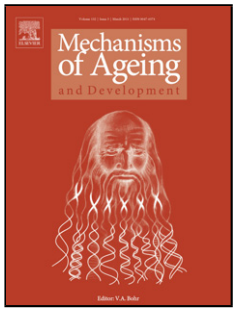

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Thyroid Hormones in Extreme Longevity

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Highlights:

Aging and longevity are complex multifactorial phenomena, in which hormonal networks play a crucial role.

Experimental evidence at the cellular and organismal level clearly showed a correlation between thyroid hormones and longevity

The involvement of thyroid hormones in aging and longevity could be explained through their effect on the oxidative stress pathway

An age-related subtle thyroid hypofunction either due to a familial component or due to a reset of the thyroid appears to be related to human longevity

Non-thyroidal illness syndrome (characterized by decreased FT3 serum concentration, increased rT3 and unchanged or inappropriately low TSH) prevalence increases with age, is associated with several age-related chronic diseases, and affects survival

ABSTRACT

The aim of the present review was to summarize knowledge about thyroid hormones (THs) and longevity. Longevity is a complex multifactorial phenomenon on which specific biological pathways, including hormonal networks involved in the regulation of homeostasis and survival, exert a strong impact. THs are the key responsible for growth, metabolism rate and energy expenditure, and help in maintaining cognition, bone and cardiovascular health. THs production and metabolism are fine tuned, and may help the organism to cope with a variety of environmental challenges. Experimental evidence suggests that hypothyroid state may favor longevity by reducing metabolism rate, oxidative stress and cell senescence. Data from human studies involving healthy subjects and centenarians seem to confirm this view, but THs changes observed in older patients affected by chronic diseases cannot be always interpreted as a protective adaptive mechanism aimed at reducing catabolism and prolonging survival. Medications, selected chronic diseases and multi-morbidity can interfere with thyroid function, and their impact is still to be elucidated.

Keywords: Longevity; Thyroid; Aging; Centenarians; Age-related diseases.

Abbreviations

AP-1: activating protein 1; **ATM:** ataxia telangiectasia mutated kinase; **BFU-E:** erythroid burst-forming unit; **CKD:** chronic kidney disease; **COPD:** chronic obstructive pulmonary disease; **DUOXs:** dual oxidases; **eGFR:** estimated glomerular filtration rate; **ESRD:** end-stage renal disease; **FT3:** free triiodothyronine; **FT4**: free thyroxine; **GH:** growth hormone; **HF:** heart failure; **HIF1α**: hypoxia-inducible factor 1 alpha; **H_2O_2:** hydrogen peroxide; **HPT:** hypotalamus-pituitary-thyroid axis; **IGF-1:** Insulin-like Growth Factor-1; **IL-1β:** interleukin-1-beta; **IL-6:** interleukin-6; **INFγ:** interferon-gamma; **MMSE:** Mini Mental State Examination; **MSH:** melanocyte stimulating hormone; **NADPH:** nicotinamide adenosine dinucleotide phosphate; **NFkB:** nuclear factor kappa B; **NMR**: naked mole rat; **NRF1:** nuclear respiratory factor 1; **NTIS:** non-thyroidal illness syndrome; **PRKAA:** adenosine monophosphate–activated protein kinase; **PVN:** paraventricular nucleus; **ROS:** reactive oxygen species; **rT3:** reverse T3; **SNPs:** single nucleotide polymorphisms; **T3:** triiodothyronine; **T4:** thyroxine; **TGB:** thyroglobulin; **THRB:** thyroid hormone receptor beta; **THs:** thyroid hormones; **TNFα:** tumor necrosis factor alpha; **TPO-ab:** thyroid peroxidase antibodies; **TRH:** thyrotropin releasing hormone; **TSH:** thyroid stimulating hormone; **TSHR:** TSH receptor.

1 Introduction

Improving health and social wellbeing is leading to progressively increased life expectancy in industrialized countries. Such a phenomenon is boosting research about mechanisms involved in the aging process and in the pathophysiology of age-related diseases. Hormonal networks involved in the regulation of homeostasis and survival emerged as crucial pathways[1]. Indeed, while longevity is of course a complex multifactorial phenomenon, selected biological pathways, including endocrine pathways (e.g. insulin, growth hormone (GH), Insulin-like Growth Factor-1 (IGF-1), and thyroid hormones (THs)), significantly affect aging[2]. THs exert their influence on almost all tissues, playing a pivotal role in development and adult life. They are the key responsible for growth, metabolism rate and energy expenditure, and help in maintaining cognition, bone and cardiovascular health. The hypotalamus-pituitary-thyroid (HPT) axis is a classical example of an endocrine feedback loop (Figure 1). Although THs have the main control on their own production, exerting a negative feedback on both thyroid stimulating hormone (TSH) and thyrotropin releasing hormone (TRH), regulation of the HPT axis is complex, and a variety of neuro-endocrine pathways are involved in the regulation of THs levels under physiological or pathological conditions[3]. Indeed, HPT axis reacts to a variety of exogenous stimuli capable to modulate THs, either environmental, such as the day-night rhythm (with a nocturnal peak secretion of TSH in humans)[4], food availability (fasting induces a decrease in both T3 and serum TSH in healthy men)[5], environmental temperature[6,7], physical or emotional stress[8,9], or pathophysiological conditions, such as acute inflammation and critical illness[10]. Thus, HPT axis regulation and TH metabolism at the tissue level (e.g. liver and muscle), are far from being fixed, and may help the organism to cope with a variety of environmental challenges[11].

Evolutionary perspective may help to understand the role of THs during aging. THs levels generally increase during development, contributing to development, maturation, and reproduction, and allowing to counterbalance the evolutionary pressure in this phase of life[12]. During late life, THs

levels tend to decline, and circadian rhythmicity and hormonal secretory patterns are deteriorated[13]. In an evolutionary perspective and in keeping with the theory of antagonistic pleiotropy[14], late life can be affected by earlier events, with long-living individuals being characterized by a less efficient peak of thyroid function during development (i.e. less strong metabolic stimulation during young age and less negative influence on aging from the optimal metabolic status required for reproduction purposes). Thus, even from an evolutionary perspective THs represent a relevant piece in the puzzle of mechanisms involved in the aging process.

Therefore, the aim of the present review is to summarize knowledge about THs and longevity. We first describe experimental studies about the role of THs. After, we summarize evidence regarding the complex relationship between THs and human longevity. Finally, THs adaptation to selected age-related chronic diseases is described.

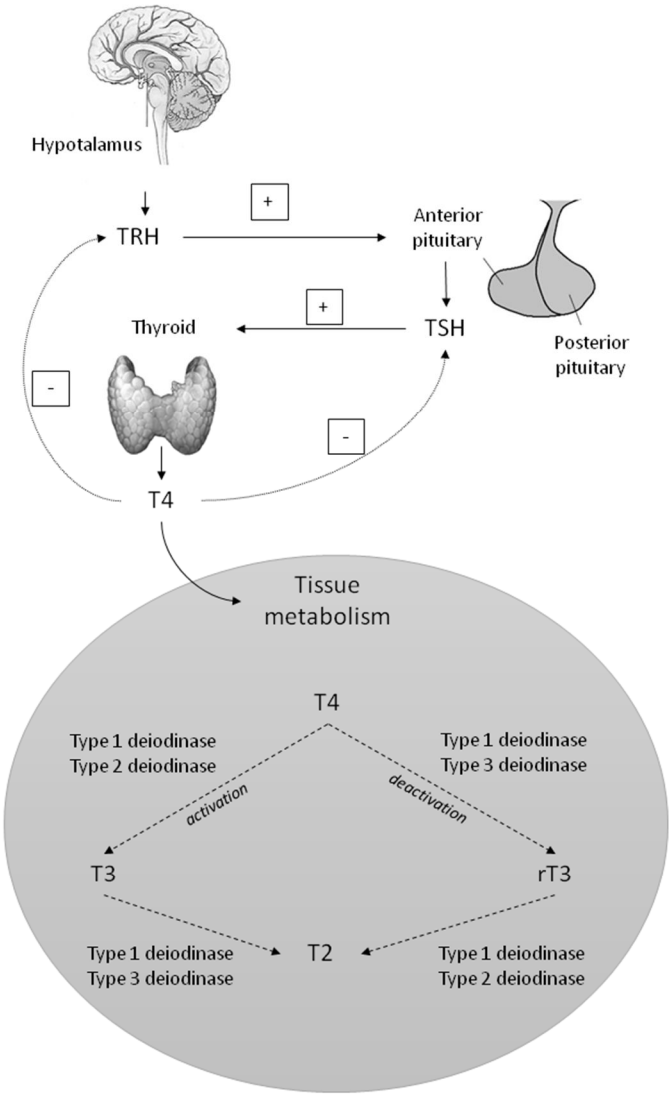

Figure 1. The HPT axis and peripheral metabolism of thyroid hormones.

Thyroid hormones (THs) secretion by the thyroid gland is under the control of thyroid-stimulating hormone (thyrotropin, TSH), produced by the pituitary when stimulated by thyrotropin-releasing hormone (TRH), released by the hypotalamus. Thyroid releases two active hormones: L-Thyroxine (T4), the most abundant, and triiodothyronine (T3), the most active. Approximately 85% of circulating T3 is produced by monodeiodination of thyroxine (T4) in tissues such as liver, muscle and kidney. This process is carried out by enzymes called deiodinases. These enzymes contain selenocysteine and are divided into three types: D1, D2 and D3. D1 and D2 induce conversion from T4 to T3, D1 is also involved in the clearance of reverse T3 via inner ring deiodination (rT3→T2), while D3 inactivates T4 e T3.

2 Thyroid hormones and longevity: experimental models

Experimental evidence suggests that THs play a key role in longevity, especially through their multiple effects on the oxidative stress pathway.

A considerable amount of hydrogen peroxide (H_2O_2) is directly produced by the thyroid during the synthesis of THs. In fact, iodide is oxidized by thyroid peroxidase in the presence of H_2O_2 (produced by dual oxidases (DUOXs) sited at the apical membrane of the thyrocyte) and then incorporated into the tyrosine residues of thyroglobulin to produce monoiodotyrosine and diiodotyrosine). Also subsequent steps leading to the synthesis of T3 and T4 are catalyzed by thyroid peroxidase[15,16]. Thyroid cells are able to counteract this potentially toxic exposition to ROS thanks to a fine tuned antioxidant system, at least until the pro- and anti-oxidant processes are well balanced[17]. However, excess in ROS production and/or inadequate production of antioxidants during aging process may contribute to cause oxidative stress and thyroid damage, including thyroid autoimmune diseases and cancer[18-21].

Additionally, THs are known to accelerate basal metabolism and increase oxygen consumption, thus leading to increased reactive oxygen species (ROS) production and oxidative stress[22,23]. Additionally, THs are able to unsaturate membrane phospholipids, leading to membrane damage and mitochondria lipid peroxidation[24,25]. Such pro-oxidant effects are tissue-dependent, with liver and heart more subject to oxidative stress than spleen and glycolytic muscle fibers[26]. However, THs can also affect the cell antioxidant status, directly (iodine compounds act as free radical scavengers able to reduce oxidative damage *in vitro*)[27,28] or indirectly, by stimulating or inhibiting the activity of antioxidant enzymes[29,30] and free radical scavengers[31]. Such an ambivalence in producing and counteracting oxidative stress has lead to controversial results about pro-oxidant or anti-oxidant activity by THs[31-38].

Recently, it has been demonstrated that binding of triiodothyronine (T3) to thyroid hormone receptor β (THRB) induces DNA damage and cell senescence. The mechanism of such a THRB-mediated disruption of cell homeostasis is related to the activation of ataxia telangiectasia mutated

(ATM)/adenosine monophosphate–activated protein kinase (PRKAA) signal transduction and nuclear respiratory factor 1 (NRF1), with consequent stimulation of mitochondrial respiration, increased production of ROS, and DNA damage ultimately leading to premature cell senescence[39].

Studies in animal models seem to confirm this view. Indeed, several mice models of longevity, either naturally long-living or manipulated and genetic mutant strains, share some commons traits, among which low levels of THs. The naked mole rat (NMR), the longest-living rodent, shows very low levels of thyroxine (0.004 ± 0.001 mg/dl)[40]. Moreover, it has been also shown that experimental hypothyroidism increased the lifespan of Wistar rats up to 28 months, while experimental hyperthyroidism reduced lifespan[41]. Hypothyroidism was found associated with reduced ROS generation and oxidative damage, while hyperthyroidism was found associated with an increase in ROS production and a compensatory increase in anti-oxidant defense enzyme levels in several studies on murine models[29,42-44].

Ames and Snell dwarf mice represent an interesting model to investigate the impact of endocrine disorders on lifespan. They are naturally mutant mice characterized by pituitary hormone deficiencies (growth hormone -GH-, prolactin and TSH, and a consequent low level of circulating THs) resulting in small body size and delayed puberty. Ames and Snell dwarf mutant mice were found to live 40-70% longer than mice with normal thyroid hormone levels[45]. It is worth noting that these mice not only live longer, but are also an example of successful aging, since they exhibit a less frequent development of age-related chronic diseases, including cataracts, kidney disease, and cancer with respect to wild type mice[45-48]. Finally, long lasting administration of thyroxine was found to shorten dramatically their lifespan, though they still lived longer than wild type mice[45].

In conclusion, the above described experimental studies clearly suggest that hypothyroid state may favor longevity by reducing metabolism rate, oxidative stress and cell senescence.

3 Thyroid hormones and longevity: human studies

Given the above described role played by THs in several vital functions, as well as changes in THs secretion during the aging process, thyroid function has been deeply investigated as a potential mechanism promoting human longevity[49]. To date, several studies have been carried out in order to demonstrate that thyroid function affects human longevity. The main problem in human studies investigating the relationship between THs and longevity is the confounding effect of age-related chronic diseases and pharmacological treatments, which affect the interpretation of thyroid function tests in older people[50]. **Iodine intake is also a major determinant of THs/TSH patterns. Overall, severely reduced iodine intake is associated with an increased risk of developing goitre and hypothyroidism, mainly because the low availability of iodine does not allow the thyroid gland to produce a sufficient amount of THs. Instead, a compensatory thyroid hyperactivity is usually able to maintain euthyroidism in subjects exposed to mild or moderate iodine deficiency. However, chronic thyroid stimulation during long lasting mild or moderate iodine deficiency may increase the risk of developing toxic nodular goitre and hyperthyroidism[51], which likely account for the observed negative relationship between age and TSH and positive correlation between age and FT4 among people with mild or moderate iodine deficiency in former cross-sectional studies[52-54]. Evidence suggests that late onset hyperthyroidism related to the exposure to mild or moderate iodine deficiency may be reverted by correcting iodine deficiency[51]. However, TSH was recently found to decrease by 5.4% and FT4 to increase by 3.7% during a 4-year follow-up period in a population with low iodine status in the past, thus suggesting that low iodine intake at young age may lead to a tendency to develop hyperthyroidism which could persist despite normal iodine intake later in life[55]. As a consequence, iodine intake should be also considered an important confounder in studies investigating the relationship between THs and longevity.**

Older people often exhibit changes in THs due to physiological and/or pathological reasons. During aging the thyroid undergoes morphological modifications, including glandular atrophy, interstitial fibrosis, reduced number of follicles, and reduced thyroglobulin (TGB) content. Such morphological changes have a significant impact on thyroid function during aging.

The prevalence of subclinical hyperthyroidism among older people was found to range between 3 and 8%, while overt hyperthyroidism was observed in 0.7-2%[56,57]. Only a small proportion of older subjects with subclinical hyperthyroidism progresses to overt hyperthyroidism (~1% per year)[58]. Nevertheless, subclinical hyperthyroidism is currently considered a harmful condition, being associated with increased risk of cardiovascular disease[59,60], insulin resistance[61], and cognitive impairment[57].

The prevalence of subclinical and overt hypothyroidism vary widely in older populations, ranging between 1 and 15%, and between 1and 10%, respectively[59,62-64]. Differences in iodine intake among populations, THs cut-off values used and sample selection methods may account for such high variability among studies[65]. Longitudinal studies showed that female sex and high TSH at baseline (within the normal range) are associated with increased risk of forthcoming subclinical hypothyroidism[66]. The risk of progression from subclinical to overt disease is highly increased in people with both high TSH and antithyroid peroxidase antibodies at baseline[67-69]. Also fasting blood glucose, total white cell count and obesity were found associated with increased risk of progression to overt disease[66].

In a longitudinal study, significant TSH increase and T3 decrease over a period of 13 years were observed in about 13% of people aged on average 85 years[70]. A significant age-related increase in thyroid peroxidase antibodies (TPO-ab), and TGB-antibodies has been also reported[71,72]. Interestingly, the age-related increase of TSH levels is not associated with a fall in circulating thyroxine free T4 (FT4) concentration, suggesting that the set point for TSH secretion may change in older people[73]. Another study showed that healthy older people had low TSH levels, with normal

free thyroxine (FT4), reduced free triiodothyronine (FT3) and increased reverse T3 (rT3) levels[56]. These findings suggest that reduced T4 degradation by peripheral/target tissue deiodinases (Figure 1) may also be involved in age-related changes in THs. Additionally, changes in deiodinases activity during aging may have some relevance in the relationship between thyroid function and longevity. Indeed, increased rT3 was observed in 8.1% of 374 older community-dwelling individuals participating in the Alsanut study, where a significant association between rT3 and mortality was also observed[74].

Centenarians seem to represent an interesting human model for investigating the relationship between THs and aging, especially because they represent a model of extreme longevity where a less relevant role of potential confounding by diseases can be supposed. Centenarians were found to have significantly higher serum TSH concentrations compared to younger controls[75,76], supporting previous observations showing that serum TSH shifts progressively to higher levels with age[71]. Additionally, nonagenarians' and centenarians' offspring were found to have higher TSH levels compared to age-matched controls without familial longevity, thus indicating that a high-TSH phenotype characterizes familial longevity[12,77]. Such interpretation is also supported by the evidence that genetic factors strongly influence thyroid function[78], and the variability of two single nucleotide polymorphisms (SNPs) in the TSH receptor (TSHR) gene, namely rs10149689 and rs12050077, was significantly associated with increased TSH levels in Ashkenazi Jewish centenarians and their offspring[77].

The above findings suggest a potentially relevant role of decreased thyroid function in promoting lifespan, likely explained by a pleiotropic effect of the HPT axis in long-lived families due to a higher TSH secretion without significant changes in circulating THs levels and whole body energy metabolism[79]. Finally, this notion does not apply exclusively to Caucasian populations, but is also found among Chinese centenarians[80].

On the contrary, studies about the relationship between THs levels and longevity provided conflicting results. A significant association between low FT4 levels and longevity has been observed in Caucasian populations[81], where relatives of centenarians also exhibit lower FT4 compared to the age matched subjects[82].

More recently, lower circulating levels of FT4 have been observed in centenarians' offsprings compared to age-matched offspring of non-long-lived parents, suggesting that subtle thyroid hypofunction may onset later during life in centenarians' offsprings as an adaptive mechanism aimed at favouring longevity[83].

The association between low FT4 and longevity was weaker in Chinese populations, and limited to the offspring generation[80]. In addition, it has been observed that centenarians exhibit slightly higher rT3 levels than control subjects[84]. Finally, an age dependent decline in circulating FT3 has been also reported[56,81].

In conclusion, an age-related subtle thyroid hypofunction either due to a familial component or due to a reset of the thyroid appears to be related to human longevity. Despite extensive research, the clinical implications of higher serum TSH observed ad advanced ages remain unclear, and it remains uncertain whether the raised serum TSH adversely affects health, has no clinical importance, or is a factor that simply contributes to healthy aging[85,86]. A slight lower thyroid function, and thus a lower basal metabolic rate, could possibly serve as an adaptive mechanism to prevent excessive catabolism in the elderly. Furthermore, lowering oxidative metabolism reduces DNA damage by ROS. The increase in TSH serum levels observed in centenarians is supposed to play a favourable role in their healthy status, regardless of the underlying mechanism.

4 Thyroid hormones and age-related chronic diseases

Chronic diseases may affect several different neuroendocrine systems, including HPT axis. Additionally, peripheral tissue metabolism of THs may be also affected by age-related chronic diseases. Indeed, the expression and activity of deiodinases are affected during illness[87], resulting in THs abnormalities known as non-thyroidal illness syndrome (NTIS). Decreased FT3 serum concentration, increased rT3 and unchanged or inappropriately low TSH usually represent the hallmarks of NTIS. In prolonged and severe NTIS low serum T4 levels may also be observed.

The aetiology of NTIS is multifactorial, involving changes in both HPT axis functionality and THs metabolism. Central hypothyroidism, with low hypotalamic TRH, was commonly observed in many models of chronic illness. Reduced TRH gene expression was found in neurons from hypothalamic paraventricular nucleus (PVN) of patients with prolonged illness and NTIS[88]. The TRH gene expression in the cells of the PVN is stimulated by melanocyte stimulating hormone (MSH), and this effect is enhanced by leptin, an adipokine involved in the regulation of food intake and energy storage[89]. Serum leptin decreases dramatically during fasting and malnutrition[90], thus leading to reduced TRH expression[91]. Malnutrition and fasting can also affect peripheral metabolism of THs. Caloric restriction is known to inhibit type 1 deiodinase[92]. Fasting causes deep changes in hepatic THs metabolism, characterized by decreased THR-β1 and type 1 deiodinase mRNA expression and increased type 3 deiodinase mRNA expression. The increase in type 3 deiodinase expression might be mediated by a decrease in leptin, independent of circulating TH levels[93]. Finally, fasting for 36 hours, or 50% reduction in food intake for three weeks, results in increased type 3 deiodinase activity in the liver[94]. It is worth noting that serum leptin levels were found significantly decreased

in chronically ill older patients affected by NTIS compared to matched patients without thyroid abnormalities, thus suggesting that a specific neuroendocrine status aimed at reducing catabolic processes may characterize select patients with chronic diseases[95].

Inflammatory cytokines also play a relevant role in the pathophysiology of NTIS. Interleukin-6 (IL-6) is known to down-regulate type 1 deiodinase. Indeed, type 1 deiodinase activity is dependent on cofactors, such as glutathione. During inflammation, IL-6 promotes the release of ROS via nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase, which results in glutathione depletion and reduced enzyme activity[96]. Interleukin-1-beta (IL-1β) induces the production of activating protein 1 (AP-1) and nuclear factor kappa B (NFkB), which "steal" the substrates for the correct transcription of the gene coding for type 1 deiodinase[87]. IL-1 β, tumor necrosis factor alpha (TNFα) and interferon-gamma (INFγ) can reduce the uptake of iodine in thyrocytes by acting on natrium/iodide symporter[97]. Inflammatory cytokines also induce the translocation of NFkB to the nucleus, where the transcription of the gene encoding type 2 deiodinase is activated. Thus, inflammation-induced up-regulation of type 2 deiodinase in the hypothalamus is likely involved in the unresponsiveness of HPT axis to low serum T3 in NTIS[98]. Finally, type 3 deiodinase expression is regulated by hypoxia-inducible factor 1α (HIF1α). During illness, decreased tissue perfusion and chronic inflammation might cause an increase of HIF1α, that activates type 3 deiodinase gene transcription in the nucleus[99].

Clinical evidence indicates that NTIS prevalence increases with age, is associated with several age-related chronic diseases, and affects survival. The following sections will describe THs abnormalities observed in the most common chronic diseases and their clinical relevance.

4.1 *Thyroid function and Chronic Kidney Disease (CKD)*

CKD may affect both HPT axis and thyroid gland functionality. CKD was formerly found associated with a higher prevalence of primary hypothyroidism, but not with hyperthyroidism[100].

More recently, hypothyroidism was observed in about one quarter of veterans with CKD, together with a significant association between estimated glomerular filtration rate (eGFR) and hypothyroidism[101]. Even the prevalence of NTIS was found to increase as renal function declines, and recent studies have reported that clinically low serum T3 can be observed in more than 75% of individuals with end-stage renal disease (ESRD)[102-104]. At variance from typical NTIS, where rT3 levels increase, patients with CKD often exhibit normal total serum rT3, likely due to an increased rT3 fractional transfer rates from serum to tissue sites, and enhanced tissue rT3 binding[104]. The specific mechanisms underlying NTIS in patients with CKD include metabolic acidosis, protein wasting and malnutrition, inflammation, and iodine toxicity. CKD-related chronic metabolic acidosis is known to be associated with reduced circulating FT3 and FT4, and treating metabolic acidosis can fully correct TH abnormalities[105]. CKD is also characterized by hypoalbuminaemia as a result of acidosis-induced protein loss and malnutrition. Additionally, inflammatory cytokines able to affect thyroid function and deiodinases, such as IL-1, IL-6, and TNF-α, were found to increase in CKD patients. Finally, increased serum iodine levels due to impaired kidney function is frequently observed in CKD patients, and accumulating iodine inhibit TPO enzyme and NAPDH-oxydase transcription, resulting in reduced production of THs[106].

4.2 *Thyroid function and Heart Failure (HF)*

The cardiovascular system is one of the most important target of THs, where they regulate cardiac contractility and heart rate, diastolic function and systemic vascular resistance. Both hyper- and hypothyroidism have a negative impact on patients with HF. In a study based on a sample of 1149 elderly women, subclinical hypothyroidism was associated with a greater risk of atherosclerosis and myocardial infarction, while subclinical hyperthyroidism was associated with increased risk of cardiac mortality and atrial fibrillation[107]. TH abnormalities were frequently found in HF patients[108], with low T3 levels observed in about 30% of patients with advanced HF[109]. Compared with other chronic diseases in which low T3 syndrome is a positive adaptation to chronic illness aimed at

reducing catabolism, in chronic HF low T3 levels exert a negative impact on the outcomes. Indeed, T3 has important cardio-protective properties[110], including reduction of myocyte apoptosis and cardiac fibrosis, induction of angiogenesis and arteriolar dilation, and prevention of hypertrophy[111]. These effects are likely due to T3-mediated regulation of miRNA expression[112]. Cardio-protective properties of T3 likely contribute to explain why low T3 levels are independent predictors of mortality in patients with chronic HF[113].

4.3 *Thyroid function and Chronic Obstructive Pulmonary Disease (COPD)*

The mechanisms by which COPD affects thyroid function is not fully understood, and likely involve hypoxemia, hypercapnia and systemic inflammation. Even in this case, both HPT axis and peripheral THs are affected. In patients with severe COPD a strong association between low T3 and hypoxemia was observed[114,115]. TSH, T3, and FT3 levels were lower in patients with severe hypoxemia when compared to patients with mild hypoxemia[116]. Increased respiratory workload was also reported as an important factor able to alter circulating THs in COPD patients[117]. Finally, increased IL-6 and TNF-α concentrations were frequently observed in COPD patients, either in stable or exacerbation phase[116]. COPD-related THs abnormalities are especially evident during exacerbation and partially regress after stabilization[116]. Furthermore, pulmonary infections were found to be more frequent among COPD patients with NTIS[118].

4.4 *Thyroid function and type 2 diabetes mellitus*

NTIS has been also observed among patients with diabetes mellitus. A significant association between rT3 and serum amyloid A, a pro-inflammatory marker synthesized in the liver in response to IL-6 and TNF-α, has been observed in diabetic patients[119]. Fontes et al recently demonstrated that hypothyroidism was more prevalent among older diabetic patients compared to age-matched non-diabetic controls, and patients taking metformin as single antidiabetic drug had lower serum TSH than those using other medications[120].

4.5 *Thyroid function and anemia*

The relationship between thyroid function and anemia has been recently reviewed[121]. Thyrotropin receptor have been found on both erythrocytes and extrathyroidal tissues, where binding of TSH could affect hematopoiesis[122]. The release of growth factors from leukocytes, as well as the proliferation of erythroid burst-forming unit (BFU-E) and erythroid cells were found to be enhanced by T3[123-125]. Finally, T4 is also able to modulate erythropoiesis by a direct β2-adrenergic receptor-mediated stimulation of red cell precursors[126].

Overt thyroid diseases have been found associated with erythrocyte abnormalities. Pernicious anemia is observed in about 20-60% of patients with hyperthyroidism and thyroiditis[127]. Hypothyroidism is more frequently associated with normochromic normocytic, hypochromic microcytic, and macrocytic anemia[127], while increased red cell plasma volume and erythrocytosis characterizes anemia of hyperthyroid patients[128,129]. Instead, there is a distinct paucity of studies about subclinical thyroid dysfunctions and anemia. Untreated subclinical hypothyroidism and primary hypothyroidism were found associated with anemia in a retrospective cross-sectional analysis of patients aged 25–60 years[130]. Additionally, lower serum iron concentrations and transferrin saturation were observed in subclinical hypothyroid patients compared to the euthyroid ones[131], thus suggesting that iron utilization and/or transport might be impaired in subclinical hypothyroid conditions.

4.6 *Thyroid function and dementia*

Several studies investigated the relationship between THs/TSH and cognitive function. Cross-sectional studies reported conflicting results about relationship between subclinical or overt thyroid dysfunction and cognitive impairment. Hogervorst et al. suggested that, even in relatively healthy elderly patients, subclinical or overt hypothyroidism are associated with lower Mini Mental State Examination (MMSE) score at baseline[132]. Similarly, subclinical hyperthyroidism was found

associated with impaired cognition[57]. Conversely, Parsaik et al. did not find any significant association between clinical or subclinical hypothyroidism and cognitive impairment[133].

In longitudinal studies, high FT4 levels have been reported to increase the risk of incident dementia[134,135], and high TSH values were found associated with increased risk of developing vascular dementia[135]. On the contrary, subclinical hyper- or hypothyroidism were not associated with cognitive decline in a large prospective longitudinal study of older subjects aged 70–82 years[136]. Finally, meta-analysis studies showed that high FT4 and low TSH levels are associated with increased risk of dementia[137,138], while a relationship between subclinical hypothyroidism and cognitive function was only documented in individuals younger than 75 years[139].

4.7 *Thyroid function and frailty*

Since thyroid plays a fundamental role in regulating homeostasis[140], it's presumable that thyroid dysfunction can contribute to pathophysiology of frailty. Nevertheless, only few studies investigated this issue until now (Table 1)[141-144].

Cross sectional studies showed that high-normal FT4 may be associated with frailty phenotype in older men[142], while women with positive TgAbs and TPOAbs antibodies were less likely to be frail[141]. Additionally, it is worth mentioning that resting metabolic rate, but not THs was recently found cross-sectionally associated with frailty among nonagenarians[145]. Finally, lower physical performance was observed among older subjects with high FT4 and rT3 concentrations[146].

Subclinical hyperthyroidism was found to be associated with prevalent but not incident frailty among 1455 men enrolled in the Osteoporotic Fractures in Men prospective cohort study[143]. Instead, the recent report from the Progetto Veneto Anziani study clearly showed that men with higher and women with lower serum TSH levels are at increased risk of frailty, either in cross-sectional or longitudinal analysis. These findings suggest important gender differences in the

association between thyroid function and frailty[144]. However, whether TSH can be considered a reliable marker of frailty deserves further investigations.

Table 1. Summary of studies on thyroid abnormalities and frailty.

Study	Design	N Age	Frailty index	Main findings
Wang et al, 2010[141]	Cross-sectional	641 women	Cardiovascular Health Study index	Community-dwelling older women with positive TgAbs and TPOAbs were found less likely to be frail than seronegative women
Yeap et al, 2012[142]	Cross-sectional	3943 men 70-89 years	FRAIL scale	High-normal FT4 level was independently associated with frailty among ageing men
Virgini et al, 2015[143]	Prospective cohort	1455 men >65 years	Cardiovascular Health Study Index	Subclinical hyperthyroidism, but not subclinical hypothyroidism, was found associated with increased odds of prevalent but not incident frailty
Veronese et al, 2016[144]	Prospective cohort	2571 (cross-sectional) 1732 (longitudinal) >65 years	Fried's index	Highest TSH quintile in men and lowest TSH quintile in women were associated with frailty in both cross-sectional and longitudinal analysis

In summary, several chronic diseases are associated with changes in thyroid function which likely represent an adaptative protective mechanism aimed at slowing metabolism and reducing oxygen consumption. However, changes in THs in patients with HF seem to represent an exception to this general rule. Indeed, T3 has important cardioprotective properties and low T3 levels may contribute to increase the risk of negative outcomes. Finally, selected thyroid abnormalities may contribute to the development of anemia and dementia (Figure 2).

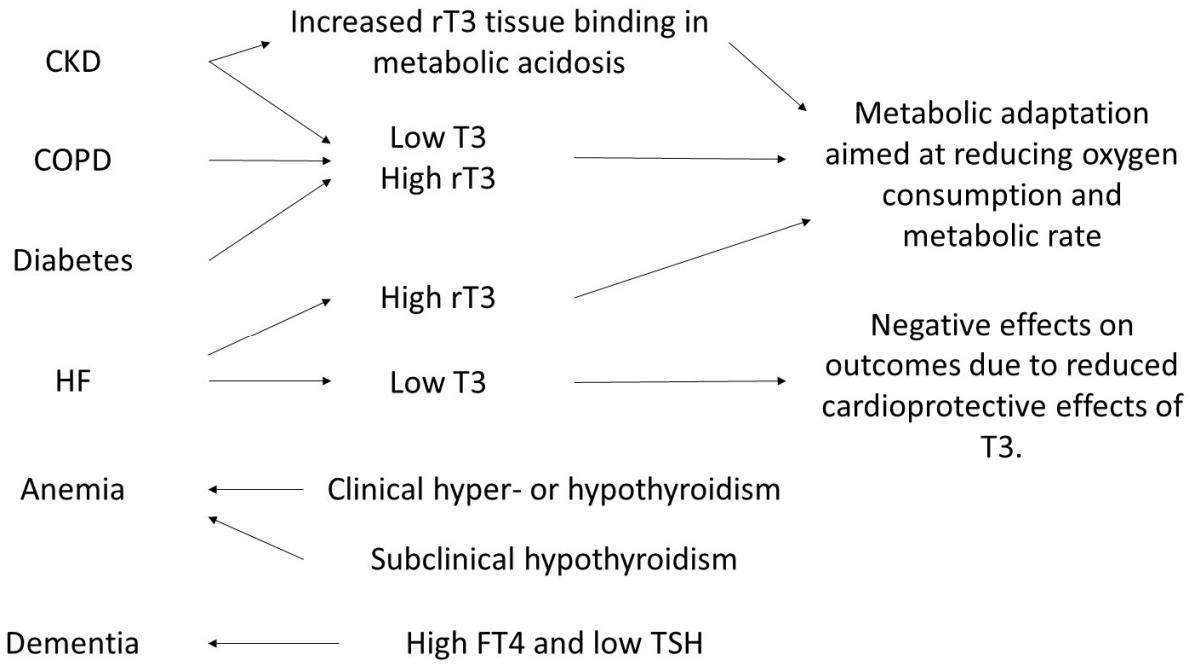

Figure 2. Summary of the relationship between selected chronic conditions and THs/TSH patterns.

5 Conclusions

In conclusion, evidence from experimental studies clearly suggests that reduced THs levels may prolong lifespan. Data from human studies involving healthy subjects and centenarians seem to confirm this view, but THs changes observed in older patients affected by chronic diseases cannot be always interpreted as a protective adaptive mechanism aimed at reducing catabolism and

prolonging survival. This is especially true for patients with heart failure where low T3 have detrimental effects on survival.

Several knowledge gaps still need to be addressed. Medications commonly prescribed to older patients (e.g. amiodarone, heparin, glucocorticoids) can interfere with thyroid function. Additionally, while evidence support the notion that selected chronic diseases may affect THs through several different mechanisms, the impact of multimorbidity on HPT axis function and peripheral THs metabolism is still to be investigated. While several factors are known to interplay to determine THs/TSH status in older and oldest old individuals (Figure 3), further studies accounting for the potential confounding by medications and multi-morbidity would be very informative. Finally, despite thyroid dysfunction can be an important determinant of frailty, only few studies investigated the relationship between THs and frailty, which is worth of future investigations.

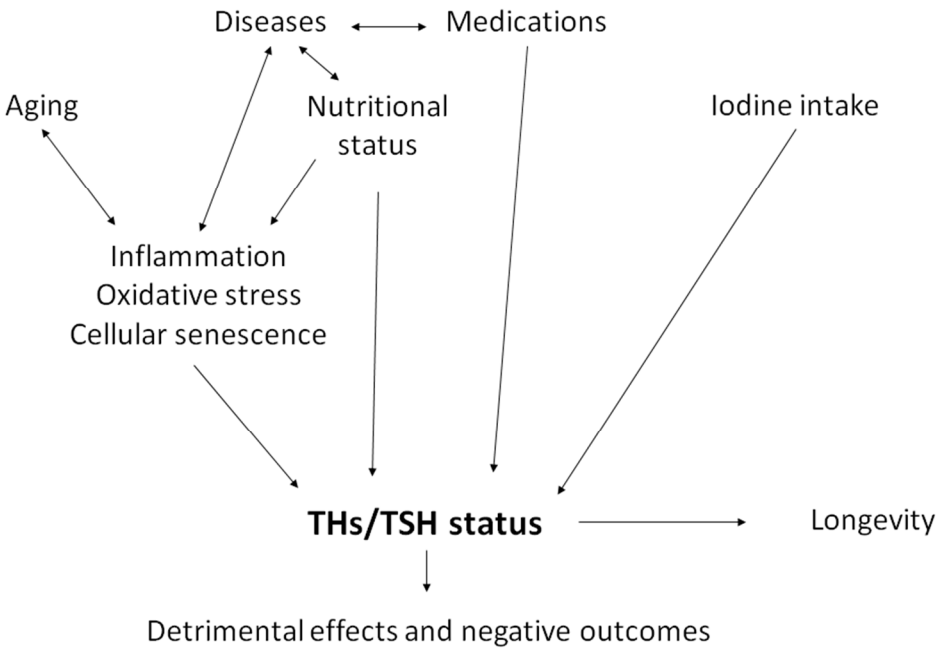

Figure 3. The complex interplay of factors conditioning THs/TSH pattern in the very old and its impact on outcomes.

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