DOI：10.6314/JIMT.202206_33(3).04 內科學誌 2022：33：203-217

Subclinical Hypothyroidism in Non-pregnant Adults Population – A Mini Literature Review

Shyh-Ching Chiou[1], Yi-Yin Huang[1], and Yuh-Min Song[1,2]

[1]Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan

Abstract

With the wide application of thyroid function tests performed in current clinical medicine, including field of preventive medicine, subclinical hypothyroidism has become an increasingly recognized clinical entity in daily practices encountered by physicians in general practice and subspecialties, including endocrinologists and geriatricians. The diagnosis may not be difficult since measured levels of thyroid-stimulating hormone (TSH), by definition higher than the upper normal limit of the laboratory references, and free thyroxine (fT4) within the normal reference range can provide enough biochemical evidence for a tentative diagnosis, although repeated tests are often required for confirmative purpose due to the largely unpredictable natural course of this endocrine disease. The presence of autoimmune antibodies (especially thyroid-peroxidase antibodies) significantly increases the risk of future development into overt hypothyroidism. Beyond that, challenges in clinical scenario, especially in the elderly population, may lie in the decision of providing optimal management by administration or not of levothyroxine supplement therapy, even when a diagnosis has been given. Indications for treating subclinical hypothyroidism include a desired improvement in symptoms, prevention of adverse events associated (especially the cardiovascular disorders), as well as prevention of overt hypothyroidism. Current guidelines from academic societies recommend that, in those with TSH levels ≥ 10 uIU/mL, small doses (eg, 25-75 μg per day) of levothyroxine usually suffice to restore normal serum thyrotropin levels in the majority of non-pregnant patients. The targets of TSH levels are recommended to set by age groups: for younger patient (< 60 years): 1-2.5 uIU/mL, whereas enlarged to 3-4 uIU/mL in patients between 60-70 years and 4-6 uIU/mL when older than 70 years. However, these potential benefits of levothyroxine supplementation should be weighed against the risks of reducing thyrotropin values below the reference range and potentially causing iatrogenic subclinical or overt hyperthyroidism. (J Intern Med Taiwan 2022; 33: 203-217)

Key Words: Anti-thyroid peroxidase antibody, Non-pregnant adults, Subclinical hypothyroidism, Thyroid-stimulating hormone

Introduction

By definition, overt hypothyroidism is diagnosed by an elevated thyroid-stimulating hormone (TSH), usually above 10 uIU/mL (unless in central hypothyroidism, in which case the TSH levels may be within or lower than the normal reference ranges), in combination with reduced circulating free thyroxine (fT4) levels. Next in the spectrum of hypo-function of thyroid gland may see subclinical hypothyroid-

Reprint requests and correspondence：Dr. Yuh-Min Song
Address：Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No.88, Sec. 1, Fengxing Rd., Tanzi Dist., Taichung City 427, Taiwan

ism which is defined biochemically as a serum TSH level above the upper reference limit but a fT4 level within normal, provided that there is no existing acute or chronic or ongoing severe illnesses, and the thyroid function has been stable for weeks before the testing, which indicates an intact hypothalamic-pituitary-thyroid axis[1]. Although higher baseline TSH levels, along with presence of autoimmune antibodies against thyroid-derived antigens (especially anti-thyroid peroxidase, TPO-Ab), age, and ultrasonography (US) findings of the thyroid gland have all been suggested as predictors of future development to overt hypothyroidism, the largely unpredictable natural course of thyroid function changes over time still gives clinical indications for repeated measurement of serum TSH for several years in follow-up in order to discern among variable thyroid function statuses and the decision-making of treatment strategy[2]. There has been clear association between overt hypothyroidism and the negative impact on health, especially those associated with cardiovascular (CV) system that warrants the treatment of this disorder with levothyroxine[3-7]. For subclinical hypothyroidism, whether to treat or not with levothyroxine is similarly based on the multiple physiological regulations exerted by thyroid hormones which, when in deficiency may cause hyperlipidemia[8,9], hypertension[10-12], various pro-atherogenic anthropometric parameters and biochemical markers[11], metabolic syndrome (MetS)[13-15], hypercoagulability[16], and impaired endothelial function[17] , risk factors that may all lead to a pro-atherogenic status. Respective discussion on the association between these factors and subclinical hypothyroidism will be given in the following text, preceded by an understanding of the natural history of this entity.

Prevalence and natural history of subclinical hypothyroidism

With the advent of TSH radioimmunoassay in the 1970s, the entity of mildly elevated TSH and normal serum thyroid hormones levels has been increasingly recognized. The prevalence of subclinical hypothyroidism is about 4 to 8.5 percent, and may be as high as 20 percent in women older than 60 years. This wide range is a result of differences in age, sex, body-mass index (BMI), race, dietary iodine intake, and the cutoff values of serum TSH that are used to define the function status[2]. After the initial assessment, there is good evidence that subclinical hypothyroidism can be associated with progression to overt disease, especially when it is associated with positive TPO-Ab[18-23].

In a community-based British cohort of over 2,000 subjects, the spectrum of thyroid disorders was analyzed first at recruitment, which was then followed for a term as long as 20 years. Minor degrees of hypothyroidism were defined on the basis of elevated serum TSH levels in the absence of obvious clinical features of hypothyroidism. Elevated TSH levels (> 6 uIU/mL) were recorded in 7.5% of females and 2.8% of males of all ages and were noted to reflect a significant lowering of circulating thyroxine levels and also a strong association with thyroid antibodies in both sexes, independent of age. While not observed in male subjects, TSH levels increased markedly in females after the age of 45 years, but this rise was abolished when subjects with thyroid antibodies were excluded from the analysis[18]. The ongoing follow-up of this cohort for the next 20 years has been conducted with one of the aims to determine the development and risk factors of overt hypothyroidism. The results showed that the mean incidence (with 95% confidence intervals, CI) of spontaneous hypothyroidism in women was 3.5/1,000 survivors/year (2.8-4.5), whereas in men was 0.6/1,000 survivors/year (0.3-1.2). Further examination of risk factors of developing hypothyroidism has identified that the odds ratios (with 95% CI) increased with (a) raised serum TSH alone: 8 (3-20) for women and 44 (19-104) for men; (b) positive anti-thyroid antibodies alone: 8 (5-15) for women

and 25 (10-63) for men; (c) both raised serum TSH and positive anti-thyroid antibodies: 38 (22-65) for women and 173 (81-370) for men. An initial serum TSH level above 2 uIU/mL increased the probability of developing hypothyroidism, which was further increased in the presence of anti-thyroid antibodies[19]. In this longitudinal follow-up study up to 20 years, rising TSH and presence of anti-thyroid antibodies together pose risk to developing overt hypothyroidism in both sexes having subclinical hypothyroidism at baseline.

The trajectory of changes in thyroid function status has been evaluated in a 13-year-long follow-up study in a cohort of health surveys program among 1,184 subjects conducted in Australia. Risk factors for hypothyroidism [TSH, fT4, TPO-Ab, and thyroglobulin antibody (Tg-Ab)] were evaluated, and the results revealed that optimal cutoffs for predicting hypothyroidism were baseline TSH above 2.5 uIU/mL, TPO-Ab above 29 kIU/L, and Tg-Ab above 22 kIU/L, when the respective reference ranges with upper limits of 4.0 uIU/mL, 35 kIU/L, and 55 kIU/L, were used. In women with positive TPO-Ab or Tg-Ab, the prevalence of hypothyroidism at follow-up (with 95% CI) was 12.0% (3.0-21.0%) when baseline TSH was ≤ 2.5 uIU/mL, 55.2% (37.1-73.3%) for TSH 2.5-4.0 uIU/mL, and 85.7% (74.1-97.3%) for TSH > 4.0 uIU/mL. The authors concluded that the use of TSH cutoffs of 2.5 and 4.0 uIU/mL in combination with presence of thyroid antibodies provides a clinically useful estimate of the long-term risk of hypothyroidism[20]. Since methods of assay on TSH or autoimmune antibodies applied in different laboratories may vary, the cutoff values used for purpose of prediction or diagnosis may only be acquired from individual dataset obtained from the study cohort.

Aging itself has been considered as a prominent factor leading to overt hypothyroidism in subjects having been diagnosed with subclinical hypothyroidism. In a Japanese study which had followed up the thyroid function in 71 individuals (mean age 70-year-old) who were atomic-bomb survivors and diagnosed with spontaneous subclinical hypothyroidism (defined as TSH > 4.5 uIU/mL and normal fT4 levels, without a history of thyroid treatment), the TSH and fT4 levels were repeatedly tested in a follow-up for an average of 4.2 years (range, 1.9-6.9). The progression of thyroid function was compared to that derived from 562 euthyroid control subjects. Analysis at study-end found that the risk for progression to overt hypothyroidism was significantly increased in subclinical hypothyroid patients (7.0%) compared with the controls (1.6%) after adjusting for age and sex (odds ratio, 4.56; p = 0.009). Higher baseline TSH levels were associated with progression from subclinical to overt hypothyroidism (p = 0.02) in the multivariate analysis, including age, sex, TPO-Ab, and thyroiditis in US findings. A TSH level > 8 uIU/mL was a predictive value for development of overt hypothyroidism (p = 0.005). During the follow-up period, serum TSH levels spontaneously normalized in 38 (53.5%) of the patients with subclinical hypothyroidism. In the multivariate analysis, normalization of TSH levels was associated with lower baseline TSH levels (p = 0.004) and normal and homogenous thyroid US findings (p = 0.04). Interestingly, this study did not find association between atomic-bomb radiation dose and occurrence of subclinical hypothyroidism or its course. The authors concluded that subclinical hypothyroidism was four times more likely to be associated with development of overt hypothyroidism than euthyroid controls in this sample population of elderly Japanese. Baseline TSH level and thyroid US findings are potential predictors of future thyroid function in subclinical hypothyroidism[21].

In another longitudinal study conducted in aged people (≥ 65-year-old), 459 individuals who were found to have subclinical hypothyroidism at baseline evaluation out of a cohort of 3,996 elderly subjects who were initially enrolled in the Cardio-

vascular Health Study were included in a 4-year follow-up study in the US. The laboratory tests on thyroid function were repeated at 2- and 4-year, and the results were stratified by baseline TSH, status of TPO-Ab, age, and sex. The results showed that persistence of subclinical hypothyroidism was 56% at 2- and 4-year. At 2-year, resolution was more common with a TSH of 4.5-6.9 uIU/mL, as compared to higher baseline TSH levels [46 vs. 10% (TSH 7-9.9 uIU/mL) and 7% (TSH ≥ 10 uIU/mL); $p < 0.001$] and with TPO-Ab negativity (48 vs. 15% for positive; $p < 0.001$). Higher TSH levels and TPO-Ab positivity were independently associated with lower likelihood of reversion to euthyroidism ($p < 0.05$). Furthermore, TSH ≥ 10 uIU/mL was independently associated with progression to overt hypothyroidism ($p < 0.05$). It was concluded that transitions between subclinical hypothyroidism and euthyroidism were common between 2- and 4-year since the initial diagnosis. Subclinical hypothyroidism may persist for 4 years in over half of the elderly individuals, but higher rate of reversion to euthyroidism was observed in subjects with lower TSH levels and TPO-Ab negativity[22].

Geographic conditions pertaining to amount of iodine consumption of the general population may also have impact on the development of subclinical hypothyroidism into an overt one. A 5-year follow-up study in China has investigated the risk factors associated with thyroid dysfunction (either hyper- or hypo-function) in three different regions where the iodine contained in the diets differ (mildly deficient, more than adequate, and excessive iodine intake, respectively.). After 5 years, an association between a higher iodine intake and higher incidence of supra-normal TSH (TSH > 4.8 uIU/mL) was found in initially euthyroid subjects who were tested positive for TPO-Ab and/or Tg-Ab at baseline ($p < 0.010$ among the three regions compared). In those initially euthyroid subjects who were positive for either TPO-Ab or Tg-Ab at study entry, those who developed to overt hypothyroidism had higher baseline TSH levels than those remaining euthyroid (median: 3.14 vs. 1.74 uIU/mL, $p < 0.0001$). Further analysis showed that subjects who were antibody positive with TSH ≥ 2 uIU/mL at baseline were more likely to develop supra-normal TSH levels than those who were antibody positive but with TSH < 2 uIU/mL (16.28 vs. 2.04%, $p < 0.001$)[23]. A higher baseline TSH level than auto-antibodies positivity seems to play a more critical role in predicting the development into overt hypothyroidism in this study.

Diagnosis of subclinical hypothyroidism

Due to the existence of wide variation in normal references of TSH levels among different ethnics, countries, and also ages, the interpretation of abnormal TSH for giving a diagnosis should be in a cautious way since it is unlikely to define a single and universal discernable cutoff point. However, other than TSH, markers such as thyroid antibodies and findings from US that are identified in population-based prospective cohort studies could help the clinician in decision-making[24].

The findings of slightly elevated TSH and normal thyroid hormone levels do not necessarily imply the presence of subclinical hypothyroidism. Other considerations before a definite diagnosis can be given may include rarely the presence of Addison's disease which may elevate serum TSH levels when supplemental steroid therapy is yet provided[25]. In addition, transient elevation of TSH within the first several hours of diverse non-thyroidal illnesses (sick euthyroid syndrome) is a common observation in patients suffering from acute illnesses[26]. Furthermore, elevation of TSH levels after an episode of subacute thyroiditis is also a common observation and the changing pattern is used to predict recovery or not of thyroid function within the first one to two years after the inflammation episode[27].

There are medications known to cause an elevation in TSH (and sometimes overt hypothyroid-

ism when the suppressive effect on thyroid function is severe enough), such as lithium, amiodarone, iodine, and interferone-α[28].

Since the elderly populations are more prone to development of thyroid hypofunction compared to the younger ones, the physiological changes with age must also be concerned. Factors could include different genetic set point, aging of pituitary gland which may affect the TSH response to normal physiological homeostasis as in negative feedback, and adaptive response to energy demands that is lower in the elderly[29]. As people age, changes occurring in the endocrine system include the amount of hormones secreted, peripheral metabolism of the hormones, or the sensitivity of target organs. There has been long-standing controversy about the thyroid function test results in the elderly. Serum TSH, fT4, and free triiodothyronine (fT3) concentrations change with aging and observational studies have suggested that serum TSH levels increase in older people. Thus, it has been suggested that a higher TSH threshold applied for decision of treating subclinical hypothyroidism in the elderly deserves concern[30,31]. In an analysis derived from the NHANES-III data of the US, Surks and Hollowell[32] had found a progressive increase in mean, median, and 97.5 centile for TSH concentration with age. Data showing that the 97.5 centile at about 3.6 uIU/mL in people aged 20- to 39-year-old, and 5.9 and 7.5 uIU/mL in those aged 70-79 and 80-year-old and older, respectively, suggested that TSH levels are age-dependent. The authors also demonstrated that about 70% of older patients who would be classified as subclinical hypothyroidism with TSH greater than 4.5 uIU/mL were within their age-specific reference range. Consequently, the authors suggested that age-based reference ranges for TSH should be of concern when giving a clinical diagnosis of hypo-function of the thyroid.

Initial diagnosis of subclinical hypothyroidism should be confirmed by reassessment of TSH, fT4 and TPO-Ab after 8-12 weeks[33]. No further evaluation is needed if the above tests were normal. Whereas in those with persistent uncertainty for a diagnosis, tests on thyroid function should be repeated every 6 months in the first 2 years, then annually[34]. The follow-up tests can be discontinued from the third year on if patients are asymptomatic of hypothyroidism, with negative results of TPO-Ab, and goiter, unless becoming pregnant or developed hypothyroid symptoms[33]. In a longitudinal follow-up study carried out in subjects aged 55 and older who had been diagnosed as subclinical hypothyroidism, a prominent decrease in thyroid function suggesting development into overt hypothyroidism was noted when TSH rises more than 40%, or when fT4 decreases by more than 15% between two consecutive tests, with TSH concentration being the most powerful predictor in this age group[34,35].

When diagnosed, subclinical hypothyroidism turns to a long-debated clinical issue of treatment or not with levothyroxine, concerning yet unanimous conclusions drawn regarding clinical benefits derived from multiple observational or clinical studies which had apply such treatment in the trials[36,37].

Association between subclinical hypothyroidism and cardiovascular outcomes

Observational studies have found association between subclinical hypothyroidism and CV outcomes, including coronary heart disease (CHD) and associated mortality. In a cross-sectional study carried out in 1,149 women (mean age ± SD, 69.0 ± 7.5 years) participating in the Rotterdam Study, data on thyroid status, aortic atherosclerosis (AS), and history of myocardial infarction (MI) were obtained. Among the 10.8% of the cohort who had subclinical hypothyroidism, there was greater age-adjusted prevalence of AS (odds ratio (OR): 1.7; [95% CI, 1.1-2.6]) and MI (OR: 2.3; [CI, 1.3-4.0]).

Associations with the CV outcomes were slightly stronger in women who also had positive TPO-Ab (OR for AS: 1.9; [CI, 1.1-3.6]; OR for MI: 3.1; [CI, 1.5-6.3]). It was concluded that subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and MI in this cohort of elderly Dutch women[38].

By using individual data from 55,287 participants with 542,494 person-years of follow-up between 1972 and 2007 that were derived from 11 prospective study cohorts, the association between baseline thyroid function and subsequent CHD events, CHD mortality, and total mortality were examined. Subclinical hypothyroidism was defined as a TSH level of 4.5 to 19.9 uIU/mL with normal thyroxine concentrations and the prevalence was found to be 6.2% of the cohort in total. The risk of CHD events and CHD mortality increased with higher TSH concentrations. In age- and sex-adjusted analyses, when compared to participants with euthyroidism, the hazard ratio (HR) for CHD events paralleled those of TSH levels as: 1.00 (95% CI, 0.86-1.18) for a TSH level of 4.5-6.9 uIU/mL, 1.17 (95% CI, 0.96-1.43) for 7.0-9.9 uIU/mL, and 1.89 (95% CI, 1.28-2.80) for 10-19.9 uIU/mL ($p < 0.001$ for trend). The corresponding HRs for CHD mortality were 1.09 (95% CI, 0.91-1.30), 1.42 (95% CI, 1.03-1.95), and 1.58 (95% CI, 1.10-2.27, $p = 0.005$ for trend), respectively; while total mortality was not increased. It was concluded that subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly when $\geq$ 10 uIU/mL[39].

Association between subclinical hypothyroidism and cardiovascular risk factors

Lipid disorder

Either overt or subclinical hypothyroidism negatively affects lipid metabolism, leading to hypercholesterolemia which progressively increases the risk for CV disease over time and, potentially, mortality. A major pathophysiology underlying hypercholesterolemia in hypothyroidism is a reduction in low-density lipoprotein (LDL) receptor activity, accompanied by concomitant diminished control by T3 of sterol regulatory element-binding protein 2, which modulates cholesterol biosynthesis by regulating rate-limit degrading enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity[7].

A meta-analysis using results obtained from 16 observational studies on the association between lipid profile and subclinical hypothyroidism has found that serum total cholesterol (T-C), LDL-cholesterol (LDL-C), and triglyceride (TG) levels were significantly increased in patients with subclinical hypothyroidism compared with euthyroidism individuals, and the calculated overall weighted mean difference (WMD) were 12.17 mg/dL, 7.01 mg/dL, and 13.19 mg/dL, respectively ($p < 0.001$ for all), while no significant difference was observed for serum high-density lipoprotein-cholesterol (HDL-C) levels. The heterogeneity in results from different studies could be caused by heterogeneous match strategies applied[40].

In view of the increased CV risk associated with subclinical hypothyroidism and the critical role of lipid disorder as major risk factor for CV events, it is prudent for physicians to evaluate lipid profile in subjects with subclinical hypothyroidism for a decision-making of relevant management.

Hypertension

Hypothyroidism has been considered a secondary cause of hypertension, mechanisms implicated include changes in circulating catecholamines, their receptors and the renin-angiotensin aldosterone system[41]. In a cohort including 66,140 adults from the Nord-Trøndelag Health Study (HUNT) conducted in Norway, a cross-sectional, population-based study investigating into the relationship between hypertension and categories of TSH levels had found that, within the reference range of TSH,

there existed a positive association between TSH levels and both systolic and diastolic blood pressure (BP)[42]. However, controversy exists whether mild thyroid dysfunction, such as subclinical hypothyroidism affects BP. The association between BP levels and subclinical hypothyroidism has been examined in a meta-analysis from results derived from 7 cross-sectional studies. The analysis found that, as compared to euthyroid controls, in subjects with subclinical hypothyroidism there existed a significant difference in both systolic BP (WMD with 95% CI; 1.89 mmHg (0.98-2.80), $p < 0.05$) and diastolic BP (WMD with 95% CI; 0.75 mmHg (0.24-1.27), $p < 0.05$)[43].

An increased incidence of target organ damage and a worse outcome in terms of CVD have been reported in the 'non-dippers' who lack the anticipated nocturnal decrease in BP[44]. In a study including 109 normotensive patients diagnosed with overt and subclinical hypothyroidism, the number of non-dippers according to systolic, diastolic and mean BPs was significantly higher in the patients with overt or subclinical hypothyroidism, as compared to 75 age- and gender-matched euthyroid control group. In linear regression analysis, TSH levels had a negative effect on the night/day ratio of the systolic, diastolic and mean BPs[45].

To investigate daily BP changes and the frequency of non-dipping patterns (defined as BP fall of < 10%) in patients with subclinical hypothyroidism, a group of 49 patients with subclinical hypothyroidism but without hypertension were compared with 50 healthy sex- and age-matched euthyroid controls using ambulatory BP monitoring. The results showed that levels of mean diastolic, daytime diastolic, nighttime diastolic and nighttime systolic BP were significantly higher in the subclinical hypothyroidism group ($p = 0.001$ for mean, daytime and nighttime diastolic and $p = 0.01$ for nighttime systolic). Diastolic non-dipping occurred more frequently in the subclinical hypothyroidism group (subclinical hypothyroidism group 49% vs. control group 26%, $p = 0.01$). On multivariate analysis, subclinical hypothyroidism was significantly and independently associated with diastolic non-dipping (95% CI, 1.162-8.053, OR 1.182, $p = 0.024$)[46].

Whether treatment with levothyroxine will benefit BP in patients with subclinical hypothyroidism has been examined in a meta-analysis using results derived from 29 RCTs or prospective follow-up studies. The analysis revealed that, in those 10 RCTs, levothyroxine supplement significantly reduced SBP in patients of subclinical hypothyroidism by 2.48 mmHg (95% CI, -4.63 to -0.33, $p = 0.024$), and in those 19 prospective follow-up studies the levothyroxine therapy also significantly decreased SBP and DBP by 4.80 mmHg (95% CI, -6.50 to -3.09, $p < 0.001$) and 2.74 mmHg (95% CI, -4.06 to -1.43, $p < 0.001$), respectively. From these findings, the authors concluded that levothyroxine supplement can reduce BP in patients having subclinical hypothyroidism[47].

In addition to dyslipidemia, changes in BP and its pattern seems also to play an important role in the CV effects in subjects with subclinical hypothyroidism.

Insulin resistance

Hyperinsulinemia and insulin resistance (IR) have long been recognized as a major risk factor for the development and progression of atherosclerotic changes of the vasculature. In an early study comparing the levels of fasting insulin and C-reactive protein (CRP) between subjects with subclinical hypothyroidism ($n = 77$) and age-matched euthyroidism ($n=80$), the results showed that there were significantly higher fasting insulin and CRP levels in the subclinical hypothyroidism group, and a positive correlation between these two parameters also existed. The presence of higher CRP levels may implicate a low grade systemic inflammation, and, along with hyperinsulinemia, both could be signifi-

cant biomarkers for atherosclerosis changes[48-50]. In a study to assess the sensitivity of glucose metabolism to insulin both in vivo (by an oral glucose tolerance test) and in vitro (by measuring insulin-stimulated rates of glucose transport in isolated monocytes with flow cytometry), 21 subjects of euthyroidism, 12 patients with overt hypothyroidism, and 13 patients with subclinical hypothyroidism were compared. The results showed that, while all 3 groups had comparable plasma glucose levels, the overt hypothyroidism and subclinical hypothyroidism had higher plasma insulin than the euthyroidism group ($p < 0.05$). Homeostasis model assessment index for IR (HOMA-IR) was increased in overt hypothyroidism (1.97 ± 0.22) and subclinical hypothyroidism (1.99 ± 0.13) versus euthyroidism (1.27 ± 0.16, $p < 0.05$), while Matsuda index, another indicator for insulin sensitivity, was decreased in overt hypothyroidism (3.89 ± 0.36) and subclinical hypothyroidism (4.26 ± 0.48) versus euthyroidism (7.76 ± 0.87, $p < 0.001$), suggesting IR in both fasting and post-glucose challenge state. At an insulin concentration of 100 mU/mL, glucose transporter type 4 levels on the monocyte plasma membrane, as well as the glucose transport rates in monocytes were found to have decreased in both overt hypothyroidism and subclinical hypothyroidism, as compared to euthyroidism subjects. These findings could justify the increased risk for IR-associated disorders, such as CVD, that has been observed in patients with overt or subclinical hypothyroidism[51].

An interesting finding regarding a possible role that IR plays in subjects with hypothyroidism was found in a clinical study in which an association existed between poor glycemic control in T2DM patients having simultaneously subclinical hypothyroidism, as compared to the euthyroid counterpart[52].

The presence of IR in subclinical hypothyroidism should be regarded significant mechanism underlying the occurrence of multiple CV risk factors in subclinical hypothyroidism, either alone or when clustering into metabolic syndrome as will be discussed below.

Metabolic syndrome

The cluster of multiple risk factors comprising MetS leads to a higher CV events and mortality. Obesity is regarded as the fundamental pathophysiology that triggers the development and formation of MetS. Clear evidences have shown that thyroid hormones play critical roles in the regulation of metabolic rate, which in turn influences adiposity. Thyroid hormones act in controlling core body temperature, appetite, and sympathetic activity. Several studies have demonstrated that weight gain and MetS development are positively associated with TSH levels. Adverse glucose metabolism, abnormal serum TG levels, higher BP could all be consequential to genomic or non-genomic action of thyroid hormones on the vasculature and in the heart[15].

In subclinical hypothyroidism, the prevalence of MetS has been found to be higher than euthyroid population. In a cross-sectional study conducted to evaluate the CV risk in subjects diagnosed with subclinical hypothyroidism ($n = 60$) and a gender- and age- matched control group of healthy volunteers ($n = 60$), parameters of MetS including BMI, waist circumference (WC), BP, fasting plasma glucose, HDL-C, and TG, were measured, along with tests on TSH, fT4, TPO-Ab, TG-Ab, T-C, LDL-C, basal insulin levels, with calculation of HOMA-IR index derived from the relevant measurements. The results showed that more frequent MetS was diagnosed in patients with subclinical hypothyroidism (46.67%) than in the control group (33.33%), although the difference did not show statistical significance. Indices like BMI, diastolic BP, T-C, TG and basal insulin level were statistically significantly higher in the subclinical hypothyroidism group, as compared to the euthyroid controls. Although the results did not confirm significantly higher presence of MetS in subclinical hypothyroidism patients in compari-

son with euthyroid counterpart, the traditional CV risk factors were more frequently present in subjects with subclinical hypothyroidism[53].

Since there has been evidence that the progression of subclinical to overt hypothyroidism is more significant in the elderly, and older persons are frequently affected by the constellation of CV and metabolic risk factors that constitute the syndrome, it is prudent to investigate into the association between subclinical hypothyroidism and MetS in this specific populaiton[21,54]. Using data from the Longitudinal Aging Study Amsterdam, which is an ongoing cohort study in a representative sample of Dutch older persons, analysis was conducted to investigate into the association between serum TSH and the MetS. A total of 1,187 subjects (M/F=590/597) between the ages of 65 and 88 years were recruited for the study. The prevalence of MetS among the cohort as a whole was 34.2%. Subjects in the upper quartile TSH levels above 2.28 uIU/mL had a significantly increased prevalence of MetS compared with subjects in the lowest quartile with a serum TSH below 1.04 uIU/mL (OR:1.68; 95% CI, 1.19-2.37)[55].

Vice versa, studies have also found a higher incidence of subclinical hypothyroidism in subjects diagnosed to have MetS. In a prospective study carried out in Taiwan, an unselected cohort of 66,822 participants with and without MetS were followed to find the association with subclinical hypothyroidism. During an average follow-up of 4.2 years, the incident rates for subclinical hypothyroidism were substantially higher in participants who already had MetS at the study entry, as compared with metabolically normal controls. After controlling for risk factors, patients with MetS were at a 21% excess risk of developing subclinical hypothyroidism (adjusted HR 1.21; 95% CI, 1.03-1.42)[56].

Among a cohort of 5,319 participants (M/F: 3,013/2,306) recruited from the general health examination program in a single medical center in China, a total prevalence of subclinical hypothyroidism was found in 3.40% of those diagnosed to have MetS. Further analysis showed that the prevalence of subclinical hypothyroidism was much higher in participants with one or two metabolic risk factors than in those with no metabolic risk factors such as BMI, SBP and DBP, regardless of age ($p < 0.01$)[57].

From the above studies, a bidirectional relationship has been noted to exist between the occurrence of subclinical hypothyroidism and MetS, implicating that the presence of either disorder may have impact on CV health due to their potential co-existence.

Endothelial function

In a study assessing carotid intima-media thickness (CIMT, as a marker of atherosclerosis) by high-resolution color-coded Doppler US, and endothelial (ED) function in patients with overt or subclinical hypothyroidism, it was found that CIMT was significantly higher not only in patients with overt but also in those with subclinical hypothyroidism, as compared to the euthyroid control subjects (0.7 ± 0.2 and 0.6 ± 0.2 mm respectively vs 0.45 ± 0.07 mm, $p < 0.001$ for both). A similar finding existed in measurement of ED function with significant impairment in patients with overt and subclinical hypothyroidism as compared with the control group (328 ± 17 and 545 ± 406% respectively vs 898 ± 195%, $p < 0.001$ for both), though the impairment was more significant in overt than subclinical hypothyroidism subjects ($p = 0.014$). The authors concluded that impairment of ED function could be a risk factor contributing to the increased risk of atherosclerosis in patients with various degrees of hypothyroidism[17].

Impaired ED function could be an early sign of and a surrogate for generalized atherosclerosis change, an implication of negative impacts from changes in lipid profile, low grade chronic inflammation, oxidative stress and insulin resistance in subjects with subclinical hypothyroidism[58].

Treatment or not with levothyroxine in non-pregnant adults with subclinical hypothyroidism?

There have been extensive studies into the treatment effect by levothyroxine supplement in subjects having subclinical hypothyroidism, aiming to find any significant clinical outcomes. The impacts on lipid profile changes with thyroid hormone supplement in patients with subclinical hypothyroidism are not consistent among different studies. In patients with thyroid cancer rendered hypothyroidism after thyroidectomy, the T-C levels in the group without levothyroxine supplementation were significantly increased 1 year after surgery than those before surgery (168.17 ± 29.19 mg/dL vs 182.50 ± 34.03 mg/dL, p=0.003). Among those receiving levothyroxine supplementation, serum TG levels were significantly decreased, while T-C and LDL-C levels showed no significant changes as compared to values after the thyroidectomy[59]. A meta-analysis using results derived from studies that were carried out in patients of overt and primary hypothyroidism and were put on levothyroxine replacement therapy, it was noted that, even when serum TSH levels have been brought into normal reference ranges, LDL-C levels were still higher than those euthyroid counterpart, with 3.31±1.64 mg/dL higher LDL-C (p = 0.044) and 9.60 ± 3.55 mg/dL higher serum T-C (p = 0.007) measured[60]. On the other hand, studies have found improvement in lipid profile after supplement of levothyroxine in patients with subclinical hypothyroidism. In a systemic review using data from 12 randomized, controlled clinical trials which had included 940 participants, levothyroxine substitution had yielded a significantly mean reduction in T-C of -11.6 mg/dL (-40 to - 6.4) and LDL-C of -8.8 mg/dL (-14.4 to - 3.6) as compared with the control group, although no significant changes was found in HDL-C or TG levels. Trials in which only patients with mild subclinical hypothyroidism (TSH < 10 uIU/mL) were enrolled showed equivalent significant effects, although with weaker magnitude. This meta-analysis revealed clear benefits of levothyroxine administration for reducing T-C and LDL-C in subclinical hypothyroidism patients with TSH levels < 10 uIU/mL[61].

Despite the favorable changes in lipid profile obtained after levothyroxine supplement, current guidelines recommend against treatment in the elderly in whom serum TSH concentrations sit between the upper normal limit of the reference range and 10 uIU/mL[62]. These recommendations are supported by a recent case control study evaluating the association between levothyroxine therapy and mortality in individuals 65 years or older with subclinical hypothyroidism and TSH values of 4.2 - 10 uIU/mL. By study design, the “cases” (n = 419) were those who died in the study years of 2012-2016, as opposed to the matched “controls” (n = 1,558) individuals who were still alive during the same time frame. On multivariate analysis, treatment with levothyroxine was associated with significantly increased mortality (HR =1.19, CI: 1.03-1.38) in this cohort of patients ≥ 65 year-old who were diagnosed to have subclinical hypothyroidism with TSH < 10 uIU/mL[63]. On the other hand, it is suggested that levothyroxine treatment may be considered in patients between 45 and 65 years, and particularly in subjects with comorbidities like dyslipidemia, arterial hypertension and/or IR[64,65].

For depressive symptoms in the elderly with underlying subclinical hypothyroidism, a recently published clinical study did not find the administration of levothyroxine for 12 months effective in evaluation score regarding depression in comparison with placebo group[66].

The evidence supporting clinical benefit from unselected levothyroxine supplementation to non-pregnant adults with subclinical hypothyroidism is yet to be elucidated, especially when this clinical entity is encountered more in aged people.

Specific concerns given to treatment of subclinical hypothyroidism in the elderly

There has been increasing attention to thyroid hypofunction, overt or subclinical, in the elderly because of its higher prevalence compared to younger age group, and the association with frailty, cognitive function, and risk for CVD[67]. There is no doubt about the benefits and indication of replacement therapy for treating overt hypothyroidism in the elderly. Thyroid hormone replacement therapy provides symptomatic relief, has positive effects on cardiac, executive and cognitive functions, which are strongly affected by overt hypothyroidism in the elderly[68]. However, the clinical outcomes of subclinical hypothyroidism, without treatment intervention, in the elderly were not found to bear a poorer prognosis than the younger counterpart. In a meta-analysis using data from 15 clinical studies investigating association between thyroid function status and ischemic heart disease (IHD) events in adults, IHD incidence and prevalence were higher in subclinical hypothyroidism subjects compared with euthyroid participants from studies including those younger than 65 year-old, but not in studies of subjects aged > 65 years. All cause together with CV mortality was also elevated in participants from the younger than 65-year studies, but, again not in studies recruiting older people. The analysis revealed that the increased risk was limited to studies including younger subjects, but not in those aged 65 and older[69]. Thus, although the detrimental effect of overt hypothyroidism on CV hemodynamics and on many of the modifiable CV risk factors for IHD is widely recognized, the clinical relevance of subclinical hypothyroidism in the elderly has been disputed[70].

As the largest clinical trial to date, the TRUST trial (a double-blind, randomized, placebo-controlled, parallel-group trial) had recruited 737 adults [F/M: 396/341 (53.7%/46.3%)] who were at least 65 years of age (mean age: 74.4 years) and who had persisting subclinical hypothyroidism (TSH: 4.60 to 19.99 uIU/mL; free T4 level within the reference range) to evaluate the clinical effects of providing levothyroxine in this elderly population. Among them, 368 patients were assigned to receive levothyroxine (at a starting dose of 50 μg daily, or 25 μg if the BW was < 50 kg or the patient had CHD), with dose adjustment according to the TSH level, while the rest of the 369 patients were assigned placebo. The results showed that there was no effect of levothyroxine on the primary outcomes of hypothyroid symptoms and fatigue scores after 12 months of therapy, and nor on the secondary outcomes of quality of life (QoL), handgrip strength, cognitive function, BP, BW, BMI, WC, CIMT, or carotid plaque thickness. Meanwhile, no excess of adverse events or hyperthyroid symptoms was observed in the treated group. The authors concluded that, from this trial, treatment with levothyroxine in older persons with subclinical hypothyroidism provided no symptomatic benefits[71]. Furthermore, a meta-analysis of 21 trials including the TRUST trial found no difference in general QoL or thyroid-related symptoms between participants with subclinical hypothyroidism treated with levothyroxine compared with placebo. No difference was found for multiple secondary outcomes, including depression, cognitive function testing, fatigue or tiredness, muscle strength, SBP, or BMI[72].

As proposed by the recent European-Thyroid-Association (ETA) guidelines, the decision to treat the elderly with subclinical hypothyroidism should be individualized and based upon the degree of TSH elevation (usually a TSH > 10 uIU/mL required), patient's age and life expectancy, potentially associated risk factors, and comorbid conditions. In old patients with milder TSH elevation (< 10 uIU/mL), a wait-and-see approach with close monitoring of thyroid function is warranted. Once the decision to treat is made, it is prudent to start with lower

doses of levothyroxine in elderly patients owing to the age-dependent decrease in thyroid hormone requirements and the increase in levothyroxine half-life. In patients who are elderly and frail, a starting dose of 12.5-25 μg/day levothyroxine should be progressively increased by 12.5-25 μg daily every 4-8 weeks with regular monitoring, and TSH should be targeted to 4-6 uIU/mL in persons older than 70-80 years[73,74].

As the debate regarding benefit of levothyroxine supplement in the elderly with subclinical hypothyroidism may still continue with need of more convincing clinical study results, the current recommendations or consensus favors the therapy in those aged 65 and younger. However, in even older subjects, treatment should be considered when TSH level is higher than 10 uIU/mL, the value above which the risk of health disorders rises, especially heart failure[75].

Conclusion

Subclinical hypothyroidism may affect up to 10% of the non-pregnant adult population. In patients who have detectable TPO-Ab, there is a greater risk of progression to overt hypothyroidism. The clinical significance resides in its association with an increased risk of HF, events and mortality from CAD. In the absence of large randomized trials showing benefit from levothyroxine therapy, the rationale for treatment is based on the potential for decreasing the risk of adverse CV events and the possibility of preventing progression to overt hypothyroidism. More than half of individuals with subclinical hypothyroidism can be observed without treatment. When indicated, treatment with levothyroxine might be administered to young and middle-aged individuals who have symptoms consistent with mild hypothyroidism. In the elderly, there is no evidence that it is beneficial in persons aged 65 years or older, and the treatment may be associated with iatrogenic thyrotoxicosis. None of the randomized trials to date has had sufficient power to examine the effects of treatment of subclinical hypothyroidism on end points such as incidence of CV events, dementia, or fracture. It is neither recommended to treat in the elderly patients aiming to improve cognitive function or QoL. Nevertheless, in patients with TSH levels persistently ≥ 10 uIU/mL, the higher risk of progression to overt hypothyroidism and increased CV risk without treatment had provided the rationale for treatment. Since the degree of thyroid dysfunction is mild, small (eg, 25-75 μg per day) doses of levothyroxine usually suffice to restore normal TSH levels in the majority of non-pregnant adults[75]. Serum TSH levels should be assessed 6 weeks after initiating the medication, then at 6-week intervals should any changes in dosage occur. The targets of TSH levels are recommended as follows, by age groups, 1-2.5 uIU/mL in patients < 60 years, which could be relaxed to 3-4 uIU/mL in patients between 60-70 years, and 4-6 uIU/mL in patients older than 70 years.

References

1. Garber JR, Cobin RH, Gharib H, et al. Clinical practice guidelines for hypothyroidism in adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocrine Practice 2012; 18: 988-1028.
2. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism- a review. JAMA 2019;322:153-60. doi:10.1001/jama.2019.9052.
3. Ning Y, Cheng YJ, Liu LJ, et al. What is the association of hypothyroidism with risks of cardiovascular events and mortality? A meta-analysis of 55 cohort studies involving 1,898,314 participants. BMC Medicine 2017; 15:21. doi 10.1186/s12916-017-0777-9.
4. Pucci E, Chiovato L, Pinchera A. Thyroid and lipid metabolism. Int J Obes Relat Metab Disord 2000; 24 (Suppl 2): S109-S112.
5. Peppa M, Betsi G, Dimitriadis G. Lipid abnormalities and cardiometabolic risk in patients with overt and subclinical thyroid disease. J Lipids 2011;2011:575840. doi: 10.1155/2011/575840.
6. Sinha RA, Singh BK, Yen PM. Thyroid hormone regulation of hepatic lipid and carbohydrate metabolism. Trends Endrocrinol Metab 2014;25:538-45. doi: 10.1016/j.tem.2014.07.001.
7. Duntas LH and Brenta G. A renewed focus on the association between thyroid hormones and lipid metabolism.

Front Endocrinol (Lausanne) 2018; 9:511. doi: 10.3389/fendo.2018.00511.
8. Khan MAH, Majumder I, Hoque MM, et al. Lipid profile in hypothyroid patients: A cross sectional study. Med Today 2013; 25: 21-4.
9. Alamdari S, Amouzegar A, Tohidi M, et al. Hypothyroidism and lipid levels in a community based study (TTS). Int J Endocrinol Metab 2016; 14: e22827. doi: 10.5812/ijem.22827.
10. Saito I, Ito K, Saruta T. Hypothyroidism as a cause of hypertension. Hypertension 1983; 5: 112-5.
11. Purohit P and Mathur R. Hypertension association with serum lipoproteins, insulin, insulin resistance and C-peptide: unexplored forte of cardiovascular risk in hypothyroidism. N Am J Med Sci 2013; 5: 195-201. doi:10.4103/1947-2714.109187.
12. Berta E, Lengyel I, Halmi S, et al. Hypertension in thyroid disorders. Front Endocrinol 2019; 10:482. doi: 10.3389/fendo.2019.00482.
13. Iwen KA, Schröder E, Brabant G. Thyroid hormones and the metabolic syndrome. Eur Thyroid J 2013; 2:83-92. doi: 10.1159/000351249.
14. Mullur R, Liu YY, Brent GA. Thyroid hormone regulation of metabolism. Physiol Rev 2014; 94: 355-82. doi:10.1152/physrev.00030.2013.
15. de Fátima dos Santos Teixeira P, dos Santos PB, Cabanelas Pazos-Moura C. The role of thyroid hormone in metabolism and metabolic syndrome. Ther Adv Endocrinol Metab 2020; 11: 1-33. doi: 10.1177/2042018820917869.
16. Ordookhani A and Burman KD. Hemostasis in hypothyroidism and autoimmune thyroid disorders. Int J Endocrinol Metab 2017; 15:426-49. doi: 10.5812/ijem.42649.
17. Saif A, Mousa S, Assem M, et al. Endothelial dysfunction and the risk of atherosclerosis in overt and subclinical hypothyroidism. Endocr Connect 2018; 7: 1075-80.
18. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: The Whickham survey. Clin Endocrinol (Oxf) 1977;7:481- 93.
19. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: A twenty-year follow-up of the Whickham Survey. Clin Endocrinol 1995; 43:55- 68. doi: 10.1111/j.1365-2265. 1995.tb01894.x.
20. Walsh JP, Bremner AP, Feddema P, et al. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: A 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010; 95: 1095-104.
21. Imaizumi M, Sera N, Ueki I, et al. Risk for progression to overt hypothyroidism in an elderly Japanese population with subclinical hypothyroidism. Thyroid 2011; 21: 1177-82.
22. Somwaru LL, Rariy CM, Arnold AM, et al. The natural history of subclinical hypothyroidism in the elderly: The Cardiovascular Health Study. J Clin Endocrinol Metab 2012; 97: 1962-9.
23. Li Y, Teng D, Shan Z, et al. Antithyroperoxidase and antithyroglobulin antibodies in a five-year follow-up survey of populations with different iodine intakes. J Clin Endocrinol Metab 2008; 93: 1751-7.
24. Mayoral LPC, Hern´andez-Huerta MT, Mayoral-Andrade G, et al. TSH levels in subclinical hypothyroidism in the 97.5th percentile of the population. Int J Endocrinol 2020; article ID 2698627. https://doi.org/10.1155/2020/2698627.
25. Ismail AA, Burr WA, Walker PL. Acute changes in serum thyrotrophin in treated Addison's disease. Clin Endocrinol 1989; 30: 225-30.
26. Langouche L, Jacobs A, Van den Berghe G. Nonthyroidal illness syndrome across the ages. J Endocr Soc 2019; 3: 2313-25. doi: 10.1210/js.2019-00325.
27. Zhao N, Wang S, Cui XJ, et al. Two-years prospective follow-up study of subacute thyroiditis. Front Endocrinol 2020;11:47. doi: 10.3389/fendo.2020.00047.
28. Rizzo LFL, Mana DL, Serra HA. Drug-induced hypothyroidism. Medicina (Buenos Aires) 2017; 77: 394-404.
29. Mammen JS. Interpreting elevated TSH in older adults. Curr Opin Endocr Metab Res 2019; 5: 68-73. doi:10.1016/j.coemr.2019.04.001.
30. Aggarwal N and Razvi S. Thyroid and aging or the aging thyroid? An evidence-based analysis of the literature. J Thyroid Res 2013; article ID 481287. http://dx.doi.org/10.1155/2013/481287.
31. Barbesino G. Thyroid function changes in the elderly and their relationship to cardiovascular health: A mini-review. Gerontology 2019; 65:1-8. doi: 10.1159/000490911.
32. Surks MI and Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the U.S. population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab 2007; 92: 4575-82.
33. Meyerovitch J, Rotman-Pikielny P, Sherf M, et al. Serum thyrotropin measurements in the community: Five-year follow-up in a large network of primary care physicians. Arch Intern Med 2007;167:1533-8. doi:10. 1001/archinte.167.14.1533.
34. Diez JJ and Iglesias P. Spontaneous subclinical hypothyroidism in patients older than 55 years: An analysis of natural course and risk factors for the development of overt thyroid failure. J Clin Endocrinol Metab 2004; 89: 4890-7. doi:10.1210/jc.2003-032061.
35. Karmisholt J, Andersen S, and Laurberg P. Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy. Eur J Endocrinol 2011; 164: 317-23.
36. Wai Ng MCW, Loo YX, Poon ZM. Subclinical thyroid disorders: clinical significance and when to treat? Proc Singapore Healthc 2014; 23: 226-40.
37. Peeters RP and Brito JP. Subclinical hypothyroidism: to treat or not to treat? Eur J Endocrinol 2020; 183, D15-D24.
38. Hak AE, Pols HAP, TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000;132:270-8.
39. Rodondi N, den Elzen WPJ, Bauer DC, et al. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA 2010; 304: 1365-74. doi:10.1001/jama.2010.1361.
40. Liu XL, He S, Zhang SF, et al. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. Med Sci Monit

2014; 20: 1432-41. doi: 10.12659/MSM.891163.
41. AK Fletcher and AP Weetman. Hypertension and hypothyroidism. J Hum Hypertens 1998;12:79-82.
42. Åsvold BO, Bjøro T, Nilsen TIL, et al. Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: A population-based study. J Clin Endocrinol Metab 2007; 92: 841-5.
43. Cai Y, Ren Y, Shi J. Blood pressure levels in patients with subclinical thyroid dysfunction: A meta-analysis of cross-sectional data. Hypertens Res 2011; 34: 1098-105; doi:10.1038/hr.2011.91.
44. de Melo ROV, Toledo JCY, Loureiro AAC, et al. Absence of nocturnal dipping is associated with stroke and myocardium infarction. Arq Bras Cardiol 2010; 94 : 74-80.
45. Inal S, Karakoç MA, Kan E, et al. The effect of overt and subclinical hypothyroidism on the development of non-dipper blood pressure. Endokrynol Pol 2012;63:97-103.
46. Canbolat IP, Belen E, Bayyigit A, et al. Evaluation of daily blood pressure alteration in subclinical hypothyroidism. Acta Cardiol Sin 2017; 33:489-94.
47. He W, Li S, Zhang J,et al. Effect of levothyroxine on blood pressure in patients with subclinical hypothyroidism: A systematic review and meta-analysis. Front Endocrinol 2018; 9:454. doi: 10.3389/fendo.2018.00454.
48. Tuzcu A, Bahceci M, Gokalp D, et al. Subclinical hypothyroidism may be associated with elevated high-sensitive c-reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocr J 2005; 52:89-94.
49. Badimon L, Peña E, Arderiu G, et al. C-reactive protein in atherothrombosis and angiogenesis. Front Immunol 2018; 9:430. doi: 10.3389/fimmu.2018.00430.
50. Beverly JK and Budoff MJ. Atherosclerosis: pathophysiology of insulin resistance, hyperglycemia, hyperlipidemia, and inflammation. J Diabetes 2020; 12:102-4. https://doi.org/10.1111/1753-0407.12970104.
51. Maratou E, Hadjidakis DJ, Kollias A, et al. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. Eur J Endocrinol 2009; 160: 785-90.
52. Cho JH, Kim HJ, Lee JH, et al. Poor glycemic control is associated with the risk of subclinical hypothyroidism in patients with type 2 diabetes mellitus. Korean J Intern Med 2016; 31:703-11. http://dx.doi.org/10.3904/kjim.2015.198.
53. Pesic MM, Radojkovic D, Antic S, et al. Subclinical hypothyroidism: association with cardiovascular risk factors and components of metabolic syndrome, Biotechnol Biotechnol Equip 2015; 29:157-63, doi: 10.1080/13102818.2014.991136.
54. Dominguez LJ and Barbagallo M. The biology of the metabolic syndrome and aging. Curr Opin Clin Nutr Metab Care 2016; 19:5-11.
55. Heima NE, Eekhoff EMW, Oosterwerff MM, et al. Thyroid function and the metabolic syndrome in older persons: a population-based study. Eur J Endocrinol 2013; 168: 59-65.
56. Chang CH, Yeh YC, Caffrey JL, et al. Metabolic syndrome is associated with an increased incidence of subclinical hypothyroidism – A Cohort Study. Sci Rep 2017;7:6754. doi: 10.1038/s41598-017-07004-2.
57. Jiang L, Du J, Wu W, et al. Sex differences in subclinical hypothyroidism and associations with metabolic risk factors: a health examination-based study in mainland China. BMC Endocr Disord 2020; 20:100. https://doi.org/10.1186/s12902-020-00586-5.
58. Lu M, Yang CB, Gao L, et al. Mechanism of subclinical hypothyroidism accelerating endothelial dysfunction (review). Exp Ther Med 2015; 9:3-10.
59. Chu CH, Kim SY, Lee YS, et al. Lipid profile change after thyroidectomy. J Endocr Surg 2020;20:41-6.
60. McAninch EA, Rajan KB, Miller CH, et al. Systemic thyroid hormone status during levothyroxine therapy in hypothyroidism: a systematic review and meta-analysis. J Clin Endocrinol Metab 2018; 103: 4533-42.
61. Li X, Wang Y, Guan Q, et al. The lipid-lowering effect of levothyroxine in patients with subclinical hypothyroidism: a systematic review and meta-analysis of randomized controlled trials. Clin Endocrinol 2017;87:1-9.
62. Pearce SH, Brabant G, Duntas LH, et al. 2013 ETA guideline: Management of subclinical hypothyroidism. Eur Thyroid J 2013; 2:215-28. doi: 10.1159/000356507.
63. Grossman A, Feldhamer I, Meyerovitch J. Treatment with levothyroxine in subclinical hypothyroidism is associated with increased mortality in the elderly. Eur J Intern Med 2018; 50:65-8. doi: 10.1016/j.ejim.2017.11.010.
64. Chrysant SG. The current debate over treatment of subclinical hypothyroidism to prevent cardiovascular complications. Int J Clin Pract 2020;74:e13499. https://doi.org/10.1111/ijcp.13499.
65. Sgarbi JA and Ward LS. A practical contemporary approach to decision-making on subclinical hypothyroidism. Arch Endocrinol Metab 2021;65:32-9.
66. Wildisen L, Feller M, Del Giovane C, et al. Effect of levothyroxine therapy on the development of depressive symptoms in older adults with subclinical hypothyroidism: an ancillary study of a randomized clinical trial. JAMA Network Open 2021;4:e2036645. doi:10.1001/jamanetworkopen.2020.36645.
67. Yeap BB, Manning L, Chubb SA, et al. Reference ranges for thyroid-stimulating hormone and free thyroxine in older men: Results from the Health in Men Study. J Gerontol A Biol Sci Med Sci, 2017; 72:444-449.
68. Biondi B and Wartofsky L. Treatment with thyroid hormone. Endocr Rev 2014; 35: 433-512.
69. Razvi S, Shakoor A, Vanderpump M, et al. The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: A metaanalysis. J Clin Endocrinol Metab 2008; 93: 2998-3007.
70. Pasqualetti G, Tognini S, Polini A, et al. Subclinical hypothyroidism and heart failure risk in older people. Endocr Metab Immune Disord Drug Targets 2013;13: 13-21.
71. Stott DJ, Rodondi N, Kearney PM, et al. for the TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 2017; 376: 2534-44. doi: 10.1056/NEJMoa1603825.
72. Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism.

JAMA 2018; 320: 1349-59. doi:10.1001/jama.2018.13770.
73. Chakera A, Pearce SHS, Vaidya B. Treatment for primary hypothyroidism: Current approaches and future possibilities. Drug Des Devel Ther 2012; 6:1-11.
74. Ruggeri RM, Trimarchi F, Biondi B. Management of endocrine disease: L-thyroxine replacement therapy in the frail elderly: A challenge in clinical practice. Eur J Endocrinol 2017; 177: R199-R217.
75. Calsolaro V, Niccolai F, Pasqualetti G, et al. Overt and subclinical hypothyroidism in the elderly: When to treat? Front Endocrinol 2019;10:177. doi: 10.3389/fendo.2019.00177.

非懷孕成年族群之亞臨床甲狀腺功能低下 - 小型文獻回顧

邱世欽[1] 黃怡瓔[1] 宋育民[1,2]

[1]台中慈濟醫院 內科部內分泌新陳代謝科
[2]慈濟大學醫學系

摘 要

甲狀腺激素在維持整體健康佔有極重要的角色，甲狀腺功能低下的影響包括血脂、血壓、體重及身體質量指數的上升、代謝症候群發生率的增加，內皮細胞功能異常，這些風險因子皆已被證實：在罹患甲狀腺功能低下的患者，會導致心血管疾病與死亡率增加，因此有必要投與甲狀腺素製劑治療。然而，因著甲狀腺功能檢測日漸普及，臨床上遇到亞臨床甲狀腺功能低下(定義為：游離四碘甲狀腺素數值正常，但是甲狀腺刺激素高於正常參考值，通常為 > 4.5 uIU/mL)的機率亦隨之增加，這個疾病雖然亦有前述各種心血管疾病風險因子的出現，但是目前並無確切證據顯示會導致心血管疾病發生率與相關死亡率的增加，且投予甲狀腺素製劑治療的臨床實驗亦未顯示在65歲以上的族群可獲致明顯療效，因此是否需積極以藥物補充治療的議題仍待大型臨床試驗釐清。依據目前的治療指引建議：若是甲狀腺刺激素 > 10 uIU/mL，因已有臨床追蹤觀察研究顯示會導致心臟衰竭風險升高，應該投與甲狀腺素製劑治療，起始劑量宜低(每日12.5-25μg，每四至八周逐漸增加12.5-25 μg)，大部分的患者以每日25-75 μg的總量可達到明顯下降甲狀腺刺激素至正常範圍。甲狀腺刺激素的治療目標值因年齡而異：60歲以下：1-2.5 uIU/mL, 60-70歲：3-4 uIU/mL，70歲以上的族群則可放寬至4-6 uIU/mL。定期檢測是必要的，要避免因劑量過高導致的醫源性甲狀腺功能亢進。