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ORIGINAL ARTICLE

Treatment of Subclinical Hypothyroidism; A Review of Literature

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is a disorder without any symptoms related with an elevated thyroid stimulating hormone (TSH) concentration > 4 mIU/l and normal T4 and T3 concentrations. It is communal in the elderly and particularly in females, with prevalence of about 11%. Some studies show no effect of the treatment, while others have found it to be beneficial, since normal TSH levels can be above 7.5 mIU/L in the elderly. As a result of these findings, the best treatment for SCH, especially in elderly patients, has been criticized.

Aim: The aim of this study was to evaluate the latest literature on the subject in order to assess the available evidence regarding this controversy in order to determine whether and under what conditions treatment of SCH is essential and how it can be prevented.

Methods: To better understand the ongoing debate regarding the treatment of SCH, a Medline search of the English-language literature was held between 2015 and 2022 using the terms subclinical hypothyroidism, hypothyroidism, treatment and prevention, cardiovascular disease, dyslipidemia and cardiac failure. From this search, 38 articles with relevant material were selected.

Results: When the data from these studies were combined, it was found that normal TSH levels increased with age, from 4 to 7.5 mIU/L in subjects under 75 years of age. Levothyroxine supplementation has also shown marked effects on the metabolic and clinical features of SCH, including decline in cardiovascular disease, heart failure, and mortality, although many of the peer-reviewed articles exhibited no treatment benefit. The drug works best in younger people who also experience fewer side effects.

Conclusions: Younger patients with TSH > 4.0 mIU/l should be treated for SCH based on available data. Treatment must be modified according to the TSH levels and existence of symptoms, and should be started with a TSH level of 10 mIU/L with moderate doses to minimize adversative cardiovascular complications in elderly patients.

Keywords: subclinical, discussion, thyroxine, treatment, hypothyroidism, hypertension, thyrotropin, dyslipidemia, heart failure, cardiovascular diseases, prevention.

INTRODUCTION

Subclinical hypothyroidism (SCH), a condition categorized by TSH levels > 4 mIU/L with normal thyroxine (T4) and triiodothyronine(T3) level and is an asymptomatic condition. It also affects women more often than men and 18% of the elderly[1]. This disease, usually asymptomatic, has the probability to rise the prevalence of cardiovascular diseases and heart failure in SCH patients. Cardiovascular diseases are the main reason of mortality and morbidity globally counting for >1.5 billion deaths annually. Although its causes are numerous, SCH, which increases in incidence with age, has recently been recognized as one of the causes of CVD[2]. The action of thyroid hormones through receptors present in tissues affects the circulatory activity of the endothelial tissue of the myocardium and vessels. Cardiometabolic abnormalities in the body, including elevated blood sugar and cholesterol levels, endothelial dysfunction due to reduced nitric oxide (NO) availability which causes elevated peripheral vascular resistance, arterial stiffness and high blood pressure (BP), all are the important risk factors[3]. For cardiovascular disease, minor variations in TSH levels have an adverse effect. To better understand the ongoing debate regarding the treatment of SCH, a Medline search of the English-language literature was held between 2015 and 2022 using the terms subclinical hypothyroidism, hypothyroidism, treatment and prevention, cardiovascular disease, dyslipidemia and cardiac failure. From this search, 38 articles with relevant material were selected. 38 relevant articles were selected. In this review, we will consider these studies and related literature.

Cardiometabolic Effects of Subclinical Hypothyroidism: Lipid abnormalities, type 2 diabetes, hypertension, heart failure, cardiovascular disease and cardiovascular mortality are associated with thyroid hormone deficiency. There are numerous cardiometabolic effects of thyroid hormones on the body. The important cardiometabolic changes induced by SCH are elaborated and discussed[4].

Metabolic Changes: Thyroid hormones have various effects of cardiometabolic activity with the help of their receptors. The thyroid produces the L-triiodothyronine (T3) and thyroid hormones L-thyroxine (T4) and secretes into the blood under the influence of TSH, which is produced by the anterior pituitary gland and binds to thyroxine-binding globulin (TBG)[5]. Intracellular deiodinases I and II convert the T4 prohormone into the functional T3 hormone. T3 then works by binding to receptors of β (TRβ). And α (TRα) Thyroid hormones lower serum cholesterol through TR receptors, promoting the excretion of bile acids from the digestive tract and reversing cholesterol transport[6]. The opposite occurs when thyroid hormones are underactive, as in SCH. Multiple researches has shown the increase in apoB, TC, HDL cholesterol, triglycerides, LDL cholesterol and HDL/ LDL ratio in SCH. In SCH, the activity of lipoprotein lipase in the adipose tissue and liver decreases, causing an increase in TG levels[7]. SCH is associated with an augmented risk of type-II diabetes, hypertension and metabolic disorders in adding to lipid disorders. When this disease coexists with hyperlipidemia, the atherosclerosis risk, cardiovascular and heart diseases increase.

Cardiovascular Changes: Numerous adverse cardiovascular hemodynamic effects are associated with SCH, including decreased cardiac output, reduced filling pressure and myocardial contractility, impaired diastolic relaxation and filling, systolic dysfunction, atherosclerosis, increased peripheral vascular resistance because of endothelial dysfunction due to low NO availability and increased SBP[8]. These metabolic and hemodynamic anomalies of SCH augmented the risk of HF, CV and CVD related mortality. The key processes by which SCH influences cardiac output and initiate the onset of heart failure have been suggested to be mitochondrion failure and quality control (MQC)[9]. The MQC is a multi-level system of surveillance that works at the mitochondrial level to biogenically replace or repair damaged mitochondria. Consequently, thyroid hormones significantly influence the regulation of several MQC components by preserving cell function and improving biogenetics of mitochondria. Various studies have shown that T3, which is also intricate in protein import and biogenesis of mitochondria, protects against coronary heart disease[10]. Low T3 profoundly affects

extracellular matrix remodeling and mitochondrial function in the ischemic reperfusion (IR) disease. The thyroid hormones are very sensitive for the myocardium, and any change in blood hormone levels can result in heart failure associated with a reduction in cardiac output due to systolic and diastolic dysfunction[11]. This has been shown in studies of heart failure patients with subclinical hypothyroidism. Previous researches have also revealed that administration of T3 reduces peripheral vascular resistance and improves cardiac output, thereby reducing left ventricular afterload.

Treatment of subclinical hypothyroidism: There is presently disagreement about the profits of treating patients with subclinical hypothyroidism, as numerous reviews, meta-analyses of randomized and cohort studies show no treatment benefit, while other comparable studies show treatment benefit[12].

Studies showing no treatment benefit: Numerous studies, mostly involving the elderly, have not shown any benefit from the treatment. The results of this study are given in Table-I are discussed below. Waring et al discussed the study results of the Osteoporotic Fractures in Men (MrOS), which involved a cohort of 1,587 American men under the age of 65 living in the community. Four thyroid function categories are discussed: euthyroidism, subclinical hyperthyroidism (SCHyper) and subclinical hypothyroidism were defined based on baseline measurements of TSH and free T4 levels[13]. TSH levels in SCH were divided into <10 mIU/L SCH and ≥10 mIU/L. After follow-up of 8.3 years and 432 deaths were documented, baseline levels of TSH and cardiovascular mortality or all-cause mortality (HR 1.02) (95% CI 0.95-1.07), HR 1.10 (96 %) were not related. Based on research results, SBC is a fairly benign condition that does not require treatment with thyroxine. Pasqualetti et al meta-analysis of 182,202 people aged 47 to 85, with an average follow-up of 9.7 years. This meta-analysis exhibited that levels of TSH rise with age and are related with an augmented risk of CHD in young people[14-15]. This increase in mortality is less pronounced in the elder, especially those over 85 years of age, even at greater than 10 mIU/l of TSH levels. This study suggests that a wait-and-see strategy should be used when closely monitoring older adults. To assess the levothyroxine effect on the proportion of cardiovascular deaths, myocardial infarction and total mortality in SCH patients, Andersen et al conducted a retrospective cohort study among 12,301 SCH patients were either stage I or stage II depending on TSH levels[16]. The patients mean age was 55.2 years, and 79.8% were females. Of the 12,301 patients, 2,501 were taking levothyroxine and 9,625 were not taking any medication. After 5.0 years of mean follow-up, a total of 1566 deaths occurred, including 766 cardiovascular deaths and 358 myocardial infarctions.

Table 1: Studies Showing no treatment Benefits of Subclinical Hypothyroidism

Author	Study type	Patients No	Age in yrs	Duration in yrs	Outcomes types
Brenta	C-S, Observ	38	62	0.6	RLP-C, LDL-C, TGs
Hennessey	Rev-Meta	1,902,019	42-87	-	CHD, HF, QoL
Niknam	RCT	50	37.8	3.0 (mos)	IMT, FMD
Zhao	RCT, O-L	380	54.2	1.	TC, LDL-C
Pandrc	Prosp, O-L	37	52.1	4.0 (mos)	BP, TC, LDL-C, Lpa, LDL/HDL, TGs, AooB
Zhao	Rev-Meta	277	36-55	2-18 (m0s)	
Abreu	Rev-Meta	733	17-80	12 (mos)	LDL-C,TGs, TC, ApoB, Lpa, BMI C-IMT, BP, FMD

Table 2: Studies Showing Treatment Benefits of Subclinical Hypothyroidism

Author	Study type	Patients No	Age in yrs	Duration in years	Outcomes types
Pasqualetti	Rev-Meta	182,202	47-85	9.6	CHD (old age)
Waring	Cohort	1587	≥ 65	8.3	ACM, CVM
Stott	RCT	737	75.1	1.0	HF, AF, WC
Andersen	Retro-Cohort	12,301	56.1	4.9	CVM, MI, ACM
Mooijaart	RCT	251	≥ 80	4.9	QoL

Reviewing the results of two clinical trials that randomized 251 people under the age of 80 to either levothyroxine or placebo, Mooijaart et al evaluate the results. With an adjusted between-group difference of 1.4 (95% CI 2.8 vs 5.4, p=0.55), the hypothyroidism symptom score decreased from 22.1 to 18.9 at 12 months in the treatment group levothyroxine. It fell from 20.5 to 16.5 in the placebo group after a median follow-up of five years[17]. The tiredness score amplified from 26.20 at baseline to 29.2 after on-year in the group given levothyroxine, while in the placebo group it rised from 25.1 at starting point to 28.7 at 12 months, with an adjusted difference of 0.0.1 (95% CI -4). 0.4 to 4.3, p = 0.96)[18-19]. In terms of drug side effects, there was one case of stroke in the group given levothyroxine and four pneumonia cases in the placebo group. The results of this analysis do not support daily thyroxine therapy in SCH patients under 80 years.

Studies highlighting the benefits of treatment: Contrary to earlier findings, numerous recent studies show that treatment has a beneficial effect on SCH patients. The studies data is given in Table 2.

In the Hennessey et al study; 1,902,019 SCH participants aged 42-85 were included in 16 analyzed studies. This detailed study provides the latest information on the benefits of treatment as well as the impact of SCH on neuropsychiatric and cardiovascular health in the elderly (CHD, HF). SCH patients in this category who would benefit from levothyroxine treatment should be carefully identified. Fewer cardiovascular events and a better quality of life in people with anti-thyroid antibodies and a TSH level <10 mIU/l are typical benefits of treatment. Careful monitoring is required after starting treatment to avoid pharmaceutical side effects. With an average age of 61, Brent et al analyzes the effect of the drug on lipid readings in 29 women with euthyroidism and 37 women with SCH[18].

Women with SCH had high levels of small dense LDL (sdLDL), residual lipoproteins (RLP), hepatic lipase and triglycerides (TG) compared to euthyroid women (control group). In adding, 23 females were treated with l 0.9 g/kg/day of levothyroxine for six months. In comparison to the group of control, management with levothyroxine significantly reduced RLP-TG (p = 0.033), RLP-C (p = 0.005) and HL, but not small dense LDL. The lipid modifications drug reduces the frequency of adverse cardiovascular events. Zhao et al. conducted a randomized, open-label, controlled trial. Determining how treatment affects plasma lipid levels in 378 Chinese patients with moderate SCH with an average age of 55.5 years. Of these participants, 369 underwent 15 months of follow-up after being randomized to levothyroxine or placebo. Treatment with levothyroxine decreased serum TC (-0.42 mmol/l vs. -0.18 mmol/l, p=0.014) and LDL-C. When patients were grouped by TSH levels, treatment effects were consistent across patient groups, suggesting that levothyroxine supplementation may be of benefit in the treatment of CVD in these patients. In the Niknam et al study, 25 controls with 37.5 years of mean age and 50 patients, 25 of whom received levothyroxine 50 g/day, were enrolled in a quasi-experimental analysis to compare the levothyroxine treatment effects versus placebo for intima-media thickness (IMD) and flow-media vasodilation (FMD)[19]. Despite equal baseline values for both IMT and FMD, afterwards two months of treatment, patients had significantly elevated FMD levels as opposed to control group (p = 0.001), but not IMT levels (p =

0.327). This study exhibited that SCH patients had dysfunction of the endothelium that was treated and that may have had long-term beneficial effects on cardiovascular health. The Levothyroxine psychosomatic effects in SCH Patients were assessed by Pandrc et al. In this analysis, levothyroxine was used to treat 35 euthyroid SCH patients with 51.6 years of mean age, normal FT4, TSH levels up to 10 mIU/L and positive antithyroid antibodies. DBP (p = 0.024), Body weight (p = 0.030), HbA1c (p = 0.001), homocysteine (p = 0.001), LDL-C (p = 0.001), apoB (p = 0.024), TG (p = 0.007), LLDL/HDL ratio (p = 0.009) and TSH (p = 0.002) were statistically significant[20-21]. According to this study, patient's treatment with SCH improves their cardiometabolic effects and physical health, which may have long-term beneficial effects on their cardiovascular system. The Abreu et al meta-analysis and review of 17 studies comprising 735 SCH patients aged 15 to 78 years with 10.5 months of mean follow-up. The study evaluated the treatment effects with levothyroxine on changes in blood lipids compared with placebo. Mild but significant decline in TC, LDL-C and TSH were observed in SCH patients receiving levothyroxine compared to placebo. This meta-analysis and review showed that the changes in lipid levels caused by SCH treatment, significant long-term benefits in reducing the incidence of CAD was noted[22]. Treatment had a good effect on IMT, FMD, CRP, PWV, BNP and ANP in addition to lipid abnormalities, which may have contributed to the beneficial effect in correcting lipid abnormalities and have beneficial effect on the cardiovascular system. In the Zhao et al study, 277 people with SCH, with a mean age of 35.9 to 50.0 years, participated in 9 short studies evaluating the drug effects of levothyroxine on carotid IMD (C-IMT), serum lipids, blood pressure and FMD. FMD (p 0.001), C-IMT (p = 0.05), DBP (p 0.001), SBP (p 0.003), LDL-C (p 0.002), TC (p = 0.03), TG (p = 0.001) 0.031) and LP(a) showed significant decreases, while serum glucose, BMI, ApoA, ApoB and HDL-C did not change significantly. Levothyroxine supplementation significantly altered lipid and clinical parameters in SCH patients, which may have significant long-term cardiovascular benefits.

DISCUSSION

The levothyroxine treatment for SCH resulted in biochemical and clinical benefits consistent with the anticipation of future cardiovascular events in some studies but not in others. In some studies, SCH treatment has failed to produce any clinical or biochemical benefit in treating people with SCH. Assessment of the study's results presented in this review made this clear[23]. The study's results did not settle the dispute about whether patients with SCD should be adequately treated. One area of discussion is recent research showing that normal values of TSH increased with age. It can be difficult to predict variations in the thyroid hormone's circadian rhythm and their baseline values for sex, age, ethnicity and race when giving treatment option for patients with SCH. Although a TSH > 4 mIU/L is considered to diagnose SCH in all age groups, recent research suggests that this TSH level should be 7.55 mIU/L for the elderly. According to additional studies, the test method, iodine level, BMI, reproductive status, age, gender, and ethnicity are independent variables that alter the range of TSH[24]. All of these issues raise questions about how to treat SCH, and a new meta-analysis and comprehensive review found no strong suggestion against treating people with SCH, especially the elderly[25]. Therefore, treatment of patients with SCH is recommended as it may cause cardiovascular side effects such as arrhythmias if not treated. Conflicting statements such as "treatment of subclinical hypothyroidism rarely makes a difference" and "treatment of subclinical hypothyroidism" appearing in numerous studies make it difficult to decide whether to treat these individuals. The SCH treatment with levothyroxine is inexpensive, easy and simple to administer as well as readily available. It may be misinterpreted that the therapy is currently not beneficial for patients with SCH[26]. Furthermore, BP improvement, lipid changes and a lower incidence of coronary heart disease and heart failure are notice with treatment. In general, SCH drugs are better for younger people than older patients (over 75) who benefit less[27]. For these patients, levothyroxine therapy should be tailored to their individual needs, preferably starting with a low dose and with a TSH level below 10 mIU/l. More randomized trials of long-term outcomes are needed to settle this debate[28].

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