Chapter 3

Aging and Subclinical Thyroid Dysfunction

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1. Introduction

1.1. Endocrinology of aging

Aging is inevitable. Although it has been intensively studied and discussed, its cause(s) are still in the realm of hypotheses. Two main theories hold the center of the stage at the moment: 1) aging occurs in accordance with genetic pre- programmed events or 2) it is not genetically programmed but results from an accumulation of random events [1, 2]. Either way, changes in cellular/molecular function are common denominators to be found in all processes that characterize biological aging, but these changes occur with different timing and specificity among different cells, tissues or organs [3]. This chapter will briefly review some important aspects of current knowledge about aging process and its impact on thyroidal function.

The endocrine system is as affected by aging as are other systems. Yet, again, not all of its components are affected at the same time or in the same way. During aging, physiologic functions decline gradually, cellular protein synthesis is diminished as well as immune function. There is also an increase in fat mass, a loss of muscle mass and strength, and a decrease in bone mineral density that contribute to declining health status.

Two important clinical changes occur in endocrine activity during aging, involving pancreas and thyroid gland. About 40% of individuals between the ages of 65 and 74 years and 50% of those older than 80 years have impaired glucose tolerance or diabetes mellitus, and in almost 50% of elderly adults with diabetes the disease is undiagnosed [4]. Pancreatic secretion, insulin receptor and insulin signaling pathways changes associated with aging are critical components of the endocrinology of aging. In addition to relatively decreased insulin secretion by the beta cells, peripheral insulin resistance related to poor diet, physical inactivity, increased abdominal fat mass, and decreased lean body mass contribute to the deterioration of glucose metabolism

[4]. Other hormonal systems exhibit lowered circulating hormone concentrations during normal aging, and these changes have been considered mainly physiologic. The decrease in human gonadic function with consequent decline in circulating estrogen and testosterone, and increase in serum gonadotropins (FSH and LH), is a classic example. A decrease in growth hormone (GH) and insulin-like growth factor-I (IGF-I) are most probably due do a decline in hypothalamic growth hormone releasing hormone (GHRH), and also a part of the aging process in mammals [4, 5]. The aged adrenal cortex is affected in its capacity to produce dehydroepiandrosterone (DHEA). In contrast the glucocorticoids produced in the adrenal cortex fasciculate layer tend to be more responsive to stimuli, have a slightly delayed clearance rate, and are less entrained to the circadian phase in aged subjects than in young ones. Although not all authors agree [6], most report that healthy elder subjects have higher cortisol levels presumably in response to increased corticotrophin (ACTH) secretion [7, 8]. It is difficult to evaluate - in humans - if this discordance is gender-related. An increased hypothalamus-pituitary-adrenal activity is also seen in aged rats, more due to an increase in hypothalamic vasopressin (AVP) synthesis and secretion than to increases in corticotrophin releasing hormone (CRH), and may be related to a decrease in glucocorticoid receptor activity both at the hypothalamus/pituitary and at peripheral tissues [9, 10].

2. Problem statement

2.1. Aging and thyroid dysfunction

Age-related thyroid dysfunction is common. Lowered plasma thyroxine (T4) and increased thyrotropin concentrations occur in 5% to 10% of elderly women [11]. Autoimmunity or an age-associated disease frequently are the primarily cause of these abnormalities rather than a natural consequence of the aging process. Several immunological abnormalities have been described in aging process. A well-recognized age-associated immune abnormality is the general production of both organ- and nonorgan-specific autoantibodies. Aging is frequently associated with the appearance of thyroid autoantibodies, but the biological and clinical significance of this is still unknown. Some data have shown that these thyroid autoantibodies are rare in healthy centenarians and in other highly selected aged populations, whereas they are frequently observed in unselected or hospitalized elderly patients, thus suggesting that these autoantibodies are not the consequence of the aging process itself, but rather are related to age-associated disease [12].

Thyroid autoimmunity and subclinical hypothyroidism have also been implicated in the pathogenesis of other age-associated disorders like coronary heart disease [13]. A major, unresolved issue is whether, and to what extent, the complex physiological changes seen in the hypothalamus-pituitary-thyroid axis contribute to the pathogenesis of age-associated diseases such as atherosclerosis, coronary heart disease and neurological disorders [11].

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With improvements in biochemical testing and increasing numbers of relatively asymptomatic individuals being subjected to blood testing, subclinical hypothyroidism and subclinical hyperthyroidism have become the most frequent thyroid disease. The clinical complications and functional consequences and effects on quality of life have been extensively addressed as well as the therapeutic options, however because of the lack of large randomized clinical trials, the evidence for choosing one treatment over another is minimal [14].

Normal aging is accompanied by a slight decrease in pituitary thyrotropin (TSH) release and especially by decreased peripheral metabolism of T4, which results in a gradual age-dependent decline in serum triiodothyronine (T3) concentrations without changes in T4 levels [11]. This slight decrease in plasma T3 concentrations occurs largely within the broad normal range of the healthy elderly population and has not been clearly related to functional changes during the aging process. The deleterious effects of overt thyroid dysfunction in elderly individuals are clearly recognized, but the clinical relevance of mild forms of hypothyroidism and hyperthyroidism are a matter of debate. The prevalence of thyroid disease increases with age and all forms of thyroid disease are encountered. However, the clinical manifestations are different from those encountered in younger patients. In the elderly, autoimmune hypothyroidism is particularly prevalent. Hyperthyroidism is mainly characterized by cardiovascular symptoms and is frequently due to toxic nodular goiters. Thyroid carcinoma is also more aggressive [15].

Molecular biology studies have considerably broadened our knowledge of thyroid tumorigenesis. Follicular cell proliferation is mainly regulated by TSH but also is controlled by extracellular growth factors that essentially modify intra- cellular signaling pathways after binding to membrane receptors. It is known that "in *vitro"* TSH stimulates cell cycle progression and proliferation in cooperation with insulin or IGF-I in various thyrocyte culture systems, including rat thyroid cell lines (FRTL-5, WRT and PCCl-3), and in primary cultures of rat, dog, sheep and human thyroid cells [16]. Park *et al.* demonstrated that the TSH proliferative effect is, at least in part, mediated by an increase in expression of an adaptor molecule of the IGF-I receptor (p66Shc) [17]. These data suggest that the synergistic proliferative effect of TSH and insulin/IGF-I on the thyroid gland may also occur "in *vivo"*.

Tumor growth occurs when the normal equilibrium of regulatory pathways is disrupted, either through enhancement of stimulatory pathways or deficient inhibitory pathways [18]. Epidemiological studies show that cancer is primarily a disease of the aged. Cancer rates increase dramatically in humans beginning in the sixth and seventh decades of life. Although the complex relationship between cancer and aging has long been recognized, a clear understanding of the mechanisms underlying this relationship has remained elusive. Recently, Hinkal and Donehower reviewing this issue focused on a decline in function of tumor-suppressing genes like p53 during aging, associated with the development of tumors in many different tissues in mice. Among the hundreds of tumor-suppressing genes now identified, p53 may be the most important. The p53 gene is mutated in over half of all human cancers, and it has been

estimated that more than 80% of human cancers have dysfunctional p53 signaling [19]. In fact, decreased expression of tumor- suppressing genes, may be associated with higher cancer incidence in aged subjects, but one can not discard higher function of genes involved in cellular proliferation probably also present in aged subjects.

Ras proteins are involved in the transduction of growth factor signals by surface receptors, and are key components of downstream signaling through several pathways. Ras activation of the Raf serine/threonine kinases, and activation of the ERK mitogen-activated protein kinases (MAPKs) is an important signaling pathway for many Ras effects [20]. Thyroidal proliferation can be induced by growth factors, and it is known that oncogenic mutations of Ras-family genes play an important role in malignant transformation and tumor progression in the follicular epithelium of the thyroid gland. In fact, De Vita *et al.* showed in FRTL5 thyroid cells that the overexpression of mutated RAS gene inhibits the expression of thyroid differentiation markers in a dose-dependent way [63]. Overexpression of three different Ras isoforms (H-, K- and N-Ras) exert similar effects on the thyroid phenotype: loss of thyroid differentiation, with decrease in thyroidal differentiation markers proteins as thyroglobulin, thyroperoxidase, Na+/I- symporter, TSH receptor, thyroid oxidase and thyroid specific combination of transcription factors, Titf 1, Foxe 2 and Pax 8 [21].

Ras proteins comprise a group of 20- to 25-KDa proteins that are involved in transduction of signals elicited by activated surface receptors, acting as molecular switches in many processes governing cellular growth and differentiation. The Ras-pERK pathway can also be modulated by thyroid hormones. In the hypothyroid rat there is a clear positive modulation of Ras, but this does not affect pERK, which shows a slight decrease. In contrast, thyroidal pERK increases in T4-induced hyperthyroidism, but there are no changes in RAS expression [22].

Effects of aging on Ras expression are still very much unexplored. In rat thyroids from both genders aging duplicated Ras expression, but its signal transduction by pERK was decreased, suggesting a failure in this pathway [23]. These results could be involved in the impaired thyroidal function observed in old rats. Ras activation of Raf serine/threonine kinases, and activation of the ERK mitogenactivated protein kinases is an important signaling pathway for many Ras effects, the others being the activation of phosphatidylinositol-3 kinase or the Ral-small GTPases. As far as we know, an increase in the protooncogene Ras expression in the thyroid from aged rats has not been detected previously. Further studies are required to elucidate the pathways involved in this increases in Ras expression during the aging process, and to correlate them with the known morphologic and functional changes that affect the aging thyroid gland.

2.2. Aging and hypothalamus-pituitary-thyroid axis

The effect of aging on the hypothalamus-pituitary-thyroid function is still a subject of controversies. The hypothalamus-pituitary-thyroid axis undergoes a significant number of complex

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physiological alterations associated with aging. However, direct age-related changes need to be distinguished from indirect alterations caused by simultaneous thyroid or non- thyroidal illness, or other physiological or pathophysiological states whose incidence increases with age. Several changes formerly believed to be a direct result of the aging process have subsequently been shown to be due to the increased prevalence of subclinical thyroid disease and/or the result of non-thyroidal illness. This makes interpretation of thyroid function tests difficult in the elderly [11].

Pituitary thyrotropin (TSH) stimulates all steps of thyroid hormones biosynthesis and is the major regulator of the thyroid gland morphology and function. TSH production and secretion are stimulated by the hypothalamic thyrotropin-releasing hormone (TRH) and suppressed by thyroid hormones, in a classic negative feedback control system.

In a revision of several population studies Surks and Hollowell report that the TSH distribution of aged humans - without thyroid disease - progressively shift to higher concentrations, suggesting that the prevalence of subclinical hypothyroidism could have been overestimated in many other studies [24]. The main point that is being discussed for some time by endocrinologists is whether the increase in the serum immunoreactive TSH of aged subjects, and related changes in thyroid function, are a "physiologic" consequence of aging on the hypothalamus-pituitary-thyroid axis or if they reflect alterations induced by acute or chronic non-thyroid illnesses and/or use of drugs, both more frequent in the elder population [25, 26].

In fact there are strong evidences pointing to a decrease hypothalamus-pituitary-thyroid axis activity with aging, be it in humans [27, 28] or in rats [29, 30, 31]. Thyroid hormone production and metabolism are altered by aging. Serum T4 and T3 are significantly reduced in old male rats, but the serum T3 seems to be less affected in elder female rat [30, 31, 32]. Decreases in serum T3, associated or not with lower T4, are present in aged humans [26], however it should be emphasized that although significantly decreased the thyroid hormone and TSH concentrations mostly remain within the range considered as normal.

The decrease in T3 levels, and in the metabolism of T4 in elder subjects has been attributed to a diminished 5'- deiodinase type I (D1) activity. In fact, we and others have found lower hepatic and thyroid D1 activity in aging rats, but males seem to be more affected than females [30, 33, 34]. The resulting lower serum T3/T4 ratio can also be attributed, at least in part, to a preferential release of T3 by the thyroid of the aged rat, both basal and after TSH stimulation [35]. The effect of aging on pituitary deiodinases type 1 and type 2 (D1, D2) is still awaiting further confirmatory studies. Donda and Lemarchand-Beraud found an increase of D1 and deiodinase type 2 (D2) activities in the pituitary of old male rats, while we found both pituitary deiodinase activities to be decreased in the old female rat [36]. No further information seems to be available, although suggestions of a "partial central hypothyroidism" and less efficient response of the hypothalamic-pituitary axis to lower circulating thyroid hormones are found often enough [32].

Hypothalamic TRH content is reduced in aged rats [32, 35] and thyrotroph response to TRH is mostly reported as decreased, both in rats [29, 32, 36] and [37, 38] in humans. Non-stimulated

TSH concentration has also been reported as relatively diminished by aging in a large population of older persons without hyperthyroidism, and in aging patients with resistance to thyroid hormone (and their non-affected relatives) [27].

In fact, Carlé *et al.* detected four-fold higher average serum TSH in younger (0-20 years) than in the older (80+ years) patients with untreated primary, spontaneous autoimmune hypothyroidism, while there was no age-dependent variation in serum T4. The well-known inverse linear correlation between T4 and log TSH was maintained in both groups, but the serum TSH/T4 ratio was lower in the elder patients than in the young ones. Thus, for the same degree of thyroid failure, the serum TSH is lower among the elderly. Since serum T4 is the parameter best associated with the degree of tissue hypothyroidism, a lower TSH at diagnosis/follow-up of elder patients may suggest that their degree of hypothyroidism is less severe than it really is. Furthermore, and of interest for the clinical endocrinologist, a longer time may be needed after thyroid hormone withdrawal before elder patients with thyroid cancer reach sufficiently high TSH values to allow an effective radioiodine treatment [28].

The increase of pituitary thyrotroph hormonal secretion, when stimulated by the low levels of thyroid hormones, is also significantly impaired in the old rat, even when the thyroid hormones levels are dramatically reduced by MMI treatment [31]. "Normal" circulating levels of TSH are frequently seen in aged rats, in spite of their low serum thyroid hormone levels [30, 31, 36]. This may be attributed to the secretion of a TSH with increased sialylation and diminished biological activity [39] as reported in some types of central hypothyroidism [40] and/or to a diminished response of the thyroid to TSH (less TSH receptors or defective transduction of its signal). A diminished effect of a less biologically active TSH can explain the low thyroid hormone concentration of the aged rat, that could be in part mediated by a decrease in the TPO and Tg expression as found by us in the thyroid gland of aged male (but not female) rat [30].

Thus, at the moment, we must consider that the hypothalamus-pituitary-thyroid axis is affected at all three levels by normal aging, and a reduced responsiveness of target cells/tissues to the effects of thyroid hormones levels rounds-off the picture of a mild state of "total" hypothyroidism that occurs during the aging process, and that may vary according to gender and species evaluated.

Aging also affect thyroid morphology, Messina *et al.* reported a reduction of the hypothalamus-pituitary-thyroid axis activity, with anatomical (weight) and physiological (uptake of iodine and hormone synthesis) age-related adaptations, that result in a reduction of thyroid function [41]. Nevertheless, the authors consider this state as different from hypothyroidism since the thyroid hormones tend to remain within the range considered as normal. In F344 rats, the follicular area and the area of the follicular lumen increased and the height of follicular epithelial cells decreased at 20.5 months, indicating low thyrocyte activity; concomitantly serum T3, T4 and TSH concentrations also decreased with age, confirming that in F344 male rats the aged thyroid shows structural and functional changes [42].

Figure 1 summarizes our current knowledge on aging process and its impact on thyroidal function and regulation.

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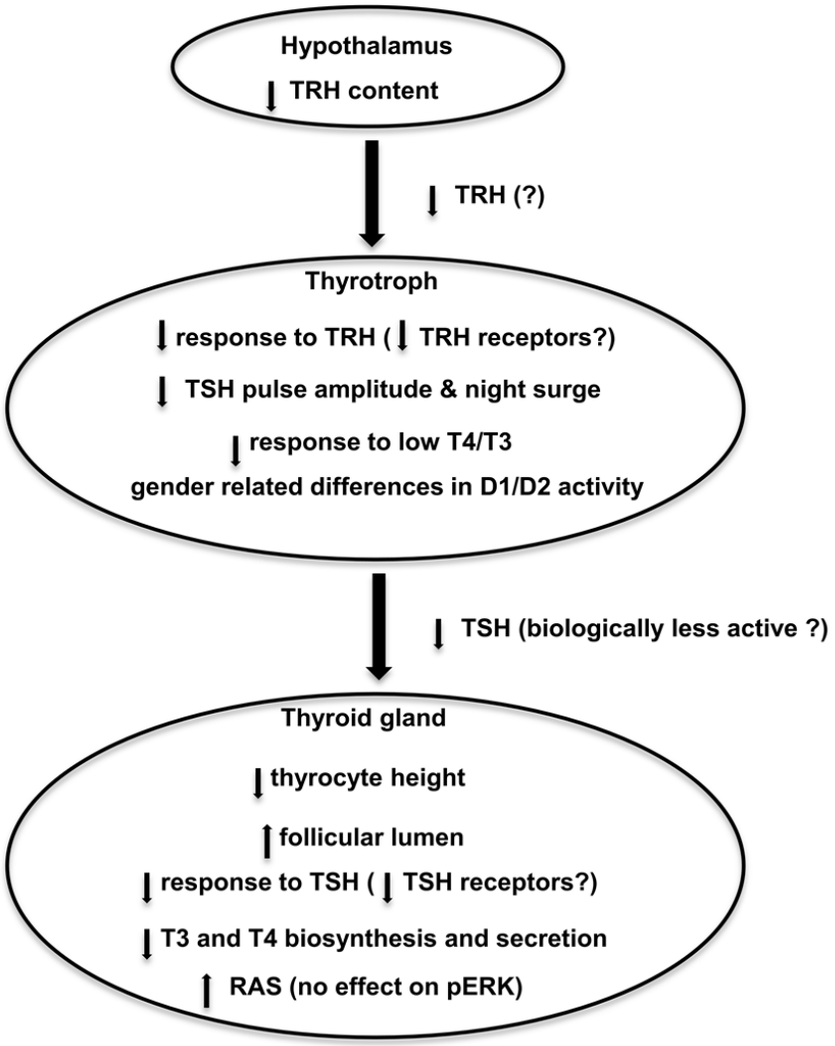

Figure 1. A schematic view of aging effects on thyroid regulation and function.

2.3. Subclinical hypothyroidism

The term "subclinical hypothyroidism" was first introduced in the early 1970s coincident with the introduction of serum TSH measurements. Subclinical hypothyroidism is defined biochemically as a high serum TSH concentration and normal serum free T4 and T3 concentrations. Some investigators also consider patients who have normal basal serum TSH and supranormal serum TSH responses to thyrotropin-releasing hormone (TRH) to have subclinical hypothyroidism. By definitions, patients with subclinical hypothyroidism cannot be identified on the basis of symptoms and signs [43].

Subclinical hypothyroidism is present in about 4% to 8.5% of adults in the United States who are without known thyroid disease [44]. Subtle thyroid dysfunction often affects the oldest-old fraction of the elderly population (i.e., those >85 years). In 85-year-old healthy individuals, hypothyroidism was in the subsequent 4 years associated with lower all-

cause and cardiovascular mortality rates compared with euthyroid individuals [45]. In a group of 400 men with a mean age of 78 years, Van den Beld and colleagues [46] showed that low serum levels of free T4 and T3 (with normal reverse T3 [rT3]) concentrations were associated with better physical performance and 4-year survival, whereas subjects with low serum levels of T3 and high rT3 concentrations did not show a survival advantage and had lower levels of physical activity. These two studies support the concept that some degree of physiologically decreased thyroid activity at the tissue level may have favorable effects in the oldest-old subjects, but caution should be exercised when interpreting the predictive value of thyroid dysfunction in the elderly, which may produce contradictory results if not considered in the appropriate context [15].

Subclinical hypothyroidism has been associated with heart failure [48] and with increased odds of metabolic syndrome [49], but the significance of increased serum TSH in elder subjects is still *sub judice*. Thus, treatment of subclinical hypothyroidism to prevent heart failure and cardiovascular disease in older people should be better evaluated in large randomized clinical trials.

Thyroid hormones have an important role in many organic functions and their deficiency causes a wide spectrum of clinical presentations and symptoms. Neuromuscular manifestations are well established in overt hypothyroidism and impaired muscle function is frequently observed. Thyroid hormone deficiency may also interfere substantially with various aspects of physical, mental and social well-being. The evidence for improvement of psychiatric symptoms with hormonal treatment of hypothyroidism, and the use of T3 to potentiate the response to treatment of depressive disorders suggest a direct relationship between thyroid hormones and psychiatric symptoms. Neurobiological evidence seems to corroborate the hypothesis of an organic basis of the effects of thyroid hormone on the brain and on psychiatric symptoms. There is some evidence that subclinical hypothyroidism may also be responsible for findings classically described in hypothyroidism. Symptoms and signs of hypothyroidism have been frequently found in subclinical hypothyroidism patients, as reported by many authors. In fact, Reuters et al described an improvement in some physical aspects of quality of life after L-T4 treatment in patients with subclinical hypothyroidism [50].

The frequency of subclinical hypothyroidism, varies from 6.5 to 15% in elder subjects [51, 52] Subclinical hypothyroidism has been associated with clustering of cardiovascular risk factors, such as hypertension, diabetes mellitus, dyslipidaemia and hyperuricaemia [53], as well as with the development of insulin resistance, which is evident both in vivo and in vitro studies. The latter may be attributed to decreased insulin-stimulated rates of glucose transport in cells, due to impaired translocation of GLUT4 glucose transporters on the plasma membrane [54].

Multiple studies, with conflicting results, have examined the association of subclinical hypothyroidism with cardiovascular risk and mortality. A recent reanalysis of the Whickham Survey suggested a clear association of subclinical hypothyroidism with ischemic heart disease and mortality [55]. However, a meta-analysis of 15 observational studies indicated that increased cardiovascular risk is evident only in younger individuals with subclinical hypothyroidism [56]. In patients with type 2 diabetes mellitus, subclinical hypothyroidism has been found to be associated with reduced all-cause mortality [57]. Furthermore, age-related subtle

thyroid hypofunction has been related to longevity [58]. Part of the heterogeneity in these studies may be related to differences in participants' age, sex or TSH level. In a recent meta-analysis combining data on 55,287 participants from 11 prospective studies, subclinical hypothyroidism was associated with an increased risk of coronary heart disease and mortality in patients with TSH levels higher than 10 IU/L, these associations did not differ in age, sex or ethnicity [51].

Treatment of subclinical hypothyroidism remains controversial [52, 53, 59]. Although there are no randomized controlled trials documenting decreased cardiovascular morbidity or mortality, some studies have suggested that treatment of subclinical hypothyroidism may result in improvement of cardiovascular risk factors, such as insulin sensitivity, glucose metabolism, soluble intercellular adhesion molecule-1 [60], endothelial progenitor cell levels [61], abnormalities in high-density lipoprotein metabolism [62], and common carotid intima-media thickness [63]. According to the American Association of Clinical Endocrinologists, treatment is indicated in patients with TSH levels above 10 IU/ml or in patients with TSH levels between 5 and 10 IU/ml along with goiter or positive anti-thyroid peroxidase antibodies, since these patients have increased rates of progression to overt hypothyroidism. However, it should be kept in mind that TSH levels are sometimes transiently elevated, due to recovery from non-thyroidal illness or medication use. As a result, it has been recommended that TSH measurement should be repeated after 6–8 weeks in order to confirm the diagnosis of subclinical hypothyroidism, prior to any consideration of initiating therapy [52].

The prevalence of thyroid disease increases with age but very often presents different clinical manifestations from those found in younger patients. Autoimmune hypothyroidism is particularly prevalent in the elderly, and may be one of the factors that underlies an increased serum TSH reported by various studies in this population [64]. Hyperthyroidism is less common in among older subject, is frequently due to toxic nodular goiters, is mainly characterized by cardiovascular symptoms, and its manifestations are generally milder than in the younger patients. The associated decrease in TSH may also be less marked than that found in Graves' disease. Thus, the question of whether changes in circulating TSH levels in the elderly indicate a "physiologic adaptation" or are a reflection of associated health disturbances is still pertinent and awaiting further evaluation.

3. Conclusion

The effect of aging on the hypothalamus-pituitary-thyroid function is still a subject of controversies. Normal aging is accompanied by a slight decrease in pituitary thyrotropin release and especially by decreased peripheral degradation of T4, which results in a gradual age-dependent decline in serum triiodothyronine concentrations without changes in T4 levels. This slight decrease in plasma T3 concentrations occurs largely within the broad normal range of the healthy elderly population and has not been clearly related to functional changes during the aging process.

The frequency of subclinical hypothyroidism, varies from 6.5 to 15% in older subjects and treatment of subclinical hypothyroidism remains controversial. However, it should be kept in mind that TSH levels are sometimes transiently elevated, due to recovery from nonthyroidal illness or medication use.

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