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Review

Subclinical thyroid disease in elderly subjects

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Abstract. Subclinical thyroid disease (STD) is defined as circulating concentrations of free T4 and free T3 within their respective reference ranges in the presence of abnormal circulating concentrations of TSH. SCD is being diagnosed more frequently in clinical practice and is reported to be more prevalent in elderly as compared to young or adult subjects. The clinical impact of subclinical thyroid dysfunction is still a matter of debate, although it has been associated with various negative clinical outcomes, such as increased cardiovascular risk, reduction in bone density, decline in cognitive function, and increased risk of overt thyroid dysfunction. The treatment of STD is controversial and there is no consensus on the TSH cutoff values which can be used as indicators for treatment, especially in elderly subjects. In the present review, we report data on the prevalence of STD and on the potential clinical consequences of these disorders. Also, data of the Literature regarding the issue of the treatment of STD in relation to the age of the patient are reported. (www.actabiomedica.it)

Key words: Aging, subclinical thyroid disease

Introduction

Changes in thyroid function participate in the overall readjustment of the hormonal milieu that occurs with aging (1). The thyroid gland undergoes several anatomical changes with age. There is a reduction in weight of the gland, in the size of follicles, and in the content of colloid, and increased fibrosis with lymphocytic infiltration. However, these changes do not correlate with thyroid function (2). The half-life of T4 increases in the seventh decade of life (2) but serum T4 concentration is not affected by this phenomenon because its production decreases with age. Different results have been reported in the Literature on the age-related modifications of thyroid hormone circulating concentrations (3). TSH has been reported to increase or decrease with age in relation to the iodine intake (4, 5). Recent reports have demonstrated that in subjects with normal thyroid function, TSH levels were slightly lower at older than younger ages. In parallel, FT3 levels were lower and FT4 levels were higher (1). These concomitant divergent changes in both FT3 and FT4 may suggest that in humans the hepatic 5' deiodinase activity declines with age, analogous to what has been reported in rats (6) with the consequence of a decreased peripheral T4 degradation. Also, the presence of an age-related altered set point of the hypothalamic-pituitary- thyroid axis may be involved in the above reported age-related modifications of thyroid hormones and thyrotropin (7).

There is an age-dependent increase in the prevalence of antithyroid antibodies. From 40 to 70% of older individuals with elevated TSH concentrations have thyroid autoantibodies, however only a minority of older patients with thyroid autoantibodies have elevated TSH. The increase in thyroid autoantibodies with age is likely due to the effect of age-associated disease rather than aging *per se* (4, 5, 8). The percent-

age of people with positive TPO antibodies decreases in subjects older than 80 yr (2). This phenomenon is not clearly explained at present, however, it has been hypothesized that, besides selection bias, survival may be associated with an unusually efficient immune system activity, devoid of the age-related abnormalities which are, on the contrary, more frequently observed in younger elderly subjects (2).

Subclinical hypothyroidism

Subclinical hypothyroidism (SHypo) is more prevalent in the elderly population, as compared to young subjects, especially in women, and may progress to overt disease (1, 5, 9, 10-14). The causes of SHypo in the elderly are similar to those of young and middle-aged patients. Autoimmune thyroiditis and treatment of hyperthyroidism are the main causes of the reduced thyroid function observed in older patients (15). SHypo may remain unrecognized in elderly patients because of the gradual decline in thyroid function. Furthermore, the effects of aging on the clinical picture of the subjects may resemble those of a thyroid hormone deficiency and may therefore represent a confounding factor in the clinical diagnosis (16, 17). Among the drugs that may induce thyroid hormone deficiency, amiodarone, lithium, and interferon are frequently administered in the elderly (16). Several studies have been focused on the clinical impact of SHypo in elderly subjects, but further investigations are needed in order to have conclusive data. At least theoretically, the main risks associated with SHypo in the elderly, like those in younger patients, are represented by dyslipidemia, atherosclerosis, decreased cardiac function.

The cardiovascular system is a major target of thyroid hormone action (18). Therefore, evaluation of the cardiovascular effects of thyroid hormone deficiency is of particular interest in SHypo. Subclinically hypothyroid patients have a more prolonged isovolumetric relaxation

time and an impaired time-to-peak filling rate (which are parameters of altered left ventricular diastolic function) (19-25) This cardiac finding may be considered as important negative prognostic factor, because left ventricular diastolic dysfunction has been associated with increased morbidity and mortality (26). The cardiovascular risk may be further increased in older subjects because they are more likely to have an underlying cardiovascular disease.

Conflicting results have been reported about systolic function in patients with SHypo (21-25, 27-30).

The association between SHypo and serum lipid profile has been investigated in several large population-based studies.

No associations between SHypo and hyperlipidemia were found in the Whickham Survey (31). In the NHANES III, cholesterol levels were higher in patients affected by SHypo than in euthyroid subjects, but there were no differences in LDL or HDL levels (32). In another study, there were no differences in TC, HDL-C, or triglycerides between patients with a serum TSH level below 4.6 mIU/liter and those with a serum TSH level between 4.7 and 10 mIU/liter (33). Overall, the data demonstrate that there are conflicting results about lipid pattern and SHypo. Besides differences in age, gender and ethnicity of the subjects evaluated in the different studies, this phenomenon might be due to differences in the population studied (i.e.: gender, ethnicity, age, and levels of TSH).

The presence of symptoms in patients with SHypo remains controversial and difficulties exist in distinguishing the clinical picture between euthyroid subjects and patients with SHypo, especially in the elderly. Moreover, the typical findings of hypothyroidism are less common in the elderly and are often attributed to chronic illnesses, depression or drugs (34, 35).

Whether or not elderly patients with SHypo should be treated remains a matter of debate (36,37). Some Authors suggest to start replacement therapy in elderly patients who have TSH concentrations greater than 10 mIU/L or in those with antithyroid antibodies (37), as well as in symptomatic elderly patients with TSH levels between 4.5 and 10 mIU/liter (36). However, concern has been raised about treating SHypo in the elderly because of potential harmful effects on cardiovascular system. On the other hand, replacement therapy could improve cardiac function, especially diastolic heart failure. Interestingly, both overt hypothyroidism and SHypo have been associated with lower mortality, and higher levels of T4 have been associated with increased mortality after adjusting for

sex, disability, and health status (15). Furthermore, recent reports demonstrated that low serum FT4 is associated with a better 4-yr survival in a population of independently living elderly men. In the same reports, there was an inverse relationship between T3 and physical performance and lean body mass, and between FT4 and mortality, which suggests that a lower activity of the thyroid hormone axis is beneficial in aging subjects and could be an adaptive mechanism to prevent excessive catabolism (38). Moreover, it has been reported that several risk factors associated with thyroid hormone deficiency (i.e., total cholesterol and and LDL-colesterol levels) are independent cardiovascular risk factors in the middle- aged, but not in the oldest-old subjects (39). In conclusion, the benefits of a replacement therapy in elderly subjects with SHypo are uncertain. Although large randomized trials are needed, recent reports suggest that treatment of SHypo should probably be avoided in patients older than 85 yr whose TSH level is between 4.5 and 10 mIU/liter (15, 40). Elderly subjects should be carefully examined for identification of who would benefit from replacement therapy. Treatment should be individualized in those with a serum TSH concentration above 10 mIU/liter with the aim of reaching a TSH serum concentration of 4-6 mIU/liter in individuals older than 70 yr (40, 41).

Subclinical hyperthyroidism

Subclinical hyperthyroidism (SHyper) is defined by low or undetectable serum TSH and normal FT4 and FT3 concentrations (42, 43). It has been reported that the most common cause of SHyper is represented by exogenous SHyper due to excessive dose of replacement therapy in hypothyroid patients or to intentional TSH suppressive therapy for benign or malignant thyroid disease (43, 44-49). Endogenous SHyper is commonly associated with Graves' disease, multinodular goiter, and autonomously functioning thyroid nodules (42-45, 48, 49). Transient TSH suppression may however occur during subacute, silent, or postpartum thyroiditis. Low circulating TSH concentrations may also be found in diseases other than SHyper (i.e.: nonthyroidal illness, psychiatric illness, pituitary dysfunction), or drug therapy (i.e., steroids, dopamine, or dobutamine) (42-44). The prevalence of exogenous and endogenous SHyper in the general population is between 0.7 and 12.4% (50). Subclinical hyperthyroidism is common during l-T4 therapy, being present in about 10-30% of patients (16, 40, 50). Endogenous SHyper is more prevalent in women than in men and in the elderly. In iodine deficient areas the prevalence of SHyper has been reported to be 15.4% in subjects older than 75 yr, in one study (51), and 7.8% in subjects older than 65 yr in another study (1). Subclinical hyperthyroidism may represent a risk factor for arrhitmias. In a prospective study, 2007 subjects 60 yr or older who did not have atrial fibrillation (AF) at the beginning of the study were followed for 10 years. The incidence of AF at 10 yr among subjects with a low TSH was 28% vs 11% among those with normal TSH (P <0.005). The relative risk for AF was calculated to be 3.1 for subjects with low TSH as compared to those with normal TSH. There was no increased mortality associated with SHyper over the study period (52). These data have been more recently confirmed by another study in which, during a 13-yr follow-up period, the incidence of AF was greater in individuals with SHyper than in the euthyroid group, with 67 events vs. 31 events per 1000 person-years with an adjusted hazard ratio of 1.98 (53).

The excess of thyroid hormones has been shown to be associated with accelerated bone remodeling, with the result of a negative calcium balance and bone loss (54, 55). In a case-control study of 37 pre- and postmenopausal women with SHyper, the bone density, evaluated at the lumbar spine, femoral neck, and midshaft of the radius, was significantly reduced in postmenopausal women as compared to premenopausal women (56). The effects of endogenous SHyper are likely influenced by the duration of the disease and other associated risk factors for bone loss which may represent confounding factors for the evaluation of the impact of thyroid hormone excess on bone metabolism. However, overall, Literature data support the hypothesis of a SHyper-related decrease in BMD, particularly in cortical bone.

Thyroid hormone excess may affect central nervous system function. Epidemiological studies that have investigated the relationship between Shyper and

impaired cognition have reported inconsistent findings. A greater risk of dementia in subjects with SHyper was previously demonstrated in the Rotterdam Study (57). In contrast, other reports have failed to demonstrate any association between thyroid dysfunction and cognition in cross-sectional or longitudinal observations (58, 15). The lack of consistency between studies may depend on different assay methods, different diagnostic criteria for thyroid dysfunction, and different assessments of cognition. A recent community-based study conducted in an iodine deficient area, demonstrated a significant cognitive impairment associated with SHyper in elderly subjects. In multivariate regression analysis adjusted for multiple confounders, the likelihood (hazard ratio) of having cognitive impairment associated with subclinical hyperthyroidism versus euthyroidism was 2.26 (1).

The need of treatment of patients affected by endogenous SHyper is still controversial (59, 60). Recommendations have been released against routine treatment for those patients whose TSH is mildly decreased; treatment was recommended for patients with circulating concentrations of TSH below 0.1 mIU/liter who were older than 60 yr, for subjects with or at increased risk of heart disease, osteopenia, or osteoporosis, or those with symptoms of hyperthyroidism (37). Treatment of SHyper should be considered in elderly subjects or postmenopausal patients, in the presence of low or undetectable serum TSH because of the increased risk of AF and the risk of osteoporosis.

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