Thyroid dysfunction in the ageing patient

Abstract. Thyroid dysfunction is a common endocrine disorder in the general population, with a reported prevalence of 10–15 %. This rate is higher in older adults, with an estimated prevalence of 25 % in some populations. Since elderly patients usually present more comorbidities than younger individuals, thyroid dysfunction may carry a synergistic negative health impact, mainly due to increased cardiovascular disease risk. Thyroid dysfunction in the elderly can be more difficult to diagnose due to its subtle or even asymptomatic clinical presentation, and the interpretation of thyroid function tests may be affected by drugs that interfere with thyroid function or by the coexistence of several diseases. Clinical experience shows that older people with hyperthyroidism display fewer signs or symptoms compared to younger people with hyperthyroidism. Moreover, older people with normal thyroid function tests have several clinical features of hypothyroidism. These observations suggest that there may be an age-related resistance to the actions of thyroid hormones. Laboratory experiments have consistently documented an age-related blunting of response to exogenously administered thyroid hormones. This resistance to thyroid hormones action has been attributed to reduced cellular transport of thyroid hormones. In light of these observations, along with epidemiologic studies, the diagnosis and treatment of thyroid disease in older people differ from the current treatment guidelines of younger people with thyroid disease. It is noteworthy that the age-related resistance to thyroid hormones is distinct from the congenital thyroid hormone resistance syndromes. This distinction is explained by the age-related changes in pituitary responsiveness to the feedback inhibition by thyroid hormones and reduced thyroid gland response to thyrotropin. The current evidence suggests that the age-related resistance to thyroid hormones is an adaptive process to prolong life span. In this review article, we summarize the current knowledge on the pathophysiology, diagnosis, and therapeutic management of thyroid dysfunction in elderly patients.

Keywords: subclinical hypothyroidism; overt hypothyroidism; hyperthyroidism; elderly; overtreatment; screening

Nowadays, people worldwide are living longer, and every country in the world is experiencing growth in both the size and the proportion of older persons. In line with this, by 2030, one in six people in the world will be aged 60 years or over (more than 1.4 billion) and by 2050, people aged 60 years and older will double (2.1 billion expected). Moreover, the number of persons aged 80 years or older is expected to triple between 2020 and 2050, reaching 426 million [1, 2].

Thyroid dysfunction is a common endocrine disorder in the general population, with a reported prevalence of 10–15 % [3]. However, this rate is even higher in older adults, with an estimated prevalence of 25 % in some populations [4, 5]. Factors involved in this increasing thyroid dysfunction in elderly patients do not only include the well-described age-dependent increase of thyroid stimulating hormone (TSH), but also some other determinants, such as a higher prevalence of autoimmune thyroiditis or autonomously functioning thyroid nodules [6, 7]. Furthermore, other mechanisms (e.g., inflammation, epigenetic changes, or gut dysbiosis) may also play a significant role [8].

Elderly patients usually present more comorbidities than younger individuals, and thyroid dysfunction may carry a synergistic negative health impact, mainly due to increased cardiovascular disease risk. Age may be considered a decisive factor in the relationship between subclinical hypothyroidism/hyperthyroidism and cardiovascular disease risk [9, 10]. Thyroid dysfunction in the elderly can be more difficult to diagnose due to its subtle or even asymptomatic clinical presentation. In addition, the interpretation of thyroid function tests may be affected by the use of drugs that interfere with thyroid function or by the coexistence of several diseases [11, 12].
Subclinical hypothyroidism (defined as elevated concentrations of TSH, along with normal values of free thyroxine) is a highly prevalent condition in the elderly population, especially among females, with a reported prevalence of 18% in women older than 65 years [13]. The prevalence of this condition in the general population is estimated to be 4–9% [14].

Normal ageing is associated with physiologically increased TSH concentrations [15]. A progressive increase in the 97.5 percentile of normal TSH serum levels with age has been described and could be set in 5.9 and 7.5 mU/L for people aged 70–79 and ≥ 80, respectively [16]. It has been estimated that about 70% of older adults with TSH levels ≥ 4.5 mU/L are within their age-specific reference range [15]. Using age-adjusted TSH ranges should be mandatory when evaluating older patients, to avoid misdiagnosis [17]. It is important to take into account that a considerable percentage of older patients with subclinical hypothyroidism may revert to euthyroid state spontaneously on repeating test; therefore, the diagnosis of subclinical hypothyroidism should be based on the confirmation on this condition [18]. The concomitant use of drugs that potentially interfere with thyroid function testing (e.g., anticonvulsants, iodine-containing drugs, heparin, or non-steroidal anti-inflammatory drugs) should be assessed, as they can lead to changes in thyroid state (including hypothyroidism and hyperthyroidism) [11].

The postulated considerations for the treatment of subclinical hypothyroidism in older patients are based on the presence of symptoms and adverse health-related outcomes, although some controversies and additional particularities regarding levothyroxine treatment in the elderly should be considered [19]. Potential symptoms related to hypothyroidism are usually non-specific and subtle in older individuals (fatigue or weakness); previous studies have shown no differences with regard to hypothyroid symptoms between older adults with and without subclinical hypothyroidism [20], and treatment with levothyroxine in several randomized controlled clinical trials did not improve these symptoms or health-related quality of life [21]. No associations between subclinical hypothyroidism and a decline in cognitive function, mood alterations or depression in older adults have been found in a number of meta-analyses [22, 23]. Physical function is not altered in older adults with subclinical hypothyroidism [24]; mild elevations of TSH (< 7.0 mU/L) may be associated with a slight functional improvement [25].

Despite initial studies raised concern about the relationship between subclinical hypothyroidism and the potential development of adverse cardiovascular outcomes, recent prospective cohorts and meta-analyses have reported mixed results [26]. An increased risk of heart failure has been observed in elderly patients (70–79 years) with TSH levels ≥ 7.0 mU/L, or in older patients with TSH ≥ 10.0 mU/L [27]. Cardiovascular events different from heart failure (coronary heart disease, stroke, and cardiovascular-related mortality) or overall mortality were not higher in older patients with subclinical hypothyroidism [28].

Randomized controlled trials did not show a significant effect of levothyroxine therapy on the reduction of cardiovascular events/mortality or the improvement of cardiac function in the elderly [29, 30]. In a data analysis from 6 prospective cohorts including more than 55,000 adult participants, TSH concentrations ≥ 10.0 mU/L were associated with an increased risk for coronary heart disease independently of age [31]. Some authors have suggested starting levothyroxine therapy in older adults (≥ 65–70 years) with TSH levels ≥ 10.0 mU/L [32]. The increased risk of progression to overt hypothyroidism in patients with subclinical hypothyroidism and higher TSH concentrations may play a part in this decision [33]. Although adults with subclinical hypothyroidism and positive anti–thyroid peroxidase antibodies have an increased risk for the development of overt hypothyroidism, antibody status in the elderly appears not to be associated with more benefits following levothyroxine therapy [34].

The prevalence of overt primary hypothyroidism, defined as elevated serum concentrations of TSH and low serum levels of free thyroxine, is estimated to be 0.3% in the general population, although this percentage can be higher among older subjects [35]. As the clinical presentation of overt hypothyroidism in the elderly is usually less evident compared to younger individuals, an accurate and early diagnosis is essential [36].

Untreated overt hypothyroidism is associated with adverse health outcomes in the elderly population, including a higher risk of hyperlipidemia, hypertension, cardiovascular disease, or depression [37]. In a recent nationwide, population-based, retrospective cohort study including more than 2,000 patients aged ≥ 65 years, hypothyroidism was associated with increased all-cause mortality, and thyroxine replacement therapy resulted in a lower risk of mortality [38]. In a meta-analysis of 4 prospective studies including 2,116 participants ≥ 80 years (5% with overt hypothyroidism), overt thyroid dysfunction was not associated with disability or impaired mental/physical performance, and there were no differences with euthyroid subjects in terms of 5-year survival [22]. Clinical significance of overt hypothyroidism in older age groups might be limited, although further research is warranted to confirm this hypothesis.

The benefits and risks of starting replacement therapy with levothyroxine should be balanced in older adults, especially in the frail elderly, since overtreatment can result in an increased risk of cardiovascular and skeletal side effects, as well as a higher overall mortality [39].

In a community-based cohort from the Baltimore Longitudinal Study of Aging, iatrogenic thyrotoxicosis was highly prevalent and incident among the study population, with the highest rates in women over 80 years [40]. In a case-control study conducted in individuals ≥ 65 years with subclinical hypothyroidism (TSH levels < 10.0 mU/L), levothyroxine therapy was associated with increased mortality, although the mechanisms leading to this outcome remained unclear, since the study did not include any information with regard to the cause of mortality [41]. The calculation of lean body mass, instead of total body weight, should be considered before the initiation of levothyroxine therapy in older patients, since it has been demonstrated to be a more accurate method to individualize levothyroxine requirements in some populations. Thus, lean body mass is the best correlate of levothyroxine daily requirements [42]. The reduction in lean body mass associated with age may result in a lower degradation of levothyroxine in the elderly and, therefore, a decrease in the daily requirements of this hormonal therapy may be expected. The frequent concomitant intake of medications that
interfere with thyroid hormone metabolism (prednisolone, carbamazepine, phenobarbital, amiodarone or tamoxifen) or absorption (bisphosphonates, proton–pump inhibitors, ferrous sulfate) along with other medical conditions can make the adjustment of levothyroxine therapy in this population even more challenging [11].

Despite thyroid disorders, including hypothyroidism, are highly prevalent in the elderly, there is a lack of consensus with regard to the screening for thyroid dysfunction in this population. Some guidelines recommend against screening of thyroid function in non-pregnant asymptomatic adults [43], while others suggest screening older patients [44]. The U.S. Preventive Services Task Force concluded that, based on the current knowledge, there is insufficient evidence to evaluate the risk-benefit of screening for thyroid dysfunction in non-pregnant asymptomatic adults [45]. Different societies contemplate that thyroid dysfunction should be considered a potential cause of different non-specific signs and symptoms and also support case finding in some scenarios (e.g., cardiovascular disease) [46]. A high stability of thyroid function has been reported among older subjects with euthyroidism; accordingly, repeating thyroid function tests should be avoided among older individuals with a recent (within 5 years) normal result, as long as no hypothyroidism-related signs or symptoms appear [47].

Although the daily oral intake of levothyroxine tablets is the most common form of administration of replacement therapy in patients with hypothyroidism, additional therapeutic alternatives are available. Newly developed formulations, such as liquid and soft gel levothyroxine, could become suitable options for older patients with swallowing difficulty, or impaired gastrointestinal absorption due to different prevalent clinical situations in this group (chronic atrophic gastritis and achlorhydria, polypharmacy and related drug interactions) [48]. Studies specifically conducted in the elderly are needed to evaluate the feasibility of such options in this population. In addition to this, alternative dosing schedules of levothyroxine tablets may be taken into consideration for patients with difficulties in maintaining compliance of daily administration.

In this regard, twice-weekly regimens have been demonstrated effective and safe in older adults [49]. Despite the fact that once-weekly administration of levothyroxine has only been tested in younger adults [50], the American Thyroid Association (ATA) also recommends this dosing strategy in the elderly presenting problems in maintaining a regular daily schedule [51]. As an alternative, intramuscular levothyroxine administration might be considered, although there is scarce evidence available in this regard [52].

Primary hyperthyroidism is a frequent disease in the elderly population. The Third National Health and Nutrition Examination Survey showed that the prevalence of TSH levels < 0.4 mU/L was between 4 and 6 % in the 70–79 years group, with a prevalence rate over 6 % in adults > 80 years [35]. In another analysis including more than 5,000 participants aged ≥ 65 from the Atherosclerosis Risk in Communities study, the prevalence of overt and subclinical hyperthyroidism was 0.26 and 0.78 %, respectively, in untreated participants, increasing this prevalence with age [4].

With regard to the different etiologies of hyperthyroidism, toxic multinodular goiter (TMG) has been described as the most common cause in older adults, followed by Graves’ disease [7]. Iodine deficiency has been demonstrated to be an important factor in the pathophysiology of TMG in the elderly population [53]. Additional causes of hyperthyroidism, such as iatrogenic thyrotoxicosis, toxic adenoma or iodine-induced thyrotoxicosis (e.g., due to the use of amiodarone), should also be considered in this population [7].

Overt hyperthyroidism is associated with severe adverse outcomes, such as cardiovascular disease, bone fragility and increased fracture risk, cognitive impairment and increased mortality [54]. Although clinical manifestations of the disease are often milder in older patients, this population have a greater risk of complications and adverse outcomes [55]. Therefore, appropriate treatment should be initiated in older patients presenting overt hyperthyroidism.

There is wide agreement in treating persistently TSH levels < 0.1 mU/L in subjects ≥ 65 years [55], since a greater risk of hyperthyroidism-related complications and progression to overt hyperthyroidism have been reported in subjects with TSH levels < 0.1 mU/L compared to those with persistent TSH levels between 0.1 and 0.4 mU/L [56]. There is less evidence supporting the treatment of subclinical hyperthyroidism in subjects with persistent TSH levels between 0.1 and 0.4 mU/L [56]. Some studies have revealed that even mild subclinical hypothyroidism could entail a higher risk of adverse outcomes in older patients, including cardiovascular disease, bone fragility and overall mortality; treatment for mild subclinical hyperthyroidism should also be considered in this population [57].

Different therapeutic modalities are available for the treatment of hyperthyroidism. On the one hand, the ATA guidelines consider radioactive iodine (RAI) as an especially suitable option for elderly patients, since TMG is the most common cause of hyperthyroidism in this population, and a high risk of relapse is observed following discontinuation of antithyroid drugs (ATD) [55]. Some studies have shown that long-term administration of ATD is effective and safe in patients with Graves’ disease and TMG, and therefore, medical treatment might be maintained indefinitely [59]. This strategy might entail a higher risk of adverse events in patients with coexisting liver dysfunction/hematologic disorders.

Only a few studies have evaluated the impact of long-term ATD therapy in the elderly population. Remarkably, in a recent randomized trial, F. Azizi et al. compared the safety and efficacy of RAI versus long-term methimazole treatment in patients ≥ 65 years with grade 2 subclinical hyperthyroidism (TSH levels < 0.1 mU/L) and nodular/diffuse goiter [58]. After 5 years, all patients in both groups attained euthyroidism with a similar safety profile and overall costs, a finding that suggests that ATD could be equally valid for the treatment of subclinical hyperthyroidism in older adults. Further trials including older participants with both overt and subclinical hyperthyroidism are needed to confirm these results.

Although RAI or ATD are often preferred in older patients with hyperthyroidism, surgery may be chosen as the first therapeutic option in patients with manifest compressive symptoms or signs. Some large series of patients undergoing thyroid surgery showed no differences in surgical outcomes between older and younger patients [59], although it is important to note that patients should be referred to high-volume thyroid surgery centers to attain these positive results.
It is recommended to outweigh the risks and benefits of this procedure in elderly patients, and the presence of important comorbidities or contraindications should also be carefully assessed before surgery.

Amiodarone-induced thyroid dysfunction (including both amiodarone-induced hyperthyroidism and amiodarone-induced thyrotoxicosis) is often observed in the elderly and can be challenging for clinicians. This medication is widely used in older adults, and this population can be particularly susceptible to the effects of amiodarone. Amiodarone-induced thyrotoxicosis has been associated with increased risk for major cardiovascular events and mortality, especially in older patients with left ventricular dysfunction. It should be pointed out that amiodarone discontinuation is not required in amiodarone-induced hyperthyroidism, and patients can be treated with levothyroxine if necessary [60]. Two types of amiodarone-induced thyrotoxicosis can be found: type 1 (iodine-induced hyperthyroidism in patients with nodular goiter/latent Graves’ disease, which can be treated with ATD) and type 2 (destructive thyroiditis, which should be treated with oral glucocorticoids).

Conclusions
Thyroid dysfunction and thyroid nodules are prevalent conditions among older adults, and their management may include some particularities in this population. These particularities should be taken into consideration to avoid pathologizing normal situations or futile treatments. Since different options in the management of thyroid dysfunction may be available, patient- and family-centered approaches should be prioritized, with a careful evaluation of their preferences and personal circumstances. It is important to note that large-scale, long-term randomized trials are needed in this population in order to deal with some unsolved questions (e.g., the potential benefits of screening for thyroid dysfunction in some patients, the management of mild subclinical hyperthyroidism, the usefulness of long-term treatment with ATD). Moreover, the term “elderly” or “older adult” may include a wide range of age groups and different health/functional status, which might result in additional differences among the individuals included in this definition. Therefore, future studies should also evaluate some of these clinical problems in specific subpopulations.

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Дисфункція щитоподібної залози (ЩЗ) — частий ендокринний розлад у загальній популяції, поширеність якого становить 10–15 %. Цей показник вищий у літніх людей: ендокринний розлад у загальній популяції, поширеність якого становить 10–15 %. Цей показник вищий у літніх людей:

- Нарушена функція ЩЗ у літніх людей відрізняється від поточних рекомендацій щодо лікування молодих людей із тиреоїдними захворюваннями.
- Епідеміологічні дослідження підтверджують, що діагностика та лікування захворювань щодо лікування молодих людей із тиреоїдними захворюваннями

Цю стійкість до дії тиреоїдних гормонів пояснюють їх зниженням реакції на екзогенне введення гормонів ЩЗ.

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Відмінності в реакції ЩЗ на гормони можуть бути визначені при оцінці реакції на введення гормонів в різних вікових груп.

- Епідеміологічні дослідження підтверджують, що діагностика та лікування захворювань щодо лікування молодих людей із тиреоїдними захворюваннями

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