

Subclinical Hypothyroidism: The Neglected Thyroid Dysfunction (Review)

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Abstract

With a global prevalence estimated at 4 - 10.5%, subclinical hypothyroidism (SCH) is the most frequent thyroid dysfunction but remains neglected and often under-diagnosed. It is defined by an increase in thyroid stimulating hormone (TSH) level with a normal free total thyroxin (FT4) and absence of specific clinical manifestations of thyroid hormone deficiency.

It has been recently demonstrated that this thyroid dysfunction is associated to a markedly increased cardiovascular risk, significant increase in all-cause mortality, and specific cardiovascular mortality.

This entity remains, however, too controversial in terms of clinical diagnosis, biological thresholds, prognostic implications, and therapeutic management.

The purpose of this review is to familiarize health professionals with the different aspects of this thyroid dysfunction: epidemiology, etiology, natural history, and management.

Keywords: Subclinical Hypothyroidism; Hypothyroidism; Thyroid Gland; Thyroid Dysfunction; Endocrinopathy

Introduction/Definition

Sub-clinical thyroid dysfunctions (hypo- or hyperthyroidism) are far more frequent than clinically symptomatic ones (overt hypo- or hyperthyroidism) [1-3]. These are biological entities characterized by abnormal blood levels of the thyroid stimulating hormone (TSH) with normal concentrations of circulating thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) [4-7]. Sub-clinical hypothyroidism is defined by an increase in plasma TSH with a normal free T4 fraction (free total thyroxin (FT4)). Clinical manifestations of thyroid hormone deficiency are by definition absent [1-8].

However, there are some controversies as to the clinical presentation of subclinical hypothyroidism since, contrary to certain authors who demand that the patient be asymptomatic, others assert that subclinical hypothyroidism may include some signs or symptoms without as much provide a specific justification for the occurrence of these symptoms/signs [9,10].

Indeed even the Billewicz scale modified by Zulewski, *et al.* which groups together 12 clinical items (symptoms and signs) specific for the diagnosis of hypothyroidism with a binary rating for each (0 = absent and 1 = present), recognizes that a score between 3 and 5 can be seen during subclinical hypothyroidism [11].

Being commonly defined as "high TSH with normal FT4", the threshold value of TSH from which the diagnosis of SCH is retained remains poorly specified (2, 4, 6 or even 10 mIU/l?) [12,13]. Therefore, it is currently recommended that the normal TSH interval in a given population be determined from hormonal assays in a representative sample of asymptomatic subjects, without abnormalities of the thyroid parenchyma on cervical ultrasound and without detectable anti-thyroid autoantibodies in their sera [14].

This variability in the possible clinical presentations of SCH can be explained by the existence of an individual “set-point” of TSH; generally determined by the hypothalamic-pituitary-thyroid axis [15,16]. The individual variability of this set-point could explain the different symptomatic spectra in subjects with the same TSH value [13].

According to the joint professional recommendations of the French Society of Endocrinology (SFE) and the French High Authority for Health (HAS) of 2007 relating to the diagnosis and management of SCH in adults, this entity is defined by a plasma TSH level > 4 mIU/l, confirmed by a second dosage at one month, with no abnormalities in the concentration of free T4 [17]. This threshold is 5 mIU/l for other countries/populations [18].

Epidemiology

Prevalence

Even if its average global prevalence is estimated at 4 - 10.5% [1-4], SCH is the most frequent thyroid dysfunction [1-7,19] and this is because it is often under diagnosed; indeed Li H., *et al.* in their work on systemic screening for thyroid dysfunction in a population of healthy Chinese adults (population size = 300) had found SCH in 14.7% of cases versus only 4% for overt hypothyroidism, 2.3% for sub-clinical hyperthyroidism, and 1% for overt hyperthyroidism [19].

SCH is far more common than overt hypothyroidism [1-4]. In fact, a national survey carried out in the United States of America had estimated the prevalence of SCH at 4.3% of the general North American population of all ages, while that of overt hypothyroidism was only 0.3% [20].

The prevalence of SCH is clearly increased in systematic screening studies in asymptomatic healthy subjects: 9.17% in the series of Zou S., *et al.* carried out in the province of Shanghai in China and including 8284 patients aged 5 to 69 years [21], 12.4% in the Ahn SY., *et al.* series of 1073 South Korean patients of different ages [22] and 19.3% in the series of 4409 Indian adults aged 18 to 90 years of Marwaha RK., *et al.* carried out in the district of Delhi [23].

Age

Like all other thyroid diseases, SCH can occur at any age [1-8], but remains particularly common in the elderly, especially after 65 years [3,5,6]. It is also far from being rare in young people and even in young children and adolescents [23,24]: Its overall prevalence in pediatrics is estimated at less than 2% [24,25]. This prevalence, as in adults and the elderly, remains clearly underestimated since Ardestani SK., *et al.* in their series of 284 Iranian schoolchildren, apparently healthy and having an average age of 10.64 years (6-14 years), had detected a SCH in 51 among them (18%) [26].

It also appears to be more common in obese young children and adolescents [27,28]; indeed Emokpae MA., *et al.* noted it in 10.7% of the 56 children and adolescents of average age 10.5 ± 4.3 years with an average body mass index of 31.2 ± 2.2 kg/m² [28].

The prevalence of SCH in a given population increases crescendo with age [1-8].

Gender

Like all the other thyroid dysfunctions which are more prevalent in women with a sex ratio of 5 to 8 women for a man [29], SCH is twice more frequent in women [1-4]; it is noted in 10 to 15% of women over the age of 50 [29] and up to 20% over the age of 60 [30].

In systemic screening studies of all ages, the female predominance is less pronounced: 21.4% in women versus 15.9% in men in the Marwaha RK., *et al.* series [23].

Race/Ethnicity

SCH is a ubiquitous disease found in all ethnicities and all populations but seems to be more common in Hispanics: 3 times more prevalent in the white race [31]. This seems logical to accept since it has been noted that alongside nutritional, immunological and extrinsic environmental factors, the nature and incidence of thyroid dysfunction are influenced by genetic factors [22]. SCHs have been reported during mutations which inactivate the TSH receptor gene (rTSH) [32] and some of which are familial with autosomal dominant transmission and variable expression [33].

Etiologies/triggering conditions

The most frequent and most common etiologies of SCH are autoimmune thyroiditis, postpartum thyroiditis, fibrous and atrophic thyroiditis in the elderly, and iatrogenism (subtotal thyroid surgery, treatment with radioactive iodine, radiotherapy, lithium salts, amiodarone, and treatment with cytokines) [2,4,6,8,14,34]. Rarer causes such as late-onset congenital hypothyroidism (thyroid ectopia or abnormal thyroid hormone synthesis) or TSH-resistance states (mutations in the TSH receptor gene and pseudo-hypoparathyroidism type IA and IC) can also be cited [2,4,32-35].

Transient SCH can exceptionally be encountered after postpartum thyroiditis, silent thyroiditis and granulomatous thyroiditis [36].

Certain clinical situations and/or conditions are associated with a particularly high risk of the development or association of SCH: external cervical radiotherapy: prevalence of SCH at 11.86% [37], cancers of the larynx and hypopharynx whatever therapeutic modalities: SCH prevalence evaluated at 27.7% [38], diabetes mellitus type 2: 16.3% [39] and type 1: 7.2% [40], celiac disease: 17% [41], polycystic ovary syndrome: 11.30 to 11.50% [42,43], major β -thalassemia: 14.80-15.40% [44,45], HIV infection: 6% [46], chronic active viral hepatitis C treated with interferon: 6.6% [47], corticosteroid-resistant nephrotic syndromes: up to 30% in children [48].

In addition, it should be pointed out that pregnant women, subjects over the age of 60, subjects with a personal or family history of thyroid dysfunction or else positive anti-thyroid autoantibodies even at very low rates, as well as heavy smoking represent sub-groups of populations at high risk and prevalence of SCH [13,49,50].

Natural history of subclinical hypothyroidism

SCH evolution is not stereotyped and depends on several factors both endogenous and exogenous, and it is estimated that globally around a third of SCH is spontaneously normalized while the third remains stable, and the other third progresses to overt hypothyroidism [30,51].

Among adult SCH, the annual incidence of overt hypothyroidism is 4/1000 for women and less than 1/1000 for men [30]. The predictors of the progression to overt hypothyroidism are: high initial TSH level (> 10 mIU/l), positive anti-thyroperoxidase (TPO) antibodies, age over 60, history of thyroid dysfunction, and thyrotoxic treatments (amiodarone, lithium, interferon, etc.) [30,51].

In subjects over 65 years of age, SCH persistence at two and four years was found in 56% of cases [52]. Spontaneous resolution of SCH was significantly associated with the negativity of anti-TPO antibodies and TSH level < 10 mIU/l. Initial TSH level > 10 mIU/l was an independent factor for secondary progression to overt hypothyroidism ($p < 0.05$) [52].

In children and adolescents, SCH is often a self-limiting condition and has very low potential for progression to overt hypothyroidism [51,53]. It often remains stable and without repercussions or evolves towards euthyroidism [51,53]: in the large systematic review of the world literature (1990-2012) by Monzani A., *et al.* the risk of progression of SCH to overt hypothyroidism in children and adolescents

was variable from 0 to 28.8%, and the predictors of this progression were: initial presence of goiter, positivity of anti-thyroglobulin auto-antibodies, association with celiac disease, progressive increase in TSH level, and gradual increase of anti-TPO autoantibodies level [51].

Management of subclinical hypothyroidism

Although it is currently accepted that SCH is a situation which is associated with a markedly increased cardiovascular risk, there is today no standardization or consensus on its management: to treat or not to treat? and the TSH threshold value from which to treat? [2-4,54,55].

Recently, the large 2019 meta-analysis of Tsai TY, *et al.* totaling 27 cohorts with 1,114,638 included patients, objectified a significant association between SCH and all-cause mortality as well as specific cardiovascular mortality [56]. Despite these findings, the treatment of SCH remains controversial, especially in the elderly [3-5,57-61].

In the latest practical clinical recommendations of 2019, the therapeutic decision for SCH in adults, especially when TSH level is less than 10 mIU/l must be discussed individually (case by case) [61]. It should therefore be considered after evaluation of the patient's age, the expected potential benefit, and the underlying comorbidities.

It is recommended if SCH is associated with clinical repercussions, ultrasound abnormalities, positive anti-thyroid antibodies, and if TSH level is > 10 mIU/l [61].

In the elderly, and even in the absence of consensus, the prescription of a low dose of thyroxine normalizing TSH level is indicated by the majority of expert clinicians since the benefit on the improvement of the overall cardiovascular risk, quality of life and general mortality is notable [62,63] ("Nothing to lose, everything to gain" as Selmer C said) [63].

Future Directions and Recommendations

SCH is frequent in the general population but its pathological significance, its prognostic implications, and its therapeutic management remain too controversial [4,60,64,65]. Several studies have reported the association of this endocrinopathy with lipid abnormalities, metabolic syndrome, increased cardiovascular risk, cognitive impairment, and obstetrical complications. However, large randomized and prospective studies are necessary to confirm these findings. In the absence of these trials, systemic treatment remains controversial [4,60,64,65]. The treatment decision is based mainly on two reasons: the potential reduction of cardiovascular complications and the prevention of progression to overt hypothyroidism [4].

Until clinical recommendations will be updated, it therefore seems important that:

- Screening for SCH in asymptomatic subjects must be indicated only for those belonging to subgroups of populations at high risk of having this thyroid dysfunction: autoimmune diseases, connective tissue diseases, systemic vasculitis, pregnant women, subjects over 60, subjects with personal or family history of thyroid dysfunction, metabolic syndrome, cardiovascular disease, and treatment that may affect the function of the thyroid gland.
- Treatment for SCH must be based on clinical judgment, cardiovascular risk evaluation, TSH level, and expert opinion. Levothyroxine might be indicated for patients with clinical symptoms and/or TSH >10 mIU/L, children in the growth phase, pregnant women, and subjects with a particularly high cardiovascular risk. For other patients, a "wait-and-see strategy" is advocated.
- Propose large prospective, randomized, multiethnic, and multicentric trials to clarify the association between SCH and cardiovascular risk, and to assess the benefit of systemic levothyroxine therapy.

Conclusion

SCH is a frequent but often neglected and underdiagnosed thyroid dysfunction due to the absence of specific clinical signs, and the lack of consensus and guidelines for its management. This thyroid dysfunction can be seen at any age and can have sometimes severe and serious repercussions. Better knowledge by all health professionals, in particular primary care physicians, is very useful for early diagnosis and appropriate management; especially that an increase in overall mortality and cardiovascular risk have been shown to be significantly associated with this disease.

Conflicts of Interest

None.

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