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SHORT REVIEW

Subclinical hypothyroidism: The state of the art

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ABSTRACT. Subclinical hypothyroidism (SH) is a common clinical problem, particularly in adulthood and the elderly. Its prevalence is conditioned by several etiological and risk factors. The highest age- and sex-specific rates are in women over 60. SH may be associated with manifestations of mild thyroid failure, which may reverse under levothyroxine (L-T_4) therapy. The risk of progression to overt hypothyroidism is distinctly higher in cases with underlying thyroid disease. A population routine screening is not generally recommended, but screening is encouraged in high-risk groups. L-T_4 therapy may be indicated in subjects with TSH levels which are repeatedly and consistently elevated (>10 μIU/ml) and may be considered in those with TSH ranging between 4.5-5.5 and 10 μIU/ml, particularly if anti-thyroid antibodies are positive and/or hypothyroid symptoms are present. Treatment should be based, at least initially, on L-T_4 low doses.

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INTRODUCTION

Subclinical hypothyroidism (SH) is a common clinical problem for which there are many controversial issues regarding definition, screening, and management.

In order to develop an evidence-based approach to the various unresolved clinical issues of SH, the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society jointly sponsored a Consensus Development Conference, which was held in 2002 (1). The expert panel of the Conference defined SH as "a serum TSH concentration above the statistically defined upper limit of the reference range when serum FT_4 concentration is within its reference range" (2) [free T_4 (FT_4)]. Although SH is the term most frequently used to define this condition, it is not necessarily apt, since many patients may disclose mild symptoms and therefore "mild hypothyroidism" may be a more appropriate term (3). Other alternative names are "compensated hypothyroidism" and "preclinical hypothyroidism".

SH is caused by the same thyroid disorders that cause overt thyroid failure, especially Hashimoto's disease (Table 1). Less common causes include overtreatment of Graves' disease, use of medications such as lithium and amiodarone, *post-partum* thyroiditis, inadequate levothyroxine (L-T_4) therapy in patients with known hypothyroidism, non-thyroidal illnesses such as diabetes mellitus, cystic fibrosis, celiac disease, chronic renal failure, and many others (4, 5). In many cases, however, no overt causes can be detected (idiopathic SH).

In 2005 SH was discussed in a number of editorials, commentaries, controversies or letters to the editor concerning the cut-off points for upper normal TSH levels and the creation of guidelines, which are sometimes in dispute (1, 6-8). In another issue of this journal, moreover, there is an "Opinion" by Niedziela concerning "SH: dilemmas in the treatment of children" (9).

The aim of the present short review is to report on the state of the art regarding this controversial question and we will preferentially cover the specific point of the "idiopathic SH".

EPIDEMIOLOGY AND RISK FACTORS

SH is a very frequent syndrome affecting about 10

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Table 1 - *Main predisposing and etiological factors for subclinical hypothyroidism.*

Predisponsing factors	Etiological factors
Female sex	Hashimoto's thyroiditis
Elderly	Non-compliance with levothyroxine treatment in primary hypothyroidism
Pregnancy	Overtreatment with anti-thyroid drugs in Graves' disease
Familial antecedents of thyroid or autoimmune diseases	Down and Turner syndrome
Antecedents of radiation to head, neck, chest	*Post-partum* thyroiditis
False positivity at congenital hypothyroidism screening	Chronic treatment with iodine containing medications
TSH receptor gene variations	Chronic non-thyroidal illnesses

million people in the USA (10). Its average worldwide prevalence has been reported to be in the range of 4-10% in large general population screening surveys (11) and 7-26% in studies of the elderly (12). Apart from the etiological pathological causes that are well known to be responsible for its development, SH prevalence is strongly conditioned by some predisposing factors (Table 1). The highest age- and sex-specific rates are in women older than 60 yr (4), approaching 20% in some reports (13). In men over the age of 74, however, SH prevalence is almost as high as in women of the same age (21%) (13).

Up to 75% of SH patients have only mildly elevated serum TSH values (between 5 and 10 μIU/ml) and 50 to 80% of them have positive thyroid antibody tests (4). Goiter is twice as prevalent in SH patients than in the general population (4).

In pediatric age, SH prevalence seems to be distinctly lower than in old people, although there are only few epidemiological studies concerning childhood and adolescence (14-16). According to one of them, SH frequency in adolescents is slightly lower than 2% (16).

There is only fair evidence to support an association between SH and pregnancy (5). However, a consensus panel for SH has recommended screening serum TSH levels in women who are pregnant or who are planning to become pregnant when there is a family or personal history of thyroid diseases or autoimmune disorders, or evidence of goiter, and/or symptoms of hypothyroidism (2). Due to a physiologic increase of L-T_4 requirements during pregnancy, women who were receiving therapeutic replacement before becoming pregnant should have their serum TSH level monitored every 6-8 weeks during gestation (2).

Another important risk factor for the development of SH is represented by a false positivity at congenital hypothyroidism screening. In fact, newborns with elevated TSH values at screening examination but with normal FT_4 and either normal or slightly elevated TSH at the recall examination are frequently (36-70%) exposed to the risk of developing SH in infancy and early childhood (17).

Finally, another risk factor for children may be represented by sequence variations of thyroperoxidase and TSH receptor genes (17, 18).

MANIFESTATION AND CLINICAL PROBLEMS

SH is, by definition, asymptomatic. The clinical signs and symptoms of thyroid failure, in fact, become evident when hypothyroid disease is fully developed. In a subclinical state, no hypothyroid manifestations should occur, at least in principle. Nevertheless, there are studies which suggest that some patients with SH do indeed have either clinical or biochemical or functional manifestations of mild thyroid failure and that mild symptoms of hypothyroidism are more prevalent in patients with SH than in age-matched controls (19, 20), but not all studies have found this to be true (21).

The abnormalities that have been most frequently reported to be associated with SH in pediatric age concern psychomotor and cognitive development (16, 22). Despite the absence of behavioral manifestations of distractibility and hyperactivity, children with a history of SH may have significant deficits in attention in clinical measures relative to normal distribution (22). On the contrary, in adolescents SH has been recently found to be associated with better performance in some areas of cognitive functions (16). Growth impairment is another adverse clinical consequence of SH that has been occasionally described in childhood. According to this report children with short stature must be evaluated for SH as well as for other causes of short stature (14).

In adulthood and in the elderly SH has been associated with other symptoms, such as depression, memory and cognitive impairment, subtle neuro-

muscular abnormalities, subtle systolic and diastolic cardiac dysfunction, raised serum levels of both total and LDL cholesterol and an increased risk of development of atherosclerosis (12, 23, 24).

NATURAL COURSE

Data from the literature concerning this issue are very controversial.
According to the results of a recent report including a large and homogeneous population aged more than 55 with no underlying thyroid diseases, the probabilities of a spontaneous TSH normalization during a 12-72 month follow-up are very high (25). According to that report early normalizers are more likely to reach lower TSH values than late normalizers (25).
According to many other follow-up studies the percentages of spontaneous TSH normalization in aged patients with SH are distinctly smaller (10, 26, 27).
Other longitudinal studies suggest that 20-50% of individuals with SH develop overt hypothyroidism within 4-8 yr (28). The risk of progression to overt hypothyroidism has been reported to be greater in those patients with goiter or thyroid antibodies, or both (4). The prognostic value of goiter and thyroid autoantobodies has been recently demonstrated even in children and adolescents (29). In the Whickham survey (30) the odds ratio of developing overt thyroid failure was calculated to be 8 in adult women with either a serum TSH value higher than 6 μIU/ml or positive antithyroid antibodies; the odds ratio was 38 when both conditions were present. The odds ratio of developing hypothyroidism was much higher in adult men with similar abnormalities (30).
All these studies documenting a high risk of developing overt thyroid failure, however, were carried out in adult populations.
Data concerning the natural course of SH in childhood and adolescence are very scanty. According to one of the follow-up studies on juvenile SH, this may be a benign and remitting process with a very low risk of evolution towards frank hypothyroidism (31).

SCREENING

Because the majority of individuals with SH have few symptoms or none at all, routine population screening has been advocated (32). Population screening, however, has not been endorsed unanimously, since the benefits of subsequent therapy have not been established in prospective clinical trials (4).
In childhood, considering the low risk of evolution towards overt hypothyroidism, SH screening may be advisable only in the subjects with several risk factors (Table 1) and particularly in those with transient neonatal hyperthyrotropinemia and/or false positivity for congenital hypothyroidism screening (17).
Due to the fact that undetected SH during pregnancy may adversely affect the neuropsychological development (33) and survival (34) of the fetus, SH screening has been proposed particularly for pregnant women (33). Although the data suggesting that SH during pregnancy may be associated with suboptimal intellectual performance of the offspring are based on relatively small numbers of cases, the importance of the recognition of SH in pregnant women might argue in favor of routine screening at the first prenatal screening (1). The American College of Obstetrics and Gynecology, nevertheless, has stated that "there are insufficient data to warrant routine screening for SH of asymptomatic pregnant women" (35).
In the overall population SH screening has been suggested to be warranted every 5 yr in women older than 35 yr of age and in men older than 65 (4).
To sum up, in 2002 the expert panel of the Consensus Conference on SH (2) recommended against population-based screening but "encouraged" assessment in high-risk groups (defined as women with a family history of thyroid disease, prior thyroid dysfunction, symptoms suggestive of hypothyroidism, abnormal thyroid gland on examination or a personal history of autoimmune disorder) (5). The same expert panel found insufficient evidence to recommend for or against screening of pregnant women or women planning a pregnancy (5). In 2004 the U.S. Preventive Services Task Force stated that "the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults" (36).

WHEN TO TREAT

This is the most controversial of all the discussions concerning SH.
The consensus expert panel recommended that subjects with an elevated TSH level have the test repeated together with a serum FT_4 measurement no sooner than 2 weeks but no later than 3 months (2). When repeated studies confirm SH diagnosis, further evaluation is required, including all the points reported in Table 1. Asymptomatic patients with TSH levels between 4.5 and 10 μIU/ml should have a test repeat every 6 months (2). The symptomatic patients with TSH concentration between 4.5 and 10 μIU/ml may try a L-T_4 treatment in order to see if the symptoms improve (2). Finally, the patients with serum TSH levels greater than 10 μIU/ml should be recommended to be treated (2).
The conclusions of that expert panel, however,

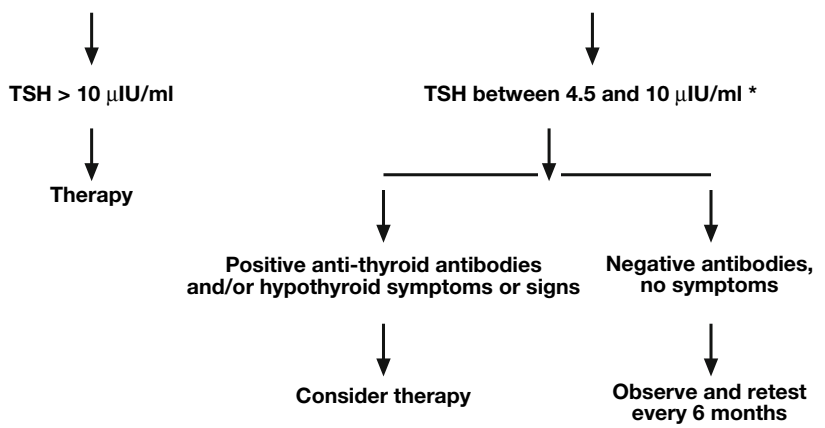
were not unanimously agreed upon (1). In fact, it has been confuted by another expert panel that, in areas where evidence-based data are not sufficient to justify reliable guidelines, the physician's judgement, in conjunction with patient input, should be paramount in this decision-making process (1).
We agree on this point that strict evidence-based strategy is not advisable in the absence of "good evidence". However, according to the literature and our experience the following algorithm may be considered as suitable and may be proposed for all cases. In short, it seems reasonable to treat patients who have a TSH level that is consistently and repeatedly elevated above 10 μIU/ml. Also patients who complain of fatigue, dry skin, constipation, muscle cramps or other common symptoms of thyroid disease (goiter, growth, and/or psychomotor development impairment) may possibly benefit from treatment even if their TSH level is repeatedly elevated only into the 4.5 to 10 μIU/ml range, especially if titers of antithyroid antibodies are increased (Fig. 1).
Our management guidelines are not very different from the ones suggested by expert panel (2) and by the American Association of Clinical Endocrinologists (37). Moreover, we agree with Niedziela on the importance of focusing also on the patients' and their families' history (9). In young children a higher TSH threshold value (at least 5.5 μIU/ml) is to be requested for treatment institution. Pre-pubertal children, in fact, are well known to have higher TSH normal values (38).

HOW TO TREAT

Therapeutic interventions must be evaluated for evidence of potential harm (1). One of the arguments against treatment is the danger of overtreatment, which could cause iatrogenic hyperthyroidism (4). A published report, in fact, indicates that up to 20 percent of patients receiving L-T_4 therapy are overtreated (13).
In adults SH may be controlled with total daily dosages as low as 25 to 50 μg. This initial dosage should be maintained for 6 to 8 weeks before a TSH measurement is repeated to guide adjustment of the L-T_4 dosage. With these initial dosages the risk of iatrogenic hyperthyroidism is very low. The thyroid replacement varies for both weight and age. Data from the literature on L-T_4 dosages in children are very scanty. According to a recent pediatric study a dosage of 2 μg/kg/day may be suitable (14). In our opinion it might be conceivable to begin treatment with an initial dosage of 1 μg/kg/day and then to modify it only in case of persistent hyperthyrotropinemia.
The goal of therapy is to maintain the TSH level within normal limits. L-T_4 dosage should be decreased if the TSH level falls below normal. Once the correct dosage has been established, the frequency of TSH measurements may be decreased to every 6 (in children) or 12 months (in adults).
A common error is to not decrease the L-T_4 dosage if the TSH is suppressed below the normal range. In these cases, in fact, undesired effects on bone density and cardiac function may be observed (19).

EFFECTS OF THERAPY

The first effect of L-T_4 therapy in SH may be the prevention of progression to overt hypothyroidism. Another probable advantage of this treatment is represented by a significant reduction in both to-



*In pre-pubertal children only a TSH value ranging between 5.5 and 10 μIU/ml is to be considered as questionable.

Fig. 1 - *Our algorithm for the management of subclinical hypothyroidism in presence of normal free T_4 levels and repeatedly supranormal TSH levels on different tests.*

tal and LDL cholesterol (32, 39). Finally, L-T_4 therapy may reverse the clinical symptoms of mild hypothyroidism (4). According to the results of randomized, prospective and placebo-controlled trials, L-T_4 therapy in SH seems to be able to significantly improve the hypothyroid symptoms (40, 41). The best therapeutic results have been reported in terms of improvement in cognitive function and memory (40-43). Cardiac function may also significantly improve in SH patients who are treated with L-T_4 compared with patients who are treated with placebo (40).
In SH children with growth retardation, therapy onset has been shown to be followed by growth acceleration and height improvement (14).

CONCLUSIONS

SH is a very topical problem, which has frequently been discussed in the last few years. The most controversial questions are whether screening and replacement treatment may be advisable or not, particularly in childhood and adolescence.
Using a cost-effectiveness model does not provide enough sufficient evidence for or against a population-based screening, even in pregnant women. Nevertheless this screening is probably to be encouraged in high-risk groups.
With regard to SH treatment, the strategy that is shared by the majority of experts is to treat individuals with TSH which is repeatedly higher than 10 μIU/ml. When TSH level is lower than 10 μIU/ml and repeatedly between 4.5 (in adults) or 5.5 μIU/ml (in prepubertal children), L-T_4 therapy is to be considered only in subjects with positive anti-thyroid antibodies and/or hypothyroid symptoms or signs, whereas the subjects with idiopathic and asymptomatic SH should only be checked and periodically retested.

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