs (warfarin, LMWH, DOACs, fondaparinux) for 7 days after surgery (9). The administration of aspirin was found to be associated with lower risk of post-operative VTE after total knee arthroplasty (adjusted odds ratio [OR], 0.34; 95% CI, 0.24-0.48]) and a similar risk of post-operative VTE after total hip arthroplasty (adjusted OR 0.82; 95% CI, 0.45-1.51) compared with conventional anticoagulant treatments.

Schab et al retrospectively compared data of 198 patients undergoing major orthopedic surgery without interrupting their aspirin therapy for cardiovascular prevention (44 unicompartmental knee arthroplasty and 154 total knee arthroplasty), with a control group consisting of 403 patients who were not taking antiplatelet agents (102 unicompartmental knee arthroplasty and 301 total knee arthroplasty) (10). No differences could be found between the two groups in early or late blood loss, as well as in transfusion rates. Notably, no difference was also observed in surgical time and length of hospital stay.

More recently, Anderson et al carried out a multicenter, double-blind, randomized, controlled study including 3424 patients undergoing total hip or knee arthroplasty, and who were then randomized to receive for 30 days once-daily oral rivaroxaban (10 mg) or the same dose of rivaroxaban during the first five days, then switched to aspirin (81 mg daily) after the fifth postoperative day. Interestingly, the results of extended prophylaxis with aspirin after five days of rivaroxaban were not significantly different from those obtained with extended rivaroxaban in the prevention of symptomatic venous thromboembolism (11).

Unlike the conclusions of Kim et al (1), recent evidence clearly attests that aspirin is more effective and safe than LMWH and warfarin for preventing VTE in patients undergoing major orthopedic surgery, and its efficacy and safety profile are globally comparable to those of DOACs in this clinical setting (7-11). Along with the well-known biological effects on both arterial and venous thrombi (12), aspirin has also some advantages compared to DOACs, including a much lower cost (i.e., an especially important aspect in low income countries) and no need for laboratory monitoring, an aspect that is now posing important challenges for clinical laboratories due to the constantly increasing number of DOACs licensed for use in many countries worldwide. Therefore, we believe that consideration should be made about increasing the use of this old but still effective drug for perioperative prophylaxis of VTE, especially in patients for whom the administration of DOACs may be challenging (i.e., in the elderly, or in patients with low compliance, impaired renal or liver function).

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Original article

Self-determination, healthcare treatment and minors in Italian clinical practice: ethical, psychological, juridical and medical-legal profiles

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Summary. *Background and aim:* The social role of the minor, as indeed that of the physician, has changed markedly. This transformation has given rise to new patterns and responsibilities in the management of healthcare procedures that involve minors. *Discussion:* According to international legislation, in the clinical setting, as in other areas of social life, minors have the right to be heard and to have their opinions taken into consideration as an increasingly determining factor, in accordance with their age and degree of maturity and discernment. The authors describe the right to information and the decision-making process when the patient is a minor and underline the role of the parties involved (physicians, parents, under-age patient, judge) in various circumstances. Specifically, the paper analyzes the ethical and legal issues relating to the entitlement to decisions concerning the medical treatment of children and assesses the importance that Italian law attaches to the will of minors in the healthcare choices that affect them. *Conclusions:* Healthcare workers are called upon to face new challenges in order to ensure that healthcare services are able to safeguard the interests of minors while, at the same time, respecting their will. How to evaluate children's competence to consent and how to balance the autonomy of parents and minors are crucial questions which the law courts in the various countries are increasingly being asked to address. These issues require close collaboration among various figures (parents, doctors, psychologists, judges) and imply the ethical need to undergo continuous training. (www.actabiomedica.it)

Key words: healthcare, minor, child, adolescent, autonomy, capacity, competence, pediatrics, surrogacy decision making

List of abbreviations
DSM, Diagnostic and Statistical Manual of Mental Disorders; NCB, National Committee for Bioethics.

Background

In the light of the enhanced role of minors, policies for their care and protection constitute a topical theme that involves several critical issues (1). Traditionally, references to minors have been associated with the categories of "protection" and "safeguard". This reflects the juridical incompetence of minors, who are regarded as the "object", rather than the "subject", of the decisions that concern them.

Within the framework of a broader trend of thought towards recognizing and safeguarding the rights of children and minors, international conventions and policies concerning adolescent health (2-4) have promoted a major transformation in the social role of the minor. Indeed, from being simply "protect-

ed subjects", minors have increasingly been regarded as holders of rights and capable of self-determination. In particular, the Convention on the Rights of the Child of 20 November 1989 expressly envisions (article 12) a fundamental right that is not only closely connected with the self-determination of minors, but is also a vehicle of their will: the right to be heard (5, 6). This new orientation is loaded with moral significance, in that it recognizes the minor as a person "as such", who is endowed not only with the rights and needs proper to every human being, but also with those specific necessities that the law defines as taking priority over the demands of parents. Moreover, the reference - required by Community legislation (EC n. 2201/2003) - to parental "responsibility", rather than "authority", imposes a new ethical value on the adult-minor relationship, in that it enhances the recognition of and respect for the minor's dignity, otherness, difference and non-belonging – in short, his/her moral equality. In parallel with this reshaping of the responsibilities attributed to parents, the areas of independence of adolescents – who are growing into citizens – are expanding. This development places boundaries on the authority of parents, who, in such areas, are called upon to engage in dialogic discussion with their children (7).

Recognition of the minor's status as a subject, however, cannot ignore the specific connotations of the "developing subject". Indeed, the precocious attribution of independence may hinder the acquisition of the true means of achieving it (8, 9). What, then, is independence? What does becoming independent mean, and under what conditions? Through the analysis of actual cases, the authors seek to provide answers to these questions.

Discussion

Decision-making competence in the maturing subject

The concept of decisional capacity is complex and multi-dimensional, and underlies many single capabilities that vary quantitatively and qualitatively in the same person on different occasions and in different situations. In neuropsychology, all the theoretical models, regardless of their complexity, describe decisional capacity as being supported by four specific abilities; regarded as four key conditions of the entire decision-making process, these are: the ability to express/manifest a choice; the ability to understand the information relevant to the choice; awareness of the meaning of the choice, and the ability to evaluate the choice rationally (10). These competencies are normally acquired at the age of about 11 or 12 years, when the individual's thought begins to operate within the framework of models of verbal ideation and becomes capable of abstraction and logical operations. Nevertheless, the crucial role of emotions in the decision-making process must be borne in mind. In this regard, the clinical and experimental findings of research in the neurosciences in recent years have revealed that – in contrast with earlier views – the lack of adequate emotional indicators (e.g. a pragmatic disorder of social communication, DSM 5) can interfere with the capacity to act and decide, even to the extent of rendering it impossible (11-13).Thus, the recognition and assessment of the minor's ability to express his/her own will, desires and opinions concerning aspects of his/her own health, from both a cognitive standpoint and an emotional and affective point of view, are clearly delicate (14).

From the juridical standpoint, Italian legislators have not yet agreed upon valid criteria for determining whether or not a minor is capable of discernment. The notion of the capacity for discernment, which is not present in the current Italian penal code (which refers to the capacity to understand and to will) is derived from Italian Law n° 149 of 28 March 2001 on the adoption and fostering of minors. This latter, in turn, derived the concept from the French text of the Convention on the Rights of the Child: "*enfant capable de discernement*". However, the English text, which is the official version, does not use the term *discernment*; rather, it refers to the concept of *level of understanding necessary for children to be considered as being capable of forming and expressing their own views* (point 36 of the explanatory report of the Convention). That is to say, it refers to minors who are able to form and express their own views, independently of the pressure exerted by third parties, as a result of the level of understanding they have reached. Moreover, it should be noted that the possession of this capacity does not require particularly well-developed or structured faculties. That

said, in the legislative sphere, in judicial proceedings and in many sectors of private life, the areas of a minor's self-determination have progressively broadened since the 1970s. This development has been accompanied by a concomitant downsizing and, especially, reinterpretation of adults' powers of upbringing and by a reassessment of parenting roles within the family (15). Indeed, although an individual's full capacity to act is legally recognized only at the age of 18 years, several laws attribute broad areas of self-determination to those who are below this age. This is particularly the case with regard to the sexual, familial and affective spheres, decisions concerning the subject's own body and person, creative capacities and status as offspring or parent. Indeed, in accordance with current legislation (Italian civil code, art. 84 and 250), at the age of 16 years a minor - if "emancipated" (children having a higher autonomy due to certain social circumstances) - can undertake paid employment, marry, acknowledge paternity/maternity of a child, and have access to voluntary abortion and contraception[a]. Moreover, the freedom and secrecy of a minor's correspondence are safeguarded both by the Italian Constitution (art. 15) and by the Convention of New York of 20 November 1989 (art. 16). In addition, Italian Law n° 281/86 grants a minor attending the second grade of secondary school the freedom to choose optional school subjects and religious education autonomously. Likewise, in accordance with general constitutional principles (articles 18, 39, 49 of the Italian Const.), minors have the right to participate in associations, join trade unions if they are working, and subscribe to political parties. Finally, the law is particularly attentive to the quality and continuity of family relationships and the need to seek the consent of the minor in the setting of those procedures that modify or orient – sometimes irrevocably – the individual's life project and the destiny of his/her personality[b].

Within the category of "minor", there is clearly a diversity of situations. Indeed, it is necessary to distinguish between the case in which the minor is a child and that in which he/she is a pre-adolescent or adolescent. A further distinction must be made between cases in which the minor possesses a given capacity for discernment specific to the issue being dealt with and cases in which this capacity appears to be premature, still developing or inadequate for the complexity of the situation under analysis.

Examination of the relevant laws reveals that legislators have ascribed ever greater autonomy to the minor, especially with regard to issues of identity, feelings and sexuality, adopting an orientation towards imposing the least possible limitation on the minor's decision-making capability. Striking a balance between the ethical principle of *benefit* and the correlated principle of *autonomy*, between the need for protection and claims to self-determination, however, finds its natural limit in cases in which the minor's choices are deemed to be irresponsible and conducive to harm or danger to the physical and/or mental integrity of the individual; in such cases, restrictive intervention on the part of the adult is invoked in the interests of safeguard and protection (16). In line with this orientation, parent-child controversies are increasingly being tackled with the aim not so much of safeguarding the parent's rights/duties as of pursuing the prevalent interest of the minor. Thus, the parent is endowed not with the power, but with the "responsibility", of bringing up the minor to become an adult capable of exercising his/her constitutional right of freedom.

The minor's opinion, discernment and consent: laws, principles and clinical practice

The informed participation of the patient is deemed to be essential to the success of medical treatment (17). Thus, the awareness and involvement of minors in therapeutic decisions, in accordance with their degree of maturity and discernment, are central to their interests. In keeping with this notion, the European Convention on Human Rights and Biomedicine of the Council of Europe (Council of Europe 1997) sets out a specific disposition regarding healthcare treatments for minors. Specifically, the text requires that "*the opinion of the minor be taken into consideration as an increasingly determining factor, in accordance with his/her age and degree of maturity*". A similar provision is contained in the latest version (2014) of the Deontological Code of Italian Physicians, Surgeons and Dentists, article 33 of which states: "*The physician is to provide minors with any information that can enable them to understand their health condition and the diagnostic and*

therapeutic procedures planned, in order to involve them in the decision-making process". Similarly, article 4 of the Nurse's Deontological Code (2009) states that: "*The nurse is to urge that the minor's opinion regarding therapeutic decisions be taken into consideration, in accordance with the individual's age and degree of maturity*". These documents, however, do not provide reference parameters for assessing the relationship between the age of the subject and his/her ability to understand. The commitment to involving the minor therefore seems to be left to the discretion of individual healthcare workers and their subjective professional resources.

This issue has been tackled with greater precision by the Italian National Committee for Bioethics (NCB) which has identified the following developmental stages (18):

1) a threshold age of 7 years, below which it is difficult to attribute to the minor the ability to understand;
2) the period between the ages of 7 and 12 years as the phase in which children begin to explore their own motivations and to compare these with what others say or do; hence the need for consent to be expressed jointly with the parents;
3) the period after the age of 12 years has been reached, during which the minor's consent or dissent can be deemed to be progressively informed.

In assessing scientific and ethical issues about reconstructive surgery in young people, the Italian NCB has highlighted the need to consider the specific vulnerabilities of these patients in relation to the particular age and physical, psychological and cognitive ongoing changes (19). Sometimes aesthetic impairment, however, may create a state of anxiety in patients and, even before that, in their parents; this condition may undermine a proper formation of a solid body image by reducing self-esteem of these patients (20). Nevertheless, legislative contributions regarding the minor's ability to express consent to medical procedures are somewhat heterogeneous and discordant.

With regard to the sphere of sex and procreation, Italian Law n° 194 of 22nd May 1978 recognizes the minor's will regarding access to the means of contraception, and grants female minors the right to request abortion, within the first 90 days, even without the consent of those exercising authority or guardianship, *when there are serious reasons that prevent or advise against consulting those persons who exercise authority or guardianship, or when such persons deny their consent or express discordant opinions.* In such conditions, the judge supervising guardianship may, *after taking into account the young woman's will and the reasons she adduces*, authorize her to decide autonomously.

Legislation concerning the transfusion of blood and blood components (Italian Law n° 219, 21st October 2005) allows *the donation of blood or blood components and the harvesting of stem cells and hematopoietic stem cells from the umbilical cord* in persons of at least 18 years of age, once informed consent has been obtained and their physical suitability has been verified. With regard to persons below the age of 18, consent must be obtained from those exercising parental responsibility, or from the legal guardian, or from the judge supervising guardianship. However, a minor who gives birth may donate hematopoietic stem cells from the umbilical cord after having provided informed consent.

Harvesting bone marrow for the purpose of transplantation, which is regulated by Law 52 of 6 March, 2001 (instituting the National Registry of Bone Marrow Donors) is apparently forbidden to minors. In reality, however, the doctrine holds that, in such cases, the above-mentioned Law 219/2005, which regulates the production and transfusion of blood derivatives, is to be applied. Indeed, the requirement that the subject be over the age of majority is deemed to apply only to non-consanguineous donors, while in the case of consanguinity, Law 219/2005 would be applicable. This broadens the spectrum of potential bone-marrow donors to encompass minors who have the consent of their parents, legal guardian or judge supervising guardianship; this is in line with the dispositions of the European Convention on Human Rights, which expressly allows minors to donate hematopoietic stem cells, though not organs, the donation of which continues to be forbidden. Allowing bone marrow to be taken from minors, without any age limit, once parental consent has been obtained, raises major ethical questions. Indeed, donations between consanguineous subjects may potentially arouse suspicion of constraint – moral constraint at least – within the family

setting[c]. As has rightly been pointed out by the National Committee for Bioethics, *current legislation does not seem adequately to consider the importance of the minor's will, which may conflict with that of the parents, nor the problem of possible abuse by parents of their power to consent to donation* (18). The doubts and controversies raised by the donation of organs and tissues by living donors persist in the case of harvesting from cadavers, not least on account of the underlying issue of the ascertainment of death. With regard to minors, the will of the individual is certified by the parents responsible; if there is disagreement between the parents, no availability for donation can be manifested. In order to avoid any abuse, the Italian law establishes that no statement of will can be provided for subjects who lack the capacity to act, nor for minors who are fostered or placed in care institutions (21).

A further area in which the minor's decision-making capability is relevant is that of experimentation. Specifically, Italian Legislative Decree 211/2003 *Implementation of the 2001/20/CE directive concerning the application of good clinical practice in the clinical experimentation of medicines for clinical use*" establishes that "*the experimenter must take into account the minor's explicit will to refuse to participate in the experimentation or to withdraw from it at any time, if the minor is capable of forming his/her own opinion and evaluating the information received*. Thus, the growing attention paid to the will of the minor finds only partial recognition in current legislation. What is seen is a weak form of self-determination which is manifested more as a right to resist healthcare treatment than as an exclusive entitlement to the right to refuse or consent to it. In Italy, unlike other countries, there is no law providing a precise indication of the age at which parental consent to decisions concerning a minor's health can be dispensed with[d]. While the indication of a general principle may leave excessive leeway for discretion in the application of the law, it nevertheless ensures the flexibility that the healthcare setting requires.

Parents in conflict over their children's health

When a parent's decision is clearly in conflict with a minor's interests, the juvenile court (JC) may impose restrictive measures on parental responsibility (articles 330, 333, 336 of the Civil Code) in order to safeguard the minor's health. If responsibility is to be limited, the JC will appoint a special guardian who, after consultation with healthcare personnel, will express the healthcare decisions deemed most suitable, and with which the parents must comply. This frequently occurs in the event of refusal of treatment, chiefly for ideological, religious or cultural reasons of the family, or when, as a result of psychiatric disorders, parents subject their children to continual treatment that is absolutely unnecessary. In this regard, the Italian Court of Reggio Emilia, when dealing with the question of the entitlement to take decisions on healthcare issues in the event of disagreement between the parents of a minor, recently adopted an absolutely innovative approach (22). The case involved a couple of separated parents who strongly disagreed between themselves as to who should take decisions concerning the health of their autistic son, thereby risking aggravating the boy's condition. The judicial authority confirmed that custody should be granted to both parents. At the same time, however, two independent subjects (the head of the institute for autism frequented by the boy and the director of the neuropsychiatry service of the Local Health Authority) were appointed to take the principal decisions concerning the process of rehabilitation and support undertaken on the basis of the minor's health. In addition, the Court entrusted implementation of this process to the social service responsible. This conclusion was motivated by the realization that the care required by the minor was so onerous and psychologically tiring as to be unsustainable by either of the parents. Custody of the minor was therefore granted to both parents, with the sole exception of the medical decisions to be taken in the interests of their son. This example, however, reveals the difficulty of actually implementing international and constitutional principles that are universally agreed upon. In practice, disagreements over healthcare choices are often settled by delegitimizing the will of parents and minor alike and assigning decisional power to the technical knowledge and medical culture prevailing at the time. Indeed, in the case cited, the judicial authority did not attach sufficient importance to the opinions of either the autistic minor or his parents, even though the etiology and treatment of the pathology in question are

frequently discussed. Further examples can be found in a whole range of cases in which minors' psychiatric and behavioral problems are dealt with by imposing restrictive measures on parental responsibility and by forcibly placing the young person in a therapeutic facility.

Conclusions

The issue of a minor's self-determination and of the legitimacy of medical procedures raises crucial problems. Not only does it touch upon the basic rights of minors, it also has legal-medical and ethical implications with regard to the questions of consent, privacy and compliance with professional secrecy (23, 24). Analysis of the literature reveals that the increasing importance assigned to the minor's opinions and will is exerting a growing influence in many spheres of civil life. Thus, in the healthcare setting, doctors are called upon to involve pediatric patients more actively in the therapeutic process, in accordance with the minor's capacity for discernment, which may even be recognized at a very early age. However, there is also an ethical imperative to ensure that this presumed autonomy does not result in the neglect of parental and medical duty or in the assignment of excessive responsibility and/or adult status to the minor. Indeed, in the absence of proper support in the making of healthcare choices, the risk is that of abandoning the minor in a state of anguished solitude at the very time in life when he/she is most vulnerable. On the other hand, we must not overlook the solitude of healthcare personnel and judges, who are increasingly obliged to take decisions, often in emergency situations, regarding highly intimate and subjective aspects of the person. On the one hand, the absence of specific legislation allows flexibility in decision-making and therefore fosters respect for the person's individuality. On the other hand, it imposes an attitude of humble prudence and the need to undertake ongoing major training.

In order to evaluate the minor's decision-making capacity in each specific situation, we need to implement measures of environmental support aimed at improving and strengthening the competences necessary for the subject's involvement. Whenever possible, the expression of the minor's will and his/her choices should always be deferred until a mediatory function has been assigned to the relationship between the doctor, the minor and his/her affective references (and legal representatives), a process that may be long and complex. This mediation should not sacrifice the will of the minor to the rights of parental responsibility and should aim to balance the interests of all the parties concerned.

Authors' contributions:
All the authors equally participated in the design of the work, drafted the manuscript and approved the final version of the manuscript.

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Notes

[a] Other competencies (prerogatives, liberties, duties, responsibilities) are granted to minors under 14 years of age, such as the autonomous right to sue, the possibility of facing legal charges, and consent to sexual intercourse. [b] The right to be heard is granted to a minor who has reached the age of 12 years (or younger, if capable of discernment) in proceedings concerning the separation of the parents (Italian Law n° 54/2006); at all stages of the adoption procedure (Italian Law n° 183/1984 and subsequent modifications); and in questions of filiation (Italian Legislative Decree 154 of 28 December, 2013). [c] We may remember the debate following the Decree of the Juvenile Court in Perugia on 26 April, 1999, which declared its lack of authority to issue a provision requested by the parents of a 14-year-old who asked to be authorized to donate bone marrow to his mother, who was suffering from a severe form of acute leukemia at high risk of recurrence, and whose bone marrow was compatible only with that of her younger son. The court ruled that Law 107/1990 did not allow this type of authorizing provision and, citing a potential conflict of interest between the parents and their son, appointed an independent guardian (with specific medical competence) who could provide consent on behalf of the young donor. This decision, however, proved controversial, in that article 3, clause 3, of Law 107/1990 allows platelets, leukocytes and bone marrow and peripheral stem cells to be harvested even from minors, once consent has been obtained from those exercising parental responsibility, the legal guardian or the judge supervising guardianship. In such cases, there is no necessity to appoint a guardian to provide consent in lieu of the parents, at least not when these latter have already explicitly expressed their consent. Others pointed out that the decision had not taken into account the will of the minor and the situation that might have arisen if the mother had died of the disease for want of transplantation: i.e., the minor's sense of guilt, the pain of bereavement and the deleterious effect of growing up without the mother. Mastrangelo G, Sellaroli V, Trattamento medico e lesioni all'integrità fisica del minore. Maggioli Editore, 2014. [d] For example, legislators in the UK and Quebec have established that minors cease to be deemed incapable at the ages of 16 and 14 years, respectively, with regard to healthcare treatment. Under Austrian law, a minor aged 14 years or over is presumed to be able to understand and to will, though parental consent is required in the event of medical intervention that may cause serious harm to the minor's physical integrity or personality. In other countries, such as the United States, Spain and Switzerland, evaluation that a minor's discernment is sufficient for the formulation of consent to highly personal acts is made on a case-by-case basis.

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Original article

Intramuscular oxygen-ozone therapy in the treatment of low back pain

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Summary. *Background and aim of the work:* Intramuscular paravertebral injections of ozone are minimally invasive, safe and efficacy in reducing pain and disability. The aim of this paper is to present the early results of paravertebral lumbar ozone injections in the treatment of low back pain. *Methods:* Between February 2011 and December 2015, a total of 109 patients underwent intramuscular paravertebral lumbar injections of ozone due to low back pain. Of them, 42 interrupted the treatment at a medium of 5.4 injections and were lost to follow-up. Of the 67 remaining patients, only 24 answered to our questionnaire. Local and radiating pain was assessed using a 10-cm horizontal Visual Analogue Scale. Perceived functional status and disability were evaluated using the Oswestry Disability Index, administered before treatment and one month after the last injection. *Results:* Visual Analogue Scale reduction was demonstrated in 23 out of 29 cycles (79%) of ozone therapy. Regarding disability evaluation, Oswestry Disability Index score reduction was assessed in all except one. No complications were recorded. Our results are similar to the other reports: 79% of patients had VAS reduction of 2.3 points and all except one patient reported ODI reduction (average reduction of 9%). *Conclusions:* Lumbar paravertebral oxygen-ozone injections are minimally invasive, safe, cheaper and effective in relieving pain as well as disability. This technique is easy to perform, it doesn't need computed-tomography or anesthesiologist support. We suggest its application in low back pain as first choice to replace intradiscal computed-tomography-guided infiltrations and to avoid or delay surgery. (www.actabiomedica.it)

Key words: low back pain, oxygen-ozone therapy, minimally invasive technique

Introduction

The efficacy of oxygen-ozone therapy in medicine is nowadays well defined and demonstrated in several fields, such as vascular diseases, infections, orthopedics and odontoiatry. Nevertheless, due to an improper empirical use by some practitioners, lack of standardization, ozone generators without appropriate photometer, and scarcity of scientific data, orthodox medicine tends to refuse ozone therapy.

The rational of its use is based on the exploitation of the chemical properties of ozone, an unstable allotropic form of oxygen. Ozone therapy has a direct (mechanical) and indirect (anti-inflammatory) effect (1). The direct effect consists in the lysis of the proteoglicans composing the disc's nucleus pulposus, which results in the release of water molecules and the subsequent cell degeneration of the matrix, which is then replaced by fibrous tissue, leading to a reduced disc volume (2). The indirect effect is realized by altering the breakdown of arachidonic acid to inflammatory prostaglandins. As result, by reducing the inflammatory components, there is a subsequent decrease in pain (3).

Regarding its use in orthopedic field, ozone can be administered through several ways, such as intra-

muscular, intradiscal, intraforaminal and periradicular. Usually, except for intramuscular way, the other need to be computed-tomography (CT)-guided and to be performed with anesthesiologist support.

Intramuscular lumbar paravertebral injections of ozone are minimally invasive, safe and efficacy in reducing pain, as well as disability and intake of analgesic drugs (2). The aim of this paper is to present the early results of paravertebral lumbar ozone injections in the treatment of low back pain (LBP) caused by several pathologies, such as discal bulging, disk herniation (DH), spondylolisthesis and lumbar stenosis.

Methods

Between February 2011 and December 2015, a total of 109 patients underwent intramuscular paravertebral lumbar injections of ozone due to LBP. Of them, 42 interrupted the treatment at a medium of 5.4 injections and were lost to follow-up. Seventeen of them had a reduced VAS, 14 had an increased VAS and 11 were stable. Finally, a total of 67 patients completed the 12 injections of ozone and were followed before and after treatment. Unfortunately, of the 67 patients, only 24 answered to our questionnaire. Their data, clinical aspects and results are summarized in table 1. There were 9 females and 15 males, with an average age of 66.2 years (range 46-88 years). All patients were studied with clinical evaluation, standard x-rays and Magnetic Resonance Imaging (MRI). All patients had a long clinical history, with an average of 6.5 years of LBP (range 1-20 years). Four of them underwent lumbar herniectomy before our treatment. LBP was due in 10 patients to lumbar discal bulging (LDB). Seven cases had LDB associated with sciatica without neurological deficits. Four patients had lumbar DH, 2 had lumbar stenosis and 1 had spondylolisthesis. Five of them underwent 2 cycles of injections.

Inclusion criteria were: LBP with or without sciatica (congruous with the level of pathology detected with MRI), VAS greater than 0 or in alternative ODI greater than 10%. Exclusion criteria were: neurological deficits, cauda equine syndrome, diabetic neuropathy, pregnancy and favism, in which ozone therapy is contraindicated. All patients were orally informed of the potential risks of treatment and written informed consent was obtained from all the subjects.

All procedures were performed in the outpatient clinic without anesthesiologist support. Each patient received 12 intramuscular injections (2/week) of an oxygen-ozone mixture (20 ml) with an ozone concentration of 27 ug/ml, obtained by means of a Multiossigen 98 HCPS generator (Multiossigen s.r.l., Gorle, Bergamo, Italy). The intramuscular injection was administered in the paraspinal lumbar muscles of the corresponding affected level, bilaterally (20 ml for each side), using an extraspinal lateral approach, under sterile conditions, with a 22-gauge needle. An injection time of 15 seconds was used, since longer injection time was deemed unsuitable because of the instability of ozone, which starts decaying after about 20 seconds (2). In order to promote homogeneous distribution of the gas through the muscular fibers, the injection site was gently massaged at the end of the procedure.

Local and radiating pain were assessed using a 10-cm horizontal Visual Analogue Scale (VAS), with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had”, administered before and after treatment. Perceived functional status and disability were evaluated using the Oswestry Disability Index (ODI), administered before treatment and one month after the last injection.

Results

All patients were retrospectively evaluated with VAS and ODI scale. The mean pre-treatment VAS score was 5.6 (range 0-10), while the mean pre-treatment ODI score was 34% (range 12-62%). After treatment, we obtained a reduction of 2.3 point of the VAS scale (mean value was 3.3) and of 9% of the ODI score (mean value 25%). Three patients underwent lumbar videoscopy after treatment, because of persistent LBP, of which 1 was a 79 year-old man with severe lumbar stenosis, 1 was a 65 year-old female with spondylolisthesis L5-S1 and the last was a 64 year-old man with multiple DH.

VAS reduction was demonstrated in 23 out of 29 cycles (79%) of ozone therapy (mean VAS score reduction 2.3); 6 of them had a VAS score increase (mean VAS score increase 2.5).

Table 1.

Patient	Gender	Age	Diagnosis	Duration of symptoms (years)	VAS pre-treatment	VAS post-treatment	ODI pre-treatment	ODI post-treatment (1 month)	Previous treatments	Treatments post-injection
1	F	48	LDB + sciatica	3	5	1	34%	22%		
2	M	48	LDB + sciatica	2	7	3	44%	20%		
3	F	65	Spondylolisthesis L5-S1	5	7	0	24%	16%		
3	F	65	Spondylolisthesis L5-S1	2	4	3	32%	22%		Lumbar videoscopy
4	F	72	LDB	1	0	2	12%	8%		
5	M	63	LDB	10	5	3	20%	4%		
5	M	64	LDB	10	5	1	30%	20%		
6	M	48	LDB	15	0	2	30%	20%		
7	F	48	LDB	2	6	5	16%	14%	Discectomy L5-S1	
8	M	87	LDB	2	5	3	38%	17%		
9	M	88	LDB + sciatica	8	7	4	44%	42%		
10	M	82	LDB	3	9	4	50%	42%		
11	M	64	HD L4-L5, L5-S1	8	8	2	42%	32%		Lumbar videoscopy
12	F	75	LDB + sciatica	2	8	5	48%	28%		
13	M	62	LDB	6	4	7	30%	30%		
14	M	79	Lumbar stenosis	4	5	9	20%	40%		Lumbar videoscopy
15	M	46	LDB + sciatica	7	8	5	62%	46%		
16	M	76	HD L4-L5	4	2	3	24%	18%	Discectomy L4-L5	
17	F	46	LDB	20	8	4	38%	20%	Herniectomy L4-L5	
17	F	48	LDB	20	4	2	26%	18%	Herniectomy L4-L5	
18	M	82	LDB	2	8	7	40%	28%		
19	F	80	Lumbar stenosis	10	8	2	58%	36%		
20	M	67	LDB	6	7	2	16%	16%		
21	M	76	HD L3-L4	1	6	1	22%	12%		
22	M	76	LDB + sciatica	5	7	5	48%	40%		
23	F	65	HD L3-L4, L4-L5	4	10	5	52%	42%		
23	F	66	HD L3-L4, L4-L5	9	1	4	44%	26%		
24	F	66	LDB + sciatica	10	7	1	26%	26%		
24	F	67	LDB + sciatica	10	2	1	26%	14%		

Abbreviations. M: male; F: female; VAS: Visual Analogue Scale; ODI: Oswestry Disability Index; LDB: lumbar discal bulging; HD: herniated disk.

Regarding disability evaluation, ODI score reduction was assessed in all except one patient (a 79 year-old man with severe lumbar stenosis). No complications were recorded.

Conclusions

LBP with or without sciatic nerve involvement affects roughly 70-80% of the population at least once

in their lifetime (4). Until 15 years ago, surgery was the treatment of choice, but conservative measures are now preferred in the wake of unsatisfactory surgical outcomes (5). The natural history of DH tends to be favorable in most cases; spontaneous regression of DH in longitudinal imaging studies has been reported (6) and a spontaneous resolution of pain within the acute phase (from 6 to 12 weeks after pain onset) has been documented in 60-80% of patients with sciatica (7). Nowadays, surgery is indicated only in patients with intolerable pain, progressive neurological deficits or risk of cauda equine syndrome (8). Surgical treatment of DH is reported to have a short-term success rate of 85-90%. The success rate tends to decrease to 70-80% during long-term follow-up (more than 6 months) as a result of the appearance of symptoms related to failed back surgery syndrome (9). Neurosurgeons have consequently tended to adopt a more conservative approach, and it is estimated that only 3-4% of all patients affected by LBP and/or sciatica receive surgical treatment in the United States (10).

Minimally invasive methods have been developed (such as corticosteroid and anesthetic injections, acupuncture, mesotherapy) in addition to physiotherapy and vertebral manipulation to treat LBP. Among them, there has been increasing use of oxygen-ozone therapy. Ozone has a double effect, direct and indirect, or mechanical and anti-inflammatory. Ozone has an oxidizing action and breaks down some of the glycosaminoglycans chains in the nucleus pulposus and reduces their ability to hold water, diminishing the size of herniation and subsequently contributing to reduce hernia impingement on the venus and arterial flow. This causes hyper-oxygenation and reduces pain by direct and indirect mechanism. Besides, ozone has an effect on the inflammatory cascade by altering the breakdown of arachidonic acid to inflammatory prostaglandins (3). Finally, the stimulation of fibroblastic activity by ozone results in the initiation of the repair process by stimulating collagen deposition (11,12).

Among minimally invasive methods, ozone can be administered through intradiscal way, intraforaminal, intramuscular (2,13,14) and periradicular. Several papers have already demonstrated good results with low costs and very rare collateral effects (1,2,13-19). While intradiscal injections seem to exploit mechanical and anti-inflammatory effect, paravertebral intramuscular injections probably use only the anti-inflammatory mechanism (3).

Periradicular and intradiscal injections have been proposed since the late 1990s as a treatment for lumbar DH (20-23). Since then, several retrospective and randomized controlled studies have been published confirming clinical success in 70-80% of patients (20-23). In 2003 Andreula et al. (1) reported the results of a study involving 600 patients, treated with intradiscal and periganglionic CT-guided injections of oxygen-ozone versus corticosteroid and anesthetic plus oxygen-ozone. They had better results in the last group with a success rate at 6 months of 78.3% and statistically significant difference between the 2 groups. In 2005 Bonetti et al. (16) described the outcomes of a randomized controlled study, reporting better results for oxygen-ozone intraforaminal injections versus periradicular infiltration of steroids. Muto et al. (17) in 2010 presented a retrospective clinical study involving 2900 patients with LBP and treated with intradiscal-intraforaminal oxygen-ozone CT-guided injections. At 1 year follow-up, they reported success rate of 75-80% for soft DH, 70% for multiple DH and 55% for failed back surgery syndrome.

We found only 3 papers dealing with intramuscular oxygen-ozone injections in LBP. The advantage of this kind of procedure is that can be performed free-hand in the outpatient clinic, without premedication or anesthesiologist support. The disadvantage is that it exploits only the anti-inflammatory effect of ozone. Melchionda et al. (14) reported the results of a matched pair study between paravertebral lumbar oxygen-ozone injections versus anti-inflammatory analgesic drugs. They had 80% success rate for oxygen-ozone treatment at 6 months follow-up versus 50% for the anti-inflammatory analgesic drug group. Paoloni et al. (2) conducted a multicenter, randomized, double-blind, simulated therapy-controlled clinical trial. Thirty-six patients received intramuscular-paravertebral ozone injections whereas 24 received simulated lumbar intramuscular-paravertebral injections with false needle. Patients who received ozone had significant lower pain scores (VAS was 0.66 in the study group and 4.0 in the control group) compared to patients who received simulated therapy. Sixty-one patients became

pain-free at a medium follow-up of 6 months. More recently, Apuzzo et al. (13) confirmed efficacy of intramuscular ozone injections in LBP: according their results, oxygen-ozone therapy was associated with better results in the short-term follow-up, whereas global postural re-education, alone or in combination with ozone, seemed to be associated with a further reduction in pain over time. Our results are similar to the other reports: 79% of patients had VAS reduction of 2.3 points and all except one patient reported ODI reduction (average reduction of 9%).

Our study has certain limitations: first of all the short term follow-up (1 month), second the small number of patients, due to a reduced compliance during treatment.

Lumbar paravertebral oxygen-ozone injections in the treatment of LBP are minimally invasive, safe, cheaper and effective in relieving pain as well as disability. In literature only a very small percentage of patients are reported to present side effects. This technique is easy to perform, it doesn't need CT or anesthesiologist support. We suggest its application in LBP (due to lumbar discal bulging, lumbar stenosis, spondylolisthesis and DH) as first choice to replace intradiscal CT-guided infiltrations and to avoid or delay surgery.

Level of Evidence: Level 4 retrospective study.

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Original article

A pilot study on sperm DNA damage in β-thalassemia major: is there a role for antioxidants?

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Summary. Excess iron deposition in patients with beta thalassemia major (BTM) causes excess free radical formation, damages the hypothalamic pituitary testicular axis and production of sperms with DNA defects. As antioxidants were reported to improve fertility in healthy males; their effectiveness to improve sperm DNA defects in adult males with BTM was studied. Twenty fully pubertal BTM patients were included consecutively, all had semen analysis; 10 were found to be azoospermic, so further analysis for sperms and DNA defects was conducted on the remaining 10 participants. Semen was analyzed for antioxidants in seminal plasma and sperms for defects including the DNA fragmentation index, sperm deformity index, teratozospermia index and acrosomal index. Participants were then given L-carnitine and N-acetylcysteine for 6 months. All semen parameters were reassessed after treatment. The sperm deformity index and teratozospermia index increased significantly after treatment from 1.90±0.33 to 2.46±0.61 and from 1.59±0.22 to 1.86±0.28 respectively. So, apparently antioxidants accentuated sperm deformities in men with BTM. Therefore, the results of this study are not in favour with the use of antioxidants in BTM patients for improving potential fertility. Larger studies, however, are needed to confirm these preliminary results. (www.actabiomedica.it)

Key words: thalassemia major, sperm analysis, antioxidants, fertility

Introduction

The improved care of patients with β-thalassemia major (BTM) poses a challenge for endocrinologists regarding their fertility potential once they reach adulthood. Hypogonadotropic hypogonadism affects 80-90% of BTM patients worldwide (1) which is largely mediated by iron deposition and generation of reactive oxygen species (ROS) (2). Oxidative stress affects the hypothalamic-pituitary-gonadal axis in a dose-dependent manner (3). The detrimental effects of ROS on sperm membrane, its structural components and nucleus are also well documented (2). Sperms are particularly vulnerable to oxidant mediated injury due to their high content of unsaturated fatty acids enriching their lipid membrane. This oxidant mediated injury, once initiated, will self-propagate into a vicious cycle culminating into loss of functionality and sperm death (4).

Functional sperm defects are by far the most common cause of human infertility identified till now (4). Only few studies addressed sperm DNA damage in patients with BTM (2, 5). It was thought to be solely related to iron overload (3) with recent evidence that desferrioxamine may have detrimental effect on spermatogenesis (5).

Antioxidant treatment in healthy males yielded controversial results (6-9) and a recent Cochrane review concluded that this form of treatment may improve the pregnancy rate and the live birth rates; however, the evidence is of low quality (10). L- carnitine increased pregnancy rates in spouses of males with idi-

opathic oligoasthenozoospermia (11). L-carnitine was lower in the seminal plasma of infertile males compared to that of fertile controls (12) and it improved sperm motility in infertile males (13-15). N-acetyl cysteine is a physiologic antioxidant that depends on reduced glutathione system to reduce the DNA fragmentation index (FI) as well as the sperm decondensation index (9).

The DNA FI is considered an indicator of improved sperm quality that is independent on morphology, count and motility (12). Antioxidants reduced oxidative stress caused by excess iron overload in BTM patients (16); however, data on the use of antioxidants for treatment of sperm DNA defects in pubertal males with BTM are lacking.

This study was an exploratory convenience interventional study that aimed at examination of potential sperm DNA damage in adult male patients with BTM and evaluation of the benefit of using L-carnitine and N-acetyl cysteine for the treatment of the existent DNA defects to fill this knowledge gap. We hypothesized that giving these antioxidants will improve sperm DNA defects in adults with BTM.

Patients

Participant recruitment into the study from the hematology/oncology and endocrinology clinics, Ain Shams University, continued over a period of 10 months from February – November 2015. Inclusion criteria included pubertal patients (Tanner stage 4 or 5) without endocrinopathies that could interfere with sperm production and willingness to participate. The exclusion criteria were: a) BTM patients with renal insufficiency; b) bone marrow transplanted patients; c) patients HIV positive and d) patients with cardiac failure.

Medical records were revised for age at diagnosis, frequency of blood transfusion, mean pre-transfusion hemoglobin level, chelation history and splenectomy. With regards to chelation therapy, 7 were using desferrioxamine while 3 were on deferiprone. Compliance of patients who were on desferrioxamine was defined as taking 30-50 mg/kg 5-7 times/week for at least 8 hours/week (17). Good compliance on oral deferiprone was defined as the patient taking the drug on >85% of days of the month, fair 50- 85% and bad <50% (18). Three patients (30%) had good compliance, four (40%) had fair compliance and three (30%) had bad compliance. The mean pre-transfusion haemoglobin level was 7.4±0.74 gm/dL.

Clinical evaluation included vital data, weight and height with calculation of standard deviation scores (SDS) (19) calculation of body mass index (20), chest, heart, abdominal examination and Tanner pubertal staging (21).

Methods

Metabolic and endocrinal investigation included fasting blood glucose (FBG), fasting insulin, serum calcium, phosphorus, parathyroid hormone (PTH), free thyroxine (fT4) and thyroid stimulating hormone (TSH), basal luteinizing hormone (LH), basal follicle stimulating hormone (FSH) and total testosterone.

Twenty fully pubertal BTM patients were included consecutively, all had semen analysis; 10 were found to be azoospermic, so further analysis for sperms and DNA defects was conducted on the remaining 10 participants, each one was followed up for a period of 6 months. Participants received L-carnitine: 2 g/day and N-acetyl cysteine: 600 mg/day for 6 months with a monthly review to check drug compliance and to provide treatment. All 10 zoospermic participants were compliant to treatment and follow up.

Semen samples were collected by masturbation after at least 3 days of abstinence at the beginning and end of study. Semen samples were examined within 30 minutes of liquefaction according to WHO guidelines (22).

Seminal plasma was obtained after centrifugation at 3500 rpm for 15 minutes, loaded into aliquots and stored at -80°C awaiting antioxidant analysis then used for measurement of superoxide dismutase, glutathione peroxidase and reductase. The deposits were used for sperm chromatin structure assay (SCSA).

Sperm motility was classified into four categories: rapid progressive motility (type a), slow progressive motility (type b), non-progressive motility and immotile spermatozoa, and was assayed at exactly 0.5 and 2h after liquefaction. Total progressive motility was

defined as the combination of type a and type b motility. Morphology was measured by recording the percentage of abnormal forms in the sample and types of abnormality (head, mid piece and tail defects).

Teratozoospermia index (TZI) was calculated as the total number of defects/number of sperms with defects. Sperm deformity index (SDI) was calculated as the total number of defects/total number of spermatozoa.

Acrosomal index (AI) was calculated as the total number of sperms-number of sperms with abnormal acrosome (sperms with absent acrosome plus sperms with small head) per 100 examined sperm (23).

Assays

SCSA was done by sperm DNA fragmentation test supplied by Halotech DNA-Bio Madrid. The method is based on the sperm chromatin dispersion test. Intact unfixed spermatozoa were immersed in an inert agarose microgel on a pretreated slide. An initial acid treatment denatured DNA in those sperm cells with fragmented DNA. Following this, the lysing solution removed most of the nuclear proteins, and in the absence of massive DNA breakage produced nucleoids with large halos of spreading DNA loops, emerging from a central core.

However, the nucleoids from spermatozoa with fragmented DNA either did not show a dispersion halo or the halo was minimal. A minimum of 500 spermatozoa per sample were studied, adopting the criteria of Fernández et al. (24). Cells close to the edge of the micro gel were not scored. Spermatozoa without DNA fragmentation were either spermatozoa with big halo; those whose halo width is similar or higher than the minor diameter of the core or spermatozoa with medium sized halo; their halo size is between those with large and very small halo. Spermatozoa with fragmented DNA were either spermatozoa with small halo; the halo width is similar or smaller than 1/3 of the minor diameter of the core, spermatozoa without halo or spermatozoa without halo and degraded; those that show no halo and present a core irregularly or weakly stained. Cell nuclei which do not correspond to spermatozoa were distinguished by the absence of tail.

Antioxidant enzymes were assayed by the commercially available manual kinetics kits supplied by RANDOX. The analysis was done spectrophotometrically on Biosystem BTS 330 supplied by MYCO.

The method used for superoxide dismutase (SOD) employed xanthine and xanthine oxidase to generate superoxide radicals which reacted with 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT) to form a red formazan dye. The superoxide dismutase activity was then measured by the degree of inhibition of this reaction. One unit of SOD is that which causes a 50% inhibition of the rate of reduction of INT under the conditions of the assay.

Glutathione peroxidase (GPX) and Glutathione reductase (GSSG) was based on the method of Paglia and Valentine (25).

Hormonal assessments

FBG, calcium and phosphorus were measured by Cobasintegra 800 autoanalyzer supplied by Roche Diagnostics. Serum FSH, LH, TSH, FT4, total testosterone, PTH, insulin and ferritin were measured by Architect I series autoanalyzer supplied by Abbott Ireland Diagnostics Division.

Ethical approval

All patients were informed about the aim and the methods of the study. All patients signed an informed consent prior to recruitment, and the study protocol was approved by the local ethics committee of Ain Shams University.

Statistical analysis

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution. Chi-square test was used in the comparison between two groups with qualitative data

and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution were done by using Independent t-test while comparison between two groups with non-parametric data was done by using Mann-Whitney test. The paired groups with quantitative data and parametric distribution were compared by using Paired t-test; while the non-parametric distribution was done by using Wilcoxon-rank test.

Spearman correlation coefficients were used to assess the relation between two quantitative parameters in the same group. The confidence interval was set to 95% and the margin of error accepted was set to 5%.

Results

Descriptive data of the included patients with comparison of azoospermic and zoospermic participants are shown in table 1. Both groups of participants differed only regarding the frequency of blood transfusion and the mean pre-transfusional haemoglobin level. Testicular volumes were significantly lower in azoospermic males with BTM as well as FSH and total testosterone.

Semen analysis data of the zoospermic participants before and after treatment are listed in table 2 and the statistical comparison is shown in table 3 where it is evident that serum ferritin didn't show significant difference after treatment and didn't correlate with any of the semen or seminal plasma parameters. All participants had a DNA FI of less than 30% before treatment. The number of mid-piece with defects, TZI and SDI increased significantly after treatment with L-carnitine and N-acetyl cysteine for 6 months. There were no significant changes in the DNA FI or the AI (table 3). Glutathione peroxidase, glutathione reductase and superoxide dismutase levels in seminal plasma didn't differ significantly before and after treatment and didn't correlate with any of the indices of sperm damage (table 3).

Table 1. Comparison between clinical and laboratory data of the included participants

	Azoospermic participants	Zoospermic participants	p
Age (years)	24.4±4.43	25.00±3.68	0.745
Weight (kg)	63.80±11.75	66.55±6.618	0.527
Height (cm)	163.60±8.76	170.3±7.79	0.087
Height SDS	-1.67±1.32	-0.662±1.172	0.088
BMI (kg/m^2)	23.81±4.1	22.914±1.191	0.515
BMI SDS	0.02±0.67	0.012±0.93	0.983
Age of onset of blood transfusion (months)	6.4±0.52	6.5±0.5	0.666
Frequency of blood transfusion (per year)	26.4±5.06	17.0±9.89	0.015*
Mean pre-transfusional haemoglobin level (gm/dl)	6.8±0.48	7.4±0.74	0.045*
Age at splenectomy (years)	7.6±2.17	10.0±3.53	0.084
Serum ferritin (ng/ml)	1328.4±477.12	2054.20±1507.10	0.164
Cigarette Smoking			
Smokers	2 (20%)	2 (20%)	0.513
Non-smokers	8 (80%)	8 (80%)	
Right testicular volume (ml)	15.9±3.07	19.5±3.69	0.029*
Left testicular volume (ml)	15.3±3.50	19.20±4.18	0.036*
Calcium (mg/dl)	8.93±0.92	9.83±0.33	0.009*
Phosphorus (mg/dl)	5.62±1.91	4.55±0.48	0.102
Parathyroid hormone (pg/ml)	41.59±20.21	47.98±19.06	0.476
Thyroid stimulating hormone (uIU/ml)	2.62±1.65	2.48±0.83	0.811
Free thyroxine (ng/dl)	1.05±0.2	0.86±0.18	0.040*
Fasting insulin (IU/ml)	5.71±4.03	5.33±1.48	0.782
Serum ferritin (ng/ml)	1328.40±477.12	2054.20±1507.1	0.164
Basal LH (mIU/ml)	5.97±4.01	4.60±1.79	0.336
Basal FSH (mIU/ml)	2.55±1.61	5.27±2.87	0.018*
Total Srum Testosterone (ng/ml)	4.21±2.88	9.15±3.66	0.003*

Table 2. Semen analysis parameters before and after 6 months of antioxidant treatment

	TMCM (1)	TMCM (2)	PM% (1)	PM% (2)	NF% (1)	NF% (2)	TZI (1)	TZI (2)	SDI (1)	SDI (2)	AI (1)	AI (2)	DNA FI (1)	DNA FI (2)
1	58.5	37.8	20%	15%	3	1	2.04	2.16	2.28	3.18	68	34	11%	15%
2	46.2	78.37	10%	10%	11	4	1.4	1.8	1.5	2.3	74	56	5%	11%
3	111.6	90	20%	25%	13	16	1.4	1.7	1.5	1.4	60	64	5%	3%
4	70.4	15	15%	10%	0	0	1.7	2.32	2.1	3.3	64	34	20%	12%
5	51.6	44.4	15%	35%	4	14	1.8	1.6	2.26	1.9	56	58	6%	7%
6	3.5	7.78	0%	5	4	4	1.52	2.25	1.88	2.84	56	46	13%	10%
7	225	205.8	35%	40%	3	6	1.69	1.5	2.26	1.88	38	60	8%	5%
8	62.8	108.8	2%	2%	2	1	1.57	1.717	2.06	2.52	50	48	8%	25%
9	70	49.5	35%	20%	7	2	1.44	1.877	1.58	2,9	78	26	5%	7%
10	174	196.5	15%	20%	2	6	1.3	1.7	1.6	2.4	72	40	14%	9%

(1)=Before treatment, (2)=After treatment, TMCM=Total motile count in millions, PM=Progressive motility, NF%=Normal forms per 100 examined sperms, TZI=Teratozospermia index, SDI=Sperm deformity index, AI=Acrosomal index, DNA FI=DNA fragmentation index

Table 3. Comparison of serum ferritin and semen analysis parameters before and after 6 months of antioxidant treatment

	Before treatment Mean±SD Median (IQR)	After treatment Mean±SD Median (IQR)	p
Serum ferritin (ng/ml)	1059 (845-3744)	1136.5 (790-2376)	0.224
Sperm count in millions/ml	29 (26)	45.5 (30-51)	0.151
Total motile count in millions	66.4 (60)	63.94 (71)	0.799
Progressive motility%	15 (10)	17.5 (15)	0.616
Non-progressive motility%	39.8%±6.7%	37.3%±8.2%	0.299
Final total motile count after centrifugation	13.54 (10.4-24)	16 (13.8-22.8)	0.248
Spermatogenic cells in millions/ml	0.36±0.08	0.44±0.25	0.343
Normal forms per 100 examined sperms	3.5 (2-7)	4 (1-6)	0.751
Abnormal forms per 100 examined sperms	95.1%±4.2%	94.2%±6.4%	0.599
Number of heads with defects per 100 examined sperms	84.20±7.02	87.20±11.12	0.379
Number of mid-piece with defects per 100 examined sperms	46.00±10.54	56.70±17.45	0.038*
TZI	1.59±0.22	1.86±0.28	0.020*
SDI	1.90±0.33	2.46±0.61	0.020*
AI	61.60±12.18	46.60±12.86	0.062
DNA FI	8 (5-13)	9.5 (7-12)	0.696
GPX (U/L)	3083±790.99	3630±1013.3	0.188
GR (U/L)	29.6±12.18	36.2±15.84	0.405
SOD (U/L)	120.8±25.5	146.7±35.53	0.106

*= significant difference.
Values are mean±standard deviation (SD) or median (IQR). TZI=Teratozospermia index, SDI=Sperm deformity index, AI=Acrosomal index, DNA FI=DNA fragmentation index, GPX=Glutathione peroxidase, GR=Glutathione reductase, SOD=Superoxide dismutase.

Discussion

This study showed that zoospermic adult males with BTM had significantly higher mean pre-transfusional hemoglobin and lower frequency of blood transfusions with no other significant differences regarding history or anthropometric measures compared to their azoospermic counterparts. Genetic modifiers which control the rate of hemolysis and the phenotypic severity of thalassemia (26) may thus have a role in the development of late onset male hypogonadism (27) that manifests by aspermia. This link between ge-

netic modifiers and sperm production in males with BTM has not been addressed before and this association needs verification by further studies.

This study shed some light on an unknown aspect regarding spermatogenesis in BTM which is still an evolving subject and very little is known about it as up to two thirds of patients with BTM have pubertal problems ranging from pubertal failure to infertility (28). Less than half of males with BTM who progress to full sexual maturity have adequate sperm count and motility (29). Moreover, chelation therapy poses some risk to normal spermatogenesis (30) which puts an additional burden on achieving normal fertility in these patients.

A previous study on 6 patients with BTM pointed to the presence of sperm DNA damage and the degree of this damage correlated with the degree of iron overload (1). However, in our study serum ferritin didn't show any correlation with markers of DNA damage and our participants had a lower median for serum ferritin than the study by Perera et al. (1). All of our participants had a DNA FI of <30% i.e. below the critical value above which DNA damage was demonstrated to reduce the pregnancy rate thus having a negative effect on fertility (31). Increased sperm DNA FI was consistently associated with reduced fertility in several studies (32-34). In this study, DNA FI didn't differ significantly after antioxidant treatment; however, other parameters of sperm damage; number of middle piece with defects, SDI and TZI increased significantly. This was considered a potential side effect of treatment with L-carnitine and N-acetyl cysteine in the studied BTM patients.

Our observations support the findings of Ménézo et al. (12) who reported some untoward effects of using antioxidants in the form of increased sperm DNA decondensation by 25%. They attributed the accentuated decondensation to the deleterious effect of the powerful antioxidant vitamin C on chromatin packaging and the tertiary structure of sperm DNA. Therefore the use of antioxidants in those whose sperm decondensation exceeds 20% is not recommended to avoid reaching the 28% threshold that adversely affect the occurrence of pregnancy due to its negative effect on sperm DNA compaction during the pre-implantation event, a process which needs good paternal gene expression in order to achieve pregnancy and avoid chromosomal anomalies (12). The increased TZI and SDI in our study advocate against the use of antioxidants in men with BTM to improve fertility as the SDI negatively correlates with the fertilization rate in conventional in vitro fertilization techniques and predicts fertilization failure (35).

Our study carries some limitations: Firstly, DNA fragmentation was normal in all men. Therefore, this made evaluation of DNA fragmentation changes challenging. Secondly, the study analysis was possible only in 10 BTM patients. Nevertheless, our study gives further information on spermatogenesis in thalassemia major patients and to our best knowledge, this pilot study is the first to evaluate the effects of antioxidants in patients with BTM.

Conclusion

Zoospermic participants with BTM had no significant sperm DNA damage as evidenced by their DNA FI; however, they showed significant increase in the SDI and TZI with the use of antioxidants. Therefore, the results of this study are not in favour with the use of antioxidants in BTM patients for improving potential fertility. Larger studies, however, are needed to confirm these preliminary results.

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Original article

The frequency of hypothyroidism and its relationship with HCV positivity in patients with thalassemia major in southern Iran

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Summary. *Introduction:* Hypothyroidism is one the most complication due to iron overload in patients with β-thalassemia major (TM). On the other hand these patients are prone to Hepatitis C virus (HCV) infection that can cause thyroid dysfunction by itself or as the side effect of treatment with interferon (INF) or IFN plus ribavirin. The aim of this study is to evaluate the association of hypothyroidism with HCV positivity and serum ferritin levels in patients with TM. *Methods:* In this cross-sectional study, 201 randomly selected patients with TM who were registered at the Thalassemia Clinic of a tertiary hospital in Shiraz, southern Iran were investigated. Thyroid function tests and serologic screening assays for HCV seropositivity (HCV Ab and HCV-RNA) were conducted for all patients. *Results:* Frequency of hypothyroidism was 22.9% including 19.9% subclinical hypothyroidism, 2% primary overt hypothyroidism and 1% central hypothyroidism. Eighty six patients (42.8%) were HCV Ab positive and 60 patients (29.9%) were HCV RNA positive. No significant relationship was found between hypothyroidism and HCV positivity or receiving IFN-α (P>0.05). Hypothyroidism showed a borderline significant association with high serum ferritin levels in TM patients (P=0.055). *Conclusion:* Our results showed no significant association between hypothyroidism and HCV infection in TM patients. It seems that the main mechanism of hypothyroidism in our patients is iron overload; however, for better evaluation a larger multicenter study is recommended. Also due to the importance of consequences of HCV infection, more careful pre-transfusional screening of blood should be considered in TM patients. (www.actabiomedica.it)

Key words: hypothyroidism, hepatitis C, iron overload , thalassemia major

Introduction

Red blood cell transfusion is the main treatment of β-thalassemia major (TM) patients but it leads to excessive iron stores and causes endocrine complications, such as thyroid dysfunctions (1-6). Prognosis and longevity in TM patients have improved in the last 20 years due to recent medical advances in transfusion and iron chelation therapy (1, 7). A chronic hepatitis, secondary to hepatitis B and C virus infections, due to the frequent blood transfusions, frequently occur in TM patients (8).

In patients with chronic hepatitis C, thyroid dysfunctions can occur with an autoimmunity mechanism. Thyroid autoantibodies such as anti-thyroperoxidase (TPO) and anti-thyroglobulin (TGA) are detected in chronic hepatitis C patients even without treatment with IFN-α and ribavirin. Innate immune system in response to viral infection can induce endogenous IFN-α and β in thyroid gland. Endogenous and exogenous IFN can cause production of thyroid antibodies by NK cells memory T cell activation (9).

Combination therapy with pegylated interferon (PEG-IFN) and ribavirin remains the choice of treatment for hepatitis C. In addition, in patients treated with IFN-α and ribavirin, thyroid dysfunctions ,including hypothyroidism, hyperthyroidism and thyroiditis, can occur. [10-12] PEG-IFN plus ribavirin can cause hypophysitis in chronic hepatitis C patients, which can cause a central hypothyroidism (9, 10). In a review article, an autoimmune thyroiditis has been reported in up to 20% of the patients during IFN treatment (11). The IFN-α molecule and ribavirin have immunomodulating properties and may act on thyroid gland through a direct toxic effect and/or autoimmune mechanism (induction of TSH receptor autoantibodies, antithyroid autoantibodies, thyroid cell apoptosis, cell mediated immunity, expression of major histocompatibility complex and cytokine production regulation).IFN-α in cultured human thyroid cells inhibited iodine organification and T4 release, and can aggravate the preexisting autoimmunity in chronic hepatitis C patients (9, 10, 12, 13).

Furthermore, the occurrence of central hypothyroidism as a possible effect of hepatitis C virus and/or adverse effect of IFN-α and ribavirin treatment is not rare (14).

Chronic liver disease can cause abnormalities in liver function tests, e.g. TBG elevation, which can cause elevation of T3 and T4. However, free T4 and TSH are usually normal. Serum T3 can be normal, increased or decreased, diminished conversion of T4 to T3 can cause low serum T3. Despite the remarkable changes of thyroid values, most patients have normal TSH and FT4 levels (15).

The aim of this study was to determine the association of the frequency of hypothyroidism with HCV positivity, antiviral therapy with IFN-α plus ribavirin, and with serum ferritin levels in TM patients.

Methods

This study was a cross sectional survey that was carried out on 201 patients older than 10 years at Thalassemia Center of a tertiary hospital in Shiraz, the capital of Fars province in the south of Iran from Feb 2014 to Feb 2015. The study was conducted at the Hematology Research Center of Shiraz University of Medical Sciences and was approved by the Ethics Committee of Shiraz University of Medical Sciences (registered with grant no 3450). Written consent form was obtained from the patients or their legal parents.

Study participants

The participants in this study were TM patients, aged 11-42 years who had regular follow-up schedule and regular blood transfusions with a frequency of 2-4 weeks.

Systematic random sampling was used to determine our sample group from all 700 registered patients at Thalassemia Center of tertiary hospital in Shiraz. The inclusion criteria were: TM patients older than 10 years, under regular follow up and regular blood transfusion; patients treated with chelating agents including deferoxamine, deferiprone or deferasirox and patients living in an iodine sufficient area (16, 17). Patients wth thalassemia Intermedia, cirrhosis, heart failure, renal failure, history of previous treatment with L-thyroxine were excluded from the study. Individuals taking medications affecting the thyroid function test (such as: steroids, anticonvulsants, propranolol, amiodarone, salicylates, furosemide, lipid lowering agent) and pregnant women were also excluded from the study.

After applying the above exclusion criteria, 201 subjects were eligible for the study.

An extensive medical history including data on age at first transfusion, duration and type of iron chelation therapy, compliance with treatment, and associated complications were obtained.

Physical examination included anthropometry (weight, height, BMI), vital signs (blood pressure, heart rate) and pubertal assessment.

Body mass index (BMI) was calculated as the body weight divided by the height squared (Kg/m^2).

A subject was considered overweight when the BMI was between 25 and 29.9 and obese when the BMI was above 30.

Biochemistry

Blood samples were drawn in the morning after an overnight fast to measure the serum concentrations of glucose, FreeT3, FreeT4, TSH, TotalT4, Total T3, urea, creatinine, electrolytes ,calcium,phosphate and total proteins.

In order to exclude severe liver injury and dysfunction, serum concentrations of alanine aminotransferase (ALT), gamma glutamyl transferase (γGT), alkaline phosphatase (ALP), total and direct bilirubin, albumin, prothrombin time (PT) and international normalization ratio (INR) were measured. Serologic screening assays for hepatitis C virus seropositivity (HCVab and HCV-RNA) were also obtained.

All biochemical and serologic tests were carried out in accordance with the routine procedures of the central laboratory.

Iron stores were assessed by an indirect method. Serum ferritin was measured by electrochemiluminescence immunoassay. Reference range values were 30-350 μg/l in males and 15-150 μg/l in females

Thyroid hormones were measured by the automated Cobas electrochemiluminescence (ECLIA) technique, using commercial kits from Roche Diagnostics (Mannheim, Germany) using Elecsys 2010 analyzer and molecular analytics E170.

The intra-assay and inter-assay coefficients of variation (CV) of our assays were between 1.6% and 3.5%, respectively.

Definition of hypothyroidism

Hypothyroidism was categorized in three categories:

A) Primary overt hypothyroidism: elevated TSH level (> 10 mIU/L) associated with low levels of thyroid hormones

B) Subclinical primary hypothyroidism: elevated TSH level (>4.2 mIU/L - <10 mIU/L) with normal thyroid hormones

C) Secondary hypothyroidism: normal-low TSH level and normal-low T4 and FT4

Statistical analysis

Data were analyzed by SPSS software version 17. Normality of data was checked by Kolmogorov Smirnov test. Descriptive data were shown as mean, standard deviation, or median, range and percentage. Comparison of qualitative data was carried out using Chi-square test. Quantitative data were compared between the two groups of patients using student t test or Mann Whitney test. P value less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics of the TM patients are summarized in Table 1. Mean age of the patients was 22.9±5.1 and ranged from 11 to 42 years, 49.3 % of them were females and 50.7% were males.

According to the patient's medical history some of these patients have had multiple endocrinopathies such as: hypoparathyroidism 27.4% [37 patients], hypogonadism 56.9% [66 patients], diabetes mellitus type I 18.2% [31 patients], and diabetes mellitus type II 7% [12 patients].

Overall 86 out of 201 patients (42.8%) were HCV Ab positive and 60 patients (29.9%) had HCV RNA positivity; of whom 56 patients received IFN-α plus ribavirin.

Overall frequency of hypothyroidism was 22.9% (46 patients) in the studied population. Including 19.9% (40 patients) with subclinical hypothyroidism, 2% (4 patients) with primary overt hypothyroidism and 1% (2 patients) with central hypothyroidism .

In Table 2, two groups of patients with and without hypothyroidism were compared based on sex, age, serum ferritin levels, HCV positivity and receiving IFN-α. Frequency of patients with HCV positivity or receiving IFN-α was not significantly different in euthyroid and hypothyroid patients. Serum ferritin levels showed a borderline significant association with hypothyroidism (median (range): 2936 (928-9500) ng/ml in hypothyroidism vs 2148 (106-19043) in euthyroid patients, P=0.055).

Table 1. Characteristics of patients with beta thalassemia major

Parameter	Value
Age (year) Mean±SD	22.9±5.1
Age at diagnosis of thalassemia (month) Median (range)	6 (2-9)
Age of HCV positive patients(year) Mean±SD	25±5
Age at diagnosis of HCV hepatitis(year) Mean±SD 18±7	
BMI (kg/m²) Mean± SD	19.5±3.3
Serum ferritin levels (µg/L) Median (range)	2256 (106-19043)
Desferoxamine (number,%)	180 (90)
Deferiprone (number,%)	80 (40)
Deferasirox (number,%)	20 (10)
Hypoparathyroidism (number,%)	37 (27.4)
Hypogonadism (number,%)	66 (56.9)
Diabetes mellitus type I (number,%)	31 (18.2)
Diabetes mellitus type II (number,%) SD: standard deviation	12 (7)

Table 2. Comparison of euthyroid β-thalassemia major patients and patients with hypothyroidism regarding sex, age and serum ferritin levels as well as HCV positivity and receiving IFN-α

	Euthyroid N=155	Hypothyroid N=46	P value
HCV RNA PCR Positive	48 (31%)	12(26.1%)	0.586
HCV Ab ELISA Positive	68 (43.9%)	18 (39.1%)	0.614
Receiving IFN-α	44 (28.6%)	12 (26.1%)	0.853
Serum ferritin (ng/ml)	2148 (106-19043)	2936 (928-9500)	0.055
Sex (Male)	74 (47.7%)	28 (60.9%)	0.131
Age (year)	23.1±5.5	22.7±3.8	0.631

All data are presented as number (percent) except age (mean ± SD) and serum ferritin levels (median and range)

Discussion

In this study, the frequency of hypothyroidism in patients with TM was determined. Also the relationship of hypothyroidism with HCV infection and iron overload were evaluated. Overall frequency of hypothyroidism was 22.9% including 19.9% subclinical hypothyroidism, 2% primary overt hypothyroidism and 1% central hypothyroidism. Our results support the fact that primary hypothyroidism is the most common form of thyroid dysfunction observed in these patients and it is resulted mainly because of abnormalities of the thyroid gland which leads to insufficient production of thyroid hormones (4). Iron overload secondary to multiple blood transfusions is the main cause of such complications hence proper and effective iron chelation therapy is essential for inducing a reduction of iron overload in various endocrine glands (1, 3, 5, 6). Similar to our study, hypothyroidism has been reported from 4% to 21.6% of TM patients with different severity, (11, 14, 18, 19). Zervas et al. reported a frequency of 4% for overt hypothyroidism, and 12.5% for subclinical hypothyroidism (3).

In the past, the reported prevalence of primary hypothyroidism in Iranian TM patients living in Shiraz was about 6% (personal observations) but in the present study the prevalence was lower (2%). On the contrary, the prevalence of subclinical primary hypothyroidism seems to be higher than before(19.9%). It is probably due to the better management (blood transfusion and chelation therapy) available in the last decade in patients followed in our Center.

Endocrine complications are mainly attributed to iron overload (1, 4, 5) and are uncommon in optimally treated patients (6). In our patients, serum ferritin levels showed a borderline significant association

with hypothyroisim; however, if we used more accurate methods such as T2MRI of heart and liver, the results were more precise and reliable. These diagnostic methods can be more helpful in early detection of iron deposition in the endocrine glands compared to serum ferritin levels (18, 19). Also if we had a larger sample size the difference probably will be more significant.

Overall 88 TM patients (42.8%) were HCV Ab positive and 60 patients (29.9%) were

HCV RNA positive. Fifty-six TM patients (28%) were receiving IFN-α and ribavirin.

It is well known that hepatitis C can induce autoimmunity as extra hepatic manifestation and hypothyroidism is more common in patients with chronic hepatitis C even in the absence of INF treatment.

This may be due to an autoimmune process that impairs thyroid hormone, however, a direct relation between HCV infection and thyroid diseases has been also suggested.

IFN has important immunomodulatory properties due to which it can induce autoimmune phenomena like autoimmune thyroiditis with hypo - or hyperthyroidism (20). Autoimmune thyroiditis has been reported in up to 20% of patients during IFN-based therapies (9). Little information are available in literature about the development of central hypothyroidism in these patients.

Zantut-Wittmann et al. evaluated 308 HCV patients treated with standard INF-α and/or PEG-IFN associated with ribavirin. FT4 and TSH levels were measured before, during and after treatment. Before treatment, 18 patients (5.8 %) presented central hypothyroidism (CH) and twelve patients developed CH during the treatment. Among the 29 patients (9.4 %) with CH, 11 patients were treated with IFN-α, six used PEG-IFN and 12 patients used two or more therapeutic schedules (14).

The prevalence of CH estimated in general population is about 1 in 80,000 to 1 in 120,000. In our study we found two cases of CH out of 201 TM patients which is higher compared to general population (21). This could be due to the population selected in our study, which included TM patients who are prone to develop thyroid dysfunction, secondary to iron deposition in the pituitary and thyroid (5, 6, 8). Furthermore, the assessment of thyroid function in our TM patients was evaluated just after treatment and, despite CH being more prevalent than normal population, there was no significant correlation between TM patients receiving INF and development of CH, and also between HCV positivity and CH.

Therefore, we believe that more studies are needed to evaluate this possible effect of HCV and IFN-α in TM patients (22-25).

In conclusion, our results showed no significant relationship between hypothyroidism and HCV infection in TM patients. It seems that the main mechanism of hypothyroidism in our patients is iron overload; however, for better evaluation a larger multicenter study is recommended. On the other hand, due to the importance of high mortality and morbidity related to HCV infection, it is recommended that more careful pre-transfusional screening of blood for anti-HCV should be introduced in our blood banks and better assessment for thyroid dysfunction is needed in HCV positive TM patients especially in those who are receiving IFN.

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Original article

One-year experience in carotid endarterectomy combining general anaesthesia with preserved consciousness and sequential carotid cross-clamping

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Summary. *Background and aim of the work:* We report 1-year single-centre experience in carotid endarterectomy (CEA) combining general anaesthesia with preserved consciousness (GAPC) and standardized carotid sequential cross-clamping, for our protocol effectiveness evaluation in reduction of perioperative stroke, death or cardiologic complications. *Methods:* We considered all patients who underwent CEA in 2016. All patients underwent superficial cervical plexus block and GAPC with Remifentanil. The surgical technique consisted of common carotid artery (CCA) cross-clamping, carotid bifurcation isolation, external (ECA) and internal carotid artery (ICA) cross-clamping. After CCA cross-clamping, we performed a neurological tolerance test (NTT); this allowed selective shunting only for positive NTT. Primary end-points were: transient ischemic attack (TIA)/stroke, myocardial infarction, death in perioperative period. Secondary end-points were: carotid shunting, peripheral cranial nerves injuries (PCNI), GAPC intolerance, other complications, reintervention in perioperative period, length of hospital stay. *Results:* 104 consecutive patients underwent CEA with this protocol in the considered period. Twenty-seven (25.9%) patients were symptomatic. Mean clamping time was 48±13.5 minutes. Five cases (4.8%) requested internal carotid artery shunting. No TIA/stroke, myocardial infarction or death were recorded in the perioperative period. PCNI were observed in 19 cases (18.2%) in the immediate post-operative period; 16 of them (84.2%) showed complete or partial resolution at discharge. Only one patient (0.9%) showed GAPC intolerance. No other complication occurred. Three patients (2.9%) underwent reintervention for neck haematoma drainage. Mean hospital stay were 3±0.9 days. *Conclusions:* GAPC associated with sequential carotid cross-clamping appeared to be safe and effective in prevention of major neurological and cardiologic complications during CEA. (www.actabiomedica.it)

Key words: carotid endarterectomy, local anaesthesia, remifentanil, preserved consciousness, carotid stenosis, general anaesthesia

Introduction

Significant stenosis of the carotid bifurcation caused by unstable atheromatous plaque can be found in around 20% of patients with transient ischaemic attack (TIA) or stroke (1). Carotid endarterectomy (CEA) remains the "gold standard" for stroke prevention in these cases, with precise indication especially for symptomatic patients (2).

Although CEA is a safe procedure, the neurologic complication rate reported in literature is between 3-7% (3-5). Although internal carotid artery

(ICA) acute thrombosis after CEA remain an important cause of perioperative TIA/stroke, two others mechanisms are mainly responsible for neurologic complications during CEA: cerebral hypoperfusion due to carotid cross-clamping and plaque embolization due to carotid bifurcation dissection and clamp releasing (6).

Local anaesthesia (LA) and general anaesthesia with preserved consciousness (GAPC) allows direct neurological monitoring in order to identify patients at risk for brain hypoperfusion.

Early common carotid artery cross-clamping before carotid bifurcation dissection should decrease the risk of plaque embolization by reducing the inflow to the internal carotid artery (7).

We report one-year single centre experience combining these anaesthetic and surgical techniques in order to evaluate the effectiveness of this protocol for neurologic and systemic complications prevention during CEA.

Material and methods

Study design

All patients who underwent CEA for symptomatic or asymptomatic primary carotid stenosis between January and December 2016 were considered for this study. CEA was performed for symptomatic patients with an ICA stenosis >50% (North American Symptomatic Carotid Endarterectomy Trial [NASCET]) and for asymptomatic patients with an ICA stenosis >70% (NASCET) or > to 65% (NASCET) if imaging analysis showed characteristics consistent with plaque instability (2).

For symptomatic patients, CEA was performed within 15 days from the onset of neurologic symptoms. When brain computed tomography (CT) showed a large ischemic lesion or neurologic and clinical patient's conditions were unstable, the treatment was deferred until stabilization of radiological and clinical findings, in order to reduce brain haemorrhage risk (8) or systemic complications after surgery.

Data Collection

All patient's data were prospectively collected in a dedicated database and retrospectively analysed. Demographic data were age and sex. Anamnestic collected data were hypertension (defined as systolic blood pressure >140 mmHg or need for specific drug for blood pressure control), diabetes mellitus (defined as need of hypoglycaemic drugs for glycaemic control), dyslipidaemia (defined as total blood cholesterol > to 200 mg/dl), coronary artery disease (defined as previous surgical or endovascular revascularization or history of myocardial infarction), history of smoking, renal failure (defined as glomerular filtration rate < to 60 ml/h), chronic obstructive pulmonary disease (COPD, defined as FEV/FVC < to 70%), previous or recent neurological symptoms (any TIA or stroke in the previous 6 months), previous endovascular or surgical ICA revascularization, parenchymal damage at CT analysis in symptomatic patients. Plaque's collected data were: ICA stenosis grade, plaque characteristic and peak systolic velocity (PSV). Anaesthesia collected data were: ASA status and tolerance to GAPC. Surgical data were: surgical technique (endoarterectomy and ICA angioplasty, eversion technique, semieversion technique or primary closure), time of ICA cross-clamping, intervention duration, need for shunt positioning and intraoperative complications.

Preoperative assessment, anaesthetic protocol and surgical treatment

A duplex ultrasound (DUS) was performed in all patients to diagnose the ICA stenosis, to define plaque echogenicity characteristics, to assess carotid bifurcation anatomy and to measure PSV. As second line examination, a computed tomography angiography (CTA) and a brain CT was performed in all patients in order to rule out recent ischemic lesion, to define plaque characteristics, to evaluate proximal segment of common carotid arteries, aortic arch, vertebral arteries, intracranial circulation and surgical feasibility of the procedure. If the plaque's distal endpoint wasn't visible at DUS analysis and CTA showed plaque extension over mandibular angle, the patient was proposed for carotid artery stenting (CAS).

All symptomatic patients underwent Neurological evaluation before surgery.

All patients underwent surgical intervention under antiplatelet therapy and statin. The dual antiplatelet therapy was discontinued before surgical intervention, except for patient with absolute cardiologic (recent myocardial revascularization) or neurologic (recent TIA/stroke or recent contralateral ICA stenting) indication. In these cases CEA was carried-out during dual antiplatelet therapy assumption. The oral anticoagulant therapy was discontinued five days before the treatment and switched to low-molecular weight heparin (LMWH) in all patients.

Before GAPC induction with intravenous Propofol bolus (2 mg/Kg), local anaesthesia of vocal chords with Lidocaine spray 4% (5 cc) was performed in all patients. After tracheal intubation, GAPC was continued with Remifentanil infusion only (0,025 γ/Kg.min). A superficial plexus block was performed with local infiltration of the posterior border of the sternocleidomastoid muscle with Naropine 0.37% (10 cc) and Lidocaine 2% (5-6 cc) in all cases. After surgical incision, CCA was firstly dissected. Before cross-clamping, Remifentanil infusion was slowly reduced until patients were awake and able to collaborate. The CCA was cross-clamped and the patient was asked to squeeze a soft toy for 2 consecutive minutes with contralateral hand as neurological tolerance test (NTT), in order to rule out neurological symptoms consistent with cerebral hypoperfusion or ischemia. The carotid bifurcation was then isolated and separately (ICA and ECA) cross-clamped. After complete ICA flow interruption, another minute of NTT was performed. If the NTT was positive for brain hypoperfusion, the Remifentanil infusion was implemented and a shunt was positioned. The endoarterectomy was then carried out with different techniques, according to operator experience and ICA anatomy. When the procedure was completed, Remifentanil infusion was reduced for a new NTT.

Follow-up was performed with clinical assessment and DUS at 30 days from surgery.

End points

Primary end points were: transient ischemic attack (TIA), stroke, myocardial infarction and death in the perioperative period (30 days).

Secondary end points were: need for carotid shunting, peripheral cranial nerves injuries (PCNI) (all patients underwent Otorhinolaryngologist on first post-operative day and after 30 days), patient's intolerance to GAPC, other systemic complications (cardiac arrhythmias, respiratory complications) in perioperative period, need of reintervention in the perioperative period and length of hospital stay.

Statistical analysis

Quantitative data are presented as mean ± standard deviation, while categorical data are given as counts and percentage. All statistical analyses were performed using SPSS software (version 13.0; SPSS Inc, Chicago, IL, USA).

Results

Population

One hundred four patients (male: 70 [67.3%]; mean age:73.3±8.1 years) underwent CEA with GAPC and sequential carotid cross-clamping. No patients were bilaterally treated in this period. Twenty-seven patients (25.9%) were treated for symptomatic stenosis with 2.1±1.3 weeks of delay between neurologic symptoms and surgical treatment. Patient's characteristics are described in Table 1 and 2.

Procedure

In the considered period, 104 CEA were performed in 104 patients with the described anaesthetic and surgical protocol. The CEA technique was chosen according with ICA anatomy and surgeon experience. Sixty-six patients (63.4%) underwent CEA and ICA angioplasty with dacron patch (Hemacarotid Patch, Maquet®, Getinge Group), 27 patients (25.9%) underwent eversion technique, 8 patients (7.7%) semieversion technique and 3 patients (2.9%) CEA and direct closure. Mean intervention time was 97.8±26.6 minutes and mean cross-clamping time was 48.2±13.5 minutes.

Table 1. Patient's characteristics

	N	%
Male	70	67.3
Age (median± standard dev.)	73.3±8.1	
Hypertension	89	85.6
Dyslipidaemia	77	74
Diabetes	32	30.7
Active Smoker	28	26.9
Coronary artery disease	27	25.9
Chronic kidney disease	18	17.3
Previous controlateral carotid treatment	22	21.1
ASA 2	9	8.6
ASA 3	88	84.6
ASA 4	7	6.7
Controlateral ICA occlusion	1	0.9
Dual antiplatelet therapy[1]	18	17.3
LMWH[2]	8	7.7

ICA: internal carotid artery; LMWH: low molecular weight heparin
1: patients undergoing CEA without dual antiplatelet therapy interruption
2: patients undergoing CEA with LMWH

Table 2. Clinical presentation of symptomatic patients

	Tot. N	%
Symptomatic	27	25.9
TIA	15	55.5
Minor Stroke	5	18.5
Major Stroke	4	14.8
Amaurosis Fugax	3	11.2
Parenchymal lesion at brain CT omolateral to carotid stenosis	19	70.4

TIA: transient ischemic attack; CT: computed tomography

End-points

No TIA/stroke, myocardial infarction or death were observed in the perioperative period.

A carotid shunt was positioned in 5 cases (4.8%). In 4 cases (3.8%) the shunt was positioned for positive NTT. In 1 case the shunt was necessary because of general anaesthesia conversion for patients intolerance to GAPC.

PCNI was observed in 19 (18.2%) patients at the end of intervention. Sixteen (84.2%) of these patient's symptoms were partially or completely resolved at 30 days.

Only 1 patient (0.9%) showed intraoperative intolerance to GAPC and conversion to GA was necessary.

No other cardiac or respiratory complications were observed during the perioperative period.

Three patients (2.8%) underwent reintervention in the first post-operative day for neck haematoma. Two (66.6%) of these patients were under anticoagulant therapy with low molecular weight heparin (LMWH) for atrial fibrillation.

Mean length of hospital stay was 3±0.9 days.

Discussion

In this experience, GAPC associated with carotid sequential cross-clamping appeared effective for prevention of neurologic and cardiologic complications, with reliable detection of intraoperative cerebral symptoms and a low rate of carotid shunting. GAPC appeared also well tolerated by patients and surgeons, with a low rate of conversion to GA (0.9%).

CEA is the first treatment option in our centre for patients with haemodynamic carotid stenosis and CAS is reserved for selected patients with specific indications (2). In the considered period 116 patients referred to our centre for symptomatic or asymptomatic carotid stenosis, and only 12 CAS procedures (10.3%) were performed.

Although CEA is a safe procedure and remains the "gold-standard" for treatment of symptomatic and asymptomatic carotid stenosis (2), 3-7% of these procedures are complicated by disabling or nondisabling strokes (3-5). Acute carotid thrombosis (ACT) after CEA remains an important cause of neurologic complications. Surgical precision during the phase of endarterectomy is crucial to avoid this complication. Two other causes of neurologic complication during CEA are plaque embolization and brain hypoperfusion during ICA cross-clamping (6). In order to limit these phenomenon and reduce the rate of perioperative neurological event, we associated GAPC for better cerebral perfusion monitoring during CEA with sequential carotid cross-clamping in order to reduce plaque embolization.

The GALA Trial showed similar results between LA and GA during CEA, with slightly lower rate of perioperative TIA/stroke occurrence, myocardial infarction and death for LA. However, these differences had no statistical significance (9).

In other experiences LA showed many advantages over GA in term of myocardial infarction reduction, haemodynamic stability and cost effectiveness (10). Kfoury et al (11) showed superiority of LA over GA in terms of reduction of neurologic (OR=2.64, 95% CI: 1.09-6.85) and cardiologic complications (OR=7.33, 95% CI: 0.82-347.3) on 1127 procedures carried out under either general or local anaesthesia (11).

GAPC demonstrated to be a safe procedure, comparable to LA in term of neurologic and cardiologic complications (12-15).

The role of NTT is not well defined in literature and no clear evidence regarding superiority of selective over routine shunting are available (1). Although this lack of evidences, some experiences provides important information about patients at high risk for neurologic intraoperative complications identified by intraoperative NTT and shows the importance of selective shunting in these patients (16, 17).

GAPC allows a reliable neurologic monitoring, with strictly selective shunting (4.8% in our experience). Internal carotid artery shunt placement, although is a safe procedure, can bring adjunctive complications due to arterial wall damage and could lead to a longer intervention time (17). In our experience, the mean internal carotid clamping time was 48.2±13.5 minutes and no perioperative TIA/stroke occurred.

These data may suggest that ICA clamping time during CEA doesn't influence perioperative neurological outcome. Also in the 27 symptomatic patients, with extremely unstable plaque, no neurological complications occurred during perioperative period, showing the effectiveness of this anaesthetic and surgical technique for reduction of complications after CEA.

Our experience showed a rate of reintervention in the perioperative period of 2.8%, aligned with other experiences (9). All reintervention were performed for neck haematoma development and consisted in surgical drainage on first post-operative day. In 2/3 of cases, this complication occurred in patients with atrial fibrillation receiving LMWH twice daily. The increased risk of haemorrhagic complications after CEA in patients receiving LMWH is been already reported in literature (18).

Also the surgical technique plays an important role for prevention of neurologic complications. The preliminary CCA dissection and cross-clamping may reduce the risk of embolic event, that are mainly responsible for hypoperfusion or intraoperative stroke during CEA (15). Once the CCA is cross-clamped and the ICA blood flow is interrupted, the ICA dissection can be performed with lower risk of plaque embolization (7).

This study present a preliminary experience limited by the small sample size and the retrospective analysis, although the data were prospectively collected.

Conclusions

CEA performed under GAPC with standardized carotid cross-clamping technique is a safe protocol for reduction of neurological and cardiologic complications, allowing reliable neurologic monitoring and stable anaesthetic management. This protocol has shown to be also well tolerated by patients and surgeons, with a low rate of conversion to GA.

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ORIGINAL ARTICLE

Diabetic ketoacidosis at the onset of Type 1 diabetes in young children

Is it time to launch a tailored campaign for DKA prevention in children <5 years?

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Summary. *Aim:* To analyze clinical characteristics associated with the occurrence of diabetic ketoacidosis (DKA) at the onset of type 1 diabetes (T1D) in children aged <5 years in order to identify early signs or symptoms useful to prevent DKA appearance. *Methods:* Data of patients with newly diagnosed TID aged <5 years (Group 1) and 6-10 years old (Group 2) coming from the province of Parma were collected in the period 2012-2016. *Results:* Mild/moderate ketoacidosis at diabetes diagnosis occurred more frequently in Group 1 than in Group 2 patients (p<0.0015). Severe DKA incidence was higher in children below 5 (21.8%) than in those over 5 years of age (3.75%; p=0.021). Latent period before overt T1D diagnosis was longer in Group 1 than in Group 2 patients (p=0.0081). During this latent period similar indicators were recorded among parents of children <3 years old: frequent use of disposable baby diapers (87%), wet baby diapers because of a large amount of urine (86%), body weight loss (79%). In children aged 3-4 years reported symptoms consisted of polyuria (89%), polydipsia (79%), fatigue (72%). In Group 2 patients predominant signs concern unusual episodes of enuresis. *Conclusions:* We believe that it is time to launch a DKA prevention campaign tailored for children under 5 years old and focused just on the above-mentioned three warning signs. Information program must involves pediatricians, pediatric nurses, new moms and nursery school teachers. (www.actabiomedica.it)

Key words: diabetic ketoacidosis, type 1 diabetes, young children, DKA prevention, baby diapers, pediatrics, polyuria, polydipsia

Introduction

Diabetic ketoacidosis (DKA) is serious complication of diabetes at diagnosis more frequently in children aged <5 years than in older subjects (1, 2). This unacceptable high prevalence conflicts with the expectation of a lowering in the occurrence of DKA, given awareness campaigns everywhere promoted to recognize the earliest symptoms of T1D at onset in childhood (3-6).

In the present paper we analyzed clinical characteristics of DKA occurring at the time of diabetes onset in children aged under 5 years in an area where a capillary awareness campaign produced an important and persistent decrease in rate of DKA in newly diagnosed diabetic children over 5 years old (3, 7, 8). The purpose of this study was to verify whether it was possible to detect in the preclinical history of younger children with newly diagnosed diabetes signs or symptoms useful to prevent the appearance of DKA.

Patients and methods

Data investigation was performed among children with newly diagnosed TID aged < 5 years (Group 1) and 6-10 years old (Group 2) coming from the same province of Parma, admitted to Children Hospital "Pietro Barilla", University Hospital of Parma, Italy, from 1st January 2012 to 31st December 2016. The province of Parma is located in Northern Italy where a campaign for DKA prevention has been launched since the Nineties according the procedures published elsewhere (3, 7, 8).

Data for this study were collected from medical files of each patient and included: age, gender, blood glucose, capillary pH, 3-beta-hydroxybutyrate (3HB) and glycated hemoglobin (HbA1c) levels, information about symptoms reported by the parents during the days preceding the overt T1D diagnosis. ISPAD criteria were used to define DKA: absent (pH ≥7.30), mild (7.2≤ pH <7.30), moderate (7.1≤ pH <7.20) and severe (pH <7.1) (9). As the clinical implications for mild and moderate DKA are similar, they are considered together in this paper. 3HB serum levels were tested on a fingerstick blood specimen by a hand-held device (Medisens Optium Xceed, Abbott Laboratories, Bedford, MA, USA). 3HB serum levels <0.5 mmol/dl were defined as normal; levels exceeding 1 mmol/dl were retained as hyperketonemia or ketosis; and levels in excess of 3.0 mmol/dl were classified as ketoacidosis (10). HbA1c levels were measured by Bayer DCA 2000 method (upper limit of normal value: 6.0 %).

The study was performed according to the criteria of the Helsinki II Declaration. Tutors or parents of all patients admitted to our department are accustomed to sign an informed consent document for the use of clinical data regarding their children for scientific purposes only. No conflict of interest exists in relation to the subject matter of the present paper.

Statistics

Data were summarized as numbers (n) and frequencies (%) if they were categorical and as mean and standard deviation (SD) if quantitative. If the data were normally distributed a two-tailed unpaired T-test or otherwise a non-parametric Mann-Whitney U-Test was applied to compare results between groups. Chi-square test (χ^2) or Fisher exact test was used to compare frequencies between groups. P-values less than 0.05 were considered as statistically significant.

Results

From 1st January 2012 to 31st December 2016, 135 children aged 1 to 18 years were admitted to the University Children Hospital of Parma, Italy, with newly recognized T1D. Sixty of these children (44.4%) were aged <10 years and came from the province of Parma: 32 patients <5 years old were recruited in the Group 1 and 28 (aged 6-10 years) in the Group 2

Characteristics of Groups patients at T1D diagnosis

Group 1 patients – Patients gathered in this Group had a mean age of 3.37±1.29 (range:1.2-4.6) years; 18 were males (56.2%) (Table 1). Twenty-one patients (65.6%) had a mild- moderate DKA and 7 patients (21.8%) a severe DKA. The remaining 4 patients did not have DKA (12.6%). Patients without DKA were 4.1-4.6 years old; those with a mild/moderate form of DKA were aged 1.9-2.8 years; and the seven patients with severe DKA had 2.2 and 2.9 years. Blood glucose average was 473,25±191,18 (858-175) mg/dl. Mean HbA1c levels were 11.03±1.78 (8.7-15.3) %. 3HB mean levels was 4,85±1,91 (0-7.3) mmol/dl. Only 7 patients (21.8%) had 3HB levels <1 mmol/dl. Analyzing the frequency of DKA over a span of 5 years, no statistically significant time trend was observed (p<0.243).

The duration of hyperglycemia-related symptoms before T1D diagnosis was quantified in 12.0±8.0 days according to what the parents reported at hospital admittance. During this latent period parents reported among children <3 years old: frequent use of disposable baby diapers (87%), wet baby diapers because of a large amount of urine (86%), body weight loss (79%), increased thirst and polyuria (76 %). In children aged 3-4 years reported symptoms consisted of polyuria (89%), polydipsia (79%), fatigue (72%).

None parent of Group 1 patients was aware of the existence of a campaign for early diagnosis of T1D and

Table 1. Characteristics of study participants at T1D diagnosis

Group of patients	1	2
N. (gender)	32 (14 girls/18 boys)	28 (15 girls/13 boys)
Age, years, mean ±SD (range)	3.37±1.29 (1.2-4.6)	8.2±2.3.(5.5-10.0)
pH	7,22±0,12 (6.91-7.37)	7,27±0,16 (6.9-7.44)
3HB, mmol/dl	4,85±1,91 (0-7.3)	3,54±2,85 (0-7.6)
DKA		
• No DKA	12.6%	75.0%
• Mild/moderate	65.6%	21.4 %
• Severe	21.8%	3.6%
Blood Glucose, mg/dl	473,25±191,18 (858-175)	282.81±126.66 (162-300)
HbA1c, %	11.03±1.78 (8.7-15.3)	9.13±1.23 (7.7-11.5)

3HB=3-beta-hydroxybutyrate, DKA= Diabetic Ketoacidosis, HbA1c=Glycated Hemoglobin

DKA prevention. Parents consulted family pediatrician only at weight loss detection, and did not inform the pediatrician about other symptoms.

Group 2 patients – Patients collected in this Group (13 males, 46.4%) had a mean age of 8.2±2.3.(range: 5.5-10.0) years (Table 1). Twenty-one (75.0%) patients did not have DKA, in 6 patients (21.4%) DKA was mild/moderate, in 1 patient DKA was severe (3.6%). Patients without DKA were 6.6-9.6 years old; patients with a mild/moderate form of DKA were aged 7.9-10 years. Mean blood glucose and HbA1c levels were 282.81±126.66 (162-300) mg/dl and 9.13±1.23 (7.7-11.5) %, respectively. 3HB mean levels were 3,54±1,85 (0-6.6) mmol/dl. Twelve patients (42.8%) had 3HB values <1 mmol/dl.

All parents of children recruited in this Group reported to know that a campaign for early T1D diagnosis was launched in their province. The duration of symptoms before overt T1D diagnosis was estimated in 6.4±1.5 days among children without DKA. Seventy-four percent of parents of these children reported that recurrent episodes of enuresis appeared a few days before, associated with frequent thirst at night (78%), polyuria (75%) and polydipsia (64%). In 18 of 28 patients (64.2%) showing unusual enuresis, the diagnosis of T1D was performed by the family pediatrician directly in his private office by capillary measurement of blood glucose. In the remaining 10 patients (35.7%) the pediatrician underestimated reported symptoms. Remembering the messages about early symptoms of T1D listed in the posters displayed in town pharmacies or at school, the parents of these children consulted spontaneously the Pediatric Emergency Department at Children Hospital of Parma where the diagnosis of T1D was quickly performed.

Comparison between two Groups of patients

During the study period, mild/moderate ketoacidosis at diabetes diagnosis occurred more frequently in Group 1 than in Group 2 patients ($p<0.0015$). Severe DKA incidence was higher in children below 5 (21.8%) than in those over 5 years of age (3.75%; $p=0.021$). Children without DKA were more numerous in Group 2 than in Group 1 ($p=0.0001$). Blood glucose and HbA1c levels were higher in patients of Group 1 than in those of Group 2 ($t=2.54$; $p= 0.016$ and $t= 3.54$; $p=0.0012$ respectively). Group 2 patients showed lower values of 3HB than Group 1 patients ($t= 3.9$; $p=0.0002$). The patients with 3HB levels <1 mmol/l were more numerous in Group 2 than in Group1 but not significantly ($t=3.4$; $p=0.08$). Latent period before overt T1D diagnosis was shorter in Group 2 than in Group 1 patients ($t= 2.83$; $p=0.0081$).

Discussion

In previous studies we demonstrated that through an educational campaign it is possible to achieve and maintain over time a marked decrease in DKA fre-

quency at diabetes onset in children over 5 years old (3, 7, 8). The findings reported in the present study showed that the goal is still reachable in this children population, but in younger children the same target seems to be still very far to be obtained, even in a province where a DKA information program for teachers, students, parents and pediatricians has been introduced since the Nineties (3).

In analyzing the medical files of children under 5 years of age recruited in this study, we found that DKA frequency occurred with a percentage (65.6%) close to that we reported in older children during the pre-campaign period (3). Among young children severe or mild DKA happened more frequently in those under 3 years old, in agreement with previous reports (11, 12). The same children showed also higher HbA1c and 3HB levels than older patients, features which may explain the long delay in their disease recognition. An optimistic finding was that in 4 patients of the same Group, diabetes has been diagnosed before the appearance of DKA. The diagnosis was performed occasionally because of suspected urinary tract infection facing numerous diapers consumed at home.

Conversely the great majority of patients aged over 5 years had a diabetes uncomplicated by DKA and a short latent period before diagnosis, as proved also by lower HbA1c and 3BH levels. These results may be ascribed to the information campaign promoted for DKA prevention in the area where the study was carried out (3, 7, 8). As expected, unusual enuresis episodes confirmed to be also in this investigation a reliable warning symptoms to promptly diagnose T1D at onset, and to maintain DKA rate low.

It has been reported that greater DKA incidence at D1T onset together with less maturity of metabolic systems combine to predispose younger children to DKA-related complications, e.g. cerebral edema which occurs in about 1% of all episodes of DKA with a high mortality and morbidity rate (13-15). It is not the case of our patients, but given the scenario described in literature, we agree on the opinion of those Authors who sustain that every case of diabetes at onset in a child aged under 5 years has to be regarded as an emergency event (16).

We warmly believe that a new information strategy has to be urgently implemented in order to spread the awareness of early symptoms of a latent hyperglycemia status also in this vulnerable young population. We are aware that early signs or symptoms of an ongoing T1D are not easy to identify in children under 5 years of age (17). We are equally conscious that the appearance of unexpected episodes of enuresis in a child usually "dry" on which we have successfully based the DKA prevention campaign in Nineties (3, 7, 8) cannot involve children whose bladders are still developing.

Among signs observed in younger children, we would like to focus attention on at least three underestimated signs that could be attributable to a latent hyperglycemia status reported in the weeks before overt T1D diagnosis: frequent use of disposable baby diapers (87%), baby diapers abnormally wet due a large amount of urine (86%), body weight loss (79%). All these signs can be linked to a relative insulin deficiency that resulted in hyperglycemia and lipolysis. The combination of hyperglycemia and lipolysis caused osmotic diuresis, dehydration and weight loss. Among these three signs only body weight loss convinced the parents to consult a pediatrician, not reporting the other two more precocious signs. This shows how much moms are sensitive to the weight growth of their children. We believe that this defect in communication has influenced the delay in T1D diagnosis in these children.

We feel it is time to launch a new DKA prevention campaign centered on children under 5 years old and focused just on the above-mentioned three warning signs that over 80% of parents have reported as early signs of the metabolic derangement that was silently happening in their children. This information program must involve pediatricians, pediatric nurses, new moms and nursery school teachers.

During routine checkup visits, it should be good practice that primary care pediatricians and nurses query the moms on how many diapers change daily, and sensitize the same moms on the need to immediately alert the pediatrician if the diapers consumption increases in an unexpected way, and first of all if diapers become abnormally wet due to a large amount of urine. The same recommendations have to be extended to nursery school teachers because they work alongside children for many hours a day, having so the opportunity to perceive an unusual polyuria.

In conclusion, we can debate if the pediatricians have to be equipped with devices for the measurement

of capillary blood glucose and glycosuria, supplies for finger pricking, reagents strips and reflectance in order to verify on real time reported signs and symptoms directly in their office. Given the experience made with "Parma campaign" in the Nineties we would be favorable of providing this equipment so useful to shorten the delay in diagnosis and hospitalization, as currently proved also in the present study.

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Original article

Comparison between self-gripping, semi re-absorbable meshes with polyethylene meshes in Lichtenstein, tension-free hernia repair: preliminary results from a single center

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Summary. Even tough inguinal hernia repair is among the commonest operations in general surgery, the choice for an optimal approach continues to be a controversial topic. Because of the low recurrence rates and low prevalence of complications, tension-free mesh augmented operation has become the standard technique in inguinal hernia surgery, significantly reducing hernia recurrence rates. On the contrary, prevalence of chronic postoperative groin pain (CPGI) i.e. pain beyond a three month-postoperative period still remains significant: as rates of CPGI may range between 15% and 53%, surgical approaches aimed to avoid chronic post-hernioplasty pain have been extensively debated, and the avoidance of CPGI has become one of the primary endpoints of surgical research on inguinal hernia repair). Recently, a sound base of evidence suggested that the entrapment of peripheral nervous fibers innervating part of the structures in the inguinal canal and stemming from ilioinguinal (Th12), iliohypogastric (L1) nerves as well as from the genital branch of the genito-femoral nerve (L1, L2), may eventually elicit CPGI (1-10). Consequently, innovative fixation modalities (e.g. self-gripping meshes, glue fixation, absorbable sutures), and new material types (e.g. large-pored meshes) with self-adhesive sticking or mechanical characteristics, have been developed in order to avoid penetrating fixings such as sutures, clips and tacks. However, some uncertainties still remain about the pros and cons of such meshes in terms of chronic pain, as new, innovative mesh apparently does not significantly reduce the rate of CPGI. Parietex ProGrip® (Medtronics™) is a bicomponent mesh comprising of monofilament polyester and a semi re-absorbable polylactic acid gripping system that allows sutureless fixation of prosthetic mesh to the posterior inguinal wall. As ProGrip® does not requires additional fixation, inguinal canal may be closed within minutes after adequate groin dissection, ultimately shortening operating time. In other words, ProGrip® has the potential for significant savings, in terms of surgical and post-operating costs as well (10). The aim of our study is therefore to compare the results of the same technique with two different mesh materials (ProGrip® mesh vs. polyethylene mesh), in terms of operative time, post-operative pain, complications, and recurrence rates. (www.actabiomedica.it)

Key words: inguinal hernia; mesh repair; self-gripping mesh

Introduction

Even tough inguinal hernia repair is among the commonest operations in general surgery (1), the choice for an optimal approach continues to be a controversial topic (2). Because of the low recurrence rates and low prevalence of complications, tension-free mesh augmented operation has become the standard technique in inguinal hernia surgery (2-4), significantly reducing hernia recurrence rates (3, 5). On the contrary, preva-

lence of chronic postoperative groin pain (CPGI) i.e. pain beyond a three month-postoperative period still remains significant (3): as rates of CPGI may range between 15% and 53%, surgical approaches aimed to avoid chronic post-hernioplasty pain have been extensively debated, and the avoidance of CPGI has become one of the primary endpoints of surgical research on inguinal hernia repair (2, 5, 6). Recently, a sound base of evidence suggested that the entrapment of peripheral nervous fibers innervating part of the structures in the inguinal canal and stemming from ilioinguinal (Th12), iliohypogastric (L1) nerves as well as from the genital branch of the genito-femoral nerve (L1, L2), may eventually elicit CPGI (1-10). Consequently, innovative fixation modalities (e.g. self-gripping meshes, glue fixation, absorbable sutures), and new material types (e.g. large-pored meshes) with self-adhesive sticking or mechanical characteristics, have been developed in order to avoid penetrating fixings such as sutures, clips and tacks (2, 3, 8, 9, 11). However, some uncertainties still remain about the pros and cons of such meshes in terms of chronic pain, as new, innovative mesh apparently does not significantly reduce the rate of CPGI (2, 3). Parietex ProGrip® (Medtronics™) is a bicomponent mesh comprising of monofilament polyester and a semi re-absorbable polylactic acid gripping system that allows sutureless fixation of prosthetic mesh to the posterior inguinal wall. As ProGrip® does not requires additional fixation, inguinal canal may be closed within minutes after adequate groin dissection, ultimately shortening operating time. In other words, ProGrip® has the potential for significant savings, in terms of surgical and post-operating costs as well (10).

The aim of our study is therefore to compare the results of the same technique with two different mesh materials (ProGrip® mesh vs. polyethylene mesh), in terms of operative time, post-operative pain, complications, and recurrence rates.

Materials and Methods

This research was conducted as a controlled, unicentric, two-cohort pilot study at the Department of Surgery of the Hospital of Codogno, Local Health Unit of Lodi - Northern Italy between April and June 2014.

Inclusion criteria

All consecutive patients with age between 18 and 80, male or female, were considered eligible for the study. Only patients having a unilateral, primary inguinal hernia were eventually included.

Exclusion criteria

Patients were excluded if they had suffered from large inguino-scrotal hernia, bilateral inguinal hernia, recurrent inguinal hernia, incarcerated hernia, irreducible hernia or with significant comorbidities (ASA >2). Patients having a poor understanding of the Italian language were also excluded.

Clinical outcomes

Primary outcomes included: early and late post-operative pain, and complications. Moreover, total number of non-steroidal analgesic used, as well as residual symptoms such as paresthesia, chronic discomfort, and chronic pain were collected at the end of the follow up. Secondary outcomes included the total operative time and the rate recurrence.

Randomization and blinding

Computer generated randomizations were communicated to the surgical team after adequate groin dissection and just before placement of prosthetic mesh.

Ethics

Informed consent was obtained from all individual participants included in the study after detailed explanation of possible complications of hernia repair. As at the time of the study both prosthetic meshes were in use at the Hospital of Codogno, but no internal or institutional recommendations guiding the choice for the appropriate prosthetic material had been put in place, and individual participants cannot be identified based on the presented material, no preliminary evaluation by the Ethical Committee was reputed necessary.

Operative details

After obtaining informed consent, patients were assessed by anesthetists for fitness of operation. The operations were performed by a single specialist (LP) in hernia surgery. Standardized procedure was utilized: 20 patients approached by standard Lichtenstein procedure as described in literature:

- Inguinal incision 1cm above pubic tubercle and horizontal (5-6cm);
- Exposure of inguinal canal by opening external oblique aponeurosis;
- Dissection and isolation of inguinal cord with nerve-sparing approach;
- Identification and management of hernia sac;
- Placement and fixation of hernia mesh (15x7.5 cm) with continuous suture to fix it at the inguinal ligament; two absorbable sutures to fix the mesh at the rectus sheath and internal oblique aponeurosis.
- Internal ring closure by closing posterior mesh with suture between posterior tails of the mesh and inguinal ligament.
- Closure of external oblique aponeurosis in continuous suture over inguinal cord.
- Closure of inguinal incision by subcutaneous and cutaneous suture.

The other 20 patients underwent the same surgical approach but we positioned a Progrip® mesh without any suture, in the same position of the Lichtenstein procedure (Figure 1); the only attention that we used was to secure a necessary overlap to the anatomic structures specially over pubic tubercle.

Data collection and follow-up

Patients were assessed in hospital before surgical procedures (i.e. T0), 3 hours after surgery (T+3), at discharge (usually, around 24 hours after surgical procedures), and then followed-up in outpatient clinical T + 7 days, T + 30 days, T + 90 days, T + 6 months, T + 1 year, T + 2 years. More specifically, patients were asked to retrieve whether they complained groin pain assessed as Visual Analogue Scale (0 to 10), discomfort and paresthesia. Moreover, they were asked about the use of non-steroidal analgesic drugs for CGPI and eventually assessed for recurrence and post-surgical complications. Healthcare professionals who performed post-surgical assessment were blinded for the mesh group assigned as treatment.

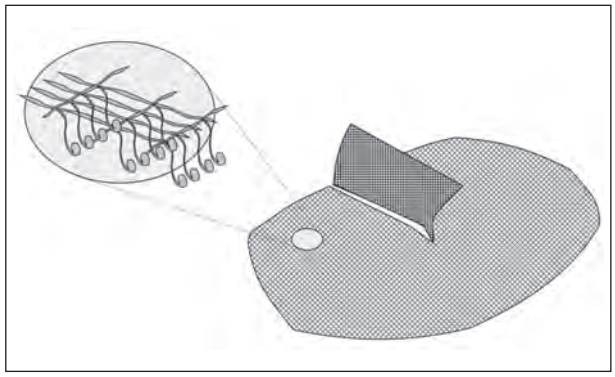

Figure 1. Schematic representation of Progrip® mesh. As shown, the surface in front of the posterior inguinal wall is characterized by many re-absorbable polylactic acid gripping peduncles that allow sutureless fixation of prosthetic mesh. In the scheme, Progrip® mesh is furtherly elaborated through an incision that allows an easily fixation of the spermatic peduncle

Statistical analysis

Student's t test for unpaired data were employed for the comparison of continuous variables, whereas association of dichotomous variables was assessed through Fisher's exact test because of the reduced number of patients included in the sample. Statistical analysis was performed by using software package SPSS 24.0 (IBM Corp. Armonk, NY). A difference with $p<0.05$ was considered statistically significant.

Results

Study population

A total of 40 patients (30 males, 10 females) with the diagnosis of a unilateral primary inguinal hernia were enrolled. Of them, 20 were assigned to the ProGrip® group and 20 were assigned to the polyethylene group. The two group were comparable concerning all demographic variables (M:F = 15:5 in both groups; mean age: 60.7 years ± 12.9 vs. 60.2 years ± 12.3 for ProGrip® and polyethylene group, respectively: $p = 0.814$).

Table 1. Characteristics of the 40 patients included in the study

	All patients (n = 40)	ProGrip® (n = 20)	Polyethylene (n = 20)	P value
Age (years; mean ± SD)	60.4 ± 12.4	60.7 ± 12.9	60.2 ± 12.3	0.891
Sex (n, %)				
Males	30; 75.0%	15; 75.0%	15; 75.0%	1.000
Females	10; 25.0%	5; 25.0%	5; 25.0%	
Operation time (minutes; mean ± SD)	35.6 ± 7.1	29.6 ± 4.1	41.7 ± 3.3	< **0.001**
Length of wound (cm; mean ± SD)	5.4 ± 0.4	5.4 ± 0.5	5.5 ± 0.4	0.214
Visual Analog Scale (mean ± SD)				
Pre operatory	4.8 ± 2.4	5.1 ± 2.4	4.6 ± 2.5	0.568
T + 3 hours	3.4 ± 1.3	3.4 ± 1.4	3.7 ± 1.3	0.556
At discharge	2.9 ± 1.0	3.0 ± 1.1	2.9 ± 0.9	0.764
T + 7 days	2.0 ± 0.9	1.8 ± 0.9	2.2 ± 0.8	0.152
T + 30 days	1.2 ± 0.7	± 0.6	1.3 ± 0.7	0.178
T + 90 days	0.8 ± 0.7	0.6 ± 0.7	1.1 ± 0.7	0.064
T + 6 months	0.4 ± 0.7	0.3 ± 0.6	0.6 ± 0.8	0.247
T + 1 year	0.2 ± 0.7	0.1 ± 0.2	0.4 ± 0.9	0.120
T + 2 years	0.1 ± 0.5	0.1 ± 0.2	0.2 ± 0.7	0.531
≥ 3 at 1 year (No.; %)	1; 5.0%	0; -	1; 5.0%	1.000
≥ 3 at 2 years (No.; %)	1; 5.0%	0; -	1; 5.0%	1.000
Residual pain, T + 2 years (No.; %)				
Any	4; 10.0%	2; 10.0%	2; 10.0%	1.000
…at rest	1; 2.5%	0; -	1; 5.0%	1.000
…on coughing	1; 2.5%	0; -	1; 5.0%	1.000
…when rising from lying to sitting	2; 5.0%	1; 5.0%	1; 5.0%	1.000
…during physical activity	4; 10.0%	2; 10.0%	2; 10.0%	1.000
Analgesic use during Follow Up				
Number of episodes (mean ± SD)	3.2 ± 1.4	2.7 ± 1.3	3.7 ± 1.3	**0.021**
3 times or more (No., %)	27, 67.5%	10, 50.0%	17, 85.0%	**0.041**

Operation time

The mean duration of the surgical procedures was 35.6 m ± 7.1. Within the ProGrip® group, the mean duration of the surgical procedure was 29.6 m ± 4.1, and resulted significantly shorter than that identified within the polyethylene group (41.7 m ± 3.3; p < 0.001).

Hospital stay

Median hospital stay for all enrolled patients was equal to 1 day (min 1; max 3). More precisely, patients assigned to the polyethylene group stayed for a mean of 1.6 days ± 1.9, whereas ProGrip® group recorded a mean hospital stay of 1.3 ± 1.6 (p = 0.598).

Surgical issues

Mean length of surgical wound was 5.4 cm ± 0.4, with no significant differences between the two groups (5.4 cm ± 0.5 vs. 5.5 cm ± 0.4 in ProGrip® and polyethylene group, respectively; p = 0.214). None among patients participating to this study suffered any intraoperative and/or early/late surgical complication.

Pain

Preoperative pain assessed by the VAS identified a mean of 4.9 ± 2.4, and although mean VAS for ProGrip® group was slightly higher than for polyethylene group, the difference was not statistically significant (5.1 ± 2.4 vs. 4.6 ± 2.5; p = 0.568). As shown in Figure

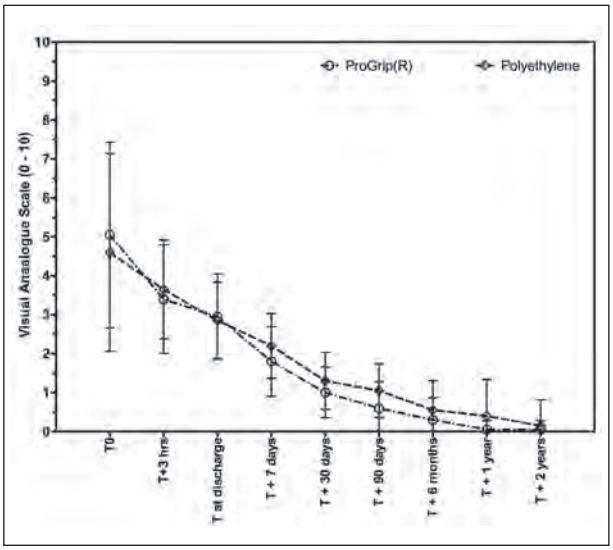

Figure 2. Change of the mean VAS score within the two groups over time

2, VAS remained somehow greater in ProGrip® than in polyethylene group also on T+3 hours (3.4 ± 1.4 vs. 3.7 ± 1.3; p = 0.556) and on the day of discharge (3.0 ± 1.1 vs. 2.9 ± 0.9; p = 0.764), but the difference was not significantly different between the two groups. On the contrary, since the first re-evaluation after 7 days, the mean VAS score for patients within the ProGrip® group was non significantly lower than that for polyethylene patients, but the difference remained constantly not significant until the end of follow-up.

Residual pain at the end of follow up was reported by a total of 4 patients (10.0%), and the shares were identical within the two groups (10.0%, p = 1.000). No significant differences were identified among the causes eliciting groin pain between the two groups. Focusing on the patients suffering from moderate-severe pain (VAS ≥ 3), such complaints were referred only by 1 patient among the polyethylene group at both 1 year and 2 years postoperatively, but again the difference was not statically significant (Fisher's exact test p = 1.000 in both cases).

Eventually, patients within ProGrip® group referred the use of analgesic during follow-up 2.7 ± 1.4 times vs. 3.7 ± 1.3 times in polyethylene group, and similarly the share of patients requiring use of analgesic during the follow-up (dichotomized as < 2 times vs. ≥ 3 times) was higher in polyethylene group than in ProGrip® group (50.0% vs. 85.0%, respectively). In both cases, the difference was statistically significant (p = 0.021, and p = 0.041).

Discussion

Since the tension-free hernioplasty was described in 1989 (12, 13), prosthetic tension free repair changed the history of groin hernia surgery, significantly reducing recurrence rates and allowing a faster recovery, mainly due to a reduced local pain. The impact of the new approach also reflected on sanitary costs, and organization of surgical units. Nowadays most of the centers, indeed, perform groin hernia surgery in outpatient basis. On the other hand, the use of prosthetic material didn't entail an increased rate of local infection, probably due to a better local and systemic prophylaxis (1-10).

Unfortunately, post-operative pain remains a significant issue (1-10, 12, 13), including both post-operative and late, chronic pain – or CGPI. Whereas management of early post-operative pain usually resides on analgesic, CGPI may ultimately require further assessment and medical or surgical intervention (12, 13). As GPCI may reduce productivity due to discomfort and absenteeism, being also associated with significant medical expenses (14-18, 19), it remains one of the unsolved issues with prosthetic repair.

Available base of evidence suggests that CGPI may found its etiology in peri-operative nerve damage, post-operative fibrosis or mesh-related fibrosis (12). Consequently, every technical improvement aimed to reduce trauma and/or inflammatory involvement of the abdominal wall has the potential to reduce its prevalence.

In the last decades, moving from outstanding results on postoperative recovery achieved in abdominal and bariatric surgery (19-27), laparoscopic (either transabdominal or totally extraperitoneal) approach to groin as well as ventral hernia (22) has been developed in order to minimize the parietal dissection and possibly quicken postoperative recovery, but its use as routine procedure is still source of debates, due to a higher operative risk and costs. To date, standard inguinotomic prosthetic repair remains the cornerstone of groin

hernia surgery, except the case of bilateral or recurrent hernias referring to units specialized in laparoscopic surgery (1-10, 12, 13, 20-27).

ProGrip® meshes, similarly to other semi-absorbable materials that incorporate self-fixing properties, are minimally invasive towards abdominal tissues, and have been shown to provide satisfactory repair both in open and laparoscopic (2, 28). However, available reports are somehow tantalizing, as the balance between pros and cons may be doubtful (4, 6, 10, 11). First at all, even though patients within ProGrip® group beneficed of shorter operation time (29.6 m ± 4.1 vs. 41.7 m ± 3.3), and during the follow-up referred a reduced GPCI-driven consumption of analgesic, differences in long-term outcomes have been minimal and not significant. Moreover, no significant differences in terms of complications, rates of relapses, and even of self-assessed pain were identified between the two study groups. As in previous reports, cost-effectiveness of new prosthetic meshes compared with more conventional materials may therefore be questioned (2). However, such analyses are beyond the scope of this study, and further investigations are needed in order to make any final conclusions.

Some limitations of our study have to be addressed. First at all, our study included a reduced number of patients: although inclusion criteria presumptively contributed to minimize confounding factors and more specifically the effects associated with comorbidities, our results may be therefore limitedly generalizable. Moreover, although VAS as a measure of pain and discomfort is extensively used in surgical research, such perceptions are significantly heterogeneous among patients and different ethnicities (29-32). In order to retrieve more objective data, we recalled the episodes of pain requiring analgesic use, but also such approach has been criticized because of a significant recall bias (29, 31). Finally, our data are affected by a relatively short follow up. Although the rate of chronic pain may not decrease significantly by the third postoperative year compared with the 6-mo follow-up (2), other reports suggest that CGPI may be a significant issue even 5 years or more after surgery, and some complications such as testicular atrophy as well as groin hernia recurrence may be more appropriately appreciated only for longer observation periods (10, 33).

Conclusion

Hernia repair with ProGrip® mesh seems to allow for an easier and equally safe surgical procedure, significantly reducing operative times. The possible effect on postoperative pain should be test on large sample size.

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Original article

Multidimensional approach usefulness in early Alzheimer's disease: advances in clinical practice

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Summary. *Background and aim:* Improving quality of life of patients with early Alzheimer's Disease (AD) is a primary concern of health professionals involved in dementia treatment. The aim of this study is to reveal associations among psychiatric symptoms and wellbeing aspects, dysfunctional lifestyles and stress-related behaviors, illness perception, personality traits, and life quality satisfaction, in order to offer a comprehensive evaluation of psychological and behavioral aspects characterizing patients with early AD. *Methods:* This is a cross-sectional study in which all the outpatients included were evaluated at the Dementia Clinic in Parma (Italy). 21 patients with probable AD were assessed by an overall cognitive screening (Milan Overall Dementia Assessment), the evaluation of personal and instrumental autonomy (Activities of Daily Living and Instrumental Activities of Daily Living), and of dementia severity (Clinical Dementia Rating Scale). After the neurocognitive assessment, a wide battery of clinical and psychological measures (Symptom Questionnaire, Pisa Stress Questionnaire, Illness Behavior Questionnaire, Sixteen Personality Factor Questionnaire and Satisfaction Profile) was administered to the patients. Spearman's rho correlations between clinical and psychological measures were performed. *Results:* A tendency to deny anxiety, depressive and somatic symptoms might be present in patients with early AD. They also present with hypochondriasis, resulting in higher level of anxiety and depression. Reduced liveliness and self-reliance as personality traits may influence the intensity of such symptoms. *Conclusions:* A comprehensive assessment including psychological and clinical measures should be routinely integrated in clinical practice for the evaluation of patients with early AD. (www.actabiomedica.it)

Key words: Alzheimer's disease, multidimensional approach, dementia care, psychological distress, quality of life

Introduction

Alzheimer's Disease (AD) is a primary neurodegenerative disease of Central Nervous System characterized by an ill-fated clinical course. During the course of neurocognitive deterioration, a heterogeneous group of neuropsychiatric symptoms consisting of disturbed emotions, mood disorders and altered personality traits affect many aspects of patients' life (1). Neuropsychiatric symptoms or 'Behavioral and Psychological Symptoms of Dementia' (BPSD) (2) are very common in AD patients and are associated with high levels of distress both in patients and their caregivers and poor Quality of Life (QoL) (3, 4). Several studies reported that neuropsychiatric symptoms are also common in patients with mild cognitive impairment, especially for anxiety, depression, apathy and irritability (1, 5).

However, behavioural and psychological manifestations may not completely refer to AD degeneration *per se* but represent difficulties of patients to adapt progressive disability effectively and to counteract frustration caused by the disease. In particular, anxiety disor-

der, depressive mood, reduced engagement in pleasant activity and reduced ability to perform activities of daily living have been recognized as remarkable factors influencing psychological distress and QoL in people with dementia (6).

According to some investigations (7, 8), patients in very early stages of AD are able and willing to report their experiences especially with cognitive decline (in particular, memory loss) and other aspects of the disease and are reliable about their own condition when they are offered a framework to help organize thoughts and feelings on the disease.

In the light of this assumption, we believe that a comprehensive evaluation of psychiatric symptoms and wellbeing aspects, dysfunctional lifestyles and stress-related behaviors, illness perception, personality traits, and life quality satisfaction may contribute to better understand the involution caused by the disease and to offer clinicians an in-depth analysis in order to plan treatment and address complex care needs of AD patients.

Methods

A total of 21 patients (M:F=13:8) with probable Alzheimer's Disease were diagnosed according to NINCDS-ADRDA criteria (9). After a complete clinical history, physical and neurological examination, neuroimaging and laboratory exams, the patients were tested by a neuropsychological battery, including:

- a global cognitive screening: Milan Overall Dementia Assessment (MODA) (10); a total global score below 85.5/100 indicates a dementia syndrome;
- the evaluation of personal and instrumental autonomy: Activity of Daily Living (ADL) (11) and Instrumental Activity of Daily Living (IADL) (12);
- the specific evaluation of the following cognitive domains:
  a. memory and visuospatial functioning: Digit Span, Corsi Span, Memory of Prose, Corsi Suvra-span learning (13), and Rey-Osterrieth Complex Figure (Copy of the Rey Figure and 10-minute Delayed Recall) (14);
  b. attention system: Trail Making Test (TMT) (15) and Visual Search Test (13);
  c. language: Phonemic Fluency (13);
  d. logical reasoning: Colored Progressive Matrices (16).

AD patients were then evaluated by the following clinical and psychological measures:

a. Symptom Questionnaire (SQ) (17): it was developed from the Symptom Rating Test (SRT) of Kellner and Sheffield (1973), with the aim of making the scales more sensitive for clinical research. The items of the SQ were derived from the original list of symptoms from which the SRT was built. The SQ is a self-reported measure based on four main scales: Anxiety (A); Depression (D); Anger/Hostility (AH); Somatic (S). It consists of 92 items of which 68 items indicate symptoms (symptom subscales: depressive symptoms -d-; anxiety symptoms, -a-; anger-hostility symptoms, -ah-; somatic symptoms -s-) and 24 items are antonyms of some of the symptoms and indicate well-being (well-being subscales: contented -c-; relaxed -r-; friendly -f-; somatic wellbeing -sw). The subject is given a rating of 1 for each symptom that is checked "yes" or "true" and for each statement of well-being that is checked "no" or "false". The more is the total score the higher is the psychological distress;
b. Pisa Stress Questionnaire (PSQ) (18): it evaluates the presence of dysfunctional lifestyles and stress-related behaviors. The items indicate characteristic behaviors of individuals with high levels of stress, similar to some patterns distinctive of the Type A personality, such as hostility, competitiveness, ambition, urgency, difficulty in expressing feelings and emotions, disturbances related to stressful situations, and checking. The main questionnaire factors are six and described as follows: Sense of Responsibility (SR), Vigor (V), Stress-induced Disorders (SD), Precision and Punctuality (PP), Leisure (L), Hyperactivity (H). The questionnaire consists of 32 items, 16 of which provide a dichotomous answer

("yes"/"no"), 15 having three possible answers ("often"/"sometimes"/"never") and 1 that requires the subject to compare his/her behavior with that of people in general. Other than scores referring to these six factors, a total score is given, by summarizing the presence of dysfunctional/stress-related behaviors and psychopathological risk factors;

c. Illness Behavior Questionnaire (IBQ) (19): it is a 62-item questionnaire that provides information about patient's attitudes, ideas, affects, and attributions in relation to illness that was originally developed as an expanded version of the 14-items Whiteley Index of Hypochondriasis of Pilowsky (1967). The IBQ evaluates the following seven scales: General Hypochondriasis (GH); Disease Conviction (DC); Psychological *versus* Somatic perception of illness (PS); Affective Inhibition (AI); Affective Disturbance (AD); Denial (D); Irritability (I). A "yes"/"no" response is required for each item. The total score is represented by the sum of positive items;
d. Sixteen Personality Factor Questionnaire - Form C (16PF-C) (20): it is a comprehensive measure of normal-range multi-level personality based on Cattell's factor-analytic theory. The form C reports 105 items and it allows to measure four second-order factors (i.e., Extraversion, Anxiety Neuroticism, Tough-Mindedness, Independence, Self-control) beyond first-order factors (i.e., Warmth -A-, Reasoning -B-, Emotional Stability -C-, Dominance -E-, Liveliness -F-, Rile-Consciousness -G-, Social Boldness -H-, Sensitivity -I-, Vigilance -L-, Abstractedness -M-, Privateness -N-, Apprehension -O-, Openness to Change -QI-, Self-Reliance -Q2-, Perfectionism -Q3-, Tension -Q4). For each item it is assigned a point of 0, 1 or 2 except for factor B, and raw scores are converted into stanines;
e. Satisfaction Profile (SAT-P) (21): it is 32-item questionnaire able to evaluate five factors globally summarizing main aspects of adult life: Psychological Functioning (PsF), Physical Functioning (PF), Work (W), Sleep-Eating-Leisure (SEL), and Social Functioning (SF). The patient is required to indicate his/her satisfaction along a continuum by drawing a perpendicular line on a segment which endpoints are represented by "no satisfaction" and "full satisfaction". For each item the scoring is made by calculating the distance between the endpoint "no satisfaction" to the point indicated by patients in millimeters. For each factor the total score is given by the mean of correspondent items. The SAT-P total score ranges from 0-100. The test was previously used in patients with dementia syndromes (22).

The neuropsychological testing and the psychological and clinical evaluation took approximately four sessions of 90 minutes to be administered to each patient by trained practitioners of the Clinic. Specifically, the sessions were made in alternate days to reduce fatigue and in relation to the cognitive and emotional tasks load. They encompassed in order:

- the global cognitive screening and the evaluation of personal and instrumental autonomy (first session);
- the specific evaluation of cognitive domains (second session);
- the administration of SQ, PSQ and IBQ (third session);
- the administration of 16PF and SAT-P (fourth session).

AD patients were included into the study if they reported a Mini Mental State Examination score of ≥20 (23) and a Clinical Dementia Rating of 1. Participants were excluded if they had any significant neurological disease other than AD or comorbid psychiatric condition, any history of significant brain lesion or head trauma and psychoactive medication intake. The participants provided written informed consent. No patients dropped out of the study during the observation period because they were exhaustively and preventively well-informed about the aims of the study directed to the investigation of psychological dimensions beyond the neuropsychological evaluation. The description of psychological dimensions of sufferance as well as their impact on daily living represented the

core of the information given to patients. They were also helped by motivated caregiver, too, during the assessment sessions.

After a descriptive analysis of neuropsychological results, Spearman's rho correlations were performed among psychological and clinical measures to detect specific associations of variables able to reveal psychological and behavioral aspects characterizing patients with early AD.

Results

Demographic data and neuropsychological evaluation scores are first shown in Table 1.

The neuropsychological assessment showed results typically depicting cognitive profile of early AD patients. As expected, of 21 patients 18 (85.7%), 17 (81%), and 19 (90.5%) reported scores below norms on Memory of Prose, Corsi Suvra-span learning and TMT Part B, respectively, highlighting an impairment of long-term episodic memory (both verbal and visuospatial) and divided attention whereas 3 patients (14.3%), 4 patients (19%), and 2 patients (9.5%) had normal performance in these tests, respectively. Selective attention was slightly impaired: 8 patients (38.1%) reported scores below the norms on Visual Search Test, 2 patients (9.5%) reported scores at inferior limits of norms whereas the majority of the sample, that is 11 patients (52.4%), had normal performance. The whole sample consisting of 21 patients (100%) performed poorly on Rey-Osterrieth Complex Figure 10-minute Delayed Recall, confirming the presence of a visuospatial memory impairment whereas the Copy of the Figure was substantially adequate although often slow. Conversely, short-term memory (both verbal and visuospatial) was relatively spared, as confirmed by scores on Digit span and Corsi Span: only 3 patients (14.3%) performed poorly on these tests while 18 (85.7%) performed normally. Moreover, a linguistic deficit was present in 5 patients (23.8%) and the remaining part of the sample, i.e. 16 patients (76.2%) showed normal performance in this test. Finally, 13 patients (61.9%) showed a deficiency of logical reasoning differently from 8 patients (38.1%) that performed normally on Colored Progressive Matrices, by revealing how frontal domains frailty may often represent a neuropsychological hallmark along with episodic memory damage in early AD.

Table 1. Descriptive analysis of socio-demographic variables and screening measures of the sample

Socio-demographic and clinical variables	Total	Males (N= 13)	Females (N= 8)
Age	70.5±6.8	70.3±6.6	70.8±7.1
Education	6.6±2.3	6.9±2.3	6.1±1,9
MODA	81.8±7.8	81.8±8.0	81.9±7.2
ADL	5.0±1.6	5.0±1.8	5.1±1.5
IADL	5.1±1.8	5.1±1.7	5.1±1.8

Note: MODA=Milan Overall Dementia Assessment; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living

As reported in Table 2, scores obtained by AD patients on SQ and IBQ overlapped with those reported Italian population (17, 19).

Moreover, AD patients showed a moderate dissatisfaction about their mental efficiency even though results on SAT-P outlined that they were globally satisfied about their QoL (Table 3).

Significantly, PSQ V scale score negatively correlated with SQ a (rho=-.81, p<.001), d (rho=-.80, p<.001), A (rho=-.78, p<.001) and D (rho=-.83, p<.001) scales scores, pointing out that patients reporting to hold vitality, energy and stress-resistance less complain of anxiety and depression symptoms. Furthermore, patients depicting themselves as being very meticulous, precise and punctual reported few somatic symptoms, as revealed by negative correlations between PSQ PP scale score and SQ s (rho=-.65, p<.01) and S (rho=-.64, p<.01) scales scores.

PSQ L scale score was positively correlated with SQ scale a (rho=.86, p<.001) and A (rho=.85, p<.001) scores. Such a result indicated that patients who are too busy and struggle to break away from commitments are those reporting more anxiety symptoms. IBQ GH scale score correlated with SQ a (rho=.78; p<.001), d (rho=.72; p<.001), A (rho=90; p<.001), and D (rho=.66, p<.01) scales scores. As expected, the patients presenting a phobic concern about their physical health experience more anxiety and depression.

PSQ V scale score was positively correlated to SAT-P SF scale score: patients who feel more vital, energetic and stress resistant are more satisfied about

Table 2. SQ and IBQ scales: Minimum, Maximum, Mean, Standard deviation and z-scores

Subscales (range)	Min	Max	Mean	SD	Z
SQ					
a (0-17)	0	11	3.48	3.84	-0.40
d (0-17)	0	10	3.90	3.42	-0.18
s (0-17)	1	13	5.19	4.29	0.19
ah (0-17)	0	7	2.62	2.48	-0.24
r (0-6)	0	3	1.14	1.15	-0.67
c (0-6)	0	5	1.76	1.26	-0.03
sw (0-6)	0	5	2.76	1.37	0.12
f (0-6)	0	1	0.62	0.50	-0.18
A (0-23)	0	13	4.62	4.59	
D (0-23)	0	12	5.52	4.11	
S (0-23)	1	16	7.81	4.53	
AH (0-23)	0	8	3.43	2.77	
IBQ					
GH (0-9)	1	7	3.81	2.18	0.13
DC (0-6)	0	4	2.05	1.43	-0.36
PS (0-5)	1	4	2.14	0.91	0.19
AI (0-5)	2	5	3.29	1.06	0.20
AD (0-5)	0	4	2.24	1.48	-0.42
D (0-5)	3	5	4.10	0.83	1.12
I (0-5)	0	3	1.05	1.16	-0.86

Note: SQ=Symptom Questionnaire; a=anxiety symptoms; d=depressive symptoms; s=somatic symptoms; ah=anger-hostility symptoms; r=relaxed; c=contented; sw=somatic well-being; f=friendly; A=Anxiety; D=Depression; AH=Anger/Hostility; S=Somatic (S); IBQ=Illness Behavior Questionnaire; GH=General Hypochondriasis; DC=Disease Conviction; PS=Psychological *versus* Somatic perception of illness; AI=Affective Inhibition; AD=Affective Disturbance; D=Denial; I=Irritability

their social functioning. In addition, PSQ total score was negatively correlated to SAT-P PF scale score (rho=-.72, p<.001): patients who have a stressful lifestyle are less satisfied about their physical functioning.

A tendency to depression was evident in patients thinking to be severely affected by the disease and not taking into account clinicians' reassurances, as shown by the correlation between IBQ DC scale score and SQ D (rho=.91, p<.001) scales scores. IBQ D scale score was negatively correlated to SQ r (rho=-.71, p<.001) and sw (rho=-.72, p<.001) scale scores. Such a result indicated that patients' tendency to deny psychological troubles result in minor relaxing and wellbeing sensations. IBQ GH scale score was negatively correlated to SAT-P SEL scale score (rho=.-72, p<.001): the patients presenting a phobic concern about their physical health are less satisfied of the quality of sleep, eating and leisure.

Table 3. Items and scales of SAT-P: Minimum, Maximum, Mean and Standard deviation

SAT-P items and scales	Min	Max	Mean	SD
1) Quality of sleep	0	86	70.3	28.7
2) Amount of sleep	0	100	71.9	30.5
3) Quality of food	80	100	89.1	7.8
4) Eating behavior	52	100	82.5	17.1
5) Resistance to physical fatigue	0	100	55.8	35.3
6) Physical wellbeing	0	100	59.2	30.4
7) Physical appearance	0	97	61.2	36.5
8) Physical mobility	0	100	66.2	36.1
9) Level of physical activity	0	93	57	36.3
10) Frequency of sexual intercourse	0	89	57.5	24.9
11) Quality of sexual intercourse	0	74	56	22.3
12) Resistance to stress	2	100	69.2	31.1
13) Mood	45	80	60.9	12.9
14) Mental efficiency	0	85	34.7	27.8
15) Emotional stability	0	87	58.2	30.8
16) Self-confidence	47	100	78	18.2
17) Problem solving ability	25	95	70.9	25.6
18) Psychological autonomy	70	100	83.8	10.9
19) Self-control	77	100	86.2	9.9
20) Type of work*	-	-	-	-
21) Organization of work*	-	-	-	-
22) Professional role*	-	-	-	-
23) Work productivity*	-	-	-	-
24) Free time	0	96	69.8	31.6
25) Free time activity	5	91	66.2	28.9
26) Social image	0	100	71.5	32.5
27) Couple relationship	0	100	70.7	31.8
28) Family role	48	100	81.7	16
29) Relationship with members of your family	70	100	88.6	11.1
30) Relationship with your friends	79	100	89.8	8.9
31) Relationship with colleagues*	-	-	-	-
32) Financial situation	45	95	76.1	16.1
PsF	44	83	69.8	13.3
PF	4	85	57.1	27.9
SEL	40	95	76.9	16.6
SF	50	82	67.9	11.7

Note: *Scores of items concerning job 20-23 and 31) were omitted because all the patients were retired); PsF=Psychological Functioning; PF=Physical Functioning; SEL=leep-Eating-Leisure

Correlations shed light on a specific description of AD patients' personality traits, too. A negative correlation was found between 16PF-C Factor F and SQ A (rho=-.81, p<.001) and D (rho=-.82, p<.001) and between 16FP-C Factor Q2 and SQ A scale

(rho=-.91, p<.001). The first result indicated that people describing themselves as introverted, reserved, rigid and inhibited experience more anxious and depressive symptoms. The latter result indicated that more people are dependent and influenced by others and need their approval more they are anxious. Furthermore, somatic symptoms are highly present in patients that are restless and intolerant, as found by the negative correlation between 16PF-C Factor Q4 and SQ S scale (rho=-.89, p<.001). Finally, 16PF-C F score was positively correlated with SAT-P PsF (rho=.80, p<.001), PF (rho=.81, p<.001) and SEL (rho=.87, p<.001). The patients who are extroverted, not inhibited and unworried are more satisfied about their psychological and physical functioning, sleep, eating and leisure quality. The patients who are more satisfied for sleep, eating and leisure quality are more self-sufficient and independent, as revealed by the correlation between 16PF-C Q2 scale score and SAT-P SEL scale score (rho=.79, p<.001).

Finally, patients thinking to be severely affected by the disease, not taking into account clinicians' reassurances and presenting affective instability reported low satisfaction about physical functioning, as shown by the negative association between SAT-P PF and both IBQ DC and D scales scores (rho=-.83, p<.001, rho=-.64, p<.01, respectively).

Discussion and conclusions

The neuropathological course of AD is characterized by a progressive decline of cognitive abilities, starting from episodic memory and executive dysfunction (24, 25). Progressive cognitive decline and functional ability reduction significantly affect patients' QoL and social care of AD patients, and non-pharmacological interventions are currently adopted for different purposes, such improving cognition, sustaining personal and instrumental autonomy of patients, reducing BPSD and alleviating caregiver's burden (26, 27).

Interestingly, along with cognitive decline a series of psychological and behavior manifestations of AD is probably due to a complex interplay of psychological, social and biological factors and a considerable part of patients' suffering and caregivers' distress relate directly to them (28).

Insight reduction occur in the majority of AD patients even at the onset of the disease and represents a predictive factor for the manifestation of severe apathy, agitation, irritability and behavioral symptoms during its course (29). A tendency to deny anxiety, depressive and somatic symptoms by AD patients accounting for their difficulty to express painful emotions might be present. Such a tendency provoking a continuous apprehensive expectation seems to reduce relaxing and wellbeing sensations and particularly affect some aspects of patients' life (i.e., sleep, eating and leisure).

Moreover, excessive worrying and misinterpretation about normal body sensations (i.e., hypochondriasis) results in a higher level of anxiety and depression, also because of the disruption of social, occupational and family functioning as a consequence of disordered thinking of patients.

The AD patients result to be satisfied about their functioning when sustained by precision, punctuality and vigor, and they do not report remarkable dysfunctional lifestyles and stress-related behaviors.

Specific personality traits have not been exhaustively examined in the context of AD (30). Our study outlines how reduced liveliness and self-reliance may play a critical role for anxiety and depressive symptoms. Conversely, liveliness and self-reliance are positively related to higher levels of satisfaction in psychological and physical functioning and sleep-eating-leisure.

Our study presents some limitations. First, as a pilot study, it should be implemented by a more extensive data collection. Second, longitudinal follow-ups are recommended for this kind of investigations to detect significant changes of psychological, neuropsychological and clinical measures during AD progression.

Management of health care needs of AD patients is influenced by many factors, such as psychiatric symptoms and wellbeing aspects, dysfunctional lifestyles and stress-related behaviors, illness perception and personality traits. Our findings support the usefulness of a multidimensional approach for a comprehensive evaluation of early AD than standardized neuropsychological assessment alone. By this way, health practitioners can be able to determine patient's medical, psychosocial and functional problems, with the aim of developing a whole plan for treatment and rehabilitation, improving clinical practice guidelines

on detection and management of dementia, and supporting caregivers dealing with the stress of caring for a loved one with AD.

Since in AD patients the occurrence of negative outcomes such as institutionalization, hospitalization and mortality results from a combination of biological, functional, psychological, pathological and environmental factors, diagnostic tools that effectively identify patients with high risk patterns should be part of a multidimensional approach routinely adopted in clinical practice.

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Original article

The economic crisis and lifestyle changes: a survey on frequency of use of medications and of preventive and specialistic medical care, in the Marche Region (Italy)

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Summary. *Background and aim:* In the words of one observer, one of the many effects of the economic downturn has been a "health system shock" marked by reductions in the availability of healthcare resources and increases in the demand for health services. The financial situation influences negatively the low-income family groups, particularly those who normally use the government provided primary prevention services. The goal of this study was to assess the impact of the global recession on the use of medicines and medical investigation recession in different areas of the Marche Region. *Methods:* An anonymous questionnaire prepared by the National Institute of Statistics, modified and validated by the University of Camerino, has been distributed to junior highschool students of Central Italy to provide a statistically representative sample of families. The questionnaire has been administered in 2016-2017. *Results:* This article examines the results about healthcare habits, specifically, regarding medicines and medical examinations. Data obtained emphasize a reduction in the use of nonsteroidal anti-inflammatory drugs (NSAIDs). The parents category showed the higher change in medicines use (72.9%). Comparing the data of the Fabriano area with that of the Civitanova Marche area, Fabriano reported a greater reduction in the frequency of taking medicine. Concerning the medical examinations, half of the respondents (62.5%), indicated that they and their family members have regular medical check-up. *Conclusions:* Respondents who admitted that the economic crisis had reduced their quality of life indicated that the parents were the ones who had experienced the greatest change. This is confirmed by the information on the reduced frequency of medicine use, which affected the parents more than the children, whom they sought to protect and safeguard the most. This reduction was most marked in the Fabriano area. In contrast, in the Civitanova Marche area, with different socioeconomic characteristics, an increase in the use of all the categories of medicines was reported. Concerning visits the situation in the Marche Region appears encouraging. (www.actabiomedica.it)

Key words: economic crisis, medications, medical care, lifestyles, prevention, drugs

Introduction

In the words of one observer, one of the many effects of the economic downturn has been a "health system shock" marked by reductions in the availability of healthcare resources and increases in the demand for health services (1, 2).

Some European countries, such as Italy, have introduced extra charges for some health services previously covered by the National Healthcare System

(NHS), and have cut expenditures on healthcare in order to reduce the deficit generated by the economic crisis (3-6).

The financial situation influences negatively the low-income family groups, particularly those who normally use the government provided primary prevention services. Therefore, in forcing governments to reduce the availability of preventive medicine, the economic downturn may have deleterious effects on the health of the population (7).

Some European countries have sought to reduce these effects by improving timely access to services, particularly those for priority groups and specific diagnostic-therapeutic pathways. Other measures include direct purchase of extra visits and tests from private providers by local healthcare units, the activation of central booking centers, the imposition of penalties for patients who do not keep appointments, and demanding that users pay for services prior to accessing care (introduced with the NHS) (8).

Studies have demonstrated a direct relationship between unemployment and attention to one's state of health. Some scholars have indicated that a steady income serves as a positive proxy for the family and a positive environmental determinant for the health of young people (9, 11).

It is well known that the social distances (income inequality) within a population produce a "gradient effect" on the health of individuals. In fact, in societies characterized by a "steep gradient" of economic inequality, the overall level of health and well-being is lower than that in societies where the differences are less pronounced.

The negative influence of income inequality is much more severe if we consider that the state of health encompasses a wide variety of physical, cognitive, emotional, behavioral, educational, occupational and mental outcomes. Therefore, the economic downturn and unemployment are elements that may increase the "gradient effect" on the health of the population and stop "the development of health"; which describes the trend within a population of all the outcomes related to a good state of health (12, 13).

The economic crisis has affected not only access to healthcare, but also the use of medicines. After the global recession, the World Health Organization (WHO) investigated the impact of the global economic crisis on the pharmaceutical sector. The largest changes, on the medicines consumption, were noted in high income countries and Europe, but no distinction was observed between the decrease in medicines for acute and chronic pathologies (14, 15), nor did any shift from licensed brands to other brands or generic medicines emerge (16). The goal of this study was to assess the impact of the global recession on the use of medicines looking a representative sample of the population in our region. A secondary objective was to investigate which medicines were affected the most and the least by the recession in areas of the Marche Region that have suffered particularly from the economic downturn, and to identify changes that may have occurred in the frequency with which families avail themselves of the services of physicians, pharmacists and dentists.

Methods

In the period 2016-2017, an anonymous questionnaire prepared by the National Institute of Statistics, modified and validated by the University of Camerino, Pharmacy and Health Products School, was distributed in the cities of Camerino, Fabriano, and Civitanova Marche, in the Marche region (Italy), which represent a cross section of regional social, economic and cultural realities. The sample is representative, owing to the fact that since the questionnaire was distributed among students in compulsory schools (lower level secondary school), we were able to reach all types of families, irrespective of their social, economic or cultural status.

The questionnaire validity was tested by administering it to 15 people of different social/economical and cultural status to value the 'face validity'. The investigators briefly explained the aim of the survey and obtained written consent before each interview. The study was conducted according to the Helsinki Declaration. The questionnaire was administered to middle school students to provide a statistically representative sample of families in the geographic area served by the University of Camerino. The questionnaire consisted of five sections: "Social and anagraphic data", "Change of the style of life" (*physical activity, consumption of al-*

cohol, smoking, consumption of drugs and the use of medicines and visits to family doctors and specialists) "Change in eating habits" (*regarding the amount of food products bought, the type of stores and the general variation of purchases observed with the increase of prices*), "Details of consumption" (*how food consumption changed in relation to specific food categories*) (17, 18), "The psychological profile of the subjects" (*the level of satisfaction with one's personal life*) (19).

The data were processed using an Excel Workbook (Microsoft Office), and analyzed using SPSS 20 (SPSS Inc); the Chi-square Test ($p<0.005$) was used to examine possible relationship.

Results

This article examines the results about healthcare habits, specifically, regarding medicines and medical examinations. 880 people answered, corresponding to a 47.3 % of the total number of questionnaires distributed. The sample was composed by 310 males (35.2%) and 570 females (64.8%). The average age ranged from 41 to 50 (57.2%) and 52.5% of sample has a high school qualification.

Table 1. The percentage of household members who take drugs.

Which drugs	n.	%
Chemiotherapics	5	1.5
NSAIDs	139	41.1
Antihypertensives	41	12.1
Antidepressants	5	1.5
Corticosteroids	4	1.2
Insulin	6	1.8
Antithyroid	20	5.9
Anxiolytics	10	3.0
Anticoagulants	2	0.6
Muscle Relaxants	2	0.6
Antihistamines	33	9.8
Antacids	4	1.2
Cortisol	25	7.4
Contraceptives	3	0.9
Antiepileptics	3	0.9
Antiparkinson's	1	0.3
Antiarrhythmics	4	1.2
Supplements	4	1.2
Homeopathic drugs	11	3.3
Spasmolytics	8	2.4
B-blockers	1	0.3
Antiplatelet agents	4	1.2
Lipid lowering drugs	1	0.3
Oral hypoglycemics	2	0.6

Table 1 summarizes the classes of drugs taken by the respondent and other members of the household (20).

The drug category with the most marked reduction was that of the nonsteroidal anti-inflammatory drugs (NSAIDs). The use of antidepressants and anxiolytics was also reduced, though to a lesser degree (21). Respondents reported that the most significant reductions were for medications prescribed by the family doctor or specialists.

To the question "*Has your family's use of medicines changed?*" 152 (17.2%) answered yes, 709 (80.5%) answered no, and 20 (2.3%) did not answer.

Specifically, for 72.9% of parents, their medicine use had changed, while this was the case for only 13.2% of children. Asked "*How has your frequency of medicine use changed?*", 47.0% indicated increased frequency, and 20.5% reported reduced frequency. Among those for whom there was an increased frequency of medicine use, 81.7% were parents and 18.3% were children, while among those who had reduced the frequency, 83.9% were parents, and 18.3% were children.

Comparing the data of the Fabriano area with that of the Civitanova Marche area, an increase in the frequency of taking medicine was noted for the Civitanova Marche population. This area was less affected by the economic recession, and its level of industrialization has remained good, as businesses here have proven more successful at adapting to socio-economic

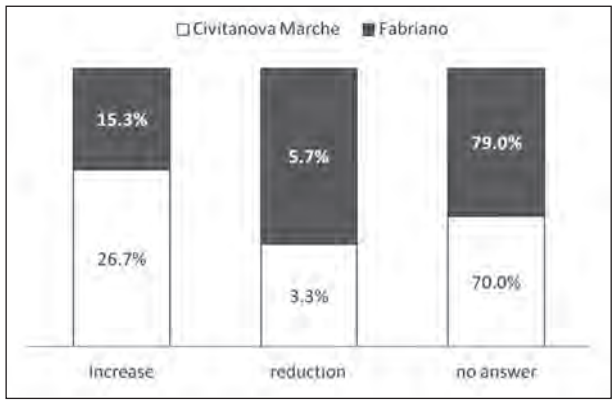

Figure 1. Increased and decreased frequency of taking medicines: Fabriano and Civitanova Marche areas

changes. Respondents from the Fabriano area, instead, reported a greater reduction in the frequency of taking medicine (Fig. 1).

As can be noted from the figure 1, the great majority of respondents chose not to answer the question about "*How frequency consumption in the family changed",* even though they answered the question about the change in medicine use in the post-crisis period.

Almost a half of respondents (39.9%) reported taking a medication recommended by a physician (GP or specialist). In 7.6% of the cases, respondents preferred to ask friends or other family members for advice on medications, rather than consulting a doctor or pharmacist (this percentage was actually 15.4% of the subjects who responded to the question) ($p<0.05$). It is also dismaying that only 1.0% of respondents asked for advice on medication from a pharmacist, significantly fewer than those who sought advice from a friend or family member ($p<0.05$). The majority of respondents (51.5%) did not provide an answer to the question.

Over half of the respondents (550 people, 62.5%), indicated that they and their family members have regular medical check-ups. The 79.9% see their family doctor or a specialist with some regularity. Only 341 (38.5%) subjects indicated that they and their family members, visit a dentist periodically. The most frequent reasons for a doctor's appointment were respiratory diseases (20.0%), cephalea (19.8%), and hypertension (16.0%), anxiety (6.8%) and gastric ulcer (6.5%). .

Discussion

As mentioned above, the sample group was surveyed in order to determine whether the economic crisis had affected how attentive respondents are to their health and that of their family.

It may be that family habits reflect a level of "lifestyle carelessness" that bears on the life of the children. In fact, in particularly critical situations such as those provoked by an economic crisis, youth are the sector of the population most vulnerable to rapid changes in lifestyle that may lead to incorrect lifestyles potentially harmful for their health, such as use of medicines without consultation of a physician or pharmacist (22-25).

In particular, we examined the use of medications, the attention to consultations and appointments with family doctors and specialists. The results regarding medicine usage are more contained then European situation. For example, our respondents indicated a quite low use of psychotropic and anxiolytic drugs, unlike the situation in Spain (26). However, a substantial number of respondents with potential psychiatric disturbances were identified in our survey. This is a worrisome observation, given this phase of an economic crisis in which one's psychological equilibrium can be put hard to the test.

Concerning the use of medications an incorrect habit has been highlighted: our data show that 15% of subjects who responded to the question about consultation with physicians or pharmacists indicated that they choose pharmaceutical products based on the recommendation of a family member or a friend, not of an expert. This may be due to mistrust of healthcare professionals and a tendency to seek an easier and less expensive solution than the one professionals would advise, which instead sometimes demand expensive or psychologically difficult diagnostic procedures, tests, and treatment regimes.

The category of NSAIDs is the one with the greatest reduction in use. This may be because families that have borne the brunt of the economic crisis may have chosen to reduce widely used drugs that are specific for certain pathologies.

More specifically, respondents who admitted that the economic crisis had reduced their quality of life indicated that the parents were the ones who had experienced the greatest change. This is confirmed by the information on the reduced frequency of medicine use, which affected the parents more than the children, whom they sought to protect and safeguard the most. This reduction was most marked in the Fabriano area. In contrast, in the Civitanova Marche area an important reduction in the use of all the categories of medicines has not been registered. A possible explanation could be given by data on unemployment which can be found on the two websites we consulted. Unsurprisingly, data referring to unemployment in the areas of Fabriano and Civitanova Marche shows youth unemployment figures in Fabriano of over 30%. Employ-

ment figures for Fabriano are equal to 36.6%, compared to Civitanova's at 41.8%.

The same can be said, even though percentages are smaller, for figures relating to women and men; the employment rate for women in the Fabriano area stands at 39.6% compared to 40% in Civitanova Marche; for men, we are looking at 54.6% compared to 58.0% in Civitanova Marche. Furthermore, a comparison of data for youth employment rates and long-term unemployment in the city of Fabriano with figures for the Marche Region, shows a reduction of 4.7% for both values (27). This evidence is reinforced by data recorded by the Job Centre in Fabriano for the period from 2010 to 2016 on the population aged 14 – 65. These data push unemployment rates over 50%, with over 5 thousand jobless in the city of Fabriano alone; an average which is well above the national figure. On the contrary, job centres in Civitanova Marche recorded a 57.1% drop in job seekers starting from 2014 (28).

Our research reveals less alarming data for access to GP and specialist medical appointments, relating to prescriptions for therapies or specialist prescriptions.

Concerning visits to the family doctor or a specialist, working on the assumption that ¼ of those who responded to the question had a medical examination with subsequent prescription of a drug for headache or anxiety, generally speaking, there seems to be a normal level of adherence to the therapy prescribed. This may be deduced from the data on visits to a specialist, and the data on specific categories of medication taken.

Instead, if one considers the situation in countries more gravely affected by the economic crisis, such as Greece, the surveys indicates insufficient compliance or even abeyance when expensive medications are prescribed, such as those for cardiovascular diseases (29).

In Italy, the national healthcare system probably deserves credit for this positive difference (universal health care coverage), because in Greece and the most part of European countries healthcare assistance is provided only on the basis of insurance.

Probably, if the Italian public health system were more similar to the one adopted by Greece, it would have meant a reduction in medicines which must be paid for, as well as in GP and specialist appointments, the cost of which would depend fully on the patient.

In countries where social and health policies are based on the principle of equality, the right to health and a decent household income, the social gap is reduced (30, 31).

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Original article

Survey about the potential effects of economic downturn on alcohol consumption, smoking and quality of life in a sample of Central Italy population

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Summary. *Background and aim of the work:* Negative health effects have been associated with the changes in lifestyles in relation with the low income of population. Consequently, in our study we investigated the frequency changes of alcohol and smoke consumption, physical activity, and quality of life in families of Marche Region in Central Italy. *Methods:* In the period 2016-2017, an anonymous questionnaire has been distributed to junior highschool students of Camerino, Fabriano, and Civitanova Marche of Marche Region. The Manchester Short Assessment of Quality of Life (MANSA), was used to assess subjective quality of life. *Results:* Data obtained in this research were used to analyze lifestyle changes, specifically those involving alcohol consumption, smoking, and physical activity, and to assess perceived general quality of life. In all categories of population, an increase of frequency in alcohol consumption was observed. On the contrary, for the tobacco smoke we observed a reduction in particular in the parents category. The MANSA mean value was 4.5 with a Standard Deviation of 1.3. *Conclusions:* As underlighted, also, by results of the MANSA test we can hypothesize a reduction in the family income produces a change of lifestyles. (www.actabiomedica.it)

Key words: economic downturn, alcohol, smoke, physical activity, quality of life

Introduction

The economic crisis started in Europe at the end of 2007 with differences in many countries.

Negative health effects have been associated with this event, and a number of studies have focused on a possible association between the economic downturn and the consequences of the changes in lifestyles, have been conducted (1).

A part of literature have expressed concern that the consequences of the job losses could be responsible for the depression states and, in addiction, for problems associated with the use of alcohol and smoking, as a response to stress (2). A 2009 study reported that an over 3% increase in unemployment had effect on suicides at ages younger than 65 years and deaths from alcohol abuse (2).

These factors can have a severe effect not only on public health but also on societal welfare (3-7). It should be remembered that incorrect lifestyles are also considered related to the development of serious diseases, such as diseases of the circulatory system, metabolic diseases, which play an important role among the main causes of death in the population and that entail significant costs for the Public Health (8). Youth unemployment is an important consequence of the economic downturn, and is also cause of psychophysical health problems and increased smoking and alcohol consumption. Moreover, recent studies have found that the effect of youth unemployment on men-

tal health remains in adulthood, independent of later unemployment experiences.

Understanding the real relationship between economic crises and adoption of less healthy lifestyles is complex because of differences in national unemployment rates (9). In fact, studies on the impact of economic crises on alcohol and tobacco consumption have produced quite varied results. Two different effects were associated with the economic downturn: one study reported increases in the prevalence of drinking and/or smoking, while another observed a dampening effect on the these behaviors, perhaps due to increased prices and decreased purchasing power (10, 11).

In this context, we surveyed parents of middle school students in an area of the Marche Region in central Italy that has been particularly hard hit by the economic crisis. Previous studies, useful for a comparative analysis of the trend pre-crisis, were conducted among high school and university students in the Marche Region, to analyze their knowledge about and use of legal or illegal substances. The results indicated that high school students regularly smoke and consume alcohol (12, 13). Other studies conducted in the same region found that 36.4% of high school students surveyed that use alcohol, tobacco and antidepressant (14), and 28.2% of university students surveyed smoked, and consumed alcohol regularly (several times a week or more often) (15).

The aims of the present study were **a)** to investigate the effect of the economic downturn on lifestyle, in terms of changes in smoking, alcohol consumption, and physical activity, and **b)** to explore the effects on the psychological profile of respondents and to assess subjective quality of life.

Methods

The research was conducted in the period 2016-2017 using an anonymous questionnaire consisting of five sections: "Social and anagraphic data", "Change of lifestyle " (*physical activity, consumption of alcohol, smoking, consumption of drugs and the need to undergo medical examinations*), "Change in eating habits" (*regarding the amount of food products bought, the type of stores and the general variation of purchases observed with the increase of prices*), "Details of consumption" (*changes in consumption of specific categories of foods*) (16, 17), "The quality of life of the subjects" (*the level of satisfaction with one's personal life*) (18, 19). The questionnaire, prepared and distributed by the School of Pharmacy, Camerino University, was first validated by administering it to a sample of people representative of different socioeconomic and cultural backgrounds.

The level of satisfaction with one's personal life was evaluated using the MANSA scale (Manchester Short Assessment of Quality of Life), an instrument that affords a fairly quick way to assess satisfaction with quality of life as a whole and also in terms of different life domains. SQOL (Subjective Quality Of Life) is the mean score of 12 satisfaction ratings. Each item is rated on a Likert type scale ranging from 1 (lowest satisfaction) to 7 (highest satisfaction) with 4 as a neutral middle point (20). We chose the MANSA scale because our group had observed its usefulness in a previous study conducted to evaluate the quality of life of the residents of post-earthquake housing in L'Aquila, central Italy (21, 22).

In the present study, a questionnaire was distributed in middle schools of Camerino, Fabriano, and Civitanova Marche in the Marche Region, cities in the geographical area served by the University of Camerino and characterized by different socio-economic and cultural backgrounds. The middle schools were chosen randomly and the questionnaire was given to the students, with the request that they ask one of their parents to fill it out.

Questionnaire answers were stored and processed using Microsoft Excel sheets, and statistical analysis was performed using SPSS 20 (SPSS Inc).

Results

Data from the 880 people who responded to the questionnaire were used to analyze lifestyle changes, specifically those involving alcohol consumption, smoking, and physical activity, and to assess perceived general quality of life. A total of 1860 questionnaires were distributed and 1091 were returned (58.7%), but about 10% of these were blank or completed incorrectly (192 blank, 19 invalid because of obvious tampering with the paper or loss of anonymity). Thus the study

analyzed 880 correctly completed questionnaires, 47.3% of the total number of those distributed.

The sample included 310 males (35.2%) and 570 females (64.8%) whose average age ranged from 41 to 50 (57.2%); 52.5% of sample has a high school qualification.

Lifestyles: alcohol consumption, smoking and physical activity

As regards the habitual consumption of alcohol, 626 (70 %) subjects responded that they do not consume alcohol habitually, while 231 (27 %) indicated that they do. Analysis of the data showed a relevant trend in alcohol consumption.

In addition, answering the question "*Which family member usually drinks alcohol?*" 231 (26.3%) subjects indicated parent 1, 626 (71.1%) indicated parent 2, while only 1 subject (0.1%) indicated that the children drink alcohol.

In particular, analyzing the change of frequency in alcohol consumption, an increase in all categories was observed. Even if the higher percentages were recorded for both parents, the 29% in alcohol consumption frequency by children is very severe (Fig. 1 a).

As for smoking habits, 297 subjects (34%) answered that someone in the family smokes. When asked, "*Which member of the family smokes?*", 605 people (68.8 %) did not answer, 187 (21.2%) indicated the parent 1, 70 (8.0%) indicated the parent 2, while only 18 (2%) indicated the children.

The "parents" category had a smaller increase in smoking than in drinking alcoholic beverages; instead, in the children category, the data pre-crisis and post-crisis appear to be unvaried (Fig. 1b).

Analyzing all groups of smokers about the reduction, parent 1 had an 87.0% reduction in smoking, parent 2 had a 73.1% reduction, and children had a 50.0% reduction, confirming the previously trend.

In addition, we investigated how the economic crisis changed the physical activity in our sample. When asked, "*Do any family members do regular physical activity?*", 524 subjects (59%) responded yes, 342 (39%) said no and only 14 (2%) did not respond.

When asked "*Which family member regularly does physical activity*?", 382 (43.4%) people did not answer, 252 (28.6 %) indicated the parent 1, while only 177 (20.2 %) reported that the children engage in physical activity.

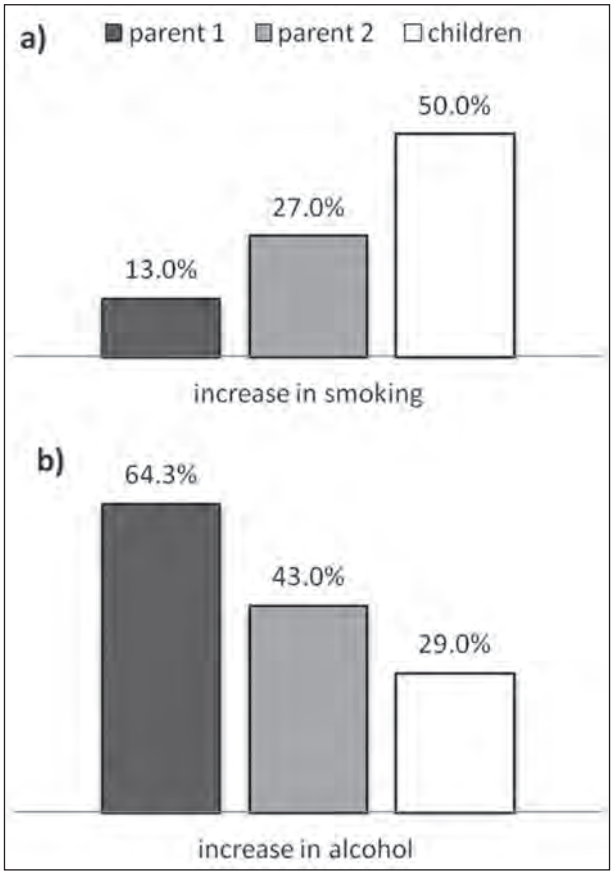

Figure 1. a) increase in smoking and b) increase in the frequency of alcohol consumption

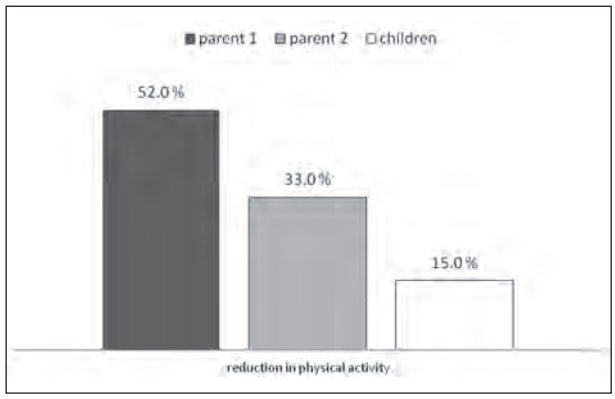

Figure 2. Reduction in physical activity

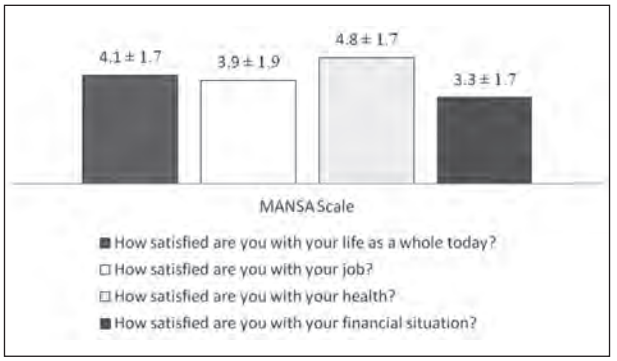

Figure 3. Quality of Life MANSA Scale Results

Furthermore, decreased frequency of physical activity was reported for all categories, in particular for the parent category (Fig. 2).

Quality of life

In order to understand the psychological status underlying changed habits of life, people were asked to provide information about their satisfaction in various fields, such as work, finances, health, etc. Respondents in this study rated their satisfaction with their quality of life at the neutral middle point, as seen in the MANSA mean value of 4.5±SD 1.3.

Prompted by the question "*How satisfied are you with your current financial situation?*" 94% of respondents indicated dissatisfaction (Fig. 3). The answers about job satisfaction confirm and reinforce those about finances: 80% of the sample indicated a level of satisfaction tending to dissatisfaction (Fig. 3).

To analyze these results, we eliminated data from Camerino, where a large part of the population holds government jobs, and has not been as severely impacted by the economic downturn as those in the more industrial cities of Fabriano and, to a lesser degree, Civitanova Marche. Fabriano has suffered the closure of factories central to the economy of the city, with consequent closure of smaller businesses that served the factories, and the city's economy has been severely harmed. In contrast, Civitanova Marche, a coastal city popular for its beaches and small businesses, has fared better during the general economic downturn, with less severe consequences. The average MANSA score for Fabriano was 3, while that for Civitanova Marche was 4. This difference, even if statistically not significant, might indicate a higher level of dissatisfaction in Fabriano than in Civitanova Marche.

Discussion and Conclusions

This paper shows some lifestyle changes trigged by the economic downturn in our Region, and indicates a need for a broader and deeper investigation of this phenomenon. In particular, comparing parents and children, we found behavior differences for every lifestyle aspect examined. Analyzing the problem of less healthy lifestyles and particularly the increased frequency of alcohol consumption and smoking and the decreased frequency of physical activity, we can point to definite changes in habits in the post-crisis period.

The results on alcohol use are very interesting, is the result about the alcohol use. Increased alcohol consumption was reported in both parents and children, in line with data reported in the literature (2).

It may be possible that the combination of youth unemployment and adult unemployment in the same household may lead to increased alcohol consumption by both categories.

The effects of the economic downturn can cause anxiety, stress, and depression, with the subsequent loss of social status and relationships (23). Two related psychological theories view increased levels of alcohol consumption and the incidence of alcohol-related health problems as crises-triggered consequences. The "stress-response-dampening theory" posits that people consume more alcohol to reduce the intensity of their response to anxiety and stress, and suffer a higher incidence of alcohol-related health problems (24, 26).

It is known that substance abuse can also lead to death, and this has been observed in some researches that have also highlighted the use of alcohol and other substances of abuse in people subjected to stress (27).

The "self-medication theory" suggests that during an economic recession, high levels of alcohol consumption can lead to the development of dependency in certain people (28, 29).

Regarding smoking habits, a clear reduction has been recorded, which certainly is a boon for the health of the smokers. However, this reduction may not represent a long-term personal choice for a healthier life-

style, but may be due to the inability to afford tobacco products. Other studies reported that during a period of economic crisis, the high price of cigarettes may deter some people from starting to smoke, or may cause others to give up smoking, and this may be interpreted to show that an economic crisis may lead to improvements in health (30-32).

The MANSA results indicate a population characterized by a lack of fulfillment, with respect to the current economic situation. The data on the level of satisfaction regarding finances and work confirm the pressure triggered by the economic downturn on the population of questionnaire respondents. This pressure emerges in the comparison between the results for the Fabriano area and the Civitanova Marche area, in reference to the different levels of economic recession. Considering previous epidemiological surveys, showing that 30.0% of youth reported alcohol consumption in the pre-crisis period, the 29.0% increase recorded in our study becomes very interesting, especially in relation to possible health problems linked to the onset of severe pathologies. In contrast, the percentage of young people who smoke (38.0%) has remained unvaried in the post-crisis period, compared to that reported in previous studies (33-35). The observation that the percentage of young smokers has not increased could be interpreted as a positive outcome. On the other hand, this stabilization of an unhealthy lifestyle choice could also be viewed as a risk for the population.

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Case report

Vascular parkinsonism sensitive to rotigotine therapy is found in aged patients: a clinical case description

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Summary. Previous and recent papers have pointed out several discussions about the so called 'Vascular Parkinsonism' (VP), particularly about some distinctive characteristics with respect to the Idiopathic Parkinson Disease (IPD); differences commonly described are sudden onset of extrapyramidal symptoms after a stroke, main involvement of lower limbs in diffuse brain microinfarcts (lower body parkinsonism), low, short in time or absent response to classic IPD therapy in all kinds of vascular brain pathologies. But few published studies have also emphasized some relationship linking brain morphological signs of vascular damage in elder patients suffering from diagnosed IPD, both 'normally' responding to classic Levodopa therapy or not. (www.actabiomedica.it)

Key words: vascular brain damage, extrapyramidal symptoms, pyramidal symptoms, vascular parkinsonism, Parkinson's disease, rotigotine

Previous and recent papers have pointed out several discussions about the so called 'Vascular Parkinsonism' (VP), particularly about some distinctive characteristics with respect to the Idiopathic Parkinson Disease (IPD); differences commonly described are sudden onset of extrapyramidal symptoms after a stroke, main involvement of lower limbs in diffuse brain microinfarcts (lower body parkinsonism), low, short in time or absent response to classic IPD therapy in all kinds of vascular brain pathologies. But few published studies have also emphasized some relationship linking brain morphological signs of vascular damage in elder patients suffering from diagnosed IPD, both 'normally' responding to classic Levodopa therapy or not.

We describe the case of D.C., 81 yrs old woman who came to physical examination owing to a typical resting tremor insidiously began at that moment about 3 month before in the distal upper left limb, subsequently involving lower left limb too, with progressive gait impairment, as she and her relatives reported. The objective examination showed a resting tremor of the left limbs, with predominance in the upper limb, slight but perceivable hypertonus of the same body side and, interestingly, pyramidal definite clinical body left side signs, like considerable hyperreflexia with enlargement of elicitable reflex areas and spastic-like internal rotation of the left foot, wich gave to the gait a clinical feature of a spastic limping streak and Babinsky sign. The foot feature was not reported as congenital. A brain magnetic resonance (RM) showed: "..vascular necrosis spotting in the white matter of brain hemispheres with prevalence of the lesional burden on the right hemisphere, the largest one being located close to the posterior white periventricular matter..". The UPDRS III score was 58, the H&Y score 2.0. The patient was treated with rotigotine transdermal patch up to 4 mg/24 h, afterwards underwent a control evaluation within two months, showing a clearcut improvement in gait, as she reported, while there was a reduction of tremor. After 6 months the UPDRS III scale showed a score of 40, H&Y resulted improved to 1.5, while the pyramidal signs were stable. It was than decided to

progressively try to increase dopamine-agonist therapy (to 6 mg/24 h and over), despite the overlapping of extrapyramidal and pyramidal clinical signs and the timing of symptoms coming out was coerent with the hypothesis of vascular parkinsonism.

This case has a double relevance due to both its slow debut and the imaging evidence of a vascular lesion charge predominant on the cerebral hemisphere contralateral to the growing extrapyramidal and pyramidal symptoms, and owing to the fact that it was necessary and successful the exclusive introduction of dopamine-mimetic therapy (i.e. rotigotine with transdermal patch) in a patient showing an intollerance to oral Levodopa: in fact the patient dropped the oral medication with L-dopa initially proposed due to dispepia, vomit, abdominal pain. We hypothesize that atherosclerosis could be one of the main factors in aethiology of Parkinson's Disease in the range of old age (i.e. over 75 yrs old); this should lead to modify the distinction between IPD and Vascular Parkinsonism (which can occur even at a very younger age after an ischemic or haemorragic stroke or vascular cerebral multiple lesions).

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Case report

Role of Transesophageal 3D Echocardiography in adult cor triatriatum diagnosis

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Summary. Cor triatriatum is a very rare congenital abnormality, symptomatic during childhood;the non restrictive form is usually diagnosed as an incidental finding. We report the case of a 88 years old man referred to our hospital for elective endovascular repair of an aortic aneurysm; transthoracic cardiac bidimensional echocardiography showed an abnormal mass into the left atrium and a the diagnosis of cor triatriatum was fully made by a three dimensional transesophageal echocardiography. 3D echocardiography is an excellent noninvasive method that provides a rapid bedside diagnosis , without having to use ionizing radiation. (www.actabiomedica.it)

Key words: cor triatriatum; three dimensional transesophageal echocardiography

Background

Cor triatriatum is a rare congenital anomaly in which the left or right atrium is divided into two parts by a membrane or a fibromuscular band and while the restrictive form tends to manifest at younger ages with symptoms of left atrial pressure overload, resembling the clinical presentation of mitral stenosis, the non-restrictive form is usually diagnosed as an incidental finding (1, 2).

We report the case of a 88 year-old man scheduled for elective endovascular repair of an aortic aneurysm, was referred to our Echocardiography Lab for a pre-operative evaluation. His cardiovascular risk factors comprised previous smoking habit, hypertension and dyslipidemia. His past medical history was remarkable for myocardial infarction treated with fibrinolysis and subsequent dual-chamber Pacemaker implantation for complete AV block.

Transthoracic echocardiography showed a non-dilated left ventricle with a mildly reduced ejection fraction, no significant valvular disease, normal right chambers and moderately dilated left atrium, which interestingly revealed the presence of a hyperechogenic formation, best visualized in the four-chamber apical view, apparently attached to the left atrial lateral wall and protruding in the atrial lumen (Fig. 1). Due to poor transthoracic windows, it was hard to throughly define the nature of the finding and we therefore decided to perform a Transesophageal two-dimensional echocardiography (TOE) for a better characterization. At visualization with TOE and 3D reconstruction, the formation appeared to be a fibromuscular band, extending from the ridge between the left atrial appendage and the left superior pulmonary vein to the posterior aspect of the interatrial septum (Fig. 2). A wide opening remained between the posterosuperior and the anteroinferior portions of the atrium and, in fact, no gradient developed across the membrane at continuous-wave doppler interrogation. Moderate regurgitation was detected (Fig. 3 A-B-C-D). The finding was therefore consistent with a diagnosis of non-restrictive cor triatriatum sinister. A conservative treatment was indicated.

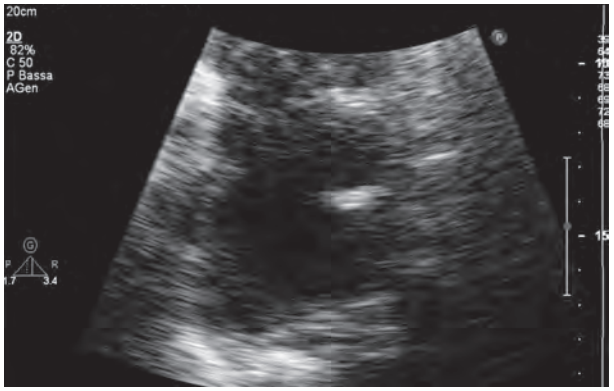

Figure 1. Transthoracic two-dimensional echocardiography showing a hyperechogenic mass, in the four-chamber apical view, apparently attached to the left atrial lateral wall and protruding in the atrial lumen

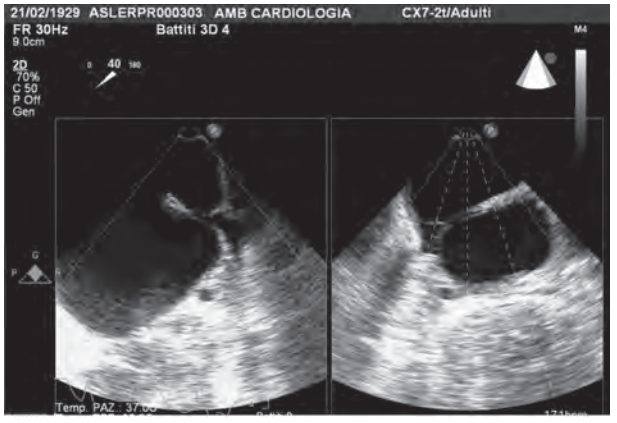

Figure 2. By TOE evaluation, the formation appeared to be a fibromuscular band, extending from the ridge between the left atrial appendage and the left superior pulmonary vein

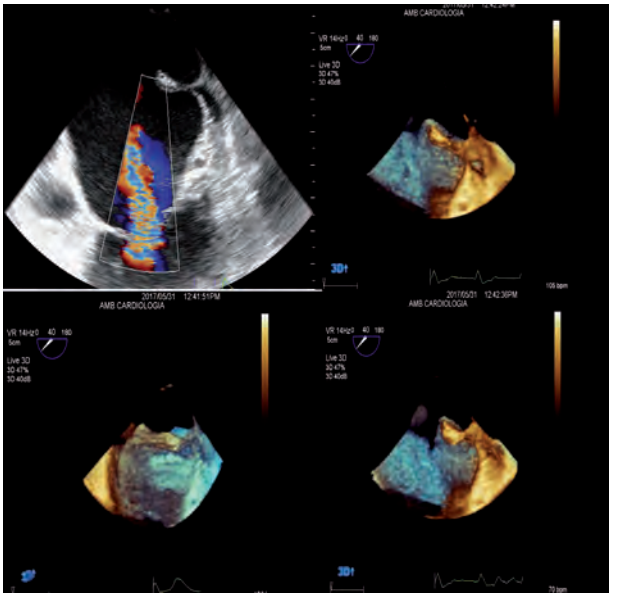

Figure 3. A-B-C-D. TOE demonstrates with 3D reconstruction a clear visualization of the the fibromuscular band, wide opening remained between the posterosuperior and the anteroinferior portions of the atrium. No gradient developed across the membrane at continuous-wave doppler interrogation. Moderate mitral regurgitation was detected

Discussion

Cor triatriatum is among the rarest of all congenital cardiac anomalies accounting for 0.1-0.4% of congenital heart disease (1, 2). In this malformation the left atrium is divided by an abnormal fibromuscular diaphragm into a posterosuperior chamber or embryonic common pulmonary vein, receiving the pulmonary veins and an anteroinferior chamber or embryonic left atrium giving rise to the left atrial appendage and leading to the mitral orifice (3). The two chambers generally communicate through one or more openings in the intra-atrial membrane. Cor triatriatum was first described by Church in 1868 (4). Several classification schemes have been proposed for describing cor triatriatum; the simplest was proposed by Loefller in 1949 (5). It is based on the number and size of fenestrations in the fibromuscular membrane dividing the left atrium.The embryologic etiology may result from incomplete incorporation of the common pulmonary vein into the left atrium (1, 4, 6). Interestingly, in this clinical scenario it was possible to reach a definite diagnosis only by means of transthoracic and transesophageal echocardiography with 3D reconstruction (7, 8). We decided not to perform further diagnostic evaluation, such as cardiac CT (9, 10) or angiography for the full evaluation of the characteristics of the abnormality by TOE3D reconstruction.

Conclusion

There are multiple imaging techniques used in the diagnosis of cor triatriatum, such as computed tomography, and magnetic resonance imaging. 3D echo-

cardiography is an excellent noninvasive method that provides a rapid bedside diagnosis, without having to use ionizing radiation.

Authors' contributions:
WS, contributed in the literature review, writing and correcting the manuscript, and echographic images acquisition GB and AB helped in the literature review and writing the manuscript. All authors read and approved the final manuscript.

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Case report

Hypochlorite accident during endodontic therapy with nerve damage – A case report

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Summary. Endodontic therapy is a routinely practised clinical procedure with few reported complications but, as a bleaching agent, inadvertent spillage of sodium hypochlorite beyond the root canal system may result in extensive soft tissue or nerve damage, and even airway compromise. Although very rare, complications arising from hypochlorite extrusion beyond the root apex are described. NaOCl causes oxidation of protein and lipid membrane and causes necrosis, hemolysis and dermal ulcerations (2-4). Neurological complication are very rare. Paraesthesia and anaesthesia may affect the mental, inferior dental and infra-orbital branches of the trigeminal nerve and normal sensation may take many months to completely resolve (6, 7). Nerve damage (the buccal branch) was described in 2005 by Witton et al. (8) and patients exhibited a loss of the naso-labial groove and a down turning of the angle of the mouth and the motor function was regained after several months. We present a case in which the extrusion of NaOCl solution during endodontic therapy led to important destructive effects on soft tissues and nerves. The arisen medico legal issues are discussed. (www.actabiomedica.it)

Key words: sodium hypoclorite, endodontic therapy, nerve damage, medical liability

Introduction

Removal of bacteria from the root canal system during shaping and cleaning is the key factor for the success of endodontic therapy. Mechanical preparation should be supported by a chemically active antibacterial irrigation solution.

Sodium hypochlorite (NaOCl) was recognized as antibacterial agent since 1920 when Crane described its use for root canal debridement and sterilization (1).

Endodontic therapy is a routinely practised clinical procedure with few reported complications but, as a bleaching agent, inadvertent spillage of sodium hypochlorite beyond the root canal system may result in extensive soft tissue or nerve damage, and even airway compromise. Although very rare, complications arising from hypochlorite extrusion beyond the root apex are described. NaOCl causes oxidation of protein and lipid membrane and causes necrosis, hemolysis and dermal ulcerations (2-4).

Treatment is determinate by the extent and rapidity of the soft tissue swelling but may necessitate urgent hospitalisation and administration of intravenous steroids and antibiotics. Surgical drainage or debridement may also be required (depending on the extent and character of the tissue swelling and necrosis (5).

Neurological complication are very rare. Paraesthesia and anaesthesia may affect the mental, inferior dental and infra-orbital branches of the trigeminal nerve and normal sensation may take many months to completely resolve (6, 7).

Nerve damage (the buccal branch) was described in 2005 by Witton et al. (8) and patients exhibited a loss of the naso-labial groove and a down turning of the angle of the mouth and the motor function was regained after several months.

We present a case in which the extrusion of NaOCl solution during endodontic therapy led to important destructive effects on soft tissues and nerves. The arisen medico legal issues are discussed.

Case report

In May 15 2013 a 34-year-old healthy woman was treated by her general dental practitioner and a non-surgical endodontic treatment was performed on her maxillary left first premolar tooth. During canal irrigation patient complained intense pain. She didn't know what kind of liquid was used but she reported to smell bleach.

At home, pain increased and patient had tense and warm swelling extending from the mandibular border to left eyelid with initial reduction in visual acuity. Patient tried to contact her general dentist but he didn't answer. The woman, worried for increasing symptoms, the same evening went to the Dental Clinic of the local Hospital and immediately transferred to the Emergency Department in the same Hospital.

On examination there was a firm left facial swelling and ecchymosis from below the border of the mandible up to the left eye. Doctors gave her antibiotic therapy and they quit on her with indication to return the next morning.

The next day, patient went again at the Civil Hospital of Brescia, where she submitted to maxillofacial visit. Doctors and patient contacted the dentist for information on the treatment performed. The dentist stated to used hydrogen peroxide at 10%. Doctor prescribed to the woman antibiotics and anti-inflammatory.

Two days later patient went back to the emergency department of the Hospital complaining alteration of vision of the eye left, an increased edema of the left cheek and an hemorrhagic episode of the oral cavity. Therefore, given the clinical, she was hospitalized at the Department of Maxillofacial Surgery of the same hospital.

Extra oral examination revealed significant soft tissue swelling extend from left intraorbital region to the mandibular border. Infraorbitally and in the region of the upper left lip, there was altered sensation. This is the area of the left infraorbital nerve. In addition the buccal branch of the facial nerve was affected. This resulted in a distinct loss of upper lip and cheek function (the corner of the mouth could not be pulled up by the mimic musculature). Eye examination revealed blepharospasm and a TC examination revealed areas of bone resorption. NaOCl accident was suspected. To prevent risk of infection orally antibiotic therapy was administered for 7 days and ibuprofen was prescribed for pain management.

Both swelling and ecchymosis kept progressively decreasing during the follow up period but neurological symptoms didn't resolved.

On neurological review one month later was found a deficit on left of the second branch of the fifth cranial nerve, of the seventh cranial nerve, of the ninth and the tenth cranial nerve. There were anesthesia and paraesthesia of the left side of the face, a detour to the left of the tongue (to the right during protrusion), deficit of left orbicularis muscle of the mouth, eye spasms during fixation and deficit of the sternocleidomastoid in the rotation of the head to the left.

One year later neurological symptoms resolved only partially. On examination it was confirmed nerve deficits on II branch of the fifth cranial nerve left, a slight deficit in the upper territory of the seventh cranial nerve left and a definite weakness in the lower area of the seventh cranial nerve left (Fig. 1a, b).

The patient filed legal claims against the dentist and the case was kept to the attention of the Penal Court.

Discussion

Irrigation during chemo-mechanical shaping is critical to the success of root canal treatment. NaOCl is used as an endodontic irrigant as it is an effective antimicrobial and has tissue dissolving capabilities. Free chlorine in NaOCl dissolves vital and necrotic tissues by breaking down proteins into amino acids. It reacts with fatty acids and amino acids in dental pulp resulting in liquefaction of organic tissue. There is no universally accepted concentration of sodium hypochlorite for use as an endodontic irrigant. The antibacterial and tissue dissolution action increases with concentration, but this is accompanied by an increase in toxicity.

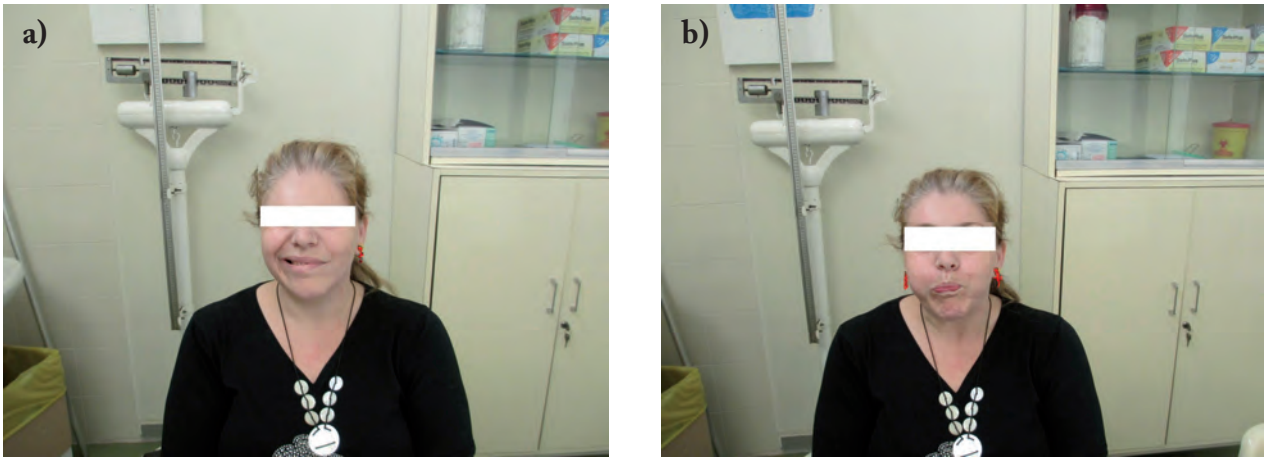

Figure 1. The neurological symptom of definite weakness in the lower area of the seventh cranial nerve left, one year later: assessed by smiling (1 a) and blowing (1 b)

It is usually used in concentrations ranging from 0.5 to 5.25% depending on the dilution and storage protocols of individual practitioners. It has been reported that 5.25% NaOCl was strong enough to kill the bacteria commonly present in the canal; however this concentration is highly toxic and irritating. The toxicity of NaOCl is due to its high alkalinity (pH 10.8-12.9) and hypertonicity (2-4).

When it comes into contact with vital tissue, it causes haemolysis, ulceration, inhibits neutrophil migration and damage endothelial and fibroblast cells.

When sodium hypochlorite extruded beyond the root canal into peri-radicular tissues, the effect is one of a chemical burn leading to a localised or extensive tissue necrosis. A severe acute inflammatory reaction of tissue develops. This leads to rapid tissue swelling both intra-orally within the surrounding mucosa and extra-orally within the skin and subcutaneous tissues. The swelling may be oedematous and haemorrhagic. Sudden onset of pain is a hallmark of tissue damage, and may occur immediately or be delayed for several minutes or hours. Associated bleeding into the interstitial tissues results in bruising and ecchymosis of the surrounding mucosa and the facial skin and may include the formation of a haematoma. A necrotic ulceration of the mucosa adjacent to the tooth may occurs as a direct result of the chemical burn, but this reaction may occur within minutes or may be delayed and appear some days later (9, 10).

The acute problems, sudden pain during root canal rinsing, the extensive swelling of the left face side, and the adverse effects to nerves and musculature, described in the case reported are typical for sodium hypochlorite and have been repeatedly published in the literature during past years (3, 11, 12).

The immediate sequel of the accidents includes severe sudden excruciating pain, probably related to tissue destruction and distension, as well as immediate swelling of the tissue in the area.

The majority of NaOCl extrusions into the periapical area are attributed to incorrect determination of the working length, excessive enlargement of the apical foramen, needle stuck within the root canal. Generally the apical anatomy of the tooth appears normal so presumably the combination of peri-apical bone destruction due to chronic infection and forced pressure irrigation lead to entry of sodium hypochlorite into the soft tissues, as well as administering lower concentrations of NaOCl decrease the risk of occurrence (6, 13).

In the case reported none of these essential measures was taken before the treatment.

There are few cases reported in the literature on post-operative altered nerve sensation and ocular complications arising from the use of NaOCl in endodontics. Few patients have reported permanent paresthesia and facial disfigurement (6). The present case is one of the few showing a permanent nerve weakness after inadvertent injection of NaOCl.

Facial nerve damage was first described by Witton et al. in 2005 (8). In those cases the buccal branch of the facial nerve was affected and both patients exhibited a loss of nasolabial groove and down turning of the angle of the mouth. Both patient were reviewed and their motor function was regained after several month. In our case instead, several month after the accident nerve deficits of the fifth and the seventh cranial nerve left were lasting.

Good medical practice indicates that after NaOCl extrusion into the tissue, local anesthesia should be administred for pain relief, and the canal should be irrigated immediately with copious amount of physiologic saline. Analgesic and antibiotics should be prescribed for postoperative pain control and to prevent secondary infections. Non-surgical management may be sufficient when treating the damage caused by misuse of NaOCl, but surgical intervention should be considered if there is progression of the ill effects.

Surgical intervention may be considered in some cases depending on the level of injury and the response to treatment. The goal of surgical intervention is to achieve decompression, ease drainage and improve prognosis (6).

The clinical features of our case were consistent with severe soft tissue damage due to a sudden chemical burn, following extrusion of NaOCl into the connective tissues. Liability issues can be found in the combination of periapical bone destruction, unfilled root canal, or high pressure during irrigation, and a high concentration of NaOCl in the irrigant solution. These presumably led to the easy entry of NaOCl into the soft tissues of the left face side. Moreover there was no immediately irrigation with solutions able to eliminate or neutralize the NaOCl. Nevertheless the permanent neurological consequences were caused by the delay in identifying the liquid used for the treatment avoiding the immediately irrigation of the canal with copious amount of physiologic saline.

Conclusions

Sodium hypochlorite can cause severe complications during routine dental treatment and must be used with extreme care. To minimize the risks and provide appropriate treatment to affected patients, dental practitioners and clinicians should have a thorough understanding of the patho-physiology and potential complications of misuse of this agent and they should execute essential preventive measures before the treatment such as accurate measurement of the working length or working radiographs.

The case presented proves that NaOCl is able to produce permanent facial and trigeminal nerve weakness. From a medico-legal point of view a correct informed consent, before endodontic treatment, should include information on the adverse reactions of NaOCl. A proper protocol and management of complications are mandatory.

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Case report

Percutaneous treatment of traumatic talus extrusion: a case report

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Summary. *Background and aim of work:* Total traumatic extrusion of talus with interruption of all ligaments (missing talus) is a very rare injury. We represent the case of a 44-years-old male who reported total extrusion of talus and Lisfranc dislocation after a motorbike accident. This rare injury has a wide choice of treatment but usually there is not a successful functional restore. *Methods:* We decided to treat the patient with an immediate reimplantation of extruded talus using 3 Kirschner wires and antibiotic therapy. We performed a temporary fixation of talus with calcaneus, tibia and scaphoid. *Results:* Usually, this kind of injuries are treated with a tibiocalcaneal arthrodesis and show common complications such as avascular necrosis and infection. Against our expectations we managed to treat successfully our patient. *Conclusions:* After 5 years of follow up the patient reported good clinical outcomes without performing arthrodesis and recording major complications. (www.actabiomedica.it)

Key words: K-wires, missing talus, total extrusion, Lisfranc fracture

Introduction

Total traumatic extrusion of Talus, as consequence of a high energy injury, is a very rare occurrence (1). This event always causes an impairment of surrounding bones and soft tissue and an impairment of slight talar vascularity (2-6). Common effects of total talus extrusion could be avascular necrosis and serious contamination of talus. There are no clear guidelines and consensus about treatment (4, 7-11). There are few reports in literature about successful reimplantation of total extruded talus (12). We herein describe our experience with 5-years follow-up of one patient, who suffered from total traumatic extrusion of talus, successfully treated with immediate replacement of talus using just Kirschner wires (K-wire). This is in contrast with similar cases, where talus reimplantation was performed using: pins, screws and external fixation and were complicated by avascular necrosis and infection.

Case report

Our patient was a 44-years-old male, who had an accident while driving his motorcycle. He received a high energy trauma that caused midfoot abduction and hindfoot eversion and pronation. Talus was totally extruded and was found seriously contaminated on ground. He was rescued and urgently moved by helicopter to the Hospital of Reggio Calabria to receive medical examination and treatment.

Physical examination showed a significant injury of left foot and ankle; we observed a wide open wound (around 6 cm) with loss of substance and a

great amount of blood on the medial side of ankle. We found an extrusion of talus bone which was intact anyway. Furthermore Patient showed a left ankle and tarsus-metatarsus dislocation (fig. 1). The functionality of left foot and ankle was impaired.

Once the patient reached the hospital, we performed oblique and lateral X-rays of left foot and ankle. These examinations revealed: the extrusion of talus bone and Lisfranc dislocation.

The patient after clinical, radiological and vascular examinations (which showed absence of posterior tibial artery pulse) was carried in the surgical room. We made antibiotic prophylaxis using Vancomycin (according to the hospital protocol of open fractures) and anti-thrombosis prophylaxis, toilette and serial lavages by saline solution of wound and extruded talus. We proceeded with immediate reimplantation of talus, restoring normal anatomic ankle and hindfoot architecture. To fix subtalar joint we used 2 K-wires placed on caudo-cranial way and one more K-wire on distal-proximal way to stabilize talo-navicular joint. Under fluoroscopic guidance, we reduced Lisfranc dislocation using 2 percutaneous K-wires (fig. 2). We verified the anterior tibial artery flow and after accurate hemostasis we sutured the wound respecting all anatomical layers. To protect the injured ankle, we made a plaster cast. We prescribed 3 weeks of antibiotic therapy (Teicoplanin 400 mg/12 h, Levofloxacin 500 mg/die and Ceftazidime 2 g/die i.v.), 90 days of anti-thrombosis therapy and no weight bearing for 90 days. The post surgery antibiotic therapy choice was made considering pre-surgery tampon outcome. After 6 weeks we removed K-wires and plaster cast. Patient underwent a rehabilitative protocol to recover left ankle R.O.M. and muscles strenght. After 90 days from the injury,

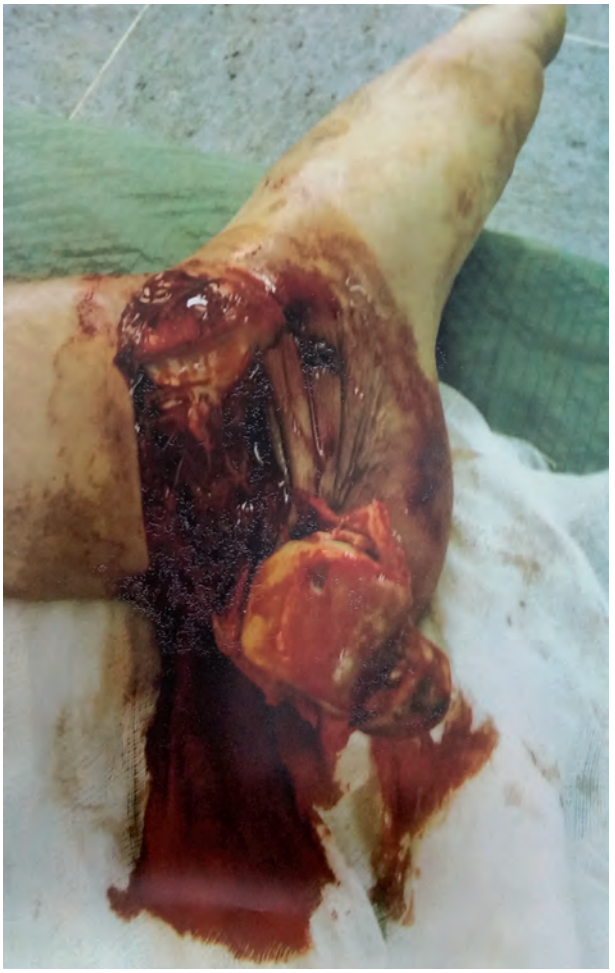

Figure 1. Total extrusion of talus after motorbike accident at the arriving at "Bianchi-Melacrino-Morelli" Hospital

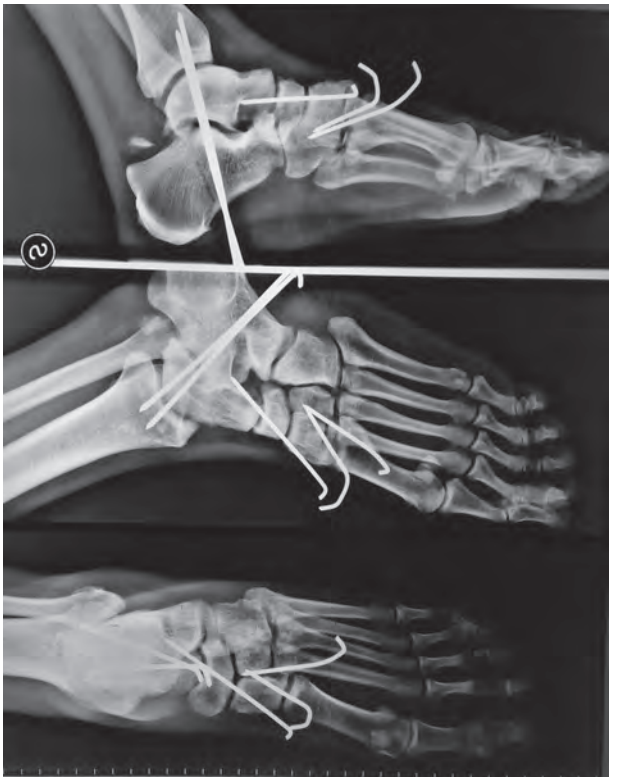

Figure 2. Post-operative X-rays (lateral, dorso-plantar and oblique projection) of talus reimplantation, fixtation and reduction of Lisfranc dislocation using K-wires

we allowed protected weight bearing using crutches. During post-operative care we did not record any complication.

The patient underwent outpatient control each month. After 1 month of follow up, the patient referred some pain and functional limitation. At clinical examination there were no signs of infection. X-rays of left foot and ankle highlighted total reduction of talus-metatarsal dislocation and successful reduction of talus fixed by K-wires to calcaneal and tibia bone. After 3 months radiological assessment (MRI, X-rays) showed spongiosa edema of hindfoot bones, scar signs of calcaneofibular, anterior talofibular ligaments and joint capsule, post-traumatic tarsal-metatarsal arthrosis and reduced calcific density (fig. 3). At clinical examination, the patient showed limitation of left ankle dorsal flexion, hindfoot eversion and inversion due to subtalar joint ankyloses. We also found hypotrophy of left leg muscles associated to edema of ankle region and post-traumatic CPRS (complex pain regional syndrome). After 24 months from injury, the patient achieved a fair clinical outcome (AOFAS Ankle Hindfoot Scale: 75). Radiological examinations (X-rays, MRI and CT) revealed normal bone structure with radiological signs of post-traumatic arthrosis (fig. 4). They also showed absence of avascular necrosis of talus and total resolution of foot CPRS. Clinically patient revealed acceptable ankle pain (VAS 2) and good range of motion with limitation of ankle dorsiflexion and severe limitation of sub-talar R.O.M.

Discussion

In literature, traumatic total extrusion of talus with interruption of all ligaments (missing talus) is a rare injury (7). It is often caused by excessive ankle plantar flexion or dorsiflexion associated with subtalar supination or pronation in high-energy trauma (13). Considering the exceptionality of this event, treatment choice is still controversial. Surgical management offers several options: immediate replacement of talus, pseudo-arthrodesis (7), amputation, primary tibiocalcaneal arthrodesis (4, 8), talar body prosthesis (9) or total ankle arthroplasty (10, 11). In our case we decided to perform immediate reimplantation, which re-

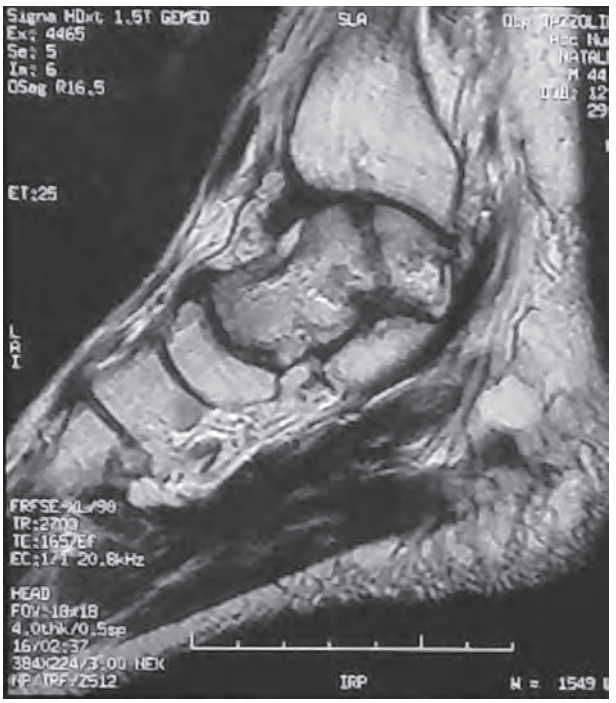

Figure 3. MRI and X-ray of left ankle and foot after 3 months of follow up. No signs of avascular necrosis were recorded

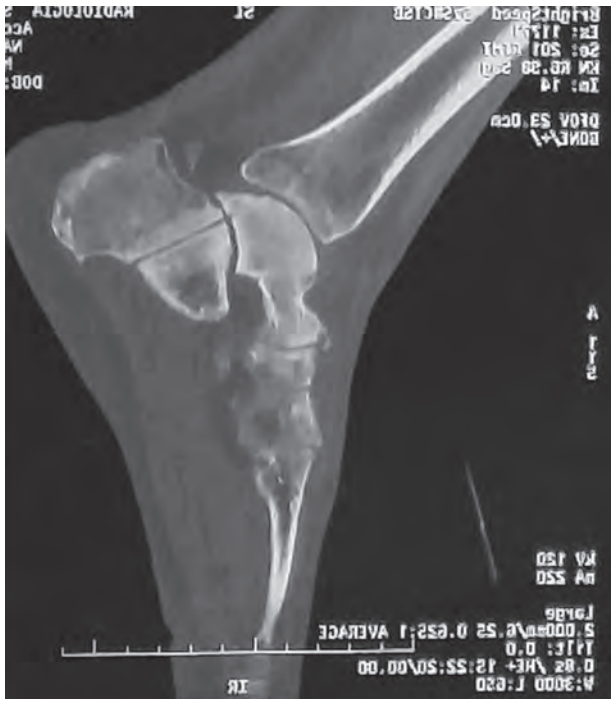

Figure 4. CT, X-ray and MRI of left ankle and foot after 24 months of follow. No signs of avascular necrosis

cent studies have suggested to be a safe treatment (11). Literature reports very few cases of successful primary reimplantation of talus. Usually talus reimplant was performed using external fixation and showed some complications such as infection or avascular necrosis of talus, promoted by damage of slight talus vascular supply. The immediate replacing need a previous plentiful debridement and serial irrigations to avoid or at least reduce the risk of infection. In a study (2) Authors preferred to delay reimplantation to avoid risk of infection and employed talus-shaped antibiotic cement while waiting for cultural results. We preferred to immediately reimplant talus under antibiotic coverage after serial irrigation and accurate debridement of wound and talus. To perform talus fixation we used just three K-wire and other two to reduce tarsus-metatarsus dislocation. After 5 years of follow up from the injury, the patient showed a satisfying functional recovery with the sole limitation of ankle dorsiflexion. However this limitation does not impair his daily life activities (fig. 5). The patient has not developed avascular necrosis, as showed by MRI exams, or infection that in many other cases required a second surgical intervention to realize a tibio-calcaneal arthrodesis.

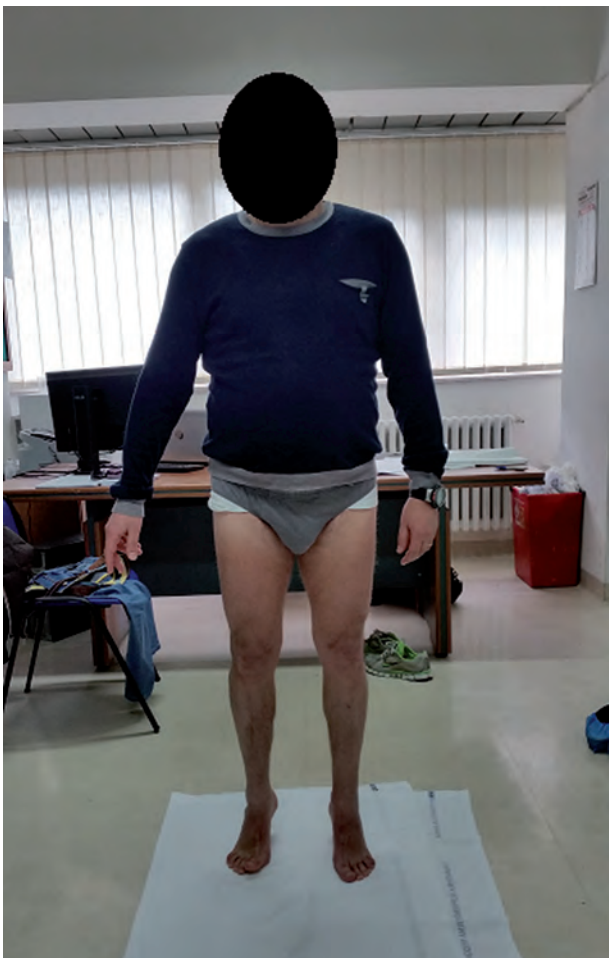

Figure 5. Clinical examination after 5 years of follow up

Conclusions

We concluded that the management of traumatic total extrusion of talus with a primary talus reimplantation and fixation with K-wires is a reasonable and treatment choice to preserve ankle fucti and normal hindfoot anatomy. Therefore this type of treatment doesn't preclude a successive ankle arthroplasty or arthrodesis. The success of such a treatment supports our therapeutic choice. Literature often cites the high probability of side effects such as avascular nescrosis, infection, talar collapse; notwithstanding we did not observe them in our case, achieving a good fuctional outcome by means of a less invasive procedure.

Informed Consent: The patient gives his informed consent to the publication of this case report.

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Case report

A rare case of giant lipomatous hypertrophy of the atrial septum

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Summary. Benign lipomatous lesion of the heart includes an heterogeneous group of entities including neoplastic, congenital and reparative phenomena. Among these lipomas and lipomatous hypertrophy of the atrial septum (LHIS) represent the most common lesion. Patients suffering from LHIS are often asymptomatic, however atrial fibrillation, congestive heart failure and supraventricular tachycardia are typical findings. Here we present a rare case of LHIS symptomatic for asthenia and dyspnea. (www.actabiomedica.it)

Key words: lipomatous hypertrophy of the atrial septum; atrial lipomas; cardiac tumor

A 80 years old women with worsening asthenia an dyspnea was referred for trans thoracic echocardiographic evaluation. A echodense mass was found in the inter atrial septum protruding in the right atrium. The mass had a diameter of 29 x 23 x 47 mm and the inferior vena cava and superior vena cava opening in the right atrium didn't seem obstructed. A trans esophageal echocardiography was effectuated and confirmed the result of the trans thoracic examination. After that a TC scan (Fig. 1) and MRI (Fig. 2) were carried out to recognize the nature of the tissue inside the heart and both the examination recognized the lesion as a adipose tissue protruding inside the right atrium. Cardiac surgery was undertaken to remove the mass. After a median sternotomy and aorta - bicaval cannulation, cardiopulmonary by-pass was instituted, ascending aorta was cross-clamped and anterograde warm blood cardioplegia was infused. After inspection we noted that the roof of the left atrium and the posterior and lateral walls of the right atrium were involved and thickened. Then we performed a right atriotomy. A mass was noted bulging from the interatrial septum and the posterior and lateral wall of the right atrium into the right atrial cavity. The fossa ovale wasn't involved by the mass and we opened it to vent the left atrium. The endocardium over the mass was incised and we looked for a cleavage plane between the endocardium and the mass, but it was firmly adherent to the endocardium and presented more like a LHIS than a atrial lipoma. So we decided to enucleate the

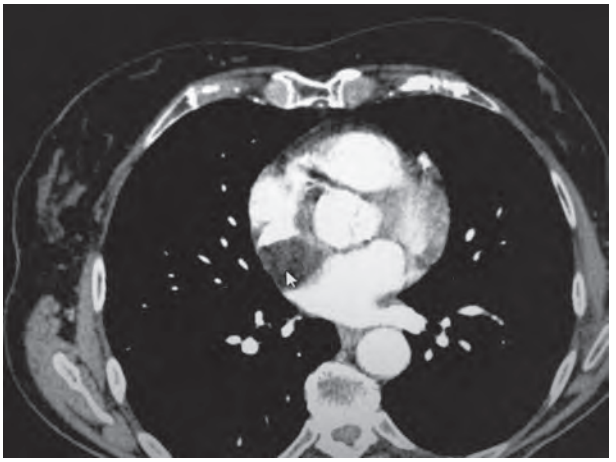

Figure 1. Arrow points interatrial septum's mass

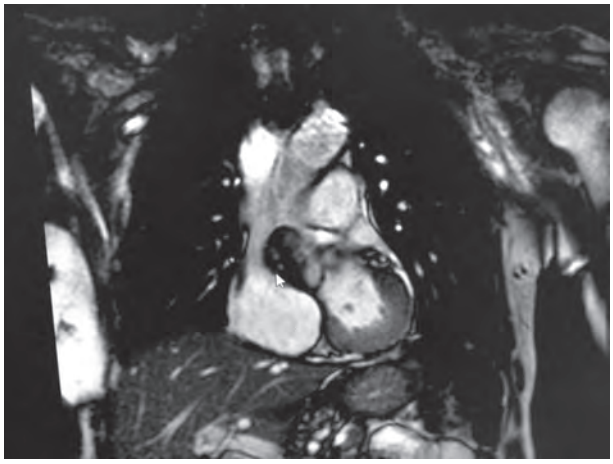

Figure 2. The mass, indicated by arrow, seems obstruct the SVC opening in the right atrium

mass. After a wedge resection of the central portion of the mass we preferred to not resect completely the lesion, because it stretched toward the floor of the left atrium and a complete resection would have required a too extended demolition of the atria. So we rebuild the integrity of the interatrial septum with a direct suture. The post operative course was eventful and the patient was discharged in 7° post operative day. The echocardiogram before the discharge showed a residual hypertrophy of the atrial septum but with a much more reduced thickness (max 9 mm); any obstruction of the vene cave or interatrial shunt was noted

Discussion

Lipomatous hypertrophy of the interatrial septum consist of a non capsulated accumulation of mature fat, multivacoulated adipose cells, and enlarged cardiac myocytes within the interatrial septum. Although the exact ethology of LHIS remains unclear, some theories have suggested the existence of embryonal, mesenchymal cells within the primitive atria that can develop into adipocyte with an appropriate stimulus, particularly obesity and advanced age. The resultant effect is adipocyte hyperplasia and fat accumulation occurring in the epicardium (1). LHIS is a very rare finding; it is often totally asymptomatic, however in some cases it can cause atrial arrhythmias and congestive heart failure. Usually the diagnosis is done by echocardiography. CT scan and cardiac magnetic resonance using fat-saturation techniques are very useful to differentiate LHIS an atrial lipomas from other cardiac masses. In our case the patient was symptomatic for asthenia, and just for this reason we suspected a neoplastic nature of the mass. So once recognized the mass in the heart we preferred investigate the nature of the mass with CT scan and magnetic resonance before perform surgery. LHIS should be surgically correct only if the patient is symptomatic, anyway a complete surgical resection should not be attempted if it will compromise vital structures, taking in consideration the slow rate of expansion, the rare malignant transformation and the absence of recurrence after excision (2). In literature some cases of complete resection of symptomatic LHIS stretched toward the superior vena cava and reconstruction of the atrium with pulmonary artery homograft (3), pericardial patch (4), and dacron patch (5) have been described but in any of this cases the masses stretched toward the floor of the left atrium. In our case the LHIS was developed in the context of the interatrial septum, right atrial posterior and lateral walls and in the floor of the left atrium so a complete resection would have required a too extended demolition of the atria. Because the age of the patients and the benign macroscopic appearance of the mass we preferred do a wedge resection of the mass protruding in the atria close to superior vena cava. Moreover the patient was symptomatic for dyspnea and we resected the portion of the mass that seemed obstruct the opening of the superior vena cava in the atrium for improve the venous return and, in this way, the clinical picture. At the follow up visit one month after the operation the patient was asymptomatic for dyspnea. To the best of our knowledge this is the first case of LHIS stretched forward the floor of left atrium.

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Endocrinopathies in celiac disease: when the endocrinologist sees what is invisible to the gastroenterologist

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Summary. Celiac disease (CD) is a systemic, immune mediated and genetically determined small intestinal disorder characterized by intolerance to dietary gluten that generally presents with gastrointestinal symptoms in young children and extra-intestinal manifestations. Furthermore, there is close association between CD and endocrine diseases, including diabetes, autoimmune thyroid diseases, growth and pubertal disorders, etc. probably due to the presence of a common genetic predisposition. The present review aims to highlight and give more insight to the endocrine changes in CD, especially when there are few or no gastrointestinal symptoms and to emphasize on screening opportunities in some endocrine diseases. (www.actabiomedica.it)

Key words: celiac disease, endocrine disorders, autoimmune thyroiditis, diabetes, adrenal insufficiency

Introduction

Celiac disease (CD), or gluten-sensitive enteropathy is a systemic immune-mediated small intestinal disorder that occurs in genetically susceptible people after ingestion of gluten containing proteins found in wheat, rye and barley grains and recovers when gluten-containing cereals are withdrawn from the diet. Patients may present with only subtle symptoms which is the main reason why the disease is highly underdiagnosed (1). Symptomatic patients present with diarrhea, malabsorption and weight loss associated with a mucosal inflammatory process in the proximal small intestine that may extend for variable distances into more distal jejunum and ileum. Thus, the disease is generally considered to affect mainly the gastrointestinal tract (2). In recent years, it has become increasingly appreciated even without gastrointestinal symptoms- thus patients may be referred initially to specialists other than gastroenterologists- being documented in up to 2% of the serologically-studied populations where typical gastrointestinal symptoms are not obvious, and perhaps, higher using endoscopic screening biopsies for some referred patients (3).

Anti-tissue transglutaminase and anti endomysial Antibodies are highly sensitive and specific for diagnosis of CD, but histologic studies are the gold standard for establishing the diagnosis (3, 4).

Hence, celiac disease or its complications have other extra-intestinal presentations, endocrine manifestation should be noted. Moreover, endocrinologists should consider celiac disease in any autoimmune condition. This manuscript aims to highlight and give more insight to the endocrine changes in CD, especially when there are few or no gastrointestinal symptoms and to emphasize on screening opportunities in some endocrine diseases.

Endocrinological diseases associated with celiac disease

1. Insulin-dependent diabetes mellitus (IDDM)

The association between celiac disease and IDDM is well recognized since long time. In the very early

reports, it was estimated that 1.0–1.5% of diabetic children suffered from celiac disease and presented with classical symptoms such as malabsorption, diarrhea and failure to thrive with poor diabetes control and frequent episodes of hypoglycemia. Diarrhea may easily have been misinterpreted as due to autonomic diabetic neuropathy or exocrine pancreatic insufficiency, and the diagnosis of celiac disease was therefore sometimes delayed or missed especially in the absence of serological screening tests (4-6). Nowadays, the frequency of celiac disease in patients with IDDM has increased to range from 3.5-7.4% in many latest studies (7-11). This is increment might be explained by greater awareness, the introduction of more diagnostic serological antibody tests and also by recognition of the non-classical presentation of celiac disease as short stature, refractory anaemia, delayed puberty, osteopenia, enamel defects, and recurrent aphthous stomatitis (12).

There is evidence of common genetic basis as both diseases are associated with the major histocompatibility complex class II antigen DQ2, DQA1*501 and DQB1*201 and seven shared non-human leucocyte antigen (HLA) loci (13).

Failure to recognize co-existing CD with longer duration of untreated patients may predispose the individuals to increased risk of growth failure, osteoporosis, infertility and gastrointestinal lymphoma. Moreover, continuous exposure to gluten may facilitate development of other autoimmune diseases apart from CD (14). Therefore, it is important to actively screen for CD in patients with IDDM at the time of diagnosis and also during follow up later in life every 1-2 years as the sequence of appearance of CD in IDDM patients cannot be predicted. This will help optimize insulin therapy, achieve good glycemic control and avert the risk of complications both due to T1DM and CD (15).

The impact of a gluten-free diet on the metabolic control of diabetes may depend on the symptoms of celiac disease in diabetic patients. In malnourished patients, the treatment of newly detected celiac disease had an unequivocal positive effect as alleviation of the intestinal symptoms, evident weight gain and improved metabolic control in particular the reduction of number of severe hypoglycemic episodes (5, 8). This positive effect of a gluten-free diet is not as straightforward as it was previously, this is due to regular screening and early diagnosis making most of celiac patients in good condition and do not suffer from malabsorption at the time of diagnosis. Therefore the impact of dieting on metabolic control in patients with IDDM and celiac disease cannot be considered unanimously positive.

2. Thyroid Diseases

There is an association between CD and thyroid disease such as graves and Hashimoto thyroiditis near 2-7% that it means 3 folds higher compared to normal population (16).

In several studies, they have suggested different mechanisms for this association such as genetics particularly HLA haplotypes B8 and DR3 which were noted to increase frequencies of children with CD as well autoimmune thyroid disease. An alternate hypothesis is also possible that thyroid gland shares a common embryonic origin during fetal development, being derived from the pharyngeal gut on the 17th day. Some autoimmune disorders may also require time to evolve, perhaps increased intestinal permeability may allow excessive amounts of antigen to enter the circulation and cross-react with other tissues, including the thyroid gland (17). Another theory is the cross reaction of tissue transglutaminase IgA (TTG- IgA) with thyroid tissue (18).

The linkage between these two disorders may have important clinical implications. Hypothyroidism may make clinical recognition of CD difficult as the severity of the diarrhea or weight loss may be more limited due to increased time for intestinal transit or fluid retention due to the reductions of circulating thyroid hormone. Also, CD reduces small intestinal surface absorptive area causing failure of hypothyroid patients to respond to oral thyroid replacement therapy. In addition, an apparent failure to respond to a gluten-free diet in CD patients may be attributed to impaired absorption and increased transit rate in hyperthyroidism. Usage of gluten free diet (GFD) is in controversy; in some studies they deny protection of GFD and in others they find that using GFD can normalize thyroid function and taper thyroxine dosage with recovery of clinical or subclinical autoimmune thyroid disease (19, 20).

Malignant thyroid lymphomas have been recorded in CD patients, it is rare T-cell lymphoma, indicating another site of extra-nodal lymphoma that may complicate the clinical course of CD, possibly due to its shared embryological developmental links with the gastrointestinal tract (21).

Thus, it is important to do serological screening for autoimmune thyroid disease in patients with celiac disease and vice versa by rigorously searching for even subclinical autoimmune thyroid conditions in celiac disease (22).

3. Other endocrine disorders

Adrenal insufficiency may occur in CD patients. Indeed, CD may be present in association with isolated autoimmune adrenocortical failure (autoimmune Addison's disease) or in the setting of polyendocrine failure that may include Addison's disease, thyroiditis, ovarian failure and CD (23, 24).

It was recommended that cases with adrenal insufficiency should be screened for CD specially if there is failure to respond to substitute hormonal treatment and also CD patients should be investigated for adrenal insufficiency specially if associated with recurrent hypoglycemia (23, 25).

Hypoparathyroidism has been rarely recorded with CD, however in celiac patients with severe hypocalcemia or tetanic seizures this rare association should be borne in mind. In a recent report, it was noted that a gluten-free diet had a beneficial effect on calcium regulation in those with concurrent CD and hypoparathyroidism (26, 27).

Anti-pituitary antibodies were detected in 42% of newly diagnosed CD patients in an Italian study (28). Interestingly, this high antibody levels were associated with height impairment, possibly mediated by a reduction in insulin-like growth factor, and suggesting that an autoimmune pituitary process may contribute in linear growth impairment in CD. A gluten-free diet reported to result in rapid catch-up growth and normalization of pituitary function (29). Growth hormone replacement may play role in children with CD and short stature, despite a gluten-free diet over a 1 year period (30).

Other evidence of alteration of pituitary gland is increased prolactin levels in recently diagnosed CD in pediatric patients and its levels were decreased over a few months with a gluten-free diet (31).

Menarche takes place later and menopause earlier in celiac women i.e. the fertility period is shortened. Also, ovarian failure causing infertility is recognized in females with CD. Moreover, serologically-based studies showed that over 4% of infertile females proved to have CD confirmed by subsequent biopsy. Some of these females showed later subsequent successful pregnancy after treatment with a gluten free diet (32). A recent meta-analysis of relevant studies indicated that CD was more prevalent in women with "all-cause" and "unexplained" infertility compared to the general population (33).

It has long been recognized that osteomalacia, osteoporosis, bone pain, and fractures are complications of celiac disease (34). The mechanisms of disturbances in bone metabolism in celiac disease are poorly understood. The initial and probably main event is calcium malabsorption which is primarily caused by villous atrophy and secondarily by coexisting vitamin D deficiency. Impaired intestinal calcium malabsorption leads to secondary hyperparathyroidism that increases bone turnover (35, 36).

Conclusions

Celiac disease is associated with many extra intestinal manifestations including diverse endocrinological disorders with symptoms being sometimes, if not mostly, subtle or atypical. This highlight the importance of awareness and early regular screening for such complications. The detection of a monoglandular endocrinopathy in CD may only be part of an evolving and dynamic process with the appearance of other endocrinopathies at a later stage in CD.

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Current treatment of hypoparathyroidism: theory versus reality waiting guidelines for children and adolescents

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Summary. The diagnosis of hypoparathyroidism(HPT)is readily made in the presence of hypocalcemia with markedly reduced or absent parathormone (PTH) levels. Currently available treatments for HPT include high dose vitamin D (ergocalciferol, D2 and cholecalciferol, D3) or, the active metabolite dihydroxy vitamin D (calcitriol), in addition to calcium supplements.This regimen, if not well monitored, can lead to hypercalciuria, as PTH deficiency impairs renal calcium reabsorption. Thus the goal of treatment, is to maintain serum calcium at the low end of the normal range. Undertreatment can cause symptomatic hypocalcemia, while overtreatment hypercalciuria, which may lead to nephrolithiasis, nephrocalcinosis, and renal insufficiency. At present, there is no consensus on the management of HPT in children and adolescents and only few studies are available on the long term outcome of patients with recombinant HPT treatment. The purpose of this article is to review, in a comprehensive manner, the major aspects of HPT management in children and adolescents waiting for authoritative guidelines for the treatment of HPT in this group of patients. Further research, addressing specific questions for this population are urgently needed to improve long-term safety of patients. Educational interventions are also needed for professionals, parents and patients to enable them to improve knowledge, quality of life and effective management care at home. (www.actabiomedica.it)

Key words: hypoparathyroidism, acute and chronic management, hypercalcemia, PTH replacement therapy, monitoring, complications

Introduction

Under physiologic conditions normal calcium homeostasis maintains within a narrow range dependent upon a complex set of regulatory mechanisms that include the effects of parathyroid hormone (PTH), vitamin D metabolites and calcitonin on calcium transport in bone, kidneys, and gastrointestinal tract. Biochemically, hypocalcemia is defined as a total serum calcium level <8.6 mg/dl, corrected for albumin concentration, [Ca corrected= 0.8 × (normal albumin − patient albumin) + serum Calcium] or and ionized serum calcium levels <1.15 mmol/L(1).

Hypoparathyroidism (HPT) is a rare disorder associated with low or no production of PTH. PTH deficiency results in abnormal mineral homeostasis that is characterized by hypocalcemia and hyperphosphatemia. In the kidneys, PTH promotes calcium reabsorption, phosphate excretion, and conversion of 25(OH)D to 1,25(OH)2Dactivating 1a- hydroxylase. In the intestine, 1,25(OH)2D enhances the absorption of calcium and, to a lesser degree, phosphate (Figure 1).

In children, HPT may present in the neonatal period or at any time during childhood and adolescence. It may be transient or permanent. Neonatal hypocal-

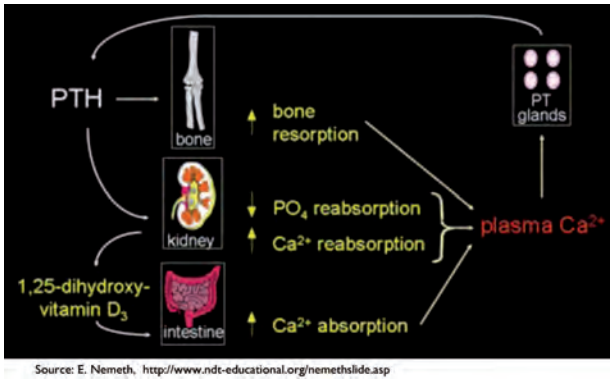

Figure 1. Regulation of systemic calcium homeostasis

cemia (NH) is common in the neonatal period. It is classified into two clinical categories: early NH occurring in the first 24-48 hours of life and late NH at the end of the first week of life. NH due to congenital HPT, either permanent or transient, is rare. The most common form of dysgenesis of the parathyroid glands in newborns and infants is that associated with the DiGeorge syndrome (DSG), a disorder with a frequency of 1:4000 births and is present in approximately 70% of children with isolated hypoparathyroidism. Another more common cause of HPT is an activating mutation of the extracellular calcium-sensing receptor (CASR) gene. A very rare syndrome is the Autoimmune Polyendocrinopathy syndrome type 1, an autosomal recessive disorder with the classic triad of **A**utoimmune **P**olyendocrinopathy, mucocutaneous **C**andidiasis and **E**ctodermal **D**ystrophy (APECED) due to loss-of-function mutations in AIRE gene (transcription factor expressed in medulla of thymus that enables differentiation of self-from foreign antigens). Major disease component of APECED are HPT, adrenal insufficiency and candidiasis (2, 3).

Hypoparathyroidism may also develop as part of chromosomal or mitochondrial disorders such as Kearns-Sayre syndrome or MELAS syndrome, and in association with Wilson disease and congenital or acquired hemosiderosis (2, 4, 5).

Another cause of HPT is the abnormally low levels of serum magnesium. This is often called functional HPT because it resolves when magnesium is restored. Less often, HPT can be caused by abnormally high levels of magnesium in the blood. Magnesium can activate the CASR protein on the hormone-secreting cells inhibiting the secretion of parathyroid hormone. Patients with the rare disorder pseudoHPT have defects of hormone function with usually elevated levels of PTH prior to therapy (6, 7).

In adults, the cause of HPT is mainly the result of a complication of neck surgery or radiation (8).Transient HPT is relatively common after thyroid surgery, with rates ranging from 6.9 to 46%; permanent HPT is defined when clinical findings persist longer than 12 months (9, 10).

Symptoms of HPT are the result of low serum calcium effect on the internal organs and correlate strongly with the degree of reduction of the absolute levels of calcium and the sharpness of onset. Presenting symptoms are variable. Mild symptoms include numbness and tingling of the extremities and perioral region, muscle cramps, and fatigue. Physical examination often reveals hyperreflexia and positive Trousseau sign (carpal spasm) by 3 minutes of occlusive pressure with a blood pressure cuff (latent tetany). In severe cases, overt tetany, seizure, altered mental status, cardiac rhythm disturbances, refractory congestive heart failure, and laryngospasm are observed (4, 11).

Traditional treatment of chronic HPT includes supplemental calcium along with active vitamin D metabolites. Although the treatment regimen appears simple, management is difficult as it is often associated with wide fluctuations in serum calcium, and risks for hypercalciuria, renal impairment, and hypercalcemia(12). Parathyroid hormone replacement is of great value in improving serum calcium and lowering serum phosphate as well as the doses of calcium and calcitriol supplementation required. Recent developments in basic sciences contributed greatly to our understanding and treatment of hypocalcemic disorders.

The purpose of this article is to review, in a comprehensive manner, the major aspects of HPT management in children and adolescents waiting for guidelines in this group of patients.

Current management of HPT

Management of hypocalcemia of HPT can be considered in two broad categories: symptomatic hypocalcemia and asymptomatic hypocalcemia, acute

and chronic. Indications, adverse reactions and dosage schedules for drugs are provided in the article, but is possible that they may change. The reader is urged to review the drug dosages before starting treatment.

1. Acute management

Symptomatic hypocalcemia (carpal or pedal spasm, seizures, broncho- or laryngospasm), can be a medical emergency requiring acute i.v. administration of calcium. If the symptoms are mild such as paresthesias, oral calcium can be tried; however, in subjects with asymptomatic hypocalcemia and total serum calcium below 7.5 mg/dL, i.v. calcium should still be preferred.

Vitamin D deficiency or hypomagnesaemia should be treated as follows: in vitamin D deficiency commence with vitamin D supplementation; in hypomagnesemia, stop any precipitating drug and administer i.v. Mg^{2+}, 24 mmol/24 h, made up as 6 g of MgSO4 (30 mL of 20%, 800 mmol/L, MgSO4) in 500 mL Normal saline or 5% dextrose. Monitor serum Mg^{2+} to achieve normal serum magnesium level(13).

a. Intravenous administration of calcium

Calcium gluconate 10% contains 93 mg of elemental calcium per 10 ml ampules. It is preferred to calcium chloride, which contains 272 mg elemental calcium per 10 ml ampules, but is irritating and potentially sclerosing the veins. In adults, usually 186 mg of elemental calcium (20 ml of calcium gluconate 10%) diluted in 50 to 100 ml of 5% dextrose is infused over ten minutes by intravenous (i.v.) root. Titrate the rate of infusion to achieve normocalcaemia and continue until treatment with vitamin D or recombinant human PTH (rhPTH) becomes effective.

Calcium should not be given rapidly because of the serious risk of cardiac dysfunction, including systolic arrest. In children and adolescents solution is infused at slow rate not greater than 2 ml (1.86 mg of elemental calcium)/kg over 10 minutes, diluted in 100 ml 5% dextrose/ 0.25 normal saline, with close monitoring of pulse rate and QT interval (4).

This dose of calcium gluconate typically increases serum Ca^{2+} concentration for only several hours. Therefore, the acute i.v. administration of calcium gluconate should be followed by a slower infusion of calcium. An i.v. solution containing about 1 mg/ml (1,023) of elemental calcium is prepared by adding 11 g of calcium gluconate (equivalent to 1023 mg elemental calcium) to normal saline or 5% dextrose water to provide a final volume of 1000 ml (14).

The i.v. solution should not contain bicarbonate or phosphate because both can form insoluble calcium salts. The solution is administered at an initial infusion rate of 50-100 ml/h (equivalent to 50-100 mg/h). The dose is adjusted to maintain the corrected serum calcium concentration at the lower end of the normal range. A typical infusion rate is 0.5 to 1.5 mg/kg of elemental calcium per hour. Over 8-10 hours, this protocol will deliver as much as 15 mg/kg body weight, raising the serum calcium levels by approximately 2 mg/dL (0.5 mmol/L). Electrocardiogram is used to monitor patients on i.v. calcium therapy when warranted by the situation, as are patients on digoxin therapy.

If hypocalcemia persists, calcium gluconate administration in the form of i.v. boluses or as a continuous i.v. infusion, may be continued for a week to ensure enterocyte recovery and adequate intestinal absorption of oral calcium.

Vitamin D supplementation is often recommended with calcium to promote its absorption. It is also important to address disease-specific problems and correct co-exiting electrolyte disturbances e.g. hypomagnesemia.

2. Chronic management

Standard therapy of HPT is oral calcium and vitamin D supplementation (both active and parent forms) at varying doses, based on clinical judgment (7). The primary goals of chronic management aim in maintaining an acceptable range of the following indexes: (a) serum total calcium (usually in the low-normal range); (b) serum phosphorus (in the high-normal range); (c) 24-h urine calcium excretion (<7.5 mmol/d) and (d) calcium-phosphate product under 55 mg^2/dl^2 (4.4 $mmol^2/L^2$) (1, 15, 16).

a. Oral calcium

The mainstay of conventional treatment of HPT is calcium supplement in combination with vitamin D,

and the therapeutic aim to obtain normocalcemia and reduce long-term complications. Supplemental calcium (1-2 grams of elemental calcium) in two to four divided doses per day, as calcium carbonate (containing 40% elemental calcium) or calcium citrate (containing 21% elemental calcium) are usually recommended in adults (1); for children and adolescents, dosage is 30-75 mg of elemental calcium/kg/day in divided doses (4, 6).When replacing calcium, it is essential to recognize that the actual amount of elemental calcium in the supplement is of major importance. As an example, calcium carbonate comprises 40% elemental calcium, so 1,250 milligrams of calcium carbonate contains 500 mg of elemental calcium. Common calcium supplements may be labelled as: calcium citrate (21% elemental calcium), calcium gluconate (9% elemental calcium), and calcium lactate (13% elemental calcium). All varieties of calcium supplements are better absorbed when taken in small doses (500 mg or less) at mealtimes. Calcium citrate is absorbed equally well with or without food. Calcium phosphate salts should be avoided.

b. Vitamin D and its analogues

Currently available treatments for HPT involve either vitamin D high doses ergocalciferol (D2) or cholecalciferol (D3) or more frequently the active metabolite 1,25-dihydroxyvitamin D3 (calcitriol). The latter is preferred in patients with hypoparathyroidism as PTH is an important facilitator of the renal conversion of 25 hydroxyvitamin D3 to 1,25 dihydroxyvitamin D3; also 1-hydroxyvitamin D3, alphacalcidol, and vitamin D analogues such as dihydrotachisterol (DHT or A.T.10) are used.

The pharmacokinetics of vitamin D analogs have been determined mainly in adults and only in small group of pediatric patients undergoing peritoneal dialysis (17). The present knowledges indicate that in healthy subjects, 25-hydroxyvitamin D3 shows a plasma half-life of about 15 days, whereas the half-life of calcitriol is of only few hours, varying from 4 to 15 hours (18, 19). These differences may be due to differences in metabolism as vitamin D binding affinity (DBP) is based on genetic factors, dose of radio labeled tracers used, timing of sample collection and the analytical method used. More studies, however, are warranted to determine the disposition of the vitamin D analogues, especially in selected populations such as pediatric patients.

As calcitriol has a rapid action (hours) it is an useful adjunct in the management of acute hypocalcemia, and is frequently used as the initial vitamin therapy. Kanis and Russell (20) showed that the half time of reduction of hypercalcemia after stopping calcitriol was shorter compared to alphacalcidol (mean 1.5 days versus 3.4 days). The highest half times were seen after ergocalciferol (mean: 29.5 days) and after AT10 (mean: 44 days). The authors concluded that, as prolonged hypercalcemia remains a serious risk with all vitamin D derivatives, the rapid reversal of hypercalcemia after calcitriol treatment makes this agent preferable to ergocalciferol and alphacalcidol.

The starting dose of calcitriol in adults is 0.25 to 0.5 μg twice daily to 0,5 μg four times a day (6) and for children and adolescents, 20 to 60 ng/kg/day (4).

Drugs interaction to calcium metabolism

Furosemide and other loop diuretics can increase renal calcium clearance and reduce serum calcium levels. Glucocorticoid antagonizes the action of vitamin D and its analogs and may also precipitate hypocalcemia. Estrogen can increase calcium absorption directly at the level of intestine and, indirectly, through the stimulation of renal 1α-hydroxylase activity, thus estrogen therapy may alter calcium homeostasis requiring dose adjustments (6).

Risks associated to conventional therapy and their monitoring

With current treatment patients may experience wide fluctuations in serum calcium and are at a substantial risk of hypocalcemia and hypercalcemia and of chronic renal failure (21).

1. Hypocalcemia

According to recent data from the USA, only 6% of patients with chronic HPT were treated with

vitamin D2, and the majority, 88%, were prescribed calcitriol (22). As calcitriol is expensive and must be administered daily, other less expensive and long-acting vitamin D preparations are frequently used, once a stable dose is reached. Ergocalciferol (D2) is the least expensive and provides a long duration of action. The usual dose is 50.000 to 100,000 IU per day. When initiating vitamin D2 therapy, calcitriol may be continued for the first 3 weeks, tapering gradually the dose until ergocalciferol becomes effective. Although only a minority of patients with HPT are treated with ergocalciferol, due to the potential toxicity related to its long biological half-life, Streeten EA et al. pointed out that no study has shown high risk of hypercalcemia with usual D2 doses of 50.000 to 100.000 IU/day (23). The authors found significantly less need for emergency care for hypocalcemia in the D2 treated group versus the calcitriol treated group. This is not unexpected due to the short half-life of calcitriol, so patients on calcitriol can become symptomatic if they miss one day of medication. There was significantly less morbidity from hypocalcemia with no evidence of higher serum creatinine in patients who were treated chronically with D2 versus calcitriol. Then treatment with vitamin D should be considered in patients with HPT, particularly those requiring medical care for repeated episodes of hypocalcemia.

2. Hypercalcemia

Hypercalcemia is of particular concern in individuals treated with large doses of parent vitamin D, ergo- or cholecalciferol, which accumulate in large amounts in fat stores and, when released, can result in prolonged parathyroid-independent hypercalcemia. Extremely large doses of vitamin D, in the order of 100,000 units per day, are required to cause hypercalcemia, because the synthesis of 1,25(OH)2 D3 is tightly regulated by serum phosphate levels and parathyroid dependent step of 1-alpha hydroxylation of 25-hydroxyvitamin D. Interestingly, changes in 1-25 (OH)2 D3 levels are modest and result from the down-regulation of the renal 1-alpha- hydroxylase by low levels of PTH, high levels of phosphate and FGF23 and 1-25 (OH)2 D3 itself. The hypercalcemia of vitamin D intoxication results from increased intestinal absorption of calcium and from the direct effect of 1,25(OH)2 D3 to increase resorption of bone. The cause of hypercalcemia in vitamin D intoxication despite a normal levels of 1-25 (OH)2 D3 is uncertain, but may reflect a) the direct action of 25OH D3 that, at pharmacological concentrations, can overcome vitamin D receptor affinity, and possibly other vitamin D metabolites which are capable of binding the 1,25 (OH)2 D3 receptor weakly; b) the total vitamin D metabolite concentrations, which can displace 1alpha, 25 (OH)2 D from vitamin D binding protein increasing its free concentration and thus increasing gene transcription, which may be locally 1-alpha- hydroxylated by non -renal 1-alpha- hydroxylase (18, 24).

De Sanctis et al. (26) reported an adolescent with thalassemia who developed severe hypercalcemia during regular clinical follow up for HPT treatment with calcitriol and calcium. On the other hand, clinicians should have a high suspicion for malignancy in patients with rapid and high elevation of serum calcium (26).

The rationale of the strategies for lowering serum calcium is based on decreasing intestinal calcium absorption, increasing renal excretion, and decreasing bone reabsorption; in very severe form removal of excess calcium may require dialysis (25). The corner stone of hypercalcemia treatment are: 1. hydration 2. saline diuresis 3. furosemide, after rehydration 4. glucocorticoids, to suppress activity of 25-hydroxy vitamin D- 1-alpha-hydroxylase, and 5. bisphosphonate in case of very elevated calcium (in consultation with endocrinologist) (24, 27).

a. Hydration: the first priority is to correct the extracellular volume depletion that is almost invariably present also in infants, particularly if hypercalcemia is long standing. Usual dose in adult is i.v infusion of 2-4 L of 0.9% Na Cl daily, for 1.5 days. Children should receive fluid volumes in order to correct fluid deficit and to provide daily maintenance requirements (1500 ml/m^2) over 24 hours, with half of the total administered in the first 8 hours. If urinary flow has been established, 20 mEq/L of K^+solution is added. Frequent measurements of serum K^+, calcium and phosphate are needed to monitor rapid adjustment of fluid and electrolyte

therapy. After dehydration has been corrected and adequate urine flow has been established, furosemide can be used i.v., (1-2 mg/kg, every 12 – 24 hours).

b. Steroids may be used to decrease the intestinal absorption of vitamin D and calcium. The usual dose is i.v. 200-300 mg hydrocortisone/1.73 m^2, daily for 3-5 days, or prednisone per os 40-60 mg/ 1.73 m^2 daily for 3-5 days.
c. In case of severe hypercalcemia (>14 mg/dl) or persistently elevated calcium, consider bisphosphonate treatment, in collaboration with endocrinologist. Bisphosphonate blocks calcium resorption correcting hypercalcemia for a longer time compared to the transitory effects of saline and diuretics. Etindronate (5 mg/kg/twice daily orally) or pamidronate (0,5 to 2 mg/kg in 30 ml of normal saline, given intravenously, over 4 hours) have been successfully employed in infants with hypercalcemia due to vitamin D intoxication (28, 29). When calcitriol is not easily available and/or is too expensive, parent vitamin D can be used with a cautionary note regarding vitamin D toxicity (30).
d. Diet management may include advice to avoid food rich in phosphate and salt as carbonated soft drinks, which contain phosphorus in the form of phosphoric acid, as well as other foods rich in phosphate like hard cheeses and whole grains. Intake of food rich in calcium are advised such as the dairy products, green leafy vegetables, broccoli. and foods with added calcium, as are some orange juice products and breakfast cereals.

3. Monitoring serum and urinary calcium, and serum phosphate

Serum calcium and phosphate should be monitored weekly or twice weekly during initial dose adjustment period, and every 3-6 months when serum levels are stable. The absence of PTH reduces the renal tubular reabsorption of calcium and thus patients treated for HPT are at risk of urolithiasis, and renal and soft tissues calcifications. Soft tissue calcification can occur in any tissue; involvement of vital organs in addition to kidney such as blood vessels and brain can result in substantial morbidity or mortality. These risks can be minimized by monitoring therapy to preserve serum calcium level in the low-normal range. Urine calcium should periodically be measured to make sure that patients do not develop hypercalciuria.Calcium 24-hour urine should be determined at least annually, once a stable dose is established (6). In children and adolescents hypercalciuria is defined as calcium excretion greater than 4 mg/kg/24 hours (4). In patient with hypercalciuria a reduction in calcium intake, a sodium restricted diet, and/or treatment with a thiazide diuretic are recommended (1).

Active vitamin D metabolites and analogs also increase intestinal phosphate absorption; when hyperphosphatemia occurs reducing dietary intake of phosphate is indicated (31). In extreme situations, phosphate binders can be used (32). Patients must avoid foods and drinks rich in phosphate; these include milk (despite being a good source of Ca), other dairy products, and canned foods.

The patient should also regularly see an ophthalmologist to screen for cataract.

PTH Replacement Therapy (PTH-RT)

The majority of cases of paediatric HPT are well controlled on conventional treatment with calcium and vitamin D analogues. However, this treatment may be inefficient, especially in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and with activating mutations in the calcium sensing receptor (CaSR) (33).

Over the past two decades, studies of teriparatide [PTH (1-34)] and the full-length natural secretory product of the parathyroid glands, PTH (1-84), ushered a new era in the management of HPT. In January 2015, the FDA approved the use of recombinant human (rh) PTH (1-84) for the management of HPT. Potential advantages of rh PTH over conventional therapy in the management of HPT include: reduction in urinary calcium, reduction in the amounts of calcium and vitamin D requirements, reduction in ectopic soft tissue calcification, and improvement in bone remodeling dynamics and quality of life. Several clinical

studies have evaluated rhPTH as a replacement therapy for HPT (34). However, due to occurrence of osteosarcoma in rat toxicology studies of rhPTH (1-34) there is some concern for long-term use in a pediatric population (35, 36).

Nevertheless, recent studies have demonstrated the advantage of using rhPTH (1-34) to control hypocalcemia in children for periods up to 3 years (35-38).

In five randomized clinical trials in adults and children with rhHPT reviewed by Sikjaer et al. (39) showed that PTH (1-34) therapy stabilizes plasma calcium at an acceptable level and abolish the need for vitamin D analogue treatment. Discrepant results, however, were reported on the urinary excretion of calcium in response to rhPTH, with most studies showing no significant effects (39). These studies included patients with different causes of HPT, including some with activating CaSR mutations. The administration of rhPTH (1-34) twice a day controlled plasma calcium levels better than once-a day (40). Three patients, two of whom were refractory to conventional therapy, were successfully treated with long-term continuous subcutaneous administration of rhPTH (1-34) (41).

Theman et al. and Diaz-Soto et al. (42, 43) treated two patients with rhPTH (a 6-year-old girl with inherited HPT with activating CASR mutation, and a 53-year-old woman with refractory HPT) for 13.5 and 5 years, respectively, with no complications.

rhPTH replacement therapy causes marked increase of bone turnover and a decrease in BMD counteracting the state of over mineralized bone. During long-term treatment, this can lead to a more physiologic bone metabolism (34).

The rationale for using rhPTH (1-84) for HPT is that, in contrast to rhPTH (1-34), it is the native hormone replacing what is truly missing in this disease. For reasons that have not been fully elucidated, the effective half-life of rhPTH (1-84) is longer than rhPTH (1-34) resulting in effective one daily dose (44, 45).

It remains to be determined if a longer acting rhPTH (1-84) molecule with favourable long-term safety and efficacy in adults would benefit children as well (46).

Conclusions

Treatment of HPT remains a challenge and no one treatment has been shown to be satisfactory for all patients. Although the therapy of acute hypocalcemia is usually readily accomplished, chronic hypocalcemia remains a very difficult therapeutic problem. There is wide consensus (1) that the best replacement treatment for HPT consists of calcium salts associated with active vitamin D analogues. However, no formal recommendations have been agreed regarding the most appropriate vitamin D analogue. If activated vitamin D analogues are not available, calciferol (preferentially D3) is recommended. Vitamin D supplementations in a daily dose of 400-800 IU to patients treated with activated vitamin D analogues has been also recommended (1). The rationale of this recommendation is that vitamin D insufficiency has been associated with adverse effects on skeletal as well as extraskeletal health (47).

Treatment of hypoparathyroid patients with calcium and vitamin D analogs increases the risk of hypercalciuria; hypercalciuria is a risk factor for nephrocalcinosis, nephrolithiasis, and impairment of renal function. Thiazide diuretics, which enhance distal renal tubular calcium reabsorption, are sometimes used as an "adjuvant" therapy. Monitoring for renal calcification through renal ultrasound and more formal measurements of creatinine clearance may be warranted. To ameliorate the renal risks, the vitamin D analog and calcium dosages are reduced to maintain serum calcium at the lowest tolerated level (Figure 2) (1).

Consequently, a higher number of hypoparathyroid patients may suffer varying degrees of hypocalcemia as a counterbalance for prevention ofhypercalciuria-induced renal damage. Therefore, for optimal management of HPT a specialist should be involved to minimize the risks of hypocalcemia, hypercalciuria, and impairment of renal function.

According to the European Society of Endocrinology (ESE) Clinical Guideline (1) biochemical monitoring of HPT patients should include serum calcium levels, phosphate, magnesium, creatinine and glomerular filtration rate every 3-6 months, and 24-h urinary calcium excretion once a year, once stable doses of supplements are established. The target for urinary

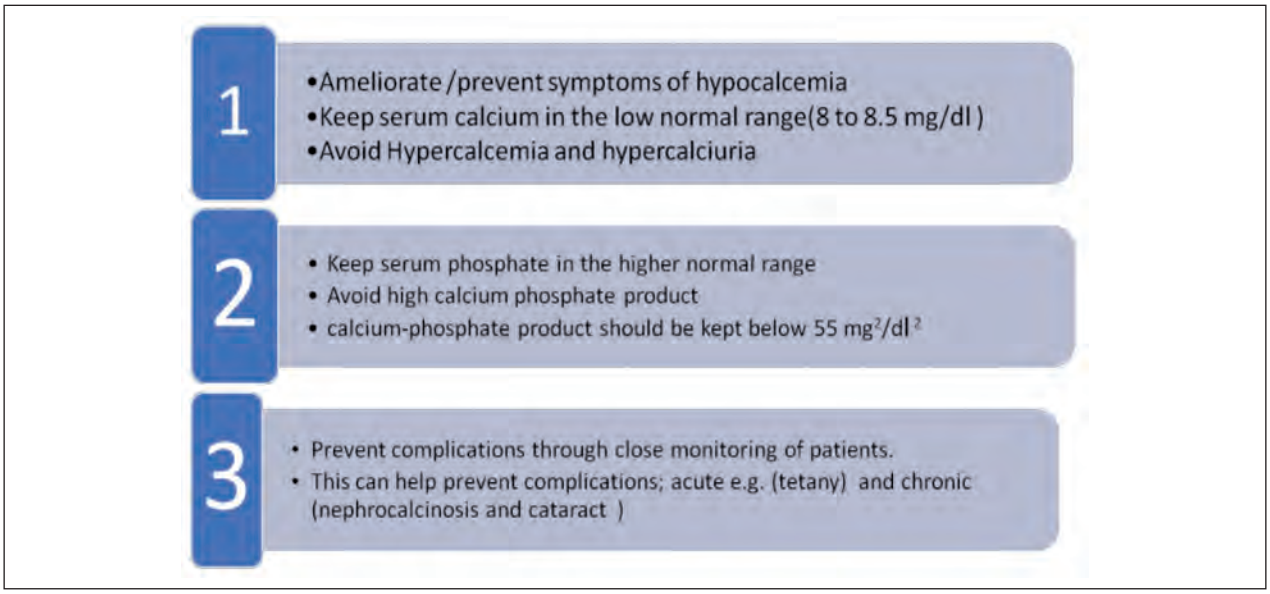

Figure 2. Goals for the management of hypoparathyroidism

calcium excretion is <4 mg/kg/24 hr. Serum levels of calcium are poor indicators of the presence of hypercalciuria and nephrocalcinosis. Thiazide diuretics are used to enhance calcium reabsorption in the distal renal tubules and to reduce calciuria, and allow reductions in the dose of calcium and calcitriol supplementation (48). Patients with HPT have abnormal bone remodeling. Bone mineral density (BMD) values are often above the average for a healthy population and at peak bone mass while serum and urine markers of bone turnover are in the lower half of the normal range or frankly low.

Based on the literature, further research is needed on hyperphosphatemia in HPT, and much more on its treatment and effectiveness. In a patient with hyperphosphatemia and/or an elevated calcium-phosphate product, consider dietary interventions and/or adjustment of treatment with calcium and vitamin D analogues (49).

The treatments showing considerable promise for the HPT patient are those with parathyroid hormone replacement. Replacement therapy with rhPTH could be a therapeutic option for refractory HPT and for patients who are not well controlled on calcium and active forms of vitamin D, and for whom the potential benefits outweigh the potential risks.

Expert opinion of Marcucci G et al. (50) inferred that the research done in the field of rhPTH "has shown that replacement treatment with rhPTH is an attractive option for subjects with HPT who are unable to maintain stable and safe serum and urinary calcium levels. However, since therapy with rhPTH is a long-term management option in HPT, more long-term data are needed".

The diagnosis of HPT is readily made in the presence of hypocalcemia with markedly reduced or absent PTH levels. At present, there is no consensus regarding the management of HPT in children and adolescents and only few studies on the long term outcome of these patients are available in the literature. Therefore, further research, addressing specific questions of this population are urgently needed to improve long-term safety of patients. Educational interventions are also needed for professionals, parents and patients to enable them to improve knowledge, quality of life, and effective management care at home.

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Thyroid disorders in subjects with Down syndrome: an update

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Summary. Down syndrome (DS) is the commonest chromosomal disorder among live born infants. DS is associated with increased risk of endocrine abnormalities particularly thyroid gland disorders. The spectrum of thyroid dysfunction in patients with DS include congenital hypothyroidism, subclinical hypothyroidism, acquired hypothyroidism (autoimmune - non autoimmune), and hyperthyroidism. This review will focus on the characteristics of the different presentations of thyroid abnormalities in DS, screening and management recommendations. (www.actabiomedica.it)

Key words: Down syndrome, hypothyroidism, subclinical hypothyroidism, autoimmune thyroid disorders

Introduction

Down syndrome (DS) is the commonest chromosomal disorder among live born infants. Its prevalence varies from 1 in 700 to 1 in 1500 live births (1). In 95 % of cases, Down syndrome is due to non - dysjunction of chromosome 21, while the remaining cases are either due to translocation or mosaicism (2-4).

DS is associated with increased risk of medical problems including gastrointestinal, cardiac, and pulmonary anomalies as well as developmental delay and endocrine abnormalities (5). Among the endocrine abnormalities, thyroid dysfunction is the commonest. It is estimated to occur in 4-8% of children with Down syndrome (6). The spectrum of thyroid dysfunction in patients with DS include congenital hypothyroidism, subclinical hypothyroidism, acquired hypothyroidism (autoimmune – non autoimmune), and hyperthyroidism (7).

Congenital hypothyroidism (CH)

Overt congenital hypothyroidism refers to elevated plasma TSH (>10 mIU/l) associated with low plasma T4 occurring at birth and in most cases diagnosed with neonatal screening (8). The prevalence of CH in DS is estimated to be 28-35 times higher than its prevalence in the general population (9). In the general population CH which is considered one of the most common preventable causes of mental retardation, is detected in 1 in 2000 to 3000 live births via neonatal screening.

The reported incidence of CH in Down syndrome is much higher, varying between 1: 113 and 1: 141 live births (10-12). Furthermore, the female preponderance observed in the general population with CH has not been found in patients with CH and DS (1).

The presence of CH increases the risk of the presence of other anomalies including congenital cardiac disease, respiratory distress syndrome, and gastrointestinal anomalies (13). The presence of CH in DS further increases the risk of congenital anomalies especially gastrointestinal and cardiovascular anomalies when compared to patients with DS without CH (5, 13-15).

A co-existence of CH and gastrointestinal anomalies is observed in DS. Jaruratanasirikul et al reported that Down syndrome babies with gastrointestinal anomalies at birth were “8.6 times more likely to have CH” (16).

Most cases of reported CH are due to thyroid hypoplasia (8, 17, 18). Other ultrasound findings included thyroid ectopia, athyreosis, or partial agenesis, but all are uncommon causes of CH (8, 9, 19). However, in most cases there is no abnormality on ultrasound scanning (17, 20-22).

Luton et al. studied the development of 13 human fetal DS thyroid glands between 23 and 33 weeks of gestation. They found that thyroid glands in DS were smaller in size and had fewer and smaller follicles compared to control thyroid glands. This was confirmed by immunohistological analysis with anti-NKX2 - 1 antibody. Fewer stained colloids were found upon antithyroglobulin staining. Furthermore, they found that TSH levels were above the 80th percentile in all foetuses and FT4 were below the 50th percentile in the majority. This supports the observation that thyroid hypoplasia is the commonest abnormality in DS patients with CH (23).

Few studies looked at the possible etiology of CH in patients with DS. Some hypotheses have been suggested including the following (1, 5):

1. Exaggerated response to TRH stimulation: delayed maturation of the hypothalamic - pituitary - thyroid axis leading to higher TSH levels with normal fT4 and fT3 levels and negative antithyroid antibodies in the first 3 years of life (24).
2. Peripheral resistance to thyroid hormones: leading to inappropriate TSH secretion. This was postulated to be due to abnormal thyroid hormone receptor function (24).
3. Inappropriate TSH release, due to a central disorder, or due to altered dopaminergic control resulting from reduction in dopamine production. Dopamine is an inhibitor of TSH (17, 24).
4. TSH insensitivity (5).
5. Reduced TSH bioactivity (5).

Subclinical hypothyroidism (SH)

SH refers to isolated elevation of TSH with normal thyroid hormone levels. Some authors refer to it as "mild hypothyroidism" (5), or "compensated hypothyroidism" or "isolated thyrotropinaemia" (10).

SH is probably the most common detected thyroid abnormality in these subjects (10). The incidence of SH varies in the literature depending mainly on the study size, and the TSH cut off for the definition of SH (1, 5, 10). Generally, TSH above 5 mIU/L is considered above the normal range in many places. Some studies refer to cases where TSH is less than 20 mIU/L as "compensated hypothyroidism" (5, 22). Others have defined two separate entities depending on whether TSH level is between 6 and 10 mIU/L or 11 and 20 mIU/L (5).

The questions that need to be answered regarding SH are many, among which are the exact definition of SH, the true incidence, its cause, whether it requires treatment or not, and at what TSH level should treatment be initiated, its natural course if left untreated, and whether treatment would have a positive impact on growth and neurodevelopment.

Elevated TSH above 5 mIU/L is widely accepted as elevated, and in the context of normal thyroid hormone levels, it is often referred to as subclinical hypothyroidism (7).

Among their 52 studied patients with SH, Pierce et al. reported that 30 patients had TSH between 5-10 μIU/mL, their mean TSH was 7.9 μIU/mL, and mean age at diagnosis was 5 years and 3 months, while 22 patients had TSH >10 μIU/mL, mean TSH level was 16.2 μIU/mL, and mean age at diagnosis was 5 years and 7 months (7).

The prevalence of SH in subjects with DS varies between 7 and 40% (1, 8, 21, 25-27). Figures between 25% and 30% have also been published (10, 22, 28). It is diagnosed irrespective of prematurity, low birth weight, or perinatal risk factors (8). In most cases, SH is asymptomatic, and is detected upon laboratory testing or neonatal screening (8, 26, 27). Some patients exhibit mild symptoms such as hypotonia or weight gain, but these symptoms often exist in patients with Down syndrome, and therefore would be difficult to rely on for diagnosis (8, 25, 29).

The cause of SH is unclear. Ultrasound scans showing goitre or thyroid hypoplasia were reported in newborns with SH (17, 21). Agenesis or ectopia is rarely reported, and in the majority of cases, normal thyroid gland is present (8). Autoimmunity is among the hypothesized causes of SH. Thyroid peroxidase (TPO) antibodies were detected in patients with SH

(10, 27, 30) and in some cases a self limiting autoimmune process was postulated (30).

In the study by Pierce et al., 37 patients out of 76 DS patients with SH were tested for thyroid antibodies. Positive antibodies were detected in 46% of the tested patients. 59% of their SH cohort had TSH level between 5-10 μIU/mL of which 25% had positive antibodies, and 35% had TSH >10 μIU/mL with positive antibodies in 66%. So the likelihood of antibody positivity was higher with higher TSH levels (7). Over expression of the gene of interferon receptor 1, which is located on chromosome 21, resulting in exaggerated response to interferon was recently suggested (10, 31, 32).

The natural course of SH is not consistent, and that is the reason debate often exists about whether or not to treat. Transient SH has been noted in several studies (10, 11, 30).

Gibson et al. studied 103 patients with DS for thyroid dysfunction. They found that 70% of those with elevated TSH normalized their TSH level 4-6 years later (30). Another study found that 27% of their DS patients (44 children) had SH, and 80 % of those retested for abnormal thyroid functions (8 out of 10) had normal TSH levels. No risk factor could be identified that favoured persistence of TSH elevation or progression to overt hypothyroidism (15).

Gibson et al. 2005 found that 8 of 17 patients with SH showed spontaneous resolution (30) . Claret al. suggested that SH in DS children less than 5 years of age is mostly transient in nature. Spontaneous resolution occurred in 73.6% of their 53 studied patients. They also stated that the presence of goitre or antithyroid antibodies is associated with lower remission rates (27). Overall, it is estimated that the incidence of progression of SH to overt hypothyroidism is less than 50% (25, 27, 30).

Treat or not to treat SH?

Because of the transient course observed in several studies, many authors are in favour of not treating SH (1, 4, 22, 27, 30, 33, 34). The rate of conversion to overt hypothyroidism has been reported to be low in a follow up study in adult patients with DS followed for 10-15 years (35).

The incidence of conversion of SH to overt hypothyroidism is estimated to be less than 50% (25, 27, 30). Furthermore, treatment does not seem to positively impact growth and development in treated compared non treated patients (4, 5, 22, 27, 30, 33, 34, 36). In the follow up of their randomized controlled trial, Marchal et al. found no difference in mental or motor development, weight, height, and head circumference between those treated with T4 and those given placebo, though treated patients were observed to be taller and with larger head circumference. This was not noted in patients with TSH level <5 mU/l. They concluded that early T4 treatment in DS did not seem to be of benefit to the motor or mental development though it may positively affect growth (37).

For all the aforementioned reasons, it was suggested that treatment of SH be reserved to patients who progress to overt hypothyroidism, and those with TSH > 10 μU/mL in the presence of goitre or positive thyroid auto antibodies (1). On the other side, some authors argue that early T4 treatment is potentially harmless, and may benefit growth and motor development in DS, a population with already delayed development (10, 28). Better intellectual outcome was also suggested with early treatment of mild cases (11). This was argued against by the work of Marchal et al and van Trotsenburg et al. (37, 38) Despite the detection of a minor benefit in growth and gross motor development with treatment during the first 2 years of life in their randomized controlled trial, the difference in motor and mental was insignificant when patients were reassessed after 8.7 years (37). Some authors also suggested that early treatment may prevent progression to severe hypothyroidism (39).

In summary, the uncertain positive impact of treatment on growth and development, the lack of clear evidence regarding the benefits of early thyroxine treatment, and the fact that elevated TSH is mild and transient in many cases are not in favour of treating patients with SH with a long life medication. Treatment of SH is only advised by most authors in case of conversion to overt hypothyroidism (1, 8). It can also be initiated in the presence of goitre, and some advocate treatment in the presence of positive thyroid antibodies as well provided TSH level is >10 μIU/mL (10).

Shifted TSH and T4 levels

Patients with Down syndrome are frequently observed to have TSH levels in the higher normal range, and T4 levels in the lower normal range (19, 40). van Trotesenberg et al. suggested that the mean plasma TSH and T4 levels in DS follow a Gaussian distribution with mean TSH shifted to right and mean T4 shifted to the left, and they considered this phenomenon as a continuum with SH (40). This may be a cause for over diagnosis of SH (7). Indeed, the data presented by Pierce et al agree with this hypothesis. The upper limit of normal TSH in their study was found to be 2.5 SD above the mean TSH value, which was 7.1 μIU/mL (7).

Autoimmune thyroid disorders

It is well known that autoimmune disorders are more common in DS patients compared to the general population (1). Among the autoimmune disorders reported celiac disease with a prevalence of 5-10%, type I diabetes mellitus which is claimed to be three times higher in DS patients (5), alopecia with recent reported rate of 11.4 % (41), and autoimmune thyroid disease (5, 10). Both hypothyroidism and hyperthyroidism are described in the literature, with autoimmune hypothyroidism or Hashimoto's thyroiditis (HT) being more common than hyperthyroidism or Graves' disease (GD) (1, 41). Thyroid auto antibodies are detected in 13-34% of patients with DS (5). Thyroid peroxidase (TPO) antibodies have been found in up to 31% of DS patients (36). In fact the presence of TPO antibodies strongly correlates with the evolution of euthyroidism and SH to overt hypothyroidism (10).

Hashimoto's thyroiditis and Graves' are recently considered as two sides of a coin (42). The commoner scenario has been conversion of GD to HT, whereas in patients with chromosomal abnormalities like Turner and DS, it was observed that the opposite scenario was more frequent (43).

Autoimmune hypothyroidism

The main features of autoimmune hypothyroidism in DS versus the general population are: 1) equal sex distribution, 2) earlier age of onset, 3) lower antibody titre at diagnosis, 4) lower rate of positive family history, 5) higher rate of progression to overt disease, 6) subclinical hypothyroidism being the most commonly observed picture on presentation, and 7) more common association with other autoimmune diseases (1, 5, 10, 41).

Autoimmune hypothyroidism in DS is equally common among both genders in contrast to the female preponderance observed in non DS population (1, 5, 10, 41). Another different point is the earlier detection of thyroid autoantibodies, though not necessarily associated with overt hypothyroidism.

Thyroid antibodies were detected in infants as young as 5 months of age (15, 44). Many authors stated that autoimmune hypothyroidism is usually diagnosed after the age of 8 years (5, 15, 39, 44). However, most of the published literature is limited by the small sample size. In their study on 146 patients with HT and DS compared to 553 patients with HT without DS.

Aversa et al. found that the mean initial age at diagnosis of HT in DS was 6.5 years compared to 11.1 years in non DS patients, 73.3% were younger than 10 years in the DS group whereas 32.5% were less than 10 years of age in the non DS group. They concluded that HT occurred at a younger age (41). It is hypothesized that this conclusion might be related to the increased awareness of the increased association of autoimmune disorders with DS among physicians, and therefore tendency to early testing of patients. Deterioration of the thyroid disease is the usual course of autoimmune thyroid dysfunction in DS. Almost all euthyroid patients studied by Aversa et al deteriorated to a state of hypothyroidism (41).The prevalence rate of SH remained constant in their cohort, while hyperthyroidism prevalence changed from 4.1% (6 patients) at initial evaluation to 8.2 % (12 patients) at re evaluation after a minimum period of 5 years. In fact, they quoted that "in 8.2% of cases HT switched to GD from presentation to re-evaluation". They emphasized that evolution of HT to hyperthyroidism is more frequent in DS (41).

Several studies tried to explain the increased incidence of autoimmune diseases in DS (1, 45, 46). Theories from different studies include the following:

- Thymic atrophy and reduction in T and B lymphocytes in the neonatal period. T lymphocytes

normalize with time but the B lymphocytopenia persists. Reduced IgM, IgG2 and IgG4, with high levels of IgA, and IgG1 and IgG3 are observed. In addition, reduction in CD4+ cells associated with increased CD8+ lymphocytes all lead to altered immune function in DS, and increased incidence of autoimmune diseases and infections (1, 45, 46).

- Mutations in the autoimmune regulator gene (AIRE) located in the 21q22.3 region. AIRE is a transcription factor involved in immune regulation, and inactivate mutations in this gene are linked to polyendocrine syndrome type 1 (APS – 1). Although hypothyroidism is not a hallmark of APS – 1, it is observed in such patients. (47) The exact link between AIRE and autoimmune thyroid disease in DS has not been clearly established, yet over expression of this gene caused by the presence of an extra copy of chromosome 21 may be the explanation (48).
- Alterations in regulation of pro and anti inflammatory cytokines due to alterations in ATP and adenosine, nucleotides and nucleosides responsible for immune regulation (15).
- The suppressive effect of interferon alpha and its toxic effect on thyroid gland. Interferon alpha down regulates the expression of genes involved in T4 synthesis in vitro. Over responsiveness to interferon is hypothesized by few authors (5).
- An association with DQA1 0301 allele which is found on chromosome 6. This allele is linked to increased association of autoimmune thyroid disease and celiac disease. Up regulation of DQA1 0301 allele by immune regulatory genes located on chromosome 21 was suggested to be the cause behind increased prevalence of autoimmune thyroiditis in DS. (49) However no specific HLA genotype has been proved to be related to thyroid autoimmunity in DS (5, 49).

Regarding the treatment of hypothyroidism, overt hypothyroidism manifested as elevated TSH combined with low free T4 requires thyroid hormone replacement. The presence of positive antithyroid antibodies in the absence of biochemical evidence and clinical symptoms does not warrant treatment but needs careful and strict follow up and more frequent biochemical testing to detect overt changes in thyroid functions (1). SH is still a debatable matter as was discussed earlier.

Autoimmune hyperthyroidism

Graves' disease is the main cause of hyperthyroidism in DS (50, 51). It is observed more frequently in DS, but without sex predilection compared to the general population (50). Its prevalence is estimated to be 0.66% compared to 0.02% in the general population (51).

Contrary to autoimmune hypothyroidism, Graves' disease in DS is usually symptomatic and easy to discover (50, 51). It commonly presents in late childhood or early adult life (5), but is generally earlier to present when compared to the general population. It is also commonly associated with other autoimmune disorders (1), and is commonly a result of progression from HT regardless of the degree of autoimmunity at presentation (43, 52).

In their follow up series of 12 DS patients initially diagnosed with HT and converted to GD over a median period of 4.2 years (9/12 were either euthyroid, SH, or overt hypothyroid, and all 12/12 had negative TRAB at initial diagnosis), Aversa et al. found that the time to conversion from HT to GD was not related to L-thyroxine treatment, and that serum TRAB concentrations did not differ between those treated with L-thyroxine and those not treated. All their patients showed long and persistent remission after an initial methimazole dose of 0.38±0.12 mg/kg/day. After a median period of 2.5 years (range 2-7 years), 8/12 patients are still being treated with a mean dose of 0.12±0.02 mg/kg/day to maintain euthyroidism (53).

From our experience, this is a reasonable dose. Hypothyroidism may develop after withdrawal of methimazole treatment and require L-thyroxine treatment (42, 53, 54). The main challenge is the treatment modality. Shorter duration of remission (50), and higher relapse rates are observed with medical treatment (5). Relapse rate after withdrawal of medication varies but rates up to 100 % have been published (50, 51). For this reason, it is suggested that treatment with radioactive iodine may be the best option (50, 51).

Several reports have been published in favour of radioactive iodine treatment in DS. However, this necessitates life - long L thyroxine replacement (51, 55).

On the contrary, De Luca et al. reported that Graves' disease in DS has less severe clinical course compared with patients without DS, they also found lower relapse rate after withdrawal of methimazole first cycle, and the persistence of remission was higher in DS after withdrawal of definitive treatment. However, their population consisted of only 28 DS patients compared with 109 controls (50). In the paediatric population, it may be difficult to use radioactive iodine as a first choice for treatment. Surgery is reported not to be the best choice in patients with DS because of the craniofacial abnormalities and the short neck that may interfere with anaesthesia (1, 5). Every treatment modality has its pros and cons and no single treatment can be generalised in all patients.

Screening recommendations

According to the American Academy of Paediatrics, it is suggested to check TSH at birth, 6 and 12 months then annually thereafter (56). The Australian and Canadian guidelines recommend the same (57, 58). In their study, Erlichman et al. emphasized the importance of TSH based screening. They concluded the total T4 based neonatal screening failed to identify many cases of congenital hypothyroidism in neonates (59). If TSH is abnormal, or there is clinical suspicion, free T4 is to be checked as well (59). For patients with SH, there are different suggestions including routine screening (15), screening every 5 years (30), and every 3 months (22).We believe that more frequent testing should be performed in patients with SH.

Regarding thyroid antibody testing, only the Irish and the UK guidelines referred to thyroid antibody measurement with each thyroid screen, which they recommended to be at least once every two years starting from age 1 throughout life (60, 61). It could be argued that patients with positive antibodies are more likely to progress to overt hypothyroidism, and therefore antibody testing can be a useful tool to anticipate progression to overt hypothyroidism (10). This would justify more frequent testing.

Conclusion

More understanding of the mechanisms behind thyroid gland dysfunction in DS has evolved over the recent years. There seems to be peculiarities regarding the presentation of autoimmune thyroid disease in DS. The metamorphism of thyroid autoimmunity in DS is common, and warrants careful follow up. The "watchful waiting" strategy is generally becoming more popular for subclinical hypothyroidism, with more frequent testing warranted for this subgroup that represents the majority. There is more evidence regarding the value of radioactive iodine treatment for Graves' disease. Up till now, there is no uniformly worldwide accepted consensus regarding the frequency of screening after the first year of life, and regarding the TSH cut off value for starting treatment.

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