The Brazilian consensus for the clinical approach and treatment of subclinical hypothyroidism in adults: recommendations of the thyroid Department of the Brazilian Society of Endocrinology and Metabolism

Consenso brasileiro para a abordagem clínica e tratamento do hipotireoidismo subclínico em adultos: recomendações do Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia

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ABSTRACT

Introduction: Subclinical hypothyroidism (SCH), defined as elevated concentrations of thyroid stimulating hormone (TSH) despite normal levels of thyroid hormones, is highly prevalent in Brazil, especially among women and the elderly. Although an increasing number of studies have related SCH to an increased risk of coronary artery disease and mortality, there have been no randomized clinical trials verifying the benefit of levothyroxine treatment in reducing these risks, and the treatment remains controversial. **Objective:** This consensus, sponsored by the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism and developed by Brazilian experts with extensive clinical experience with thyroid diseases, presents these recommendations based on evidence for the clinical management of SCH patients in Brazil. **Materials and methods:** After structuring the clinical questions, the search for evidence in the literature was initially performed in the MedLine-PubMed database and later in the Embase and SciELO – Lilacs databases. The strength of evidence was evaluated according to the Oxford classification system and established based on the experimental design used, considering the best available evidence for each question and the Brazilian experience. **Results:** The topics covered included SCH definition and diagnosis, natural history, clinical significance, treatment and pregnancy, and the consensus issued 29 recommendations for the clinical management of adult patients with SCH. **Conclusion:** Treatment with levothyroxine was recommended for all patients with persistent SCH with serum TSH values ≥ 10 mU/L and for certain patient subgroups. Arq Bras Endocrinol Metab. 2013;57(3):166-83

Keywords
Hypothyroidism; subclinical hypothyroidism; consensus; guidelines

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RESUMO

Introdução: O hipotireoidismo subclínico (HSC), definido por concentrações elevadas do TSH em face de níveis normais dos hormônios tireoidianos, tem elevada prevalência no Brasil, particularmente entre mulheres e idosos. Embora um número crescente de estudos venha associando o HSC com maior risco de doença arterial coronariana e de mortalidade, não há ensaio clínico randomizado sobre o benefício do tratamento com levotiroxina na redução dos riscos e o tratamento permanece controverso. **Objetivo:** Este consenso, patrocinado pelo Departamento de Tireoide da Sociedade Brasileira de Endocrinologia e Metabologia e desenvolvido por especialistas brasileiros com vasta experiência clínica em tireoide, apresenta recomendações baseadas em evidências para uma abordagem clínica do paciente com HSC no Brasil. **Materiais e métodos:** Após estruturação das questões clínicas, a busca das evidências disponíveis na literatura foi realizada inicialmente na base de dados do Medline-PubMed e posteriormente nas bases Embase e SciELO – Lilacs. A força da evidência, avaliada pelo sistema de classificação de Oxford, foi estabelecida a partir do desenho de estudo utilizado, considerando-se a melhor evidência disponível para cada questão e a experiência brasileira. **Resultados:** Os temas abordados foram definição e diagnóstico, história natural, significado clínico, tratamento e gestação, que resultaram em 29 recomendações para a abordagem clínica do paciente adulto com HSC. **Conclusão:** O tratamento com levotiroxina foi recomendado para todos os pacientes com HSC persistente com níveis séricos do TSH ≥ 10 mU/L e para alguns subgrupos especiais de pacientes. Arq Bras Endocrinol Metab. 2013;57(3):166-83

Descritores

Hipotiroidismo; hipotiroidismo subclínico; consenso; diretriz

INTRODUCTION

Subclinical hypothyroidism (SCH) has been biochemically defined by the presence of elevated serum thyroid stimulating hormone (TSH) levels despite normal serum concentrations of thyroid hormones (1-3). The prevalence of SCH in the general population is approximately 4%-10%, being higher in women and the elderly and inversely proportional to the iodine content in the diet (4-7). In Brazil, the prevalence of elevated TSH in a representative sample of 1,220 adult women of Rio de Janeiro city was 12.3% and reached 19.1% among women who were over 70 years of age (8). In the metropolitan area of São Paulo, the prevalence of hypothyroidism in 1,085 individuals was 8% (9). Among 1,110 individuals from a Japanese-Brazilian population of Bauru ≥ 30 years old, the prevalence of hypothyroidism was 11.1% in females and 8.7% in males (10), and in an elderly population of São Paulo city, the prevalence of SCH was 6.5% and 6.1% for females and males, respectively (11).

In the last decade, a growing number of studies have associated SCH with increased risk of coronary artery disease and mortality (12,13). However, strong and conclusive evidence has not been found from randomized prospective double-blind studies for the potential benefits of levothyroxine therapy.

Recently, the American Thyroid Association in conjunction with the American Association of Clinical Endocrinologists published recommendations (14) for hypothyroidism; however, there were few specific recommendations for the subclinical dysfunction. In Brazil, there is currently no consensus on SCH diagnosis and treatment.

The present consensus unifies the efforts of the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism to develop recommendations based on available evidence in the literature with the clinical approach to SCH patients in our country. The main objectives were to develop recommendations to assist clinicians in delivering the best health care possible to patients and avoid unnecessary procedures within the context of the Brazilian health care system.

METHODS

This consensus follows the strategic policy of the Thyroid Department of the Brazilian Society of Endocrinology and Metabolism in the development of

national consensus for major thyroid diseases, directed at this population and in the context of the Brazilian health care system.

The model used was based on the Guidelines Program (15) of the Brazilian Medical Association (*Associação Médica Brasileira*, AMB) and the Federal Council of Medicine (*Conselho Federal de Medicina*, CFM) because this program represents a genuinely national initiative and is already known by the medical and academic community in the country. After choosing the participants with recognized academic performance and extensive clinical experience with thyroid diseases, the clinical questions were developed. The publications were obtained by searching the Medline-PubMed, Embase and SciELO – Lilacs databases. The keywords were identified by different means such as accessing the "Citation" (PubMed) after obtaining known publications that provided answers to the specified questions. The Oxford classification was used to classify the degree of recommendation or the strength of evidence of the work (Table 1) (15); this classification establishes the strength of the evidence based on the experimental design used, considering both the best available evidence for each question and the Brazilian experience. This system was chosen primarily because it is the same used by the Guidelines Program of AMB/CFM (16), with which the Brazilian medical community and academia are familiar.

Table 1. Definition of the strength of recommendation of the evidence according to the Oxford classification (modified from references 15 and 16)

Recommendation	Strength of evidence
A	Experimental and observational studies of best consistency
B	Experimental and observational studies of less consistency
C	Case reports (uncontrolled studies)
D	Opinion without critical evaluation, based on consensus, physiological studies or animal models

DEFINITION AND DIAGNOSTIC

What is the definition of SCH?

Recommendation 1

*Although the subclinical term is associated with the absence of obvious symptoms of hormone production failure by the thyroid gland, SCH is defined biochemically by elevated serum TSH values in the presence of normal serum free T4 (FT4) (1,2) (**D**).*

What is the normal TSH value in the general population according to age and in specific populations?

The reference limits for TSH, similar to any other test, are obtained by averaging the TSH values from a supposedly healthy population without thyroid disease within a 95% confidence interval (between the 2.5 and 97.5 percentiles) (17). Ideally, normal TSH levels should be based on values determined from fasting samples collected in the morning, from individuals without a personal history or a family history of thyroid disorders, without goiter, without thyroid disorders observed on the ultrasound and with negative anti-thyroperoxidase (TPOAb) and anti-thyroglobulin (TgAb) antibodies (18). However, it is difficult to obtain this ideal population, and the reference limits commonly used today for all races, genders and ethnicities were provided by large North-American population studies, which defined the reference limit of serum TSH for a normal adult to be between 0.4 and 4.5 mU/L (4,19).

A statistical reanalysis of the North-American population data, considered the effects of age, race/ethnicity, gender and body weight in individuals who had neither thyroid disease nor goiter; were not taking medication; were not pregnant; were not taking estrogens, androgens or lithium; had normal urinary concentrations of iodine; and in whom antithyroid antibodies were undetectable. This reanalysis showed that the mean normal TSH values are between 1.40 and 1.90 mU/L and are 1.0 mU/L higher in the White population than in the Black population (19). Table 2 shows the mean levels and the 2.5 and 97.5 percentiles obtained by the analysis of 13,296 individuals of different ages without apparent thyroid disease (19).

Table 2. The distribution of average and 2.5 and 97.5 percentiles of the TSH values obtained from 13.296 individuals of all races and both sexes. who were thyroid disease free (modified from reference 19)

Age (years)	2.5 Percentile	Median	97.5 Percentile
All ages	0.42	1.40	4.30
13-19	0.41	1.30	3.78
20-29	0.40	1.30	3.60
30-39	0.38	1.25	3.60
40-49	0.44	1.40	3.90
50-59	0.49	1.50	4.20
60-69	0.46	1.66	4.70
70-79	0.47	1.74	5.60
80 +	0.44	1.90	6.30

TSH values expressed in mU/L.

A national study was performed on 960 adults between 18 and 60 years of age (excluding pregnant women), without goiter or detectable antithyroid antibodies, who did not use drugs that potentially interfere with thyroid function or status, had no personal or family history of thyroid disorders and had normal levels of serum FT4. In this study, the mean TSH value was 1.52 mU/L, with a 2.5 percentile value of 0.43 mU/L and a 97.5 percentile value of 3.24 mU/L (20).

The effect of age on the upper limit of what is considered normal should always be considered, especially when the treatment with levothyroxine is debated for elderly individuals in whom the physiological increase of serum TSH may represent a cardiovascular protective factor (21) and may be associated with greater longevity (22).

The reference limits in the pediatric population are higher shortly after birth, decreasing quickly over the first days and then progressively with increasing age (23,24). Table 3 shows the percentiles obtained in a population of 654 boys and girls aged up to 18 years of age (23).

Table 3. The reference percentiles of TSH in children (modified from reference 23)

Age	Percentile				
	2,5	25	50	75	97,5
7 days	0,32	1,66	3,11	5,30	12,27
14 days	0,34	1,64	3,01	5,06	11,44
21 days	0,35	1,61	2,89	4,76	10,43
28 days	0,36	1,58	2,80	4,55	9,75
3 months	0,32	1,78	3,25	5,32	11,21
1 year	0,38	1,55	2,62	4,10	8,14
4 years	0,66	1,52	2,18	3,02	5,15
7 years	0,80	1,69	2,35	3,19	5,24
12 years	0,66	1,48	2,11	2,90	4,88
18 years	0,49	1,22	1,79	2,51	3,38

TSH values expressed in mU/L.

During pregnancy, there is a decrease in serum TSH values (25). However, the complexity and dynamics of the hormonal changes occurring during pregnancy, especially in the first trimester, make the establishment of reference values more difficult. Changes in iodine metabolism, the production of chorionic gonadotropin (beta-hCG), increases in thyroid hormone carrier proteins, changes in excretion and elevation of thyroid hormones levels *per se*, alter the reference values (26). Thus, it is important that laboratories establish reference ranges for each population, particularly in regions where there may be iodine deficiency. In the absence of local standards, the upper limits of normal TSH values can be up to 2.5 mU/L in the first trimester and up to 3.5 mU/L in the following two trimesters, as described in studies with a large number of pregnant women (27,28).

Recommendation 2

*The reference value for serum TSH for healthy adults is between 0.4 and 4.5 mU/L (4,19) (**A**). For pediatric (23) (**B**) and elderly patients (22) (**B**), it is important to evaluate the values according to the normal ranges suggested for each age. During pregnancy, TSH values up to 2.5 mU/L in the first trimester and 3.5 mU/L in the following two trimesters should be considered the normal upper limits in the absence of a local laboratory reference (27) (**B**).*

How should SCH be diagnosed?

In general, a laboratory investigation for thyroid dysfunction is performed in individuals with a clinical suspicion of a thyroid disorder. SCH can be associated with symptoms of hypothyroidism (5); however, the clinical manifestations are not usually evident, and when they occur, they may be rather non-specific. Thus, an investigation should be performed when there is a suspicion of SCH or as a screening in individuals from specific groups such as women over 35 years of age every 5 years, patients with previous personal or family history of thyroid disease, undergoing thyroid surgery, previous therapy with radioiodine or external radiation in the neck, type 1 diabetes, personal or family history of autoimmune disease, Down and Turner syndromes, lithium or amiodarone treatment, depression, dyslipidemia and hyperprolactinemia (1,14).

The diagnosis of SCH is biochemical and consists of the detection of elevated serum concentrations of TSH despite normal levels of FT4, when other causes of high TSH are excluded (Table 4) (2,17). Although an exact and absolute upper cutoff level of TSH cannot be defined (28), TSH values between 4.5 mU/L and 20 mU/L have been accepted as the cutoff (4,19) and upper level (13), respectively, for the SCH diagnosis.

SCH must also be differentiated from other causes (Table 4) of elevated TSH with normal serum FT4 concentrations such as the following: the physiological elevation of TSH with increasing age (29); use of recombinant TSH in patients undergoing cancer thyroid

Table 4. Causes of increases in serum TSH concentrations despite normal FT4, that should be differentiated from SCH

Causes
Temporary increase in TSH
Recent adjustments in the dose of levothyroxine
Hypothyroidism under-treated with levothyroxine
Recovery from subacute thyroiditis
After administration of radioiodine for Graves' disease
Recovery phase from Graves' disease
Other causes of TSH elevation
TSH elevation with increasing age
Use of recombinant TSH in patients undergoing thyroid cancer surgery
Untreated primary adrenal insufficiency
Cross-reaction of TSH with heterophilic antibodies against rat proteins
Mutations in the TSH receptor

surgery (30); untreated primary adrenal insufficiency (31); cross-reaction of TSH with heterophilic antibodies against rat proteins (32); and mutations in the TSH receptor (33). In most cases, a careful patient history helps the clinician establish the correct diagnosis.

Recommendation 3

*SCH is biochemically diagnosed by serum TSH ≥ 4.5 mU/L despite normal FT4 levels (4,19) (**A**), when other causes of high TSH are excluded. The consensus accepts values up to 20 mU/L as the upper limit for TSH in the diagnosis of SCH (13) (**D**).*

Recommendation 4

*The determination of serum TSH should be requested in situations where there is clinical suspicion of SCH (5) (**A**) or as a screening in specific groups of high-risk individuals (1) (**D**).*

How should persistent and progressive SCH be differentiated from transitional SCH?

Only patients with persistent SCH should be considered for treatment. Thus, persistent SCH should be differentiated from the situations associated with temporary increases in TSH (Table 4) including recovery from subacute thyroiditis (34), after administration of radioiodine to treat Graves' disease (35) and during recovery from debilitating diseases (36).

A significant proportion of patients with SCH show normal TSH levels during the first 2-5 years of follow-up (37), especially those with serum TSH value ≤ 10 mU/L (38). Thus, when there is a suspicion of SCH, the determination of TSH should be repeated after 3-6 months to exclude laboratory error or temporary causes of TSH elevation.

Recommendation 5

*Persistent or progressive SCH must be differentiated from temporary causes of high TSH, which may regress during follow-up (37) (**A**) especially in patients with serum TSH ≤ 10 mU/L (38) (**B**). TSH should be repeated initially within 3 months to confirm persistent SCH (1) (**D**).*

How should SCH be classified according to TSH levels?

SCH has been classified according to the magnitude of the increase in serum TSH concentrations, the risk of progression to overt hypothyroidism and the association with comorbidities. Serum TSH values ≥ 10 mU/L are associated with a high risk of progression to overt hypothyroidism (39), coronary artery disease and death (13). Thus, some authors have proposed the sub-classification of SCH according to severity into mild-moderate SCH (TSH values 4.5-9.9 mU/L) or severe SCH (TSH values ≥ 10 mU/L) (2).

Recommendation 6

*Considering the rates of progression to overt hypothyroidism (39) (**B**) and the risk of coronary events and mortality (13) (**A**), SCH should be classified according to serum TSH concentrations into mild-moderate (TSH values 4.5-9.9 mU/L) and severe (TSH values ≥ 10 mU/L) (2) (**D**).*

NATURAL HISTORY

What are the predictors of progression to overt hypothyroidism?

SCH may progress to overt hypothyroidism, remain relatively stable for long periods or regress to a normal thyroid function depending on individual and population characteristics (40). In the Whickham study (7), women with elevated TSH levels (> 6 mU/L) and positive antithyroid antibodies had an annual rate of progression to overt hypothyroidism of 4.3%, while for women with high levels of TSH and negative thyroid antibodies, this rate was only 2.6%. In at least one other longitudinal study, the combination of elevated TSH and positive antithyroid antibodies was predictive of progression to overt hypothyroidism in females (41).

Prospective studies in a cohort of patients showed higher rates of progression that were generally also associated with serum TSH concentrations and the presence of thyroid autoimmunity. Diez and Iglesias (39) observed that patients with SCH and TSH levels < 10 mU/L had a lower incidence rate (1.76%) of overt hypothyroidism compared with patients with TSH levels ranging from 10 to 14.9 mU/L (19.7%) and 15 to 19.9 mU/L (73.5%). Huber and cols. (42) showed that the annual incidence of overt hypothyroidism ranged from 3.3% (TSH values 6-12 mU/L) to 11.4% (TSH values > 12 mU/L) and also depended on the presence of positive antithyroid antibodies. In Brazil, Rosario and cols. (43) showed that not only the presence of TPOAb antibodies but also ultrasonographic aspects indicating autoimmune thyroiditis are associated with an increased risk of progression to overt hypothyroidism. Similarly, Marcocci and cols. (44) concluded that patients with autoimmune thyroiditis and hypoechogenicity on thyroid ultrasound were more likely to progress to overt hypothyroidism. Increased iodine intake was also a risk factor for progression in a Chinese population study (45).

Conversely, in a significant proportion of patients, elevated serum TSH levels observed in the first evaluation might progress to normal levels in a second evaluation. In a large Israeli population study (37), the normalization rate was 62% in 5 years of follow-up; therefore, it is imperative to repeat TSH measurements before making treatment decisions. The return to euthyroidism tends to be more frequent in patients with serum TSH levels 4-6 mU/L, while TSH values between 10-15 mU/L are associated with a low frequency of thyroid function normalization (38,39,46,47).

The majority of elderly patients with SCH remain in this condition after 12 (76.7%) (38) and 24 months (56%) (48), and TSH values ≥ 10 mU/L was an independent predictor of risk for progression to overt hypothyroidism (39,48).

Children and adolescents appear to have low risk of SCH progression to overt hypothyroidism (49,50). In a prospective study, most patients (88%) experienced normalization or stabilization of their TSH levels (49). The presence of goiter, celiac disease, positive antithyroid antibodies, higher TSH levels in the initial presentation or progressive elevation of TSH levels appear to be predictors of overt hypothyroidism in this age group (51,52).

Recommendation 7

*In females (7,39) (**B**), serum TSH levels (39) (**B**), thyroid autoimmunity (7,39,41) (**B**), and increased iodine intake (45) (**A**) are risk factors associated with progression to overt hypothyroidism.* TSH levels ≥ 10 mU/L are associated with an increased risk of progression to overt hypothyroidism in adults (38,39,41,42) (**B**) and in the elderly (48) (**A**). *There is no evidence of risk in males, possibly because of the low prevalence of hypothyroidism among men.*

Recommendation 8

*The risk of progression to overt hypothyroidism is low among children and adolescents (49,50) (**B**), but it may be higher in the presence of goiter, celiac disease, positive antithyroid antibodies and higher TSH levels (51,52) (**B**).*

Recommendation 9

*The determination of TPOAb antibodies (7,39,41) (**B**) and a thyroid ultrasound (43,44) (**A**,**B**) may be useful in determining SCH etiology and predicting the risk of progression to overt hypothyroidism.*

CLINICAL SIGNIFICANCE

Does SCH affect quality of life and neurocognitive function?

The effects of overt hypothyroidism on patient quality of life are well established but remain controversial in SCH patients. Only 24% of patients with SCH were classified as having overt hypothyroidism in a study aimed at developing a clinical index based on scores to assess the severity of hypothyroidism (53). In a cross-sectional study conducted in Colorado (USA) (5), SCH patients reported more symptoms of hypothyroidism compared with euthyroid controls; however, the sensitivity and the positive predictive value were low. In a study of an Australian community (54), SCH was not associated with a worsening of the quality of life, which is a result similar to the one obtained in Brazil (55). In specific elderly populations (56-58), SCH was not associated with significant effects on cognition, depression and anxiety.

In Brazil, the results obtained from cross-sectional studies have been controversial. Almeida and cols. (59) did not find differences in the neurocognitive evaluation between 65 patients with SCH and 31 healthy

controls. The same group found in another study that, although symptoms of depression and anxiety were positively associated with TSH levels in SCH patients, levothyroxine replacement did not have any benefits (60).

Recommendation 10

*SCH can be symptomatic in a small proportion of patients (5,53) (**A,B**); however, there is no overwhelming evidence regarding the effects of this disorder on quality of life and cognitive function (54) (**A**). In the elderly, SCH is not associated with effects on cognitive function, depression or anxiety (56-58) (**A,B,A**).*

Is there an association between dyslipidemia and SCH?

Thyroid hormones act in different pathways of lipid metabolism, and overt hypothyroidism may be associated with dyslipidemia through different mechanisms (61). It has been hypothesized that these changes may occur in patients with SCH, but the results of different studies are conflicting. In the Rotterdam study (62), no significant differences were found in serum total cholesterol levels and non-HDL cholesterol (triglycerides and LDL-c were not assessed) between individuals with SCH and those with euthyroidism, although a strong association of SCH with the risk of atherosclerosis and myocardial infarction in elderly women was observed. The data obtained from the study National Health and Nutritional Examination Survey (NHANES) (63) in the North American population have reinforced these findings because no evidence of an association between SCH and dyslipidemia was found. Likewise, no association of SCH with lipid profile abnormalities was found in a Japanese-Brazilian population (10). In a large cross-sectional study (64) with 7,000 consecutive outpatients, there was no association of SCH with changes in serum total cholesterol levels, LDL-c and triglycerides.

Moreover, other population studies found an association between SCH and dyslipidemia. In the Health, Aging, and Body Composition Study (65), there was a significant association between SCH and increased serum total cholesterol levels, but only among Black women. In the Australian study conducted in Busselton (66), elevated serum LDL-c levels were associated with SCH even after adjusting for sex and age. In the Tromso study (67), a positive correlation between serum TSH levels and lipid parameters was also found. The study performed in Colorado (USA) (5) with more than 25,000 participants (2,336 with SCH) showed a significant association of SCH with high serum total cholesterol levels and a positive correlation between serum TSH levels and total cholesterol; however, the analyses were not adjusted for age and sex. More recently, an association of SCH with dyslipidemia was shown in a Chinese population (68). Factors that appear to contribute and strengthen the association of SCH with dyslipidemia include TSH levels > 10 mU/L (69,70), a smoking habit (71) and insulin resistance (72,73). Moreover, population studies involving euthyroid individuals suggest that small elevations in serum TSH, even within the normal range, may be associated with elevated lipid parameters (74,75).

Recommendation 11

*There is a discrepancy among the population studies regarding a potential association of SCH with dyslipidemia; however, serum TSH levels > 10 mU/L (69,70) (**A**), a smoking habit (71) (**B**) and insulin resistance (72,73) (**B**) are associated with an increased risk for dyslipidemia in SCH patients.*

What are the effects of SCH on the vascular endothelium?

Thyroid hormones exert effects on the endothelium and vascular smooth muscle cells, which in turn, play a major role in the modulation of vascular tone (76). In addition, the TSH receptor is expressed in the vascular smooth muscle cells (77), and TSH has direct effects on human endothelial cells (78,79).

Lekakis and cols. (80) were the first to describe a negative relationship between SCH and endothelium-dependent vasodilation, measuring the brachial artery flow-mediated dilation that was subsequently confirmed by other studies (81,82). In a randomized double-blind crossover study, Razvi and cols. (83) showed that replacement therapy with levothyroxine increased the flow-mediated dilatation of the brachial artery in SCH patients. More recently, Traub-Weidinger and cols. (84) observed a reversible coronary microvascular dysfunction after treatment with levothyroxine in 10 patients with SCH due to autoimmune disease.

Recommendation 12

There are few studies in the literature regarding the effects of SCH on the vascular endothelium. The majority of studies have a sample with an insufficient number of

patients, thereby limiting the strength of the evidence regarding the cause-effect relationship.

What are the effects of SCH on cardiac function?

Thyroid hormones have important effects on cardiac physiology through genetic and non-genetic mechanisms, and it has been speculated that changes in these mechanisms as a result of SCH could be associated with changes in the cardiac structure and function as occurs in overt hypothyroidism (76).

Changes in systolic and diastolic functions have been reported in patients with SCH in small studies with methodological limitations (85-91), while no structural or functional alterations were associated with SCH in 2 population studies (92,93).

Conversely, the association of SCH with heart failure has been demonstrated more consistently in epidemiological studies and meta-analyses, especially for serum TSH levels > 10 mU/L (94-97) and in the elderly (94,95,97). However, in a single cohort with repeated measurements of thyroid function over time, the association of persistent SCH with heart failure in elderly patients was not confirmed, suggesting that the temporary SCH effects could mask those from the persistent SCH in studies based only in one determination of thyroid function (98).

Recommendation 13

*There is no consistent evidence regarding the effects of SCH on cardiac structure and systolic and diastolic functions in population studies (92,93) (**B**,**A**).*

Recommendation 14

*There is evidence showing a significant association of SCH with congestive heart failure, especially in the elderly (94,95,97) (**A**) and in patients with TSH levels above 10 mU/L (96) (**A**).*

Is SCH associated with cardiovascular risk and mortality?

Several prospective population studies (10,12,62,94-107) have explored the potential associations of SCH with cardiovascular risk and mortality; however, the results are conflicting, possibly due to multiple factors including the following: differences in the definitions used for SCH and coronary artery disease; inclusion of populations with specific characteristics, with different ethnicities and ages; different inclusion and exclusion criteria; and different adjustments of the confounding factors that interfere with the prognosis, among others (108).

In Brazil, in one prospective population study in the Japanese-Brazilian community of Bauru (10), SCH was significantly associated with an increased risk of death from any cause in 7.5 years of follow up, but not with cardiovascular causes. However, the number of events was small, which most likely limited the statistical power to determine significance. Moreover, because it was a specific population of Japanese-Brazilians, the data cannot be generalized for the entire Brazilian population.

The impact of SCH on cardiovascular risk has also been investigated in different meta-analyses (109-112), but the results were also conflicting, possibly because of the heterogeneity of the studies. However, more recently, a complex meta-analysis (13) based on individual data from 11 prospective studies included 55,287 subjects with homogeneous criteria for inclusion and exclusion and a single definition for SCH and coronary artery disease. In this study (13), SCH was significantly associated with both increased risk and death from coronary artery disease. The risks for both outcomes were higher for TSH levels ≥ 10 mU/L, but death as a result of coronary artery disease was also significant with TSH levels ≥ 7 mU/L.

In the elderly, however, a meta-analysis (21) did not find any association of SCH with cardiovascular risk and mortality, suggesting that the SCH does not exert the same effect on cardiovascular risk in the elderly compared to a younger population.

Recommendation 15

*There is consistent evidence for an association of SCH with risk of coronary artery disease and death from coronary artery disease, especially for TSH values ≥ 10 mU/L (13) (**A**), but this is not observed in elderly patients aged > 65 years (21) (**A**).*

TREATMENT

When should SCH be treated?

The risk of progression to overt hypothyroidism is the first parameter to consider in the clinical decision regarding treatment. Therefore, patients with persistent SCH, especially with serum TSH levels ≥ 10 mU/L (38,39,41,42), positive TPOAb (7,39,41) and/or with ultrasonographic changes (44) that suggest thyroid au-

toimmunity would be candidates for treatment because of the characteristics associated with a higher rate of progression to overt hypothyroidism.

The presence of symptoms related to hypothyroidism is often considered by clinicians to indicate the treatment. However, the effects of replacement therapy with levothyroxine in patients with SCH on mood, cognition and quality of life vary among the different studies according to the type of population, with the definition of SCH and methods of measuring outcome. There are few clinical, randomized and placebo-controlled trials that have evaluated the impact of treatment on these outcomes. Some trials have demonstrated beneficial effects (113-116), while others did not confirm these results (117-120). In the elderly with SCH, a randomized study showed that treatment with levothyroxine does not improve cognitive function compared with a placebo (120), although only 27 of the 42 placebo-treated patients completed the study, which may have influenced the results.

Another possible benefit of levothyroxine treatment in patients with SCH would be in regard to dyslipidemia. However, few randomized placebo-controlled trials have evaluated the effect of levothyroxine on the lipid profile of SCH patients. Some trials did not observe a reduction in the levels of lipid parameters with the treatment (113-115,118), while others demonstrated favorable effects (67,83,121-123). Two meta-analyses also assessed the effects of levothyroxine replacement on the lipid profile of SCH patients (69,70). The first meta-analysis (69) was favorable to treatment, but most of the selected studies were not randomized. Conversely, in the second meta-analysis (70), which selected only placebo-controlled randomized studies, the beneficial effects of levothyroxine were slight and only affected total cholesterol. Both meta-analyses (69,70) showed that the potential benefits of the treatment occurred in patients with TSH levels > 10 mU/L. Later, a few randomized trials have been published with the same goal, but all presented with methodological limitations. In a randomized crossover study, Ravzi and cols. (83) observed the beneficial effects of levothyroxine treatment on total cholesterol LDL, but without differences compared with the placebo group, and at the end of 3 months, only 71/100 patients had TSH levels within the target range.

In a study of paired analysis (pre and post intervention), Adrees and cols. (124) demonstrated favorable effects of levothyroxine treatment on women with SCH, and in a randomized placebo-controlled trial conducted in Brazil, Teixeira and cols. (125) demonstrated that the levothyroxine replacement reduced the levels of LDL-c and total cholesterol, especially in postmenopausal women with positive antithyroid antibodies and serum TSH levels > 8.0 mU/L. However, only 38 of the 60 subjects completed the 6 months of treatment.

There are also few randomized placebo-controlled trials that demonstrated a beneficial effect of SCH treatment on endothelial function (83,122) (**A**) or cardiac structure and function, and the studies had methodological limitations and conflicting results (83,87,88,126-129).

However, there is consistent evidence (13) for an association of SCH with increased risk and death from coronary artery disease, especially for TSH levels above 10 mU/L. Death as a result of coronary arterial disease was also significantly higher for TSH values from 7 mU/L. In a meta-analysis (21), the association of SCH with increased cardiovascular risk and mortality was significant only for individuals aged less than 65 years. Despite these data on the association of risk between SCH and cardiovascular outcomes and death, no randomized placebo-controlled clinical trials have been conducted to evaluate the impact of levothyroxine treatment on these outcomes in patients with SCH. However, there is indirect evidence of potential benefits obtained from population-based cohort studies data to assess these outcomes, where one group of SCH patients was treated and another was not. In the Cardiovascular Health Study cohort, individuals with SCH treated with levothyroxine had a lower risk of cardiovascular events compared with untreated individuals (97). A reanalysis of the Whickham study (12) demonstrated that the treatment of SCH was associated with a reduction in total mortality after 20 years of follow up, even after multiple adjustments for other factors that influence prognosis. In the study Preventive Cardiology Information System (PreCIS; Cleveland Clinic – USA) (106), patients with moderate SCH (TSH > 6.0-10 mU/L) and overt hypothyroidism had a higher risk of mortality from all causes, especially in individuals under 65 years that did not receive levothyroxine throughout the cohort. Finally, in a UK cohort (130), young adult patients (40-70 years old) recently diagnosed with SCH (TSH, 5.01 to 10 mU/L) that had received levothyroxine treatment were less likely to have coronary artery disease events and less likely to die as a result of all causes at 7.6 years of follow-up compared with patients who did not

receive levothyroxine. However, no positive effect was observed in the elderly subjects (> 70 years old).

Recommendation 16

*SCH treatment remains controversial, and it is not supported by evidence because of the lack of randomized and placebo-controlled studies with sufficient numbers of patients to demonstrate the benefits of the treatment on cardiovascular risk and mortality risk. Thus, treatment should be considered in specific situations, depending on the available evidence regarding the clinical significance of SCH, in subgroups of patients who might benefit from treatment and based on individual clinical judgment (**D**).*

Recommendation 17

*Treatment for SCH should only be considered for patients with persistent SCH and after confirmation of serum TSH levels after 3 - 6 months (37) (**A**).*

Recommendation 18

The consensus recommends levothyroxine treatment for all patients with persistent SCH and serum concentrations of TSH ≥ 10 mU/L (Table 5) because of the higher risk of progression to overt *hypothyroidism (39,41,42) (**B**), heart failure (96) (**A**), coronary artery disease and mortality (13) (**A**). There are also cohort studies with indirect evidence showing the benefits of SCH treatment on cardiovascular risk and mortality (12,97,106,130) (**B**). Furthermore, there is evidence (70) (**A**) suggesting a favorable effect of levothyroxine treatment on serum total cholesterol in patients with SCH and TSH levels > 10 mU/L.*

Recommendation 19

For patients with persistent SCH and serum TSH levels < 10 mU/L (Table 5), treatment may be considered for subgroups of patients with specific characteristics, as follows:

*Female patients (7,39) (**B**) with positive TPOAb (7,39,41) (**B**) and/or with ultrasound changes that suggest Hashimoto's thyroiditis (43,44) (**A,B**) and with a progressive increase in serum TSH levels due to the higher risk of progression to overt hypothyroidism.*

*Patients with preexisting cardiovascular disease or high cardiovascular risk (e.g., metabolic syndrome, dyslipidemia, diabetes, arterial hypertension), especially patients aged < 65 years (21) (**A**) and with TSH levels > 7 mU/L (13) (**A**), due to the higher cardiovascular risk and death from cardiovascular disease.*

*The consensus did not find evidence to support the recommendation of levothyroxine treatment in patients with SCH to relieve symptoms or improve quality of life and cognitive function. However, dependent on individual clinical judgment, the consensus agrees with the previous recommendation (1) (**D**) of performing a therapeutic test with levothyroxine for a short period of time. If the clinical manifestations remain unchanged after normalization of TSH, the treatment should be discontinued.*

When should elderly patients with SCH be treated?

Large population studies did not demonstrate an association of SCH with cognitive dysfunction, anxiety or depression in patients older than 65 years (56-58), and a randomized placebo-controlled trial (120) did not find any benefit of levothyroxine treatment replacement on the cognitive function of patients > 65 years and with SCH.

Evidence from population-based cohort studies (94,95,97) associates SCH with an increased risk of heart failure in elderly patients with TSH levels > 10 mU/L. However, in a recent study of a population-based cohort with determinations of thyroid function over time, the association of SCH with persistent heart failure in elderly patients has not been confirmed (98). Furthermore, there has been no study on the potential benefits of the SCH treatment in elderly on the heart failure risk.

Table 5. Recommendations (R) for the treatment of persistent subclinical hypothyroidism

Parameter	TSH (> 4.5 < 10 mU/L)	TSH (≥ 10 mU/L)
Age ≤ 65 years		
Without comorbidities (R18)	No	Yes
Risk of progression to overt hypothyroidism (R 19A)	Consider to treat	Yes
Preexisting cardiovascular disease or cardiovascular risk (R 19-B)	Consider to treat if TSH ≥ 7 mU/L	Yes
Hypothyroidism symptoms (R 19-C)	Therapeutic test should be considered	Yes
Age > 65 years (R 20, R 21)	No	Yes

It is postulated that mild-moderate SCH (TSH levels > 4.5 and ≤ 10 mU/L) in the elderly may be associated with benefits, either as a protective factor against cardiovascular risk and mortality (21,22,99) or by demonstrations that such patients have better physical function and gait speed as shown by a 2-year follow-up study of patients aged 70-79 years (131). Furthermore, population-based cohort studies (97,106,130) showed that although the SCH treatment has a favorable effect on the reduction of cardiovascular risk and/or mortality in young adults, the same was not observed in elderly patients.

Recommendation 20

*SCH treatment in elderly patients > 65 years is recommended only when TSH levels > 10 mU/L are sustained (Table 5) due to a lack of association with cardiovascular risk and mortality in this age group (21) (**A**), the lack of favorable effects of the treatment in population-based cohort studies (106,130) (**B**) and because of the higher risk of heart failure in elderly patients with SCH and TSH levels > 10 mU/L (94,95,97) (**A**).*

Recommendation 21

*There is no recommendation for treatment for elderly (> 65 years old) SCH patients to relieve symptoms and improve quality of life (120) (**A**).*

What are the treatment risks?

It is estimated that a significant proportion of patients undergoing levothyroxine replacement may be using supraphysiological doses resulting in subclinical or overt hyperthyroidism. In a study performed in Colorado (USA) (5), approximately 40% of the patients with hypothyroidism were treated with supraphysiological doses of levothyroxine, while in Brazil (132), a recent multicenter study showed that this situation occurred in approximately 14.4% of patients. The induced subclinical hyperthyroidism in these cases is associated with an increased risk of atrial fibrillation (133), especially in the elderly over 65 years of age (134), and reduced bone mass in postmenopausal women (135).

Recommendation 22

*The risks of SCH treatment are inherent to the use of high doses of levothyroxine, with special clinical relevance in the elderly due to increased risk of atrial fibrillation (133,134) (**A**) and in postmenopausal women due to the risk of osteoporosis (135) (**B**).*

SUBCLINICAL HYPOTHYROIDISM IN PREGNANCY

How is SCH diagnosed during pregnancy?

The diagnosis of SCH during pregnancy results from laboratory findings characterized by high concentrations of TSH despite normal levels of FT4 for the gestational age (136).

There is strong evidence that the reference range for TSH is lower during pregnancy (17,18) compared with the normal reference range in non-pregnant women (approximately 0.45 to 4.5 mU/L). A larger decrease in TSH levels is observed in the first trimester, and it is temporary, depending on the beta-hCG concentrations, which can stimulate the TSH receptor. The TSH concentrations rise gradually in subsequent trimesters. The reference values of TSH during pregnancy (median and 2.5% and 97.5% percentiles) obtained from several studies (25,28,137) are shown in table 6.

The best methods for the FT4 determination during pregnancy are tandem mass spectrometry, liquid chromatography and equilibrium dialysis. The usual methods of FT4 measurement are influenced by the increase in the thyroxine-binding globulin (TBG) and the decrease in albumin concentrations that occur during pregnancy. These changes may influence FT4 immunoassays, which can also occur for the total T4 and the FT4 index (138). Caution in interpreting their values and establishing the normal range for each trimester by laboratories is recommended (139).

Table 6. References values of TSH (mU/L) in the different trimesters of pregnancy

Study	Trimesters of pregnancy		
	First	Second	Third
Stricker and cols.	1.04 (0.09-2.83)	1.02 (0.2-2.79)	1.14 (0.31-2.9)
Soldin and cols.	0.98 (0.24-2.99)	1.09 (0.46-2.95)	1.2 (0.43-2.78)
Bocos-Terraz and cols.	0.92 (0.03-2.65)	1.12 (0.12-2.64)	1.29 (0.23-3.56)

Values expressed as median and percentiles (2.5-97.5%).

Recommendation 23

*Reference values for TSH should be determined for each trimester of pregnancy by the local laboratory. If these values are not available, the following reference values should be used: first trimester, 0.1-2.5 mU/L; second trimester, 0.2-3.5 mU/L; and third trimester, 0.3-3.5 mU/L (27) (**B**).*

Recommendation 24

*If the best methods to measure FT4 are not available, clinicians should use the usual methods for its determination. However, clinicians should be aware of the limitations of these methods and of the reference values according to the method used (138,139) (**B**).*

Recommendation 25

*For the diagnosis of SCH in the first trimester of pregnancy, TSH values ranging between 2.5 to 10 mU/L associated with FT4 values within the normal range for the gestational age should be considered (136) (**D**).*

Does SCH increase maternal risk?

Most studies in pregnant women with SCH that analyzed complications during pregnancy suggest that the SCH is associated with adverse effects during pregnancy. Fetal loss was the most frequently associated obstetric complication. Benhadi and cols. (140) found a positive linear relationship between fetal loss and increased TSH concentrations. Negro and cols. (141) found an increased rate of fetal loss in women with negative TPOAb and TSH values between 2.5 to 5.0 mU/L compared with those who had TSH values < 2.5 mU/L. Allan and cols. (142) also observed that women with elevated TSH levels (> 6 mU/L) had a higher percentage of fetal death compared with controls. Other complications associated with SCH were gestational hypertension or preeclampsia, preterm delivery, low birth weight, placental abruption and postpartum hemorrhage (143). However, in a cohort of 10,990 pregnant women (144), SCH detected in the first and second trimesters was not associated with adverse effects.

Recommendation 26

*Although retrospective, several studies (142,143) (**B**) have suggested that SCH is associated with higher risk of pregnancy complications. Only 2 prospective studies (140,141) (**B**) have suggested that the treatment of pregnant women reduces the risk of these complications, but these studies require confirmation by other randomized studies.*

Does SCH increase fetal risk?

Thyroid hormones are essential for brain development, and their deficiencies can cause deficits in neuronal differentiation and migration, axonal and dendritic growth, myelin formation and synaptogenesis (145).

However, the deleterious effects of SCH on fetal neurocognitive development are still unknown. Two studies have shown that low concentrations of thyroid hormones in the early stages of pregnancy were associated with decreased intelligence quotient (IQ) in children tested at 10 months and 7 years (146,147).

A large study (Controlled Antenatal Thyroid Study; CATS) performed in England (148) evaluated pregnant women until the 16th week of gestation. Those with TSH levels above the 97.5% percentile and/or FT4 levels below the 2.5% percentile were treated or not treated with levothyroxine. The results showed no difference in the IQ of the children evaluated at 3 years of age between the 2 groups. However, this study evaluated only children at 3 years of age, which may have limited the significance of the findings because of the technical difficulty of assessing IQ in this age group. Moreover, the percentage of children with an IQ < 85 was higher in the group of pregnant women with SCH that were not treated compared to the treated group.

Recommendation 27

*There is little evidence suggesting potential deleterious effects of SCH on fetal neurocognitive development (146,147) (**B,C**), and there is no evidence of benefit from the levothyroxine treatment in pregnant women with SCH (148) (**A**).*

Should we screen SCH during pregnancy?

There is controversy regarding the universal screening for hypothyroidism in all pregnant women. The consequences for the mother and fetus are well established when overt hypothyroidism is not diagnosed and treated during pregnancy. However, these consequences are not defined for SCH because there is only one randomized prospective study evaluating the effects of levothyroxine treatment and subsequent child development (148). Thus, the American College of Obstetricians and Gynecologists (149) does not recommend the universal screening of pregnant women, but only for those women at high risk for thyroid dysfunction.

Recently, the American Thyroid Association (136) also stated that there is not enough evidence to recommend or not recommend universal screening of TSH in pregnant women in the first trimester.

In one study (150) comparing the detection of thyroid dysfunction through the universal screening of pregnant women with the active search approach in high-risk pregnancies noted that 30% of pregnant women with thyroid dysfunction were not detected with the latter approach.

The pregnant women at high risk for developing thyroid dysfunction present with one of the following conditions: 1) history of hyperthyroidism or hypothyroidism or previous postpartum thyroiditis; 2) history of cervical irradiation; 3) goiter; 4) family history of thyroid disease; 5) positive antithyroid antibody; 6) type 1 *diabetes mellitus* or other autoimmune disease; 7) history of miscarriages or premature births; 8) symptoms and signs of thyroid dysfunction including anemia, high cholesterol and hyponatremia; and 9) treatment with amiodarone (150).

Recommendation 28

*There is insufficient evidence to recommend or not recommend universal screening for hypothyroidism with TSH in pregnant women in the first trimester of gestation, but the consensus agrees with the recommendation of an active search in pregnant women at high risk for thyroid dysfunction (136,149-151) (**D,D,B,B**).*

When and how should SCH be treated during pregnancy?

Most retrospective studies (142,143) suggest an association of SCH with adverse effects during pregnancy, but there are no prospective randomized studies on the potential benefits of SCH treatment during pregnancy. However, it is known that levothyroxine treatment during pregnancy is safe when used carefully.

Once started, the doses of levothyroxine should be lower than those prescribed for overt hypothyroidism treatment. The concentrations of TSH and FT4 should be measured 4 weeks after the beginning of the treatment (151) and monthly until the middle of pregnancy and at least in the 26th and 32nd weeks of gestation (149). The goal is to maintain concentrations of TSH lower than 2.5 mU/L in the first trimester of pregnancy or 3.5 mU/L in the second and third trimesters (27).

Recommendation 29

*There is no consistent evidence to recommend for or against SCH treatment during pregnancy. However, this consensus accepts that the treatment should be initiated at the time of diagnosis due to retrospective studies suggesting adverse effects during pregnancy and low risk of treatment (142,143) (**B**).*

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