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AGING, THYROID GLAND AND LONGEVITY

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ABSTRACT

The endocrine system, in particular endocrine gland, undergoes inevitable functional changes with advancing of age. The prevalence of thyroid disorders increases with age and abound morpho-physio architectural alteration of the gland during the process of aging are well-known. Pronounced differences in clinical course of thyroid disorder is observed in elderly compared to younger individuals, as symptoms are more subtle and are often attributed due to normal aging. Subclinical hypo- and hyperthyroidism, as well as thyroid neoplasms, require special attention in elderly subjects. Intriguingly, decreased thyroid function, as well as thyrotrophin (TSH) levels progressively shifting to higher values with age – may contribute to the increased lifespan. This review explores literature on recent findings concerning the alterations in thyroid function with aging that may potentially lead to extended longevity, both in humans and animals.

KEYWORDS: Thyroid gland; Aging; Subclinical thyroid dysfunction; Thyroid cancer; Longevity.

INTRODUCTION

Aging is an inevitable process in any life surviving in this nature. Endocrine system that includes collection of endocrine gland including the thyroid gland, undergo crucial functional change with advancing age, morphological and physiological alteration of the thyroid gland during the process of aging are well-known fact. TSH secretion in response to thyrotropin-releasing hormone (TRH) is reduced with aging, and thus serum TSH level is usually lower in older than in young people in response to decreased thyroid hormone concentrations, suggesting a certain level of insensitivity of thyrotrophic cells in anterior pituitary, occurring with age;[1,2] prevalence of thyroid diseases in the elderly, differ essentially from that observed in younger subjects relies on the presence of subtle symptoms

which are often attributed to normal aging. Therefore, subclinical hypo- and hyperthyroidism, as well as thyroid neoplasms which increases with age, require special attention in elderly subjects.[3]

Thyroid dysfunction with aging

The process of aging affects both the prevalence and clinical presentation of hypo- and hyperthyroidism. Importantly, subclinical disturbances of thyroid function are more frequent than overt diseases in elderly people. [4,5] Consistently, the prevalence of subclinical hypothyroidism, which is characterized by normal free thyroxine (FT_4) and elevated thyrotropin (TSH) levels, increases with aging, the largest TSH increase is observed in people with the lowest TSH at baseline, and people with higher baseline TSH levels had proportionally smaller increases in TSH concentrations .[6 -12] and ranges from 3 to 16% in individuals aged 60 years and older. [13]

Overt thyroid disorders has negative impact on physical and cognitive function in elderly people such as impairment of attention, concentration, memory, perception, language, and executive functions are the common manifestation.[14]Moreover subclinical hypothyroidism is not associated with impairment of physical and cognitive function or depression in individuals aged 65 years and older, as compared to euthyroidism.[15,16] Contrary to this, some study has demonstrated the presence of – at least – mild cognitive impairment in people with subclinical hypothyroidism at mean age under 65 years with less mortality rate, [17,18] although the risk of coronary heart disease (CHD) events and of CHD mortality increased with TSH levels 10 mIU/l or higher. [18]

Undoubtedly, there are obvious indications for treatment of overt hypothyroidism. On the other hand, indications for treatment of subclinical hypothyroidism are still controversial. Although appropriate treatment of subclinical hypothyroidism demonstrated significant progress of lipid profile but, there is no clear evidence that this beneficial effect can be associated with decreased cardiovascular or all-cause mortality in elderly patients [19] However study of Parle et al.[20] documented L-thyroxine replacement therapy has no improvement role in cognitive function in elderly individuals with subclinical hypothyroidism. Also subclinical hypothyroidism evaluated in the elderly, dependent on the presence or absence of thyroid antibodies and degree of TSH concentration. Therefore lower baseline TSH levels and negativity of antithyroid peroxidase antibody (TPOAb) is presented in higher rate by subclinical hypothyroidism reverted to euthyroid status in adults aged at

least 65 years. [21] In turn, higher TSH level and TPOAb positivity were independently associated with lower chance of reversion to euthyroidism.[21]Moreover, TSH levels ≥ 10 mIU/l were independently associated with progression to overt hypothyroidism. [21]Recently similar findings was reported by Imaizumi et al.[22] showing that higher baseline TSH levels are associated with progression from subclinical to overt hypothyroidism and that higher TSH level (> 8 mIU/l) is a predictive value for development of overt hypothyroidism.[22] On the other hand, there is strong evidence that thyroid hypofunction may contribute to increased lifespan,[22] Therefore, taking into account all mentioned observations, the replacement therapy with L-thyroxine is not uniformly recommended in elderly people with subclinical hypothyroidism.

In turn, subclinical hyperthyroidism, characterized by serum TSH levels below lower limit of the reference range and normal serum FT_4 levels, is observed in about 8% of individuals aged 65 years and older.[23] Subclinical hyperthyroidism may be associated in older adults with decreased bone mineral density and fractures or cognitive impairment. [23-25] Furthermore, subclinical hyperthyroidism is associated with increased risk of total, as well as CHD mortality and atrial fibrillation (AF) [26]. The highest risks of CHD mortality and AF are observed in the case of TSH levels lower than 0.1 mIU/l. [26] Unexpectedly, de Jongh et al. [15] have reported that subclinical hyperthyroidism is not associated with impairment of physical and cognitive function or depression in elderly people, aged 65 years and older.. Interestingly, Rosario [27] has recently shown that progression of subclinical hyperthyroidism to overt hyperthyroidism in elderly patients is an uncommon observation. Nevertheless, since subclinical hyperthyroidism (and obviously, overt hyperthyroidism with increased T_4 level) may lead to increased risk of total, as well as CHD mortality, patients older than 65 years, with low TSH levels – particularly in case of toxic multinodular goitre or a solitary autonomous thyroid nodule – require proper medical treatment.[11]

It should also be stressed that during aging, gender-specific alterations in TSH and free thyroid hormone levels were observed, with increasing age in males there were decreases in free thyroid hormones but not in TSH concentrations. In turn, in females, the free thyroid hormone levels were not changed with aging but TSH level increased in age-dependent manner. [28]

Most recent results indicate that even in euthyroid older men with normal levels of TSH, differences in FT_4 levels within the normal range predict specific health outcomes relevant to

aging. For example, higher FT_4 within the normal range was independently associated with frailty in euthyroid men aged ≥70 years. [12] Moreover, higher FT_4 levels within the normal range were associated with lower hip bone mineral density, increasing bone loss and fracture risk in postmenopausal women. [29] Therefore, it seems that further studies are required to explain whether higher FT_4 levels contribute poorer health outcomes. Moreover, it is of interest to clarify whether FT_4 levels in the low-normal range could be considered as potential biomarkers for healthy aging. [12]

Although numerous studies demonstrate that the increased TSH level resulting from subclinical hypothyroidism further rises with aging, other findings suggest that aging is associated with lower TSH levels. [30-35] It is worth noting that TRH and FT_4 serum levels do not differ between young, middle-aged and elderly subjects. [34]

Thyroid dysfunction and longevity

As it has been mentioned above, the alterations in levels of hormones related to pituitary-thyroid axis are associated with the process of aging and, thus, may impact longevity.However, a direction of these changes, which may lead to increased lifespan, still seems to be not fully determined. [30-35]

Studies performed on centenarians have documented conducive discovery that expresses potential contribution of TSH and thyroid hormones to lifespan regulation, In 2009, Atzmon et al. [7]published the results of studies on thyroid disease-free population of Ashkenazi Jews, characterized by exceptional longevity (centenarians) with observation of higher serum TSH level as compared to the control group. Moreover, inverse correlation between FT_4 and TSH levels in centenarians and Ashkenazi controls was depicted and thus finally, concluded that increased serum TSH is associated with extreme longevity [7] indicating that serum TSH shifts progressively to higher levels with age. [36] In another study, a role of genetic background, was presumed to be potentially responsible for the changes, considering two (2) single nucleotide polymorphisms (SNPs) in TSH receptor (TSHR) gene, namely rs10149689 and rs12050077, assumed to be associated with increased TSH level in the Ashkenazi Jewish centenarians and their offspring.[37]

The above-mentioned inverse correlation between FT4 and TSH in centenarians may suggest a potential role of decreased thyroid function in lifespan regulation, leading to remarkable longevity. Such a hypothesis seems to have been confirmed by the findings obtained in the

Leiden Longevity Study, demonstrating the associations between low thyroid activity and exceptional familial longevity.[38]

Corsonello et al,demonstrated that age is associated with a decrease in free triiodothyronine (FT_3) and FT_4 but not with increased TSH levels. Moreover, children and nieces/nephews of centenarians had lower FT_3, FT_4 and TSH levels as compared to the age-matched subjects, at least partially, confirming an important role of low thyroid function in the regulation of lifespan.[39]

An experiment in rodents demonstrated a very severe thyroid hypo-function with reduced core body temperature, as observed in Ames dwarf (df/df) and Snell mice with mutations at the Prop-1 and Pit-1 gene, exhibited lack of growth hormone (GH), prolactin and TSH), ascribed to contribute remarkable longevity,[40] thus reduced thyroid function with low levels of T_4 is associated with extended longevity in animals.[42,43]

The findings in animals are consistent with the results obtained in humans, confirming relevant role of thyroid hypo-function in lifespan extension.

Thyroid carcinoma with Aging

The prevalence of thyroid nodules and thyroid neoplasms is increased in the elderly. Among elderly people, males are at higher risk of cancer and thyroid cancer is more aggressive in men than in women. Follicular thyroid carcinoma (FTC) is second most common finding in older people and is the second least aggressive cancer likely to metastasize hematogenously to distant sites, worsening prognosis. [44]Moreover, rapidly growing and typically very aggressive anaplastic (undifferentiated) thyroid carcinoma (ATC) is rare. By the time of diagnosis, most patients have widespread local invasion and distant metastases.[44]

Papillary thyroid carcinoma (PTC) is the most common endocrine malignant neoplasm in the older individuals. Women are affected by PTC two to three times more often than men .Nevertheless, female-to-male ratio seems to decline with the process of aging.[45] Importantly, the mortality rate of PTC is usually higher in the elderly. Presumably, it is a consequence of increased mitotic activity of these tumors and increased likelihood of distant metastases. [46] It is known that in general population patients with aggressive variants of PTC have higher risk for the metastatic disease development. [47] The potential role of NDRG2 gene expression in the development and progression of PTC is also raised. It is worth

recalling that mutated BRAF gene is an independent predicting factor of poor outcome in PTC and is related to advanced age.[48,49]

Medullary thyroid carcinoma (MTC), which derives from the para-follicular cells (C cells) of the thyroid gland, constitutes up to 5% of all thyroid malignancies. Its sporadic form, more frequent than is familial MTC, occurs more commonly in the older population.[49]

CONCLUSIONS

The process of aging strongly affects entire endocrine system with no exception to thyroid gland. One should emphasize that thyroid disease associated symptoms in the elderly people are very similar to symptoms of the normal aging. Therefore, broadening the knowledge on alterations in thyroid function, which may be observed during aging, appears to be very important and constitutes a challenge for thyroid researchers, given that some specific thyroid dysfunctions may contribute to lifespan extension.

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