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Editorial Comment

Thyroid Alterations with Aging

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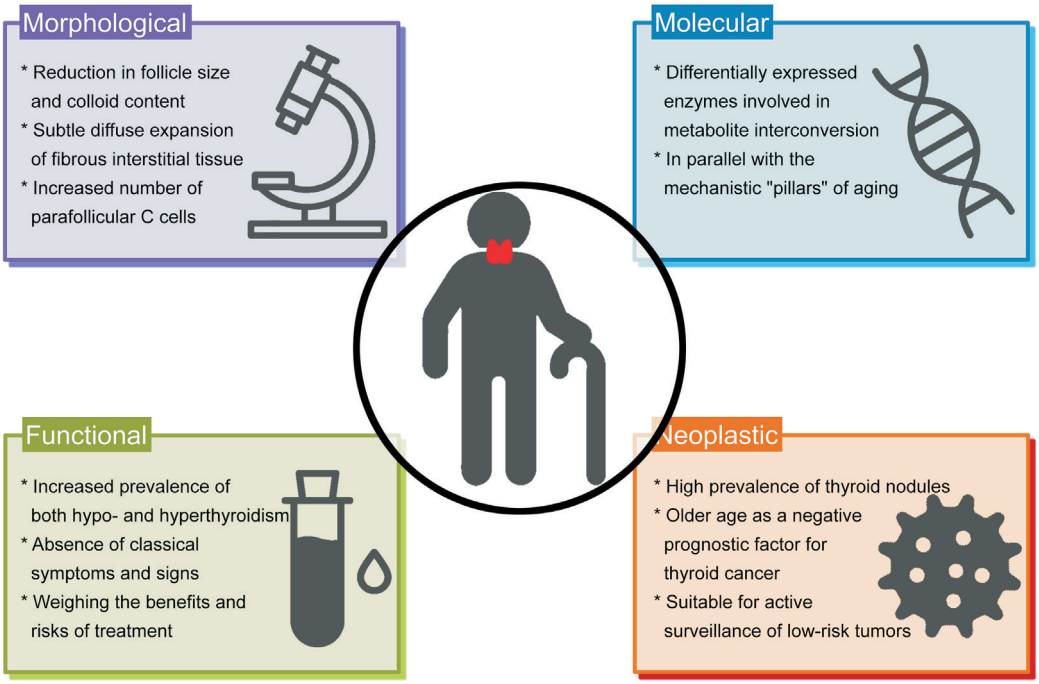

Central Illustration. Various aspects of age-related changes in the thyroid gland.

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The thyroid gland, like other organs and systems, undergoes age-related changes in the elderly. As a key regulator of metabolism and homeostasis, thyroid hormone interacts intricately with various biological processes and has been shown to have inverse associations with longevity in some studies.[1] Here, different aspects of age-related changes in the thyroid gland are briefly reviewed.

1. Morphological alterations

A general trend of thyroid gland atrophy, characterized by reduced weight and size, has been reported with advancing age. In contrast, other studies have found that thyroid size and weight may increase due to a higher prevalence of nodular goiter among the elderly. Histological studies of apparently normal glands show reduced follicle size and colloid content, degeneration and flattening of epithelial cells, subtle diffuse fibrous interstitial expansion, and varying degrees of lymphocytic infiltration.[2] These morphological changes may result from age-related failure of endocytosis, as there is a marked reduction in the density and polymerization of microtubules and microfilaments in the thyroid follicular cells of aged rats. Additionally, an increased number of parafollicular C cells, along with the formation of clusters and micronodular hyperplasia, is often observed.

2. Functional alterations

As people age, changes occur in thyroid hormone production, metabolism, and action. In most iodine-proficient populations, the distribution curve of thyroid-stimulating hormone (TSH) shifts to higher values in older adults. The prevalence of positive anti-thyroperoxidase and anti-thyroglobulin antibodies increases with age, particularly among women, but appears unrelated to fully developed thyroid autoimmune disease. Altered thyroid status includes reduced sensitivity of thyrotrophs to negative feedback from thyroid hormone, decreased TSH bioactivity, diminished responsiveness of the thyroid gland to TSH, and variations in tissue-specific thyroid hormone availability or activity.[3] These mechanisms may help the organism adapt to aging by lowering the metabolic rate and reducing protein catabolism.

Subclinical hypothyroidism, defined as a TSH concentration

above the reference range with normal free thyroxine levels, is often observed in older individuals but may be temporary.[4] Clinical judgment is crucial when selecting therapeutic options for the elderly with subclinical thyroid disorders, and using age-specific TSH reference ranges may help prevent misclassification in this population. In contrast, a high index of suspicion is essential when diagnosing hypothyroidism in the elderly, as signs and symptoms such as cold intolerance, constipation, fatigue, weakness, reduced appetite, hair loss, and dry skin can easily be mistaken for normal aging. Additionally, depression and lethargy are often prominent in this group. The potential benefits of treatment — such as symptom improvement, prevention of overt hypothyroidism, and avoidance of adverse outcomes — should be weighed against the risks of iatrogenic subclinical or overt hyperthyroidism.

The prevalence of hyperthyroidism also increases with age. Toxic multinodular goiter is the most common cause in older adults, particularly in iodine-deficient regions. Elderly patients often lack classical symptoms and signs of hyperthyroidism; instead, atrial fibrillation, cardiovascular complications, and weight loss occur more frequently. Gastrointestinal or neuropsychiatric symptoms, such as cognitive impairment and affective disorders, may signal hyperthyroidism in the elderly. Treatment for subclinical hyperthyroidism is recommended for patients over 65, as well as for those with cardiac risk factors, heart disease, osteoporosis, and individuals exhibiting hyperthyroid symptoms.

3. Molecular alterations

Few studies have analyzed the gene expression signature in the aging thyroid. Using transcriptome data from normal-appearing thyroid tissues in The Cancer Genome Atlas and the Genotype-Tissue Expression project, we identified that the overrepresented protein class of aging-correlated genes primarily consists of metabolite interconversion enzymes.[5] Moreover, pathway enrichment analysis suggests changes in immune and inflammatory responses, mitochondrial functions, cytoskeletal proteins, and amino acid and cytochrome P450 metabolism. The complexity and multisystem interactions of age-related thyroid pathologies have been integrated into a unified framework that encompasses key mechanistic “pillars” of aging, including inflammation, immune adaptation, cellular senescence, stem cell exhaustion, loss of proteostasis, metabolic derangement, and epigenetic modifications.[6]

4. Neoplastic alterations

Age affects the incidence, prevalence, and behavior of thyroid neoplasms, as well as treatment options. Thyroid nodules are common in older adults, with about half of individuals over 60 years of age showing nodules in ultrasonography assessments.[7] While prevalence rises with age, the risk of thyroid cancer may decrease. However, mortality associated with thyroid cancer is generally higher in the elderly. Aside from pediatric oncology, thyroid cancer is the only tumor type for which age is considered a prognostic factor for staging. One possible reason for this phenomenon is that the expression of the sodium-iodine symporter may be downregulated in older patients, while younger patients are more likely to have radioiodine-avid disease.

The papillary subtype is the most common histology of thyroid cancer. For small papillary thyroid carcinoma, a conservative approach involving active surveillance has been proposed as an alternative to immediate surgery for low-risk tumors. Interestingly, older age may be associated with a reduced risk of tumor growth during active surveillance.[8] Conversely, the transformation of differentiated thyroid cancer into poorly differentiated or undifferentiated forms, which carry a dismal prognosis, is more frequently observed in the elderly. These dual characteristics of thyroid cancer emphasize the need for tailored management in older patients. Our analyses indicate that age is positively linked to glycolytic pathways and negatively linked to immune-related functions in papillary thyroid cancer.[9]

5. Conclusions

Numerous changes in thyroid characteristics occur with aging, most of which are considered physiological. When evaluating thyroid dysfunction, various confounding factors, such as comorbidities, nutritional status, and polypharmacy, can complicate the interpretation of results. Clinical symptoms might be atypical or subtle, and weighing the benefits and risks requires careful therapeutic decision-making. Additionally, the prevalence of thyroid nodules among the elderly is high, warranting special attention to both indolent and aggressive malignancies.

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