REVIEW

Clinical and therapeutic controversies on subclinical hyperthyroidism

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Subclinical hyperthyroidism is defined as low or undetectable serum thyrotropin concentration in the presence of levels of free thriiodothyronine and thyroxine within the reference range. Despite the conflicting results from many observational studies, this thyroid disorder has been associated with an increased risk of developing atrial fibrillation, left ventricular hypertrophy, increased heart rate and diastolic function impairment. In addition, a relation between subclinical hyperthyroidism, skeletal disorders and cognitive changes has been reported. Treatment of subclinical hyperthyroidism remains controversial, given the lack of prospective randomized studies showing clinical benefits with restoration of the euthyroid state. Nevertheless, this review recommends the treatment of subclinical hyperthyroidism to individuals aged over 65, postmenopausal women, patients with cardiac risk factors, heart disease, osteoporosis or hyperthyroidism symptoms, whenever TSH is persistently suppressed (<0.1 mU/L). When TSH is between 0.1 – 0.5 mU/L, treatment should be considered for individuals over age 65, patients with heart disease or hyperthyroidism symptoms.

KEYWORDS: Subclinical hyperthyroidism; atrial fibrillation; bone mineral density; management.

Salles F, Salles D. Clinical and therapeutic controversies on subclinical hyperthyroidism. MEDICALEXPRESS. 2014 Oct;1(5):251-256.

Received for publication on May 8 2014; **First review completed on** May 20 2014; **Accepted for publication on** July 30 2014

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INTRODUCTION

Subclinical hyperthyroidism (SH) is defined as a condition in which the serum concentrations of thyroid stimulating hormone (TSH) are reduced or undetectable, associated with triiodothyronine (T3) and free thyroxine (T4) values within the reference limits.[1] Several authors agree that it is important to distinguish between a low TSH value (between 0.1-0.4 mU/l) and an essentially suppressed TSH (<0.1 mU/l).[1,2,3]

The causes of subclinical hyperthyroidism do not differ from those usually related to clinical thyrotoxicosis, and can be classified as endogenous or exogenous, as shown in Table 1.

The most common etiologies are those associated with the use of levothyroxine, whether in thyroid nodular disease therapy, differentiated thyroid carcinoma post-surgical follow-up - aiming to prevent metastasis - or even in hypothyroidism treatment.[4] It should also be pointed out that the employment of excessive doses of thyroid hormone for the purpose of fast and easy weight loss is still frequent, since these drugs can be manipulated and sometimes sold freely in pharmacies.[5]

Prevalence varies according to ethnicity, gender, age and content of dietary iodine. The Framingham study shows that among the 2575 selected individuals over 60 years, 4% had low concentrations of TSH (<0.1 mU/l), and the predominance was in females.[5] Moreover, the III NHANES (III National Health and Nutrition Examination Survey) estimated that 1% of individuals between 60 and 80 years have SH (TSH <0.4 mU/l), increasing to 3% in individuals above 80 years.[6]

Endogenous SH is not a common clinical condition. This becomes evident when we consider that more than half of the cases in which a first test shows low TSH levels, but a repeat test detects a reversion to normal levels.[3] Thus, according to data from the USA, and considering a TSH level below 0.4 mU/l, only 2-3% of the general population is diagnosed with the condition in question. These epidemiological values increase exponentially in the case of exogenous SH, but its prevalence has not been defined.[2,6,7]

Regarding the natural history of the disease, published reports[8,9] state that a TSH below 0.1 mU/l is an important risk factor of the evolution of SH to clinical thyrotoxicosis. However, several studies show that the majority of individuals with a initial test showing low serum TSH progress to two different outcomes: either this TSH value remains reduced, or evolves towards normalization of thyrotropin values.[8,9,10]

Clinically, an association between low levels of TSH and several comorbidities is observed. Despite being a subclinical condition, non specific signs and symptoms such as nausea, tachycardia, and nervousness have been reported.[11] Patients with SH, both endogenous and exogenous, showed a higher prevalence of palpitations, tremors, heat intolerance, sweating, anxiety, weight loss, decreased sense of well-being, fear, hostility and difficulty concentrating, interfering with the quality of life.[3,12,13]

DOI: 10.5935/MedicalExpress.2014.05.07

Table 1 - Etiology of Subclinical Hyperthyroidism

ENDOGENOUS:
• Toxic multinodular goiter
• Graves' Disease
• Toxic Adenoma
• Acute and subacute thyroiditis
• Gestational Hyperthyroidism
EXOGENOUS:
• Use of levothyroxine suppressive doses
• Hypothyroidism treatment
• Factitious etiology
• Use of drugs such as glucocorticoids, opioids and levodopamine
• Amiodarone administration
• Use of iodine contrast
RARE:
• Pituitary gland disease
• HCG (human chorionic gonadotropin) secreting tumor

Some reports suggest an association of neuropsychiatric abnormalities and the SH. An increase in the risk of developing dementia (especially of vascular origin) and Alzheimer's disease was observed.[14,15]

Because thyroid hormones influence the skeletal and cardiovascular systems, associations have been described between SH and osteoporosis,[16,17,18] atrial fibrillation,[3,19,20,21] hypertrophy of the left ventricle (LV), tachycardia, impaired diastolic function and increased rate of cardiovascular mortality.[12,13,22,23]

Laboratory diagnosis is made through the finding of a low plasma concentration of TSH and normal levels of free T3 and T4, usually obtained during routine screening. The clinical picture common to classic hyperthyroidism (weight loss, insomnia, psychomotor agitation, fine tremor, excessive sweating) is rarely evident.[24]

There is still no consensus on whether a patient diagnosed with SH should or should not be treated. Given the possible consequences of an untreated SH, it would be logical to implement a therapy. However, factors such as degree of TSH suppression (<0.1 vs. 0.1-0.4 mU/l), patient age and absence of comorbidity may not be indicative of treatment. Furthermore, it is possible that the suppression of TSH is transient and that there will not be any evolution towards a clinically evident hyperthyroidism, obviating the need of intervention.[25]

Given the reported controversies, this work aims to compare different studies and their results and describe the clinical manifestations of SH and its effects on health, facilitating a critical analysis about the most appropriate therapeutic approach regarding SH for each patient.

METHODS

For the preparation of this systematic review, a thorough search of information was conducted; publications were selected according to their impact on the scientific community and relevance to the project at issue.

At first, we defined what databases would be used to obtain papers and journals: the Medline/PubMed, SciELO, Capes, UpToDate and Google Scholar virtual. The following keywords were used in the search: "*Subclinical Hyperthyroidism*", "*Management of subclinical hyperthyroidism*", "*Treatment of subclinical hyperthyroidism*", "*Subclinical hyperthyroidism and bone effects*", "*Subclinical hyperthyroidism and dementia*" and "*Subclinical hyperthyroidism and heart effects*".

The decision to review papers published from the nineties onward is justified by the fact that until the mid-eighties, the laboratory diagnosis of thyroid dysfunctions was obtained by radioimmunoassay; this was unable to detect very low levels of TSH. By the late eighties, immunometric assays had been introduced, and proved to be a better cost effective test for the screening of thyroid disease. The second generation of immunometric assays detects TSH levels down to 0.1 mU/l and the third generation is able to detect even lower thyrotropin values (down to 0.01 mU/l). Thus, the advance in diagnostic tests of thyroid disease created a new category of diseases represented by subclinical hyper- and hypothyroidism;[26] consequently, significant research on these hormonal disorders only dates from the nineties.

NATURAL HISTORY

A study by Parle et al including 66 individuals with an initial laboratory screening pointing to SH showed that approximately 60% eventually had evolved toward a normal range of TSH; 39% remained at the same TSH values, while 1% developed thyrotoxicosis.[10] Another prospective study by Rosario examined a sample of 102 patients with TSH between 0.1-0.4 mU/l and monitored these for a period of approximately 41 months. Three of these patients progressed to clinical hyperthyroidism, 4 evolved towards essentially suppressed TSH levels (<0.1 mU/l), 24 evolved toward normalization of TSH levels, while 71 continued with TSH between 0.1 to 0.4 mU/l.[8]

These studies also concluded that a TSH level below 0.1 mU/l is an important risk factor for the evolution of SH toward a clinical thyrotoxicosis, and this progression occurs at a rate of 2 to 5% per year.

COGNITIVE DISORDERS

The mechanisms by which SH leads to the development of cognitive disorders and dementia are still unknown. However, some hypotheses have been raised. One states that SH can lead to dementia by a direct effect of thyroid hormones on neurons, leading to increased oxidative stress and, consequently, neuronal apoptosis.[14] A second hypothesis is that there is the possibility of coexistence between low blood levels of TSH and TRH (thyrotropin releasing hormone) on the hypothalamus. This fact could lead to a relative scarcity of site acetylcholine, since TRH increases synthesis and release of this neurotransmitter in the synapses.[14]

The first major study linking subclinical hyperthyroidism with the risk of developing dementia was published in 2000 by Kalmijn. This is a prospective cohort study, in which 1,843 participants aged 55 years or older were selected from the Rotterdam Study. Elderly patients with SH had an increased risk of developing dementia and Alzheimer's Disease, and this would be even higher for patients with positive dosing for anti-peroxidase antibodies.[14]

A later study, conducted by Ceresini et al, sought to ascertain whether SH could cause cognitive disorders.[27] From the InChianti Study, they selected 1,171 participants of both sexes aged 23 to 102 years. They analyzed the plasma concentrations of TSH, free T3 and T4, as well the cognitive status by the MINI-MENTAL test. Patients were divided into two groups by ages: younger and older than 65 years. They found that SH is more prevalent in the elderly and that

the group aged over 65 years received lower scores on the MINI-MENTAL with a significantly higher risk of developing cognitive disorders.[27]

In 2010, Benseñor presented SH as a risk factor for developing dementia of vascular origin. A sample of 1276 subjects aged 65 years or older were submitted to laboratory evaluations of TSH, free T4 and several tests for the diagnosis of dementia according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders). In contrast with data from the Rotterdam Study, no relation was observed between SH and Alzheimer's disease. However, the results obtained suggested a consistent association between subclinical thyrotoxicosis and an increased risk of developing dementia of vascular origin.[15]

The results relative to SH and the development of cognitive disorders are often confusing and discordant. Although the reviewed studies have been well-conducted and indicate an association between the diseases, the notion that SH could increase the risk of dementia is still intriguing because its mechanism of action is merely explained by hypotheses.

SKELETAL ANOMALIES

Thyroid hormones are necessary for normal skeletal growth, metabolism, maturation and bone remodeling. Open hyperthyroidism is a risk factor for osteopenia and osteoporosis, because increases in serum concentrations of T3 and free T4 result in high rates of bone remodeling, with a disproportionate increase in bone resorption over bone formation, which results in the loss of approximately 10% of bone mass per remodeling cycle.[28] In spite of these data, the effects of SH on bone mineral density are less well known.

Faber and Galløe[16] investigated whether patients treated with thyroxine at doses high enough to suppress TSH concentrations in plasma would develop significant reductions in bone mass when compared with normal subjects. Bone density was analyzed in the distal forearm, femoral neck and lumbar spine in pre and postmenopausal women with SH triggered by the administration of levothyroxine. Results were compared to controls. Patients of reproductive age, presenting subclinical hyperthyroidism or not, did not exhibit significant changes in bone mass. In contrast, postmenopausal women with SH showed excessive reduction of bone mineral density when compared to the control group of postmenopausal patients.

In 1997, Bauer et al[29] stated that there was no consistent evidence showing that low levels of TSH are associated with increased bone loss in elderly women. However in 2001, they again studied the relation between TSH levels and their effects on the skeletal system in women aged over 65 years and found partially divergent results: in the more recent work, they reported that women with TSH levels ≤ 0.1 mU/l have a threefold higher risk of developing hip fracture, and a fourfold higher risk for vertebral fracture when compared to patients with normal TSH levels. However, for the patients in the 0.1 to 0.5 mU/l range of TSH, they continued to assert that there is no increased risk of fractures.[17]

Faber et al treated 16 women with postmenopausal SH due to multinodular goiter with radio-iodine therapy. As a control group, 12 women were followed without treatment. The goal was to evaluate whether normalization of serum TSH concentrations exerts a protective effect on the loss of bone mass. Two years later, they observed that the treated group did not show any change in bone density of the spine and hip, while in the control group there was a continuous reduction in bone mass at a rate of 2% per year.[30]

In 2007, Belaya et al[18] evaluated whether the etiology of subclinical thyrotoxicosis would adversely affect bone density in postmenopausal women. To this end, 88 female participants were selected who were already at least five years postmenopausal. These participants were categorized into four different groups: (1) 20 women with multinodular goiter, (2) 25 undergoing suppressive therapy with levothyroxine after thyroidectomy due to differentiated thyroid cancer, (3) 21 with Graves' disease under treatment with anti-thyroid drugs and (4) 22 without thyroid dysfunction, functioning as the control group. Biochemical markers of bone turnover were significantly increased in patients with SH. However, only participants who were postmenopausal and with SH of endogenous etiology (groups 1 and 3) had a reduction in bone density. In the cases of exogenous SH (group 2) no significant skeleton change was observed.[18]

In a more recent study on the effect of SH on bone density, Flynn et al[31] stated that there was an increased risk of fractures in patients with suppressed TSH (≤ 0.03 mU/l). This study included 17,684 people from the city of Tayside, Scotland, who were making use of levothyroxine for at least six months. These subjects were divided into 4 groups: suppressed TSH (≤ 0.03 mU/l), low TSH (0.04-0.4 mU/l), normal TSH (0.4 to 4.0 mU/l) or elevated TSH (> 4.0 mU/l) and then followed for a period of approximately 4.5 years. They concluded that participants with suppressed TSH had a higher risk of developing fractures, which did not occur with cases of low TSH.[31]

In summary, SH is a risk factor for osteoporotic fractures, especially in postmenopausal women with TSH level equal to or less than 0.1 mU/L. In this case there is an enhancement of bone resorption which already occurs on a large scale due to the absence of estrogen. However, there is no evidence that a TSH level between 0.1-0.4 mU/L is associated with reduced bone mineral density.

The association between the SH and fracture risk seems biologically plausible, because an increase of thyroid hormones, even within the reference values, would lead to increased bone remodeling and therefore to the loss of bone mass, predisposing to skeletal fragility fractures. One should also consider the work of Faber, who showed no progression of bone loss in postmenopausal women and with SH who underwent treatment.[30] Wiersinga suggested the existence of a continuous risk: the more suppressed TSH, the lower the bone density and the greater the risk of fractures; however, treatment of SH can prevent this evolution.[32]

CARDIOVASCULAR EFFECTS

In the case of overt hyperthyroidism, excess circulating T3 and T4 leads to chronotropic changes such as increased heart rate, palpitations and irregular heart rhythm, as well as to inotropic changes such as alterations in heart contractility and reduced ejection fraction.[33] As for SH, there is still much discussion in the literature about the presence of these cardiovascular effects.[34,35]

Sawin et al[21] reported a prospective study to determine the frequency of development of atrial fibrillation in patients clinically asymptomatic and with thyrotropin levels below the reference values. Two thousand and seven people aged

60 years or older, who had never had a previous episode of atrial fibrillation, were followed for a period of 10 years. After statistical analysis, subjects with inicial values of thyrotropin <0.1 mU/l showed a threefold higher risk of developing atrial fibrillation. A low but detectable level of TSH (0.1 mU/l-0.4 mU/l) was not associated with an increased risk of this arrhythmia.[21]

Biondi et al stated that the endogenous SH etiology affects quality of life as well as cardiac morphology and function in young and middle-aged individuals. They studied patients with endogenous SH from areas with iodine deficiency and who were not positive for anti-thyroglobulin and anti-peroxidase antibodies. The sample consisted of 23 patients, of which 15 had multinodular goiter and 8 had thyroid nodule of autonomous functioning. Twenty three other subjects were selected as the control group. All underwent morphological and functional thyroid evaluation; they answered the SRS (Symptom Rating Scale) and SF 36 questionnaires (Short Form 36 health survey) on the quality of life. Morphological and functional analysis of the heart included standard Electrocardiogram (ECG), Holter (24 hour ECG) and Echocardiogram with Doppler (Echo-Doppler).[12] The questionnaires showed that SH patients had a higher prevalence of palpitations, nervousness, tremors, heat intolerance and sweating than the control group and indicated further deterioration of health among the patients, interfering with the quality of life. Significant increases in heart rate, left ventricular mass, diastolic function as well as myocardial relaxation abnormalities with a prolonged isovolumetric relaxation time were also present in SH patients.[12]

As a consequence, Biondi et al recommend the early treatment of persistent endogenous SH in young people, to improve the quality of life and avoid the consequences of long term exposure of the cardiovascular system to the excess of the thyroid hormone.[12]

Petretta et al analyzed the cardiac structure and function, as well as the autonomic control of the heart in patients with subclinical and overt hyperthyroidism. The studied population consisted of 30 patients with SH and 30 patients with clinically evident disease, none ever treated by endocrinologists. Twenty healthy subjects were selected for the control group. TSH, T3 and T4 serum levels were measured; cardiac function was evaluated by Echo-Doppler and 24 hours of Holter monitoring. Patients with overt hyperthyroidism showed increased contractility and LV mass, and lower parasympathetic control over the heart. In the subclinical disease, no change in cardiac structure was observed, but the reduction in the parasympathetic control was present. The mechanism of reduction of vagal control in patients with SH is unknown, but it certainly contributes to the symptoms. The authors support the idea that the treatment of patients with SH may prevent cardiac arrhythmias and improve quality of life.[36]

Sgarbi et al[37] studied the cardiac effects of normalization of serum TSH levels in 10 patients with endogenous SH compared to 10 healthy controls. All participants underwent clinical and cardiological evaluation. Patients were subjected to pharmacological treatment (methimazole 20 mg/day) and reassessed six months after reaching a state of euthyroidism. The main symptoms related to SH were palpitation, fatigue, excessive sweating, nervousness and weakness. The clinical manifestations significantly improved or disappeared after reaching euthyroidism. They also reported a significant heart rate reduction with decreased supraventricular and ventricular premature beats after normalization of serum TSH levels. Left ventricular mass and thickness of the interventricular septum and posterior wall of the left ventricle were increased but became similar to the control group upon reaching the euthyroid condition.[37] In contrast, Pearce et al reported no association between serum TSH levels and left ventricular structure in 1,376 participants selected from the original Framingham Study. However, the absence of peripheral thyroid hormone levels makes it impossible to definitively diagnose the disorder.[38]

Völzke et al[39] performed a longitudinal study investigating the relation of this thyroid disorder to blood pressure, pulse pressure and to the risk of developing hypertension. No association was found between SH and changes in blood pressure, pulse pressure and incidence of hypertension.

Very recently Kaminski et al[40] evaluated the impact of SH in the heart through echocardiographic parameters. Patients were subjected to treatment with radio-iodine therapy. The echocardiographic assessment occurred at two different times: upon SH diagnosis and six months after reaching euthyroidism. The subclinical disease was associated with an increased volume of cardiac chambers, the diameter of the ascending aorta, LV mass and changes in left ventricular relaxation phase. All these disturbances were reversed with the return of patients to the euthyroid state.

Sgarbi[37] and Kaminski[40] performed similar analyses of cardiac disturbances before and after treatment of SH, using similar methods and arriving at concordant results. Both propose an early therapy of the SH, in order to prevent cardiac dysfunction and progression to advanced disease and to more concerning clinical effects.

The renin-angiotensin system appears to be activated in cases of cardiac hypertrophy induced by hyperthyroidism. The left ventricle is also hypertrophic because of the direct effects of thyroid hormones on synthesis of contractile proteins in cardiomyocytes.[33,41] This hypertrophy is associated with increased risk of cardiovascular morbidity and mortality and may worsen the ventricular filling in the elderly population in which the cardiac compliance is already reduced due to interstitial fibrosis.[41]

MORTALITY RISK

As shown, SH obviously coexists with increased morbidity, but data on mortality are controversial.

Haentjens et al[42] reported that patients with SH had a 41% increase in overall mortality when compared with the control group consisting of euthyroid individuals. Mortality was found to depend on age, with a larger number of cases over the age 60, and on gender, affecting men more than women.

Ittermann et al[43] analyzed data from 3,651 Germans aged 20-79 years followed for approximately 8.5 years, during which 299 people died. The number of deaths was higher among subjects with TSH levels below the reference values. However, after comparing the results with parameters such as age and sex, no association was found between low levels of TSH and all causes of mortality.

Sgarbi et al[44] followed 1,110 Brazilian subjects of Nipponese origin for 7.5 years. Unlike the findings of Itterman et al,[43] this study confirms an association between SH and increased general mortality and of cardiovascular origin.

Thus the relation between SH and mortality remains in the balance.

DIAGNOSTIC CONDUCT

As for the diagnostic approach, the following steps are suggested, following a preliminary diagnosis:

First step: Confirm the laboratory diagnosis of SH after a period of 3 to 6 months. Spontaneous normalization of TSH can often occur.
Second step: Establish the presence or absence of thyroid disease.
Third step: Stratify the individual by the value of TSH (TSH <0.1 mU/L $\times$ TSH between 0.1-0.4 mU/L). The current recommendation is to start treatment in all the patients with TSH <0.1 mU/L, because of the risk of atrial fibrillation and osteoporotic fractures in both endogenous and exogenous SH. Furthermore, patients with suppressed TSH have a high risk for progressing to overt hyperthyroidism, while TSH levels between 0.1-0.4 mU/L are more likely to evolve to the normalization of TSH.
Fourth step: Stratify the individual risk factors. Emphasis on age ≥ 65 years, postmenopausal, previous or current history of osteopenia/osteoporosis, cardiovascular disease, atherosclerosis or other cardiac risk factors.[32]

TREATMENT

The treatment of SH is controversial due to the lack of controlled interventional studies that demonstrate general benefits to patient health.

Conduct is largely intuitive, but the *American Association of Clinical Endocrinologists* (AACE) and the *American Thyroid Association* (ATA) offer a guide for the management of hyperthyroidism which includes recommendations regarding subclinical hyperthyroidism.[45]

Persistently suppressed TSH (<0.1 mU/L) should be treated (i) in all individuals aged 65 years or older; (ii) in postmenopausal women who are not under hormone replacement therapy with estrogen or do not use bisphosphonates; (iii) in patients with cardiovascular risk factors, heart disease and osteoporosis, and individuals with hyperthyroidism symptoms.

In SH patients where TSH is between 0.1-0.5 mU/L, treatment should be considered in individuals aged 65 years or older, in patients with cardiac disease or in the presence of hyperthyroidism symptoms.

Upon the decision to treat, the principles applying to overt hyperthyroidism therapy should be followed.

CONCLUSIONS

Subclinical hyperthyroidism reduces the quality of life by exerting various deleterious effects on the health of individuals. The extent of clinical manifestations is related to the magnitude of the excess of thyroid hormone, but also to the individual sensitivity to exposure to this hormonal excess, disease duration and age of the patient.

This review recommends the treatment of subclinical hyperthyroidism in the following cases:

a) When TSH level is persistently suppressed (<0.1 mU/L) and the patient:
- is aged 65 years or older
- is a postmenopausal woman
- has cardiovascular risk factors
- has risk factors for osteoporosis
- manifests hyperthyroidism symptoms

b) When the TSH level is slightly reduced (between 0.1-0.5 mU/L) and the patient:
- is aged 65 years or older
- has heart disease
- manifests hyperthyroidism symptoms

Finally, more randomized clinical trials are needed to evaluate if, in the long-term, treatment of subclinical hyperthyroidism brings benefits to the health of the individual.

RESUMO

Hipertireoidismo subclínico é definido como a condição que ocorre quando a concentração de tirotropina sérica é baixa ou indetectável na presença de níveis de triiodotironina livre e tiroxina dentro dos respectivos intervalos de referência. Apesar dos resultados conflitantes de vários estudos observacionais, este distúrbio de função tireoidiana tem sido associado com um risco aumentado de fibrilação atrial, hipertrofia ventricular esquerda, aumento da frequência cardíaca e comprometimento da função diastólica. Além disso, tem sido relatada uma relação entre hipertireoidismo subclínico e alterações esqueléticas ou cognitivas. O tratamento do hipertireoidismo subclínico permanece controverso, dada a falta de estudos prospectivos randomizados mostrando benefício clínico com a restauração do estado normal. No entanto, esta revisão recomenda o tratamento de hipertireoidismo subclínico de indivíduos com idade superior a 65 anos, em mulheres na pós-menopausa, e em pacientes com fatores de risco cardíaco, com sintomas de doenças cardíacas, osteoporose ou hipertireoidismo, sempre que a tireotropina esteja persistentemente abaixo de $<0,1$ mU/L. Quando estiver entre 0,1-0,5 mU/L, o tratamento deve ser considerado para os indivíduos com idade superior a 65 anos, portadores de doença cardíaca ou sintomas de hipertireoidismo.

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