

Subclinical Hypothyroidism and Anti-Thyropoxidase Antibodies

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Abbreviations: SCH: Subclinical Hypo-
thyroidism; TSH: Thyroid-Stimulating Hor-
mone (or Thyrotropin); LT4: Levothyroxine;
T3: Triiodothyronine; DNA: Deoxyribo-
nucleic Acid; ADCC: Antibody-dependent
Cellular Cytotoxicity; EBT: External Beam
Therapy; TCR: T cell Receptor; MHC: Ma-
jor Histocompatibility Complex; DNA:
Deoxyribonucleic Acid; APC: Antigen-Pre-
senting Cell; TPO: Thyropoxidase; Tg:
Thyroglobulin.

ABSTRACT

Subclinical hypothyroidism (SCH) refers to the serum thyrotropin (or TSH) concentration above the reference range with normal serum free levothyroxine (fT4). The leading cause for raised thyrotropin concentration in SCH is not due to iodine deficiency but rather due to excessive intake of iodine that results in the development of anti-TPO antibodies towards thyroid peroxidase enzyme. Most common symptoms reported are muscle cramps, slowness of thinking, throat harshness and constipation. Most of the clinicians believe that those individuals having thyrotrophic concentration greater than 10 mIU/L should undergo the treatment of levothyroxine (LT4). The results of many epidemiological studies states that, greater the concentration of Anti-Thyropoxidase antibodies then greater the susceptibility of having overt hypothyroidism in SCH individuals.

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as altered blood serum thyrotropin concentration with no change in blood serum free levothyroxine (fT4) and T3 concentration ^[1].

INCIDENCE AND PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM

In India, it is estimated that about 42 million people were suffering from thyroid diseases ^[2]. In women prevalence is about 11.4%, whereas in men it is about 6.2%. Prevalence of subclinical hypothyroidism is higher in men when compared to women after 60 y of age whereas in the woman of below 60 y of age prevalence of SCH is higher in women when compared to the men. As the

age increases the prevalence of SCH also increases and it is greater in the woman^[3,4]. In a population without a known thyroid disease prevalence of SCH is about 3-8% whereas in the developed countries it is about 4-15%^[5-7].

THYROID PEROXIDASE (TPO) ANTIBODIES

Thyroid hormones are majorly synthesized with the help of TPO enzymes. Calculating the anti-TPO autoantibodies levels in the blood is important to diagnose and predict the clinical course of autoimmune thyroid disease^[8]. The existence of anti-TPO antibodies in subclinical hypothyroidism contributes to the etiological diagnosis. Anti-TPO antibody seems to be positive in around 53% of SCH subjects^[9]. Even at the top of the autoimmune process in the thyroid gland, about 10-15% of SCH subjects have a result of negative antibody screening.

Autoimmunity is triggered by the genetic factors, environmental factors such as Infections, stress, trauma, infections, and smoking, hormonal influences and in the progression of Hashimoto's thyroiditis iodine plays a major role^[10-16]. Exalted levels of anti-thyroid peroxidase antibodies are seen in about 75% of Graves' disease cases and more than 90% cases of Hashimoto thyroiditis and 10% in healthy people and it may reach 30% in the elders^[17,18]. Upon exposure to anti-TPO antibodies, thyrocytes are damaged due to the activation of the complement system and antibody-dependent cellular cytotoxicity (ADCC)^[19].

PROGRESSION TO OVERT HYPOTHYROIDISM

Overt hypothyroidism is not so as common as SCH and depending on the presence of anti-Thyroperoxidase autoantibodies, progression to overt hypothyroidism can vary. For instance, 2.3% of SCH subjects with negative anti-TPO antibody screening and 4.3% of SCH subjects with positive anti-TPO antibody screening advances to overt hypothyroidism each year^[20]. Progression to overt hypothyroidism can be halted by the early diagnosis and treatment of the condition^[21]. Some of the epidemiological studies have determined that the presence of high anti-TPO autoantibody concentration tunes these subjects of SCH to be more susceptible to convert to overt hypothyroidism.

SYMPTOMS OF SUBCLINICAL HYPOTHYROIDISM

Most of the patients with mild-Subclinical hypothyroidism are asymptomatic and only few of them have typical hypothyroid symptoms. The most common symptoms reported were the problems with memory, puffy eyes, muscle cramps, muscle weakness, slowness of thinking weariness, dry skin, feeling colder, throat harshness and more constipation^[22,23].

AETIOLOGY OF SUBCLINICAL HYPOTHYROIDISM

Before the actual diagnosis of subclinical hypothyroidism, other aetiological factors for exaggerated thyrotropin concentration such as the existence of Forssmann antibodies, recovery from non-thyroidal illness, thyroid hormone (T3 and T4) resistance and the subjects of central hypothyroidism with inactive thyrotropin should be ignored.

Anyhow, the most common aetiological factor causing exaggerated thyrotropin concentration is due to autoimmune thyroid disease. Previous external beam therapy (EBT), Radioactive iodine (I-131) therapy, Thyroidectomy can result in SCH. In some cases, SCH lasts for a short period of time such as in postnatal and Granulomatous or DeQuervains thyroiditis. According to some reports, iodine exposure results in the dysfunction of the thyroid gland (thus causing the hypothyroidism and hyperthyroidism [Goitre]) and thyroid autoimmunity. Currently, iodine deficiency in SCH is no more appreciable due to the availability and supplementation of iodine-rich nutritious food (Milk, Fish etc.)^[24,25]. People who live in coastal areas have the high prevalence of SCH. As discussed earlier that iodine deficiency plays an important role in causing SCH but in coastal areas in spite of usage of iodine water these people are subjected to SCH. So the exact cause for the higher rate of prevalence in coastal areas is not known and on another side this is very helpful to exclude autoimmune thyroiditis and also helps to guess the presence of thyroid autoimmunity against thyroid peroxidase.

MECHANISM OF SUBCLINICAL HYPOTHYROIDISM

Even though several hypotheses have been put forward to explain the mechanism of how excessive iodine is linked to the development of thyroid autoimmunity but the exact mechanism is not known. Intake of large quantities of iodine results in the increased iodine incorporation in the thyroglobulin molecule and this is characterized by the change in the stereochemical conformation which further results in the change in its properties such as loss of antigenic determinants and this leads to the formation of Novel, iodine-containing thyroglobulin molecules. Iodination of thyroglobulin molecule at the critical points such as tyrosine amino acids results in the creation of new antigenic epitopes^[26,27]. When this altered thyroglobulin molecule (with new antigenic epitopes) introduced to receptors of T and/or B cells by the Antigen-presenting cell (APC) with the help of Major histocompatibility complex (MHC) proteins then this presentation causes the T cell receptor (TCR) on T cells and MHC proteins on APC to increase their affinity towards the altered thyroglobulin molecule. Overall increased affinity results in Increase in the presentation of thyroglobulin by APC to T cells/B cells which leads to the activation of T cells and B cells thereby initiating the process of autoimmunity. In a nutshell, increasing the thyroglobulin iodination can amplify the process of autoimmunity when compared to the thyroglobulin molecule with decreased iodination.

Another proposed mechanism of SCH is direct iodine toxicity to thyrocytes which as a result of oxidative stress. Increased concentration of iodine in the dysplastic thyrocytes is rapidly oxidized by thyroid peroxidase enzyme and this causes the generation of oxidative intermediates of iodine. These oxidative intermediates are over reactive where it causes damage to thyrocytes and to the mitochondrial membrane by forming iodo compounds due to the binding of proteins, lipids and nucleic acids. Generation of these oxidative intermediates causes oxidative stress thus causing thyrocyte necrosis. So excessive iodine intake causes the thyrocytes to trigger the death pathway or apoptotic pathway and also causes the development of thyroid autoimmunity [28-30].

THYROID PROFILE OF SUBCLINICAL HYPOTHYROIDISM

80% of patients with SCH whose TSH is less than 10 mIU/L has thyroid antibodies and it is predicted that these individuals have higher rate of progression (Table 1). Individuals whose TSH is below 6 mIU/L anticipates the decreased progression. Some studies conclude that the normal thyrotropin levels are seen in 52% of SCH subjects having a serum thyrotropin concentration of 10 mIU/L [31].

Table 1. Levels of TSH and FT4 in various thyroid conditions.

S.no	Condition	TSH (mIU/L)	FT4 (ng/dl)
1.	Euthyroid	0.4-4.2	0.8-2
2.	Hypothyroidism	>4.2	<0.8
3.	Mild Subclinical hypothyroidism	4-10	No Change
	Severe Subclinical hypothyroidism	>10	
4.	Hyperthyroidism	<0.4	>2
5.	Subclinical hyperthyroidism	0.8-2	<0.4

MANAGEMENT OF SUBCLINICAL HYPOTHYROIDISM

The main objective of the treatment is to bring back the individual to a euthyroid state, with resolution of signs and symptoms of Subclinical hypothyroidism. Levothyroxine (LTX) refers to the artificial thyroxine (T4), a thyroid hormone which is endogenously produced and released by the thyroid gland into the bloodstream. Once it is released into the bloodstream peripherally it is converted to L-triiodothyronine (T3) which is the active metabolite of T4. Tetraiodothyronine (T4) and Triiodothyronine (T3) binds to nuclear receptors called thyroid hormone receptors which were found in the nucleus of peripheral cells and this causes the metabolic effects by controlling the transcription of DNA thereby protein synthesis [32].

Most of the clinicians agree that the individuals having TSH levels greater than 10 mIU/L is managed with levothyroxine (LT4) but there is uncertainty regarding the fact of use of LT4 in SCH subjects with Thyrotropin concentration between 5-10 mIU/L [33,34]. If Thyrotropin concentration is greater than 10 mIU/L, physicians believe that the levothyroxine therapy is appropriate [35-37]. The levothyroxine daily dose is 50 to 75 µg [38]. However, managing the SCH subjects with a serum thyrotropin concentration below 10 mIU/L is controversial [39].

According to the meta-analysis studies conducted in 2007 reports that, replacement of levothyroxine in patients of SCH do not show any improve in survival or cardiovascular morbidity. Some studies reports that replacement of LTX helps in upgrading the lipid profiles and function of left ventricular parameters (Figure 1) [40].

ADVERSE EFFECTS OF LEVOTHYROXINE THERAPY

The earliest clinical response to LT4 replacement is usually diuresis and weight loss, leading to mobilization of interstitial fluid as glycosaminoglycan are degraded. In patients who receive LT4 therapy for TSH suppression, the risk of arrhythmias and bone loss is hampering factor and the use of a medication with TSH-lowering effects has a more acceptable safety profile that would be an attractive alternative. During the LT4 treatment in SCH patients who have abnormal thyrotropin levels, failure to decrease LT4 dosage expose the patient to undesirable side effects of LT4 on density of the bones and function of the heart [41,42].

LIFESTYLE MODIFICATIONS

- » Limiting the goitrogenic food (Cruciferous vegetables like cabbage, cauliflower and broccoli).
- » Eating a healthy diet containing the adequate amount of iodine.
- » Regular exercise.
- » Distress the mind with Yoga, Meditation and Deep breathing.
- » Proper sleep.

» Drinking more water that will help to rejuvenate the thyroid metabolism.

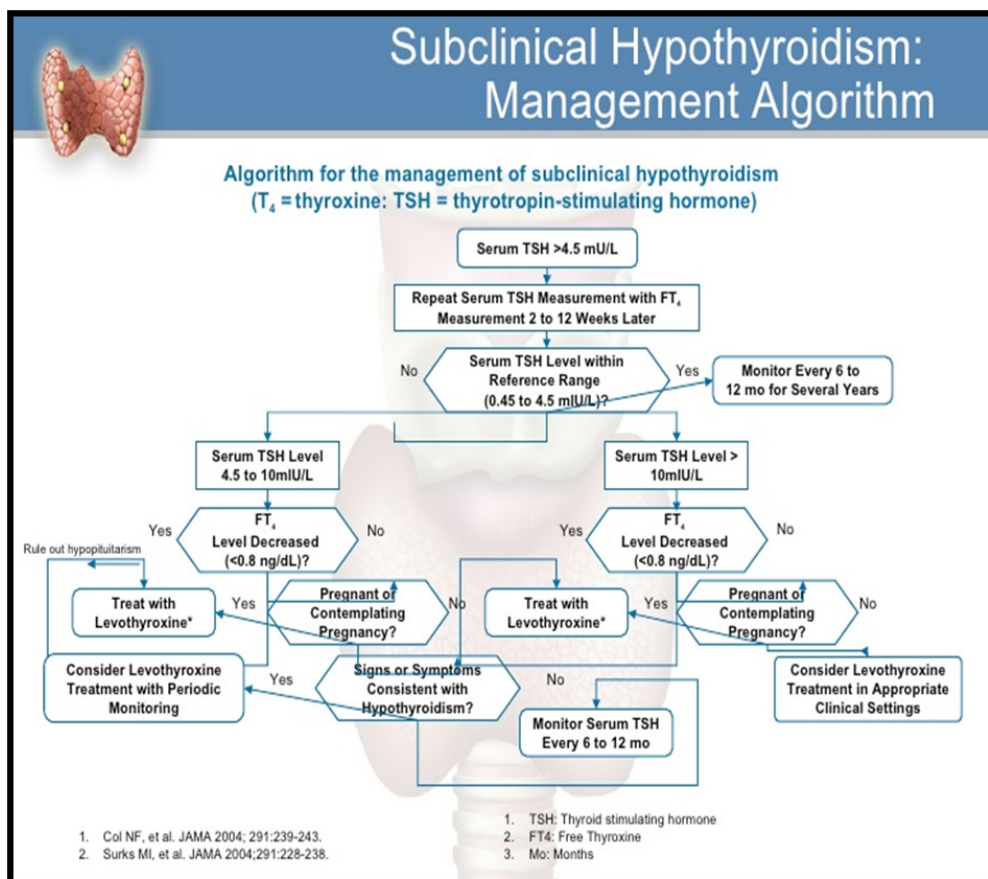


Figure 1: SCH management algorithm.

CONCLUSION

Interpretation of serum thyrotropin concentration, no change in T3 and T4 and anti-TPO antibodies helps in determining the etiology and risk of SCH patients progressing to overt hypothyroidism. It may be treated with levothyroxine sodium along with lifestyle modification and metformin is also used as adjunctive therapy for management of subclinical hypothyroidism need to be evaluated.

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