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Low-grade systemic inflammation in subclinical hypothyroidism

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Abstract

Background: Hypothyroidism is the deficiency in the production of thyroid hormones to meet the requirements of peripheral tissues. Subclinical hypothyroidism (SCH) is defined biochemically as normal serum free thyroxin concentration in the presence of an elevated serum thyroid-stimulating hormone (TSH) concentration. SCH may be associated with low-grade systemic inflammation (increased high sensitivity-C reactive protein (hs-CRP), one possible explanation may be that TSH in adipocytes promotes the release of interleukin-6 (IL-6). Studies have confirmed inflammatory biomarkers like hs-CRP and IL-6 to be a predictor of cardiovascular (CV) events. However, the treatment of SCH remains subject to debate.

Conclusions: It is increasingly evident that SCH has prognostic values and crucial clinical effects, which leads to the view of SCH not being a compensated biochemical change *sensu strictu*. Even a modest but consistent fluctuation in the circulating thyroid hormone levels can create a response from the human heart. Well-timed treatment should be considered as a precaution to avoid the unfavourable CV diseases. The inflammatory biomarkers, namely CRP and IL-6 are exceptionally robust markers of cardiovascular risk. Thus, using these biomarkers may be helpful in assessing the cardiovascular risk in patients with subclinical hypothyroidism.

Key words: subclinical hypothyroidism, low-grade inflammation, levothyroxine treatment.

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Introduction

Hypothyroidism is the deficiency in the production of thyroid hormones to meet the requirements of peripheral tissues. Subclinical hypothyroidism (SCH) is defined biochemically as normal serum thyroxin (T4) concentration in the presence of an elevated serum thyroid-stimulating hormone (TSH) concentration. The incidence of SCH reaches 10-12% in women, 2-5% in men, and after the age of 70, it varies between 15 and 20% [1-3]. In recent years, the attitude of specialists towards the problem of SCH, especially regarding the diagnosis and management of patients has been revised [4]. SCH is recognized as an independent medical condition that requires increased attention.

SCH may be associated with low-grade systemic inflammation (increased C-reactive protein (CRP) and thereby, an increased cardiovascular (CV) risk. However, the treatment of SCH remains subject to debate.

The major bibliographic sources were collected from the PubMed online database. Key search terms were "subclinical hypothyroidism", "inflammation biomarkers" and "levothyroxine treatment". All English-language research articles or translations published on the topic were reviewed. Full-length English articles are only included in this review.

Subclinical hypothyroidism

Hypothyroidism is a frequent endocrine disease that, if left untreated, can have major health consequences, including cardiovascular disease – coronary heart disease and heart failure [5]. The definition of subclinical hypothyroidism is principally biochemical. TSH concentrations above the standard range and free thyroxine concentrations below the reference range are considered overt or clinical primary hypothyroidism. In primary hypothyroidism, an increase in the production of TSH via a feedback mechanism is present to balance the low thyroid hormones level [6].

TSH values above the reference range and free thyroxine concentrations within the normal range constitute mild or subclinical hypothyroidism [7], which is widely seen as a symptom of early thyroid failure. SCH is mild in nature and the patients are usually asymptomatic. The only abnormal hormone level is an increased TSH [8]. The most frequent cause of hypothyroidism is Hashimoto thyroiditis or autoimmune thyroiditis, which involves self-attack of the thyroid gland through inflammation and damage [6, 9]. Other causes include thyroid surgery in the past, radiation to the front of the neck, drugs like lithium and amiodarone [10]. The prevalence of SCH is about 1-2% among the general population and this value increases in iodine-

deficient areas [11]. The prevalence is up to 20% in older individuals (> 65years) [12].

SCH can be divided in 2 forms, mild and severe [13]. In the mild form, the upper limit of TSH is 9.9 mIU/L, while in the more severe form TSH values are above 10 mIU/L. Approximately 80-90% of patients fall in the mild form of SCH [14]. Annually 2-5% of cases of untreated SCH progress to overt hypothyroidism [15]. SCH patients with positive thyroid peroxidase antibodies (TPO) show a high tendency to convert to overt hypothyroidism (two-fold increased risk) [16].

The treatment of SCH with levothyroxine (LT4) is recommended to begin under any of the following circumstances by the American Thyroid Association (ATA) and American Association of Clinical Endocrinology (AACE) [17]:

– TSH >= 10 mU/L.
– TSH between 7 and 9.9 mU/L in younger persons and only with symptoms of hypothyroidism in patients > 65 years.
– TSH above upper limit of normal to 6.9 mU/L in patients < 65 years and symptoms of hypothyroidism. High TPO antibody titer may also be an argument for treatment [18].

In SCH the LT4 therapy is started at a dose of 25-50 mcg and then up-titrated as required, keeping the goal of normalizing TSH.

Some authors suggest that patients with ultrasonographic findings that show chronic thyroiditis even in the absence of TPO should receive levothyroxine therapy [19]. Even though a large number of studies have shown that levothyroxine therapy is helpful in treating patients with SCH, there is a lack of evidence from randomized controlled trials. Hence, it is still ambiguous whether to treat a patient with SCH LT4 therapy or not [20].

Hypothyroidism is the least defined known risk factor of cardiovascular disease. Subclinical hypothyroidism and overt hypothyroidism show almost the same cardiovascular consequences [9]. Even though the entire pathophysiological mechanisms are unknown, the most known causes include insulin resistance, hypertension, disturbed lipid balance, and endothelial dysfunction [12, 21].

SCH is associated with hypercholesterolemia, atherosclerosis [22] and increased carotid intima-media thickness [5]. SCH is also associated with elevated levels of C-reactive protein, homocysteine, TNF-α, MPO-Myeloperoxidases, IL-6, and other inflammatory markers [14], so that over time untreated SCH can contribute to heart disease [22]. There is a higher risk of CV disease especially in younger population (aged < 65years) compared to the older ones [23]. Kvetny J. et al. have shown that SCH is an independent predictor of cardiovascular disease in patients younger than 50 years [24]. An important factor in CV disorders in hypothyroidism is the change in peripheral vascular resistance and elasticity of the arterial wall [25]. The researchers established a close correlation between TSH levels and the thickness of the intima media, a correlation that is interpreted as a link in the pathogenesis of atherosclerosis [25]. Ghasemi M. et al. found correlations between hypothyroidism and the average intimate thickness of the carotid vessels [26]. Cardiovascular diseases, being a leading cause of death globally, appropriate measures have to be taken regularly to identify and stratify individuals. Usually this stratification is done based on evaluating the risk factors [27]. A long list of CV disease risk factors has been identified. The list is still expanding with the addition of numerous novel biomarkers. This includes various biochemical markers, as well as genetic and inflammatory markers. The successful quantification of these risks is helpful in ascertaining that the patients receive proper treatment on time. Thus, the integration of novel as well as existing risk factors into the therapeutic guidelines is necessary to prevent and reduce the globally leading cause of death [27].

Low-grade inflammation

The current definition of inflammation is "a response to infections and damaged tissues that bring cells and molecules of host defence from the circulation to the sites where they are needed in order to eliminate the offending agents" [28]. Acute inflammation is characterized by the 5 cardinal signs – redness (*rubor*), heat (*calor*), pain (*dolor*), swelling (*tumor*), and loss of function (*functio laesa*).

Inflammation is an important constituent of innate immunity. Low-grade inflammation is the innate immune response to potentially harmful stimuli, such as pathogens, injury, and metabolic stress [29]. Subclinical inflammation is associated with increased risk of several metabolic diseases, such as obesity and diabetes mellitus. In addition, modest elevation in the level of acute phase protein – CRP between 3 – 10 mg/L is also associated with inflammation [29, 30].

Low-grade inflammation is also associated with cigarette smoking, sleep deprivation, lack of physical activity, hypertension, PCOS, and a large variety of unhealthy diets [29].

Table 1 shows a comparison between acute inflammation and low-grade inflammation.

Table 1. Comparison of acute and low-grade inflammation [2]

Parameter	Acute inflammation	Low-grade inflammation
Cause	Pathogens, trauma, tissue infarction	Metabolic malfunction
Mediators	Molecules and cells of the innate immune response	Molecules and cells of the innate immune response
Classic signs of inflammation	+++	None
CRP response	+++	+
Purpose	Healing and repair	Restoration of Homeostasis
Triggering mechanisms	PAMPs and DAMPs	UPR

Note: UPR – unfolded protein response, DAMP – damage-associated molecular patterns,

PAMP – pathogen-associated molecular pattern. In addition, symbols indicate magnitude.

Biomarkers of low-grade inflammation

C-reactive protein

CRP, a pentameric protein, with a discoid shape, is synthesized in the liver. It is a member of the pentraxin family, family of innate immune response proteins [14]. The monomer has 22 amino acids and a molecular mass of 25106 Da. The overall mass of the whole protein, which is made up of five monomers, is around 120000 Da [31]. The location of CRP gene is 1q23.2 [31]. CRP plays a vital role as a dynamic and sensitive marker of inflammation [32]. During acute responses to serious changes in the body like acute infection or tissue damage, a significant increase is usually noticed in a time span of 48 hours [30-33]. There could be chronic or acute rise in the levels of CRP depending on the situation. Acute rise in CRP could be a result of acute bacterial or viral infections, burns or even trauma or exercise, and the chronic rise in CRP is noticed as a result of elevated blood pressure, elevated body mass index, diabetes mellitus, cigarette smoking, cancer, or chronic bacterial or viral infections [34].

CRP is a non-specific inflammatory marker that mediates atherosclerosis [35]. Independent of other cardiovascular risk factors, studies in both men and women of different age groups have shown that there is an association between inflammatory biomarkers like CRP, IL-6 and cardiovascular events [36, 37]. Recent investigations have confirmed inflammatory biomarkers like CRP and IL-6 to be a predictor of cardiovascular events.

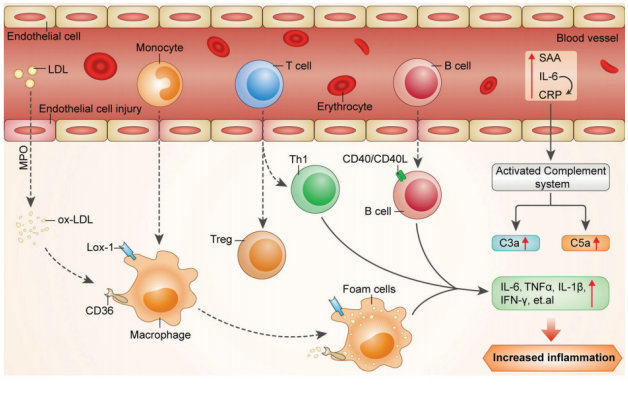

Fig. 1. Cascade of inflammation in atherosclerosis [38]

In a study done by Oemrawsingh RM. et al. it was found that the patients who undergo percutaneous coronary intervention (PCI), and with a high level of hs-CRP at the time of the procedure, have a predictive value for myocardial infarction and 10 year mortality [40]. Thus, hs-CRP being a valuable biomarker, is helpful in assessing subsequent risk in patients having PCI [40]. Even though CRP has been confirmed to be a predictor of cardiovascular events and have direct associations with cardiovascular events, hs-CRP is not a causative factor of cardiovascular diseases [14].

The standard examinations measures CRP in a range of 10-10000 mgL, while the range of high-sensitivity C-reactive protein (hs-CRP) is between 0.5 and 10 mg/L. This indicates that the trace amounts of CRP in the blood can be measured by estimating hs-CRP [39]. In comparison with other acute-phase reactants, hs-CRP have many advantages which include excellent assay precision, availability, accuracy. Due to these, hs-CRP is the analytic element of choice for CV disease risk assessment [34]. Table 2 shows the risk of CV diseases based on the hs-CRP levels [34].

Table 2. The CV disease risk based on hs-CRP level [34]

RISK	hs-CRP level (mg/L)
Low	<1
Average	1-3
High	>3

In a meta-analysis by Tellechea M, an association between CRP and hypothyroidism has been found [12]. Nevertheless, LRT in overt hypothyroidism patients showed significant effect in decreasing the level of CRP, but not in patients with SCH.

Taking into consideration that SCH may progress to overt hypothyroidism, monitoring for TSH and hs-CRP may be useful [9, 12]. Thus, these patients could benefit from early interventions [9].

IL-6

IL-6 is a circulating cytokine with pleiotropic effects (both neurodegenerative and neuroprotective properties) [41] and on inflammation, immune response, and haematopoiesis [42]. The locus of IL-6 is mapped on the chromosome 7p21. The structure comprises 212 amino acids and a core protein of ~ 20 kDa. The synthesis of acute phase proteins, such as CRP, fibrinogen, serum amyloid A and inhibition of albumin is induced by IL-6. Continuous dysregulated production of IL-6 leads to the onset of several diseases.

IL-6 is secreted by activated macrophages, lymphocytes and adipocytes and gets activated by binding to high-affinity receptor complexes [43]. The level of IL-6 is increased in circulation during conditions like obesity (a risk factor for coronary heart disease (CHD) and diabetes mellitus). In systemic inflammation, the level of IL-6 is increased, which in turn increases the level of CRP in CHD prone patients. Elevated IL-6 levels in acute coronary syndrome patients are a strong independent predictor of increased mortality.

IL-6 plays the core role in vascular inflammation. In patients with autoimmune thyroiditis, an increased level of IL-6 is noticed. Even in patients with SCH, a positive correlation is found between SCH and IL-6 [44].

IL-6 being a pro-inflammatory cytokine, increases hepatic production of CRP and thereby promoting atherogenesis [45]. The studies conducted by Turemen EE. et al. and Taddei S. et al., concluded that the presence of high amount of CRP and IL-6 is seen in patients with SCH [46, 47]. One possible explanation may be that TSH in adipocytes promotes the release of IL-6 [1].

Conclusions

It is increasingly evident that SCH has prognostic values and crucial clinical effects, which leads to the view of SCH not being a compensated biochemical change *sensu strictu* [48]. Even a modest but consistent fluctuation in the circulating thyroid hormone levels can create a response from the human heart. Well-timed treatment should be considered as a precaution to avoid the unfavourable CV diseases.

The inflammatory biomarkers, namely CRP and IL-6 are exceptionally robust markers of cardiovascular risk. Thus, using these biomarkers may be helpful in assessing the cardiovascular risk in patients with subclinical hypothyroidism.

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Authors' contributions
SV designed the study, revised the manuscript; GDK conducted literature review, collected the data, interpreted the data, wrote the manuscript. Both authors revised and approved the final version of the manuscript.

Ethics approval and consent to participate
No approval was required for this study.

Conflict of Interests
The authors have no conflict of interests to declare.