WHAT'S NEW ABOUT THE THYROID GLAND AND AGING?

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Abstract: *As people age, significant functional changes occur in the endocrine system and specific endocrine organs, such as the thyroid. Thyroid diseases are more common as people age, and it is well known that the thyroid gland undergoes a number of morphological and physiological changes as people age. It should be emphasized that the clinical course of thyroid problems in the elderly is fundamentally different from that seen in younger people since the symptoms are more subdued and frequently mistaken for the signs of aging. In older people, additional care is needed for thyroid neoplasms and subclinical hypo- and hyperthyroidism. Interestingly, a longer lifespan may be attributed to both diminished thyroid function and thyrotropin (TSH) levels, which gradually increase with age. Recent research on the changes in thyroid function with age, including those that might result in longer lifespans in both people and animals, is the main topic of this brief overview.*

Keywords: *Aging, subclinical thyroid malfunction, thyroid cancer, longevity, and thyroid gland*

Introduction.

As with other organ systems, the endocrine system and specific endocrine organs, such as the thyroid gland, experience important functional changes as people age. Many morphological and physiological changes of the thyroid occur during the aging process, and a specificity of thyroid diseases in the elderly, which differs essentially from that observed in younger subjects, depends on the presence of subtler symptoms that are often attributed to normal aging. Therefore, subclinical hypo- and hyperthyroidism, as well as thyroid neoplasms, the prevalence of which rises with age, need special attention in elderly subjects. It's interesting to note that altered thyroid function may contribute to longer lifespans. The current review focuses on the most recent findings regarding the changes in thyroid function during the aging process.

Aging-related thyroid dysfunction

The frequency and clinical manifestation of hypo- and hyperthyroidism are impacted by age.Crucially, in the general population and among the elderly, subclinical thyroid dysfunction is more common than overt illnesses [4,5]. Subclinical hypothyroidism, characterized by normal free thyroxine (FT4) and increased thyrotropin (TSH) levels, is

consistently more common as people age [6–12] and varies between 3 and 16% in those 60 years of age and older [13]. In contrast to euthyroidism, subclinical hypothyroidism is not linked to depression or impairment of physical and cognitive function in people 65 years of age and older, despite the fact that overt thyroid disorders are known to have a negative impact on physical and cognitive function in the elderly. For instance, overt hypothyroidism is linked to impairment of attention, concentration, memory, perceptual functions, language, and executive functions [14]. Additionally, Park et al. [16] have shown that subclinical hypothyroidism in older adults is not linked to meta- bolic abnormalities, depression, poor quality of life, or cognitive impairment. However, other research showed that those with subclinical hypothyroidism at mean age ≤ 65 had at least minimal cognitive impairment (reviewed in [17]). Furthermore, subclinical hypothyroidism was not linked to an elevated risk of overall mortality, according to de Jongh et al. [15]. Similar results were found by Rodondi et al. [18], who examined data from multiple large prospective cohorts and showed that while the risk of coronary heart disease (CHD) events and CHD mortality increased with TSH levels 10 mIU/l or higher, overall mortality was not elevated in subjects with subclinical hypothyroidism. There are unquestionably clear indications for treating overt hypothyroidism. However, recommendations for treating subclinical hypothyroidism remain debatable. Although treating subclinical hypothyroidism improves lipid profiles, there isn't enough proof to link this positive outcome to lower cardiovascular or all-cause mortality in older individuals [19]. Additionally, L-thyroxine replacement treatment does not enhance cognitive performance in older adults with subclinical hypothyroidism, according to Parle et al. [20]. The presence or lack of thyroid antibodies and the degree of elevated TSH concentration were the determining factors in the evaluation of the natural history of subclinical hypothyroidism in the elderly. Therefore, among persons aged 65 years or older with lower baseline TSH levels and antithyroid peroxidase antibody (TPOAb) negative, a rather significant incidence of reversal of subclinical hypothyroidism to eu-thyroid state was noted [21]. Conversely, a decreased likelihood of reverting to euthyroidism was independently linked to greater TSH levels and TPOAb positive [21]. Furthermore, the development of overt hypothyroidism was independently linked to TSH levels > 10 mIU/l [21]. Imaizumi et al. recently revealed similar results, demonstrating that a greater baseline TSH level is linked to the progression from subclinical to overt hypothyroidism and that a higher TSH level (> 8 mIU/l) is a predictive value for the development of overt hypothyroidism [22]. However, there is compelling evidence that thyroid hypofunction may be linked to longer lifespans (see the text for more details). Thus, considering all of the aforementioned observations, L-thyroxine replacement treatment is not always advised for older adults with subclinical hypothyroidism. Conversely, around 8% of people 65 and older have subclinical hyperthyroidism, which is defined by serum TSH levels below the lower limit of the standard range and normal blood FT4 levels [23]. In older persons, subclinical hyperthyroidism may be linked to cognitive impairment [23] (reviewed in [25]) or reduced bone mineral density and fractures [24]. Additionally, subclinical hyperthyroidism is linked to a higher risk of atrial fibrillation (AF) episodes, CHD mortality, and overall risk [26].

TSH levels below 0.1 mIU/l are associated with the greatest risks of AF and CHD mortality [26]. Surprisingly, de Jongh et al. [15] have found that depression and impairment of cognitive and physical performance in older adults (65 years of age and above) are not linked to subclinical hyperthyroidism. Additionally, these scientists have shown that there is no correlation between subclinical hyperthyroidism and an elevated risk of overall mortality [15]. It is quite hard to explain such outcomes. This uncertainty in observations is presumably caused by variations in the number of participants in specific research or by the length of follow-up. It's interesting to note that Rosario [27] recently demonstrated that it is rare for older people to proceed from subclinical hyperthyroidism to overt hyperthyroidism. However, patients over 65 with low TSH levels, especially in cases of toxic multinodular goitre or a single autonomic thyroid nodule, need appropriate medical treatment because subclinical hyperthyroidism (and clearly, overt hyperthyroidism with elevated T4 level) may increase the risk of both overall and CHD mortality (e.g. [11]). It should be emphasized that gender-specific changes in TSH and free thyroid hormone levels were noted as people aged [28]. Specifically, free thyroid hormone levels decreased while TSH concentrations did not as males aged. Conversely, in females, TSH levels rose in an age-dependent manner whereas free thyroid hormone levels remained unchanged with aging [28]. According to the most recent findings, variations in FT4 levels within the normal range predict certain aging-related health outcomes, even in euthyroid older men with normal TSH levels. For instance, among euthyroid males aged ≥70 years, frailty was independently linked to increased FT4 within the normal range [12]. While several studies show that the elevated TSH level caused by subclinical hypothyroidism increases with age [6–12], other research indicates that aging is linked to decreased TSH levels even when there is no thyroid illness [30–35]. TSH secretion in response to thyrotropin-releasing hormone (TRH) has been shown to decrease with age, and serum TSH levels are typically lower in older adults than in younger adults due to decreased thyroid hormone concentrations. This suggests that thyrotrophic cells in the anterior pituitary become less sensitive with age, and that the elderly lose their nocturnal surge of TSH to varying degrees (reviewed in [1]).

Thyroid issues and lifespan

As previously stated, changes in pituitary-thyroid axis hormone levels are linked to aging and may thus affect longevity. The course of these alterations, which might result in a longer lifetime, is yet unclear, though [6–12, 30–35].
It should be noted that research on centenarians (and almost centenarians) produced the most startling results on the possible role of thyroid hormones and TSH in regulating lifespan. The findings of research on Ashkenazi Jews who are free of thyroid illness and have extraordinary lifespan (centenarians) were reported in 2009 by Atzmon et al. [7]. Comparing these people to the control group, which was made up of younger, unrelated Ashkenazi Jews, and to another control group derived from the National Health and Nutrition Examination Survey (NHANES) program of investigations, they found that their serum TSH levels were higher [7]. Consequently, our results seem to corroborate earlier data, suggesting that serum TSH gradually increases with age (e.g., [36]). Additionally, the

authors found a significant correlation between FT4 and TSH levels in Ashkenazi controls and centenarians, and they have concluded unequivocally that elevated serum TSH is linked to exceptionally long lifespans [7]. Another study evaluated the potential contribution of genetic background to the aforementioned alterations [37]. It was discovered that the Ashkenazi Jewish centenarians and their descendants have higher TSH levels due to two (2) single nucleotide polymorphisms (SNPs) in the TSH receptor (TSHR) gene, specifically rs10149689 and rs12050077 [37]. The aforementioned negative relationship between FT4 and TSH in centenarians raises the possibility that a reduced thyroid function contributes to the control of lifespan and results in exceptional longevity. The results of the Lei-den Longevity Study, which showed a correlation between low thyroid activity and remarkable familial longevity, appear to support this theory [38].
On the other hand, Corsonello et al. [39] have shown that while TSH levels do not rise with age, free triiodothyronine (FT3) and FT4 do. Furthermore, FT3, FT4, and TSH levels were lower among centenarians' progeny and nieces/nephews than in age-matched participants [39]. It should be emphasized that prolonged longevity in animals is linked to decreased thyroid function and low T4 levels [40–42]. For instance, it is thought that a significant factor in the exceptional longevity of Ames dwarf (df/df) and Snell mice is their extremely severe thyroid hypofunction with decreased core body temperature, which is characterized by mutations at the Prop-1 and Pit-1 genes, respectively, and a lack of growth hormone (GH), prolactin, and TSH [40]. Additionally, mice with mild thyroid hypofunction and severe hypothyroid Ames dwarfs who have targeted disruption of the growth hormone receptor/growth hormone binding protein gene (GH receptor knockout; GHRKO) have smaller thyroid follicles, which could account for the lower thyroid hormone levels in these mutants [43].

In conclusion, the results in animals are in line with the findings in people and might support the idea that thyroid hypofunction plays a significant part in extending life.

Aging mechanisms and thyroid cancerogenesis
The elderly are more likely to have thyroid nodules and thyroid cancers. Men are more likely than women to get cancer in their later years, and thyroid cancer is more aggressive in men [44].
The most common endocrine malignant tumor in elderly individuals is papillary thyroid cancer (PTC). PTC affects women two to three times more frequently than it does males [45]. However, as people age, the female-to-male ratio appears to decrease [45]. Significantly, older adults often have a greater PTC death rate [46]. It is presumably a result of these cancers' elevated mitotic activity and higher risk of distant metastases [46]. It is well established that people with aggressive PTC variations are more likely to acquire metastatic disease in the general population [47]. It is also suggested that NDRG2 gene expression may play a part in the onset and course of PTC [48]. It is important to remember that a mutant BRAF gene is linked to advanced age and is an independent predictor of a bad outcome in PTC [49].

Follicular thyroid carcinoma (FTC), the second most prevalent and second least aggressive kind of thyroid cancer, is also frequently found in elderly adults. Compared to PTC, this cancer has a poorer prognosis because it is more prone to spread hematogenously to distant locations [44]. Up to 5% of all thyroid cancers are medullary thyroid carcinomas (MTC), which are derived from the thyroid gland's parafollicular cells (C cells). The elder population is more likely to experience its sporadic form, which is more prevalent than familial MTC [50].
Anaplastic (undifferentiated) thyroid cancer (ATC) is uncommon and usually exceedingly aggressive. HPV is important to note, nevertheless, that elderly individuals are far more likely to have HPV than younger people. Most patients have distant metastases and extensive local invasion by the time of diagnosis. In ATC, age seems to be a reliable indicator of a bad prognosis [44].

Conclusions

The entire endocrine system is significantly impacted by the aging process. Age consistently affects the thyroid gland as well. It should be emphasized that the symptoms of thyroid problems in older adults are strikingly similar to those of normal aging. Given that some specific thyroid dysfunctions may contribute to lifetime extension, expanding our understanding of changes in thyroid function that may be seen as we age looks to be crucial and a challenge for thyroid researchers.

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