

**A STUDY ON SUBCLINICAL HYPOTHYROIDISM IN
FEMALES OVER FIFTY YEARS OF AGE**

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled “**A STUDY ON SUBCLINICAL HYPOTHYROIDISM IN FEMALES OVER FIFTY YEARS OF AGE**” is a bonafide work done by Dr.K.S.GOPAKUMAR, post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of regulations of **The Tamilnadu Dr.M.G.R.Medical University** for the award of M.D.Degree Branch I (General Medicine) during the academic period from May 2006 to March 2009.

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INTRODUCTION

The term subclinical hypothyroidism was originally used to describe the patient with a low-normal free T4 but a slightly elevated serum TSH level. Other terms for this condition are mild hypothyroidism early thyroid failure, preclinical hypothyroidism, and decreased thyroid reserve. The TSH elevation in such patients is modest, with values typically between 4 and 15 mU/L, although patients with a TSH above 10 mU/L more often have a reduced free T4 and may have some hypothyroid symptoms.

The definition of this syndrome depends significantly on the reference range for a normal TSH concentration.

This syndrome is most often seen in patients with early Hashimoto's disease and is a common phenomenon, occurring in 7% to 10% of older women.^{1,2,3}

Subclinical hypothyroidism may have endogenous causes (chronic autoimmune thyroiditis, subacute thyroiditis, postpartum thyroiditis) or exogenous causes (thyroidectomy, ¹³¹I therapy, antithyroid drugs, inadequate thyroid hormone replacement therapy). The prevalence of subclinical hypothyroidism is rather high. In the classical population-based study among adults in the English county of Whickham the prevalence was 75 per 1000 women and 28 per 1000 men¹; similar figures have been obtained in other studies. The higher prevalence of subclinical hypothyroidism in females than

in males and in older than in younger subjects is in agreement with the higher prevalence of thyroglobulin and thyroid peroxidase (microsomal) antibodies in women and in elderly people.

The natural history of subclinical hypothyroidism is reasonably well known. Spontaneous return of increased TSH values into the normal range occurs in 5.5% after 1. year.⁴ Progression to overt hypothyroidism ranges from 7.8% to 17.8% in various studies.^{4,5,6}

Another report indicates that approximately 30% of patients with subclinical hypothyroidism had developed overt hypothyroidism after 10 years; the higher the initial TSH, the greater the risk.⁷

Clinical manifestation of subclinical hypothyroidism include abnormal lipid metabolism^{8,9,10}, cardiac dysfunction^{11,12} and neurologic and mental dysfunction¹³ and several cross-sectional studies have suggested that it confers an elevated risk for atherosclerosis and coronary heart disease.^{14,15} However, neither of these associations have been confirmed by others^{16,17}. This discrepancy may reflect small size of the study or participation in these study limited to one sex. Also, few longitudinal studies have been conducted. The relationship between subclinical hypothyroidism and cardiovascular disease is therefore controversial and possible outcomes of the conditions remain unclear. Importantly several previous studies suggesting that thyroid

autoimmunity is a risk factor for coronary heart disease^{15,18,19} remain surrounded by controversies.^{17,20}

Women with subclinical hypothyroidism didn't differ from controls with regard to BMI, Hypertension and Diabetes Mellitus in previous studies.^{14,21}

This study has been performed to estimate the prevalence of subclinical hypothyroidism and its relation to Hypertension, Diabetes and Ischemic heart disease among women above the age of 50 years attending medical out patient clinic at Government Kilpauk Medical College and Hospital.

AIM OF THE STUDY

- To estimate the prevalence of subclinical hypothyroidism among women above the age of 50 yrs
- To study the relationship of subclinical hypothyroidism to Hypertension, Diabetes and Ischemic Heart Disease in those patients

REVIEW OF LITERATURE

PHYLOGENY, EMBRYOLOGY, AND ONTOGENY

Phylogeny

Thyroid tissue is confined to, and is present in, all vertebrates. The phylogenetic association of the thyroid gland and the gastrointestinal tract is evident in several functions. The salivary and gastric glands, like the thyroid, are capable of concentrating iodide in their secretions.

Structural Embryology

The human thyroid anlage is first recognizable at E 16-17. The primordium begins as a thickening of epithelium in the pharyngeal floor. The primitive stalk connecting the primordium with the pharyngeal floor elongates into the thyroglossal duct , the primordium assumes a bilobate shape, coming into contact and fusing with the ventral aspect of the fourth pharyngeal pouch when it reaches its final position at about E50. Cells of the lower portion of the duct differentiate into thyroid tissue, forming the pyramidal lobe of the gland. At this time the lobes contact the ultimobranchial glands, leading to the incorporation of C cells into the thyroid. Concomitantly, histologic alterations occur throughout the gland, and by 13 to 14 weeks the follicles begin to fill with colloid.

Functional Ontogeny

Future follicular cells acquire the capacity to form thyroglobulin (Tg) as early as the 29th day of gestation, whereas the capacities to concentrate iodide and synthesize thyroxine (T4) are delayed until about the 11th week. As a consequence of hypothalamic maturation and increasing secretion of thyrotropin-releasing hormone (TRH), the serum TSH concentration increases between 18 and 26 weeks.

ANATOMY AND HISTOLOGY

The thyroid is approximately 15 to 20 g in weight .The normal thyroid is made up of two lobes joined by a thin band of tissue, the isthmus. The individual lobes normally have a pointed superior pole and a poorly defined blunt inferior pole that merges medially with the isthmus.

Blood supply is by the superior thyroid artery and the inferior thyroid artery.

Thyroid blood flow range from 4 to 6 mL/min/g.

The gland is composed of follicles .Thyroid tissue appears as closely packed ring-shaped structures consisting of a single layer of thyroid cells surrounding a lumen. The follicular cells are columnar when active and cuboidal when

inactive. The thyroid also contains parafollicular cells, or C cells, that are the source of calcitonin.

IODINE AND THE SYNTHESIS AND SECRETION OF THYROID HORMONES

Dietary Iodine

Formation of normal quantities of thyroid hormone requires the availability of adequate quantities of exogenous iodine to allow thyroidal uptake of approximately 60 to 75 μg daily, taking into account the fecal losses of about 10 to 20 μg iodine of iodothyronines as glucuronides and about 100 to 150 μg as urinary iodine in iodine-sufficient populations. At least 100 μg of iodine per day is required to eliminate all signs of iodine deficiency . Iodine deficiency is common in mountainous regions.

Iodide Metabolism by the Thyroid Cell

The process of iodide trapping is accomplished by a membrane protein, the sodium-iodide symporter (NIS or SLC5A). In addition to the active transport of iodide from the extracellular fluid, intracellular iodide is also generated by the action of the iodotyrosine dehalogenase (Dhal) enzymes. The iodide thereby released is immediately reconstituted to newly synthesized thyroglobulin after exiting the apical membrane of the cell.

Iodide Oxidation and Organification

Oxidation of iodide and incorporation of the resulting intermediate into the hormonally inactive iodotyrosines MIT and DIT is known as organification. Oxidation of thyroidal iodide is mediated by the heme-containing protein thyroid peroxidase (TPO) and requires the H₂O₂ generated by the calcium dependent Duox1 and 2 enzymes. The rate of organic iodinations is dependent on the degree of thyroid stimulation by TSH .

Iodothyronine Synthesis

The MIT(mono iodothyronine) and DIT(di iodothyronine) formed via oxidation and organic binding of iodide are precursors of the hormonally active iodothyronines T₄ and T₃. Synthesis of T₄ from DIT requires the TPO-catalyzed fusion of two DIT molecules to yield a structure with two diiodinated rings linked by an ether bridge (the coupling reaction). Efficient synthesis of T₄ and T₃ in the thyroid requires Tg.

Storage and Release of Thyroid Hormone

There are approximately 250 µg T₄ per gram of wet weight in normal human thyroid. This is sufficient to maintain a euthyroid state for at least 50 days. Thyroglobulin is present in the plasma of normal individuals at concentrations up to 80 ng/mL. The first step in thyroid hormone release is the endocytosis of colloid from the follicular lumen by two processes: macropinocytosis by

pseudopods formed at the apical membrane and micropinocytosis by small coated vesicles that form at the apical surface. Both processes are stimulated by TSH. Following endocytosis, endocytotic vesicles fuse with lysosomes, and proteolysis is catalyzed by cathepsin D and D-like thiol proteases, all of which are active at the acidic pH of the lysosome. The iodotyrosines released from Tg are rapidly deiodinated by an NADPH-dependent iodotyrosine deiodinase, and the released iodine is recycled. The thyroid hormone transporter MCT8 in the thyroid gland could be involved in the exit of T4 and/or T3 from the phagolysosome or thyroid cell. Stimulation of D1- and D2- (type 1 and 2 deiodinases) can catalyze 5'-deiodination of T4. T4 release from the thyroid cells is inhibited by several agents, the most important of which is iodide.

Role and Mechanism of Thyrotropin (TSH) Effects

All steps in the formation and release of thyroid hormones are stimulated by TSH secreted by the pituitary thyrotrophs . Thyroid cells express the TSH receptor (TSHR), a member of the glycoprotein G protein–coupled receptor family. Although the TSHR mainly couples to Gs, when activated by high concentrations of TSH, it couples also to Gq/11, activating the inositol-phosphate diacylglycerol cascade. The induction of signal via the phospholipase C (PLC) and intracellular Ca²⁺ pathways regulates iodide

efflux, H₂O₂ production, and Tg iodination while the signal via the protein kinase A (PKA) pathways mediated by cAMP regulates iodine uptake and transcription of Tg, TPO, and the sodium-iodide symporter (NIS) mRNAs leading to thyroid hormone production . The TSHR, in addition to TSH, also binds thyroid-stimulating antibody (TSAb), thyroid-blocking antibodies (TBAb), and neutral antibodies to the TSHR .

THYROID HORMONES IN PERIPHERAL TISSUES

Plasma Transport

T₄ arises solely from direct secretion by the thyroid gland. In normal humans, T₃ is also released from the thyroid but approximately 80% is derived from the peripheral tissues by the enzymatic removal of a single 5' iodine atom from T₄. The remaining iodothyronines and their derivatives are generated in the peripheral tissues from T₄ and T₃. Principal among them are 3,3',5'-triiodothyronine (reverse T₃, or rT₃) and 3,3'-diiodo-L-thyronine (3,3'-T₂). The major iodothyronines are poorly soluble in water and thus bind reversibly to plasma proteins. The plasma proteins with which T₄ is mainly associated are thyroxine-binding globulin (TBG) and transthyretin (TTR) and albumin . About 75% to 80% of T₃ is bound by TBG, and the remainder by TTR and albumin.

Thyroxine-Binding Globulin (TBG).

TBG is a glycoprotein SERPIN family of serine antiproteases of with a molecular mass of about 54 kd. Normal human serum concentration is 270 nmol/L (1.5 µg/dL). The half-life of the protein in plasma is about 5 days.

Free Thyroid Hormones

Because most of the circulating T4 and T3 is bound to TBG, its concentration and degree of saturation are the major determinants of the free fraction of T4. Binding of the thyroid hormones to the plasma proteins alters their metabolism. The negligible urinary excretion of T3 and T4 is due to the limited filterability of the hormone-binding protein complexes at the glomerulus. The free fraction of T4 ($T4/T4 \cdot TBG$) is inversely proportional to the concentration of unoccupied TBG binding sites.

Estimates of the free T4 concentration in serum can be generated by direct or indirect assays. It is the free hormone that is available to the tissues for intracellular transport and feedback regulation, that induces its metabolic effects, and that undergoes deiodination or degradation. The bound hormone acts merely as a reservoir. If an increase in TBG occurs, the free T4 concentration and T3 concentrations can be maintained at normal levels only

if the bound hormone increases. The plasma concentration of T4 is determined by its rate of entry into, and exit from, the plasma.

For any level of T4 production, be it increased, normal, or decreased, the total plasma T4 level varies inversely with its MCR (Metabolic Clearance Rate).

Intracellular free T3 and T4 are in equilibrium with the free hormone pool in plasma. In the steady-state, the rate of T3 and T4 metabolism is rate-limiting in the exit of hormones from the plasma.

T4 and T3 Transport across Cell Membranes and Intracellular T3 Binding

MCT8 is a T-type amino acid transporter belonging to the monocarboxylate transporter family and facilitates transport of T3, T4, rT3 across cell membranes in vitro.

Iodothyronine Deiodination

The most important pathway for T4 metabolism is its outer ring (5') monodeiodination to the active thyroid hormone, T3. This reaction is catalyzed by the type 1 and 2 deiodinases (D1 and D2) and is the source of more than 80% of the circulating T3. Inner ring deiodination, an inactivating step, is catalyzed primarily by the type 3 (D3) deiodinase, which inactivates T3 and prevents activation of T4 by converting it to reverse T3. The structures of the three deiodinases are similar, and contain the amino acid

selenocysteine in the active catalytic center . Selenium is thought to be the iodine acceptor during deiodination reactions.

Quantitative and Qualitative Aspects of Thyroid Hormone Metabolism

Thyroid Hormone Turnover

In the normal adult, T₄ has a distribution volume of approximately 10 L . Because the concentration of total T₄ in plasma is approximately 100nmol/L (8µg/dL), the extrathyroidal T₄ pool is approximately 1mmol (800µg). In the adult, the fractional rate of turnover of T₄ in the periphery is about 10% per day (half-life, 6.7 days). Thus, about 1.1 L of the peripheral T₄ distribution space is cleared of hormone daily, a volume containing approximately 110 nmol (85 µg) of T₄.

The kinetics of T₃ metabolism differ from those of T₄, partly because of its 10- to 15-fold lower affinity for TBG. The volume of distribution of T₃ in the normal adult is about 40 L. At a mean normal serum T₃ concentration of 1.8nmol/L (120ng/dL), the daily production of T₃ is approximately 50 nmol (33µg).The rapid metabolic clearance rate of the product of inner ring T₄ deiodination, and the low concentration in plasma (0.25nmol/L, 15ng/dL) combine to yield daily production rates for rT₃ of about 45nmol. 80% -85%

of T3 and all of rT3 production can be accounted for by peripheral deiodination of T4.

Mechanism of Thyroid Hormone Action

Thyroid hormone acts by binding to a specific nuclear thyroid hormone receptor (TR), which, in turn, binds to DNA usually as a heterodimer with retinoid X receptor at specific sequences (thyroid hormone response elements, or TREs) dictated by the DNA binding-site preferences of the RXR-TR complex. Triiodothyronine has a 15-fold higher binding affinity for TRs than does T4, explaining its function as the active thyroid hormone. In humans, there are two TR genes, α and β , found on different chromosomes (TR α , chromosome 17; TR β , chromosome 3). There are several alternatively spliced gene products from each of these genes forming both active and inactive gene products. The active proteins are TR α 1, and TRs β 1, β 2, and β 3.

REGULATION OF THYROID FUNCTION

The Hypothalamic-Pituitary-Thyroid Axis

The thyroid participates with the hypothalamus and pituitary in a classical feedback control loop. In addition, there is an inverse relationship between the glandular organic iodine level and the rate of hormone formation. Autoregulatory mechanisms within the gland, in turn, tend to maintain a constant thyroid hormone pool. Finally, the hypothalamic-pituitary feedback

mechanism senses variations in the availability of free thyroid hormones, however small, and acts to correct them. There is a close relationship between the hypothalamus, the anterior pituitary, the thyroid gland, and still higher centers in the brain, the function of the entire complex being modified in a typical negative-feedback manner by the availability of the thyroid hormones.

Thyrotropin-Releasing Hormone (TRH) Synthesis and Secretion

TRH, a modified tripeptide (pyroglutamyl-histidyl-proline-amide), is derived from a large prepro-TRH molecule. The parvocellular region of the paraventricular nuclei (PVN) of the hypothalamus is the source of the TRH that regulates TSH secretion. TRH travels in the axons of the peptidergic neurons through the median eminence and is released close to the hypothalamic-pituitary portal plexus. T₃ suppresses the levels of prepro-TRH mRNA in the hypothalamus, but normal feedback regulation of prepro-TRH mRNA synthesis by thyroid hormone requires a combination of T₃ and T₄ in the circulation. In addition to inhibiting the synthesis of prepro-TRH mRNA, thyroid hormone also blocks the capacity of TRH to stimulate TSH release from the thyrotroph.

Thyrotropin (Thyroid-Stimulating Hormone) Synthesis and Secretion

It is a glycoprotein secreted by the thyrotrophs in the anteromedial portion of the adenohypophysis. TSH is composed of an α -subunit of 14 kd (92 amino

acids) and a specific β -subunit synthesized in thyrotrophs, which is a 112-amino-acid protein. The quantity of β -subunit is rate-limiting for TSH secretion. TRH increases and thyroid hormone suppresses the transcription of both subunits.

In normal serum, TSH is present at concentrations between 0.4 and 4.2 mU/L. The level is increased in primary hypothyroidism and reduced in thyrotoxicosis. The plasma TSH half-life is about 30 minutes, and production rates in humans are 40 to 150 mU/day. Circulating TSH displays both pulsatile and circadian variations. Both T4 and T3 mediate the feedback regulation of TSH secretion, and TRH determines its set-point. There is a linear inverse relationship between the serum free T4 concentration and the log of the TSH, making the serum TSH concentration an exquisitely sensitive indicator of the thyroid state of patients with an intact hypothalamic-pituitary axis.

Somatostatin decreases TSH secretion in vitro and in vivo, but prolonged treatment with a somatostatin analogue does not cause hypothyroidism. Dopamine is a regulator of TSH secretion, but chronic administration of dopamine agonists do not cause central hypothyroidism, indicating that compensatory mechanisms negate these acute effects. Glucocorticoids in high doses transiently suppress TSH secretion, although prolonged therapy is

not associated with central hypothyroidism. Bexarotene, a retinoid X receptor agonist used for treatment of T-cell lymphoma, suppresses TSH sufficiently to cause central hypothyroidism, presumably by reducing TSH- β gene transcription.

Iodine Deficiency

In humans compensatory alterations in thyroid function come into operation when total iodine intake falls below 75 $\mu\text{g}/\text{d}$.

Effects of Increased Iodine Intake on Thyroid Hormone Synthesis

The quantity of iodine organified in thyroglobulin which includes T4 and T3 displays a biphasic response to increasing doses of iodide, at first increasing and then decreasing as a result of a relative blockade of organic binding. This decreasing yield of organic iodine from increasing doses of iodide, termed the Wolff-Chaikoff effect, results from a high concentration of inorganic iodide within the thyroid cell. The mechanism for organification inhibition may involve inhibitory effects of high iodide concentrations on TPO and THOX2.

Effects on Thyroid Hormone Release

An important practical effect of pharmacologic doses of iodine is the prompt inhibition of thyroid hormone release. The mechanism is unknown, but the effect is mediated at the thyroid cell level, rather than through an action on TSH.

Aging and the Thyroid

In the healthy elderly patient, there is a normal free T4 but a relatively lower serum TSH than in younger individuals. The requirement for complete levothyroxine replacement is reduced about 20% by the eighth decade.

LABORATORY ASSESSMENT OF THYROID STATUS

Tests of the Hypothalamic-Pituitary-Thyroid Axis

The rate of TSH secretion is exquisitely sensitive to the plasma concentrations of free thyroid hormones. The normal range of the serum TSH concentration by immunometric assay varies slightly in different laboratories but is most commonly 0.4 to 4.2mU/L. The free α -subunit common to TSH, FSH, LH, and hCG is generally detectable in serum with a normal range of 1 to 5 μ g/L, but the TSH β -subunit is not.

TSH in Patients with Thyroid Dysfunction

Patients with hyperthyroidism (excess thyroid hormone secretion) and/or thyrotoxicosis (excess thyroid hormone from any cause) will virtually always have a subnormal TSH. Patients with hypothalamic or pituitary hypothyroidism often have normal or even slightly elevated serum TSH. The circulating TSH generally has reduced biologic activity due to abnormal glycosylation, reflecting the impaired access of TRH to the thyrotroph. In

general, the degree of TSH elevation correlates with the clinical severity of the hypothyroidism. Patients with serum TSH values in the range of 5 to 15 mU/L have few if any symptoms²³, and the serum free T4 is typically low-normal while serum free T3 concentrations are normal.^{22 24} Such individuals with modest TSH elevation are said to have subclinical hypothyroidism if the serum free T4 is in the normal range. An elevation in both serum TSH and free T4 is unusual and indicates either autonomous TSH production as with a TSH-secreting pituitary tumor, resistance to thyroid hormone (RTH), or hyperthyroidism with an artifactual elevation in TSH.

QUANTITATION OF SERUM THYROID HORMONE CONCENTRATIONS

Total T4 and T3

The normal range for total T4 is 64 to 142 nmol/L (5 to 11 µg/dL). Normal serum T3 concentrations are 1.1 to 2.9 nmol/L (70 to 190 ng/dL).

Concentrations of Free T4 and T3.

The absolute concentration of free hormone is the product of the total hormone concentration and the fraction that is dialyzable or ultrafiltrable . About 0.02% of T4 and 0.3% of T3 is free or unbound . The normal ranges

for free T4 and T3 are 9 to 30 pmol/L (0.7 to 2.5 ng/dL) and for free T3, 3 to 8 pmol/L (0.2 to 0.5 ng/dL).

There are two general categories of methods for estimating free thyroid hormones: Comparative free T4 methods and so-called free T4 index methods. Three general approaches are used: (1) two-step labeled hormone methods, (2) one-step labeled analogue methods, and (3) labeled antibody approaches. In general, two-step labeled hormone back titration methods are less subject to artifacts due to abnormal binding proteins, changes in albumin, TBG, or increases in free fatty acids than are one-step hormone analogue methods.^{25 26 28} All general approaches are subject to artifacts from endogenous antibodies to T4, abnormal binding proteins, or illness.^{27 29}

The Free T4 Index (FT4I).

Particularly useful in estimating the free T4 in severely ill patients is the determination of the thyroid hormone-binding ratio (THBR), multiplying this result by the total T4 (or T3) to obtain a free hormone index (FT4I or FT3I).

Causes of a Suppressed TSH.

The most common cause of a reduction in serum TSH is an excess supply of thyroid hormone due to either increased endogenous thyroid hormone production or excessive exogenous thyroid hormone. Because the concentration of TSH is inversely proportional to the degree of thyroid

hormone excess, patients with clinical symptoms almost invariably have serum TSH concentrations below 0.1 mU/L. Such patients nearly always have an increase in the serum free T4. The hypothalamic-pituitary axis may remain suppressed for up to 3 months after complete resolution of the thyrotoxic state.^{30 31} The best test for assessing the physiologic state in such patients is the free T4 or FT4I. In severe illnesses, with or without dopamine infusion or excess glucocorticoid, TSH is suppressed, making assessment of thyroid functional status difficult. Because the FT4I may also be reduced in such patients, astute clinical judgment is required to assign thyroid status.

Causes of an Elevated TSH

Elevations in TSH nearly always imply a reduction in the supply of T4 or T3, which may be permanent or transient. Primary hypothyroidism is far and away the usual explanation. Other causes include acutely ill patients as in renal insufficiency³² or the asynchronous return of the hypothalamic-pituitary and thyroid axes to normal as critically ill patients recover.³³ Iodine deficiency is the most common cause of an elevation in TSH worldwide.

Patients with hypothalamic-pituitary dysfunction may have clinical and chemical hypothyroidism, but low, normal, or even elevated serum TSH concentrations. The explanation for this paradox is that the biologic

effectiveness of the circulating TSH is impaired due to abnormal glycosylation secondary to reduced TRH stimulation of the thyrotrophs.

In adrenal insufficiency, TSH may be modestly elevated but returns to normal with glucocorticoid replacement

Tests That Assess the Metabolic Impact of Thyroid Hormones

Basal Metabolic Rate

Basal metabolic rate (BMR) measures oxygen consumption under specified conditions of fasting, rest, and tranquil surroundings. Under these conditions, the energy equivalent of 1 L of oxygen is 4.83 kcal. Values in patients, calculated as a percentage of established normal means for gender and age, normally range from -15% to +5%. In severely hypothyroid patients, values may be as low as -40%, and in thyrotoxic patients, these may reach +25% to +50%.

Biochemical Markers of Altered Thyroid Status

Occasionally markedly elevated creatine kinase MM isoenzyme or low-density lipoprotein (LDL) cholesterol lead to the recognition of hypothyroidism.

Serum Thyroglobulin

The mean normal values vary with the assay used but are on the order of 30 pmol/L (20 ng/mL). Values are elevated in both endemic and sporadic nontoxic goiter, and the degree of elevation correlates with the thyroid size.

Tests for Thyroid Autoantibodies

Autoantibodies to Thyroid Peroxidase and Thyroglobulin

Tg and TPO autoantibodies appear to be a secondary response to thyroid injury and are not thought to cause disease themselves. TPOAb autoantibodies correlate with thyroidal damage and lymphocytic infiltration. The disease widely most associated with TgAb and TPOAb is autoimmune thyroiditis, or Hashimoto's disease. Both TgAb and TPOAb are found in almost 100% of such patients. Antibodies to Tg and TPO are also detectable in 50% to 90% of patients with Graves' disease.

Thyroid Autoantibodies in Nonautoimmune Thyroid Disorders

Antibodies to Tg and TPO are more common in patients with sporadic goiter, multinodular goiter, and isolated thyroid nodules and cancer and in other autoimmune diseases, particularly insulin-dependent diabetes mellitus (IDDM).

Radioiodine Uptake

Several factors make this test less frequently used than in the past. The first is the improvement in indirect methods for assessing thyroid status. The second is the decrease in normal values for thyroid RAIU consequent to the widespread increase in daily dietary iodine intake.³⁴

¹³¹I (half-life 8.1 days) and ¹²³I (half-life 0.55 day) both emit gamma radiation, which permits their external detection and quantitation at sites of accumulation, such as the thyroid.

Measurements of RAIU are generally made at 24 hours. The RAIU usually indicates the rate of thyroid hormone synthesis and the rate of thyroid hormone release into the blood.

States Associated with Increased RAIU

Hyperthyroidism, aberrant hormone synthesis, abnormal thyroglobulin synthesis, iodine deficiency, rebound increases in RAIU are seen after withdrawal of antithyroid therapy, after subsidence of transient or subacute thyroiditis, excessive hormone losses as in nephrotic syndrome and chronic diarrheal states.

States Associated with Decreased RAIU.

Exogenous thyroid hormone(thyrotoxicosis factitia), disorders of hormone storage,the early phase of subacute thyroiditis and in chronic thyroiditis with transient hyperthyroidism, exposure to excessive iodine.

HYPOTHYROIDISM

CLINICAL PRESENTATION

Hypothyroidism can affect all organ systems. The term myxedema, formerly used as a synonym for hypothyroidism, refers to the appearance of the skin and subcutaneous tissues in the patient in a severely hypothyroid state.

Skin and Appendages

Hypothyroidism causes an accumulation of hyaluronic acid in the dermis and other tissues.³⁵ Myxedematous tissue is characteristically boggy and non pitting and is apparent around the eyes, on the dorsa of the hands and feet, and in the supraclavicular fossae. The skin is pale and cool as a result of cutaneous vasoconstriction. The secretions of the sweat glands and sebaceous glands are reduced, leading to dryness and coarseness of the skin.

Cardiovascular System

The cardiac output at rest is decreased because of reduction in both stroke volume and heart rate, reflecting loss of the inotropic and chronotropic effects

of thyroid hormones. Peripheral vascular resistance at rest is increased, and blood volume is reduced.^{12 36 37 38}

In severe primary hypothyroidism the cardiac silhouette is enlarged, and the heart sounds are diminished in intensity.³⁹ These findings are the result largely of effusion into the pericardial sac of fluid rich in protein and glycosaminoglycans.

Electrocardiographic changes include sinus bradycardia, prolongation of the PR interval, low amplitude of the P wave and QRS complex, alterations of the ST segment, and flattened or inverted T waves. Pericardial effusion is probably responsible for the low amplitude in severe hypothyroidism. Systolic time intervals are altered; the preejection period is prolonged, and the ratio of preejection period to left ventricular ejection time is increased. Echocardiographic studies have revealed resting left ventricular diastolic dysfunction in overt, and in some studies, subclinical hypothyroidism.³⁸ The combination of large heart, hemodynamic and electrocardiographic alterations, and the serum enzyme changes has been termed myxedema heart. Hypothyroidism has been shown to be a risk factor for atherosclerosis and cardiovascular disease by several studies, although others have not shown this association.

Respiratory System

Pleural effusion is usually evident only in radiological examination. Lung volumes are usually normal, but maximal breathing capacity and diffusing capacity are reduced. Obstructive sleep apnea is common but is reversible with restoration of a euthyroid state.

Alimentary System

Although most patients experience a modest gain in weight, appetite is usually reduced. Peristaltic activity is decreased and together with the decreased food intake, is responsible for constipation. The latter may lead to fecal impaction (myxedema megacolon). Gaseous distention of the abdomen (myxedema ileus), if accompanied by colicky pain and vomiting, may mimic mechanical ileus.⁴¹

Central and Peripheral Nervous Systems

All intellectual functions, including speech, are slowed. Dementia is seen in elderly patients. Psychiatric disorders are common and are usually of the paranoid or depressive type and may induce agitation (myxedema madness).⁴²

The tendon reflexes are slow, especially during the relaxation phase and is due to a decrease in the rate of muscle contraction and relaxation.

Skeletal System: Calcium and Phosphorus Metabolism

Deficiency of thyroid hormone in early life leads to both a delay in the development of, and an abnormal, stippled appearance of the epiphyseal centers of ossification (epiphyseal dysgenesis). Impairment of linear growth leads to dwarfism in which the limbs are disproportionately short in relation to the trunk but cartilage growth is unaffected.

Renal Function

Renal blood flow, glomerular filtration rate, and tubular reabsorptive and secretory maxima are reduced. Blood urea nitrogen and serum creatinine levels are normal, but uric acid levels may be increased. There is impaired renal excretion of water and the retention of water by the hydrophilic deposits in the tissues result in an increase in total body water, even though plasma volume is reduced.

Hematopoietic System

In response to the diminished oxygen requirements and decreased production of erythropoietin, the red blood cell mass is decreased; this is evident in the mild normocytic, normochromic anemia that often occurs.

Reproductive Function

In adult women, severe hypothyroidism may be associated with diminished libido and failure of ovulation. Secretion of progesterone is inadequate, and

endometrial proliferation persists, resulting in excessive and irregular breakthrough menstrual bleeding.

Hypothyroidism in men may cause diminished libido, impotence, and oligospermia.

Energy Metabolism: Protein, Carbohydrate, and Lipid Metabolism

Both the synthesis and the degradation of protein are decreased. The decrease in protein synthesis is reflected in retardation of both skeletal and soft tissue growth.

Hypothyroidism is associated with a reduction in glucose disposal to skeletal muscle and adipose tissue.⁴³ Hypothyroidism is also, however, associated with reduced gluconeogenesis.⁴³ The net effect of these influences is usually a minimal effect of hypothyroidism on serum glucose levels. Degradation of insulin is slowed and the sensitivity to exogenous insulin may be increased.

An elevation in serum LDL cholesterol has been associated, in most studies, with overt and subclinical hypothyroidism.⁴⁰ According to most studies, serum HDL and triglycerides levels, are not influenced by hypothyroidism.^{40,44}

CLASSIFICATION OF HYPOTHYROIDISM

Acquired

Hashimoto's thyroiditis

Iodine deficiency (endemic goiter)

Drugs blocking synthesis or release of T4 (e.g., lithium, ethionamide, sulfonamides, iodide)

Goitrogens in foodstuffs or as endemic substances or pollutants

Thyroid infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedel's struma, cystinosis, scleroderma)

Postablative due to ¹³¹I, surgery, or therapeutic irradiation for nonthyroidal malignancy

Congenital

Iodide transport or utilization defect (NIS or pendrin mutations)

Iodotyrosine dehalogenase deficiency

Organification disorders (TPO* deficiency or dysfunction)

Defects in thyroglobulin synthesis or processing

Thyroid agenesis or dysplasia

TSH receptor* defects

Thyroidal Gs protein abnormalities (pseudohypoparathyroidism type 1a)

Idiopathic TSH unresponsiveness

Transient (Post-thyroiditis) Hypothyroidism

Following subacute, painless, or postpartum thyroiditis

Consumptive Hypothyroidism

Rapid destruction of thyroid hormone due to D3 expression in large hemangiomas or hemangioendotheliomas

Defects of Thyroxine to Triiodothyronine Conversion

Selenocysteine insertion sequence–binding protein (SECIS-BP2) defect

Drug-Induced Thyroid Destruction

Tyrosine kinase inhibitor (sunitinib)

Central Hypothyroidism

Acquired

Pituitary origin (secondary)

Hypothalamic disorders (tertiary)

Bexarotene (retinoid X receptor agonist)

Dopamine and/or severe illness

Congenital

TSH deficiency or structural abnormality

TSH receptor defect

Resistance to Thyroid Hormone

Generalized and “Pituitary” dominant

TREATMENT

Treatment is nearly always with levothyroxine, and the proper use of this medication has been reviewed extensively.^{45 46 47} A primary advantage of levothyroxine therapy is that the peripheral deiodination mechanisms can continue to produce the amount of T3 required in tissues under the normal physiologic control.

Pharmacologic and Physiologic Considerations

Levothyroxine has a 7-day half-life; the typical dose of levothyroxine, approximately 1.6 to 1.8 μ g/kg ideal body weight per day (0.7 to 0.8 μ g/pound). Because of the 7-day half-life, approximately 6 weeks is required before there is complete equilibration of the free T4 and the biologic effects of levothyroxine. Return of the serum TSH level to normal is the goal of levothyroxine therapy in the patient with primary hypothyroidism.

Institution of Replacement Therapy

The initial dose of levothyroxine prescribed depends on the degree of hypothyroidism and the age and general health of the patient. Patients who are young or middle-aged and otherwise healthy with no associated cardiovascular or other abnormalities and mild to moderate hypothyroidism (TSH concentrations 5 to 50 mU/L) can be given an initial complete

replacement dose of about 1.7 $\mu\text{g}/\text{kg}$ of ideal body weight. The resulting increase in serum T4 concentration to normal requires 5 to 6 weeks, and the biologic effects of T3 are sufficiently delayed that these patients do not experience adverse effects.

At the other extreme, the elderly patient with heart disease, particularly angina pectoris, without reversible coronary lesions, should be given a small initial dose of levothyroxine (25 $\mu\text{g}/\text{day}$), and the dosage should be increased in 12.5- μg increments at 2- to 3-month intervals with careful clinical and laboratory evaluation. The serum TSH should be evaluated 6 weeks after a theoretically complete replacement dose has been instituted to allow minor adjustments to optimize the individual dose.⁴⁸ In patients with central hypothyroidism, serum TSH is not a reliable index of adequate replacement and the serum free T4 should be restored to a concentration in the upper half of the normal range. Such patients should also be evaluated and treated for glucocorticoid deficiency before institution of thyroid replacement .

The interval between the initiation of treatment and the first evidence of improvement depends on the strength of dose given and the degree of the deficit. An early clinical response in moderate to severe hypothyroidism is a diuresis of 2 to 4 kg. Thereafter, pulse rate and pulse pressure increase, appetite improves, and constipation may disappear. Later, psychomotor

activity increases and the delay in the deep tendon reflex disappears. Hoarseness abates slowly, and changes in skin and hair do not disappear for several months. In individuals started on a complete replacement dose, the serum free T4 level should normalize after 6 weeks; a somewhat longer period may be necessary for serum TSH levels to return to normal, perhaps up to 3 months.

Monitoring Replacement Therapy

Monitoring the adequacy of, and compliance with, thyroid hormone therapy in patients with primary hypothyroidism is easily done by measurement of serum TSH. Based on analysis of the NHANES III reference group,² a reference TSH range with an upper limit of 2.5 mU/L (The normal serum TSH concentration varies between 0.5 and 4.0 mU/L) has been suggested.

After the first 6 months of therapy, the dose should be reassessed because restoration of euthyroidism increases the metabolic clearance of T4. A dose that was adequate during the early phases of therapy may not be adequate when the same patient is euthyroid owing to an acceleration in the clearance of thyroid hormone. The finding of a normal serum TSH level on an annual basis is adequate to ensure that the proper levothyroxine dose is being taken by the patient. If the serum TSH level is above the normal range and noncompliance is not the explanation, small adjustments, usually in 12- μ g

increments, can be made with reassessment of TSH concentrations after the 6 weeks required for full equilibration have passed.

CONDITIONS THAT ALTER LEVOTHYROXINE REQUIREMENTS

Increased Levothyroxine Requirements

Pregnancy

Gastrointestinal Disorders

Mucosal diseases of the small bowel (e.g., sprue), After jejunioileal bypass and small bowel resection, Impaired gastric acid secretion (e.g., atrophic gastritis).

Therapy with Certain Pharmacologic Agents

Drugs That Interfere with Levothyroxine Absorption

Cholestyramine, Sucralfate, Aluminum hydroxide, Calcium carbonate, Ferrous sulfate.

Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4)

Rifampin, Phenytoin, Carbamazepine, Estrogen, Sertalin

Drugs That Block T4 to T3 Conversion

Amiodarone

Conditions That May Block Deiodinase Synthesis

Selenium deficiency, Cirrhosis

Decreased Levothyroxine Requirements

Aging (65 years and older), Androgen therapy in women

Adverse Effects of Levothyroxine Therapy

Excessive doses of levothyroxine causes accelerated bone loss in postmenopausal patient^{49 50} Administration of excessive doses also increases cardiac wall thickness and contractility and, in elderly patients, increases the risk of atrial fibrillation.^{36 38}

HEART DISEASE AND THYROID HORMONE THERAPY

Patients with coronary artery disease and primary hypothyroidism cardiac function is improved in response to levothyroxine therapy because of a decrease in peripheral vascular resistance and improvement in myocardial function.^{36 37} However, patients with preexisting angina pectoris should be evaluated for correctable lesions of the coronary arteries and treated appropriately before levothyroxine is administered.^{51 52 53}

MYXEDEMA COMA

This state, which almost invariably affects older patients and is associated with a high mortality rate. It is usually accompanied by a subnormal temperature. The external manifestations of severe myxedema, bradycardia, and severe hypotension are invariably present. Seizures may accompany the

comatose state. Factors that predispose to its development include exposure to cold, infection, trauma, and central nervous system depressants or anesthetics. Alveolar hypoventilation, leading to carbon dioxide retention and narcosis, and dilutional hyponatremia resembling that seen with inappropriate secretion of arginine vasopressin (AVP) may also contribute to the clinical state. The importance of the difficulty in diagnosing myxedema coma is that a delay in therapy worsens the prognosis. Consequently, the diagnosis should be made on clinical grounds, and, after sending serum for thyroid function tests, therapy should be initiated without awaiting the results of confirmatory tests because mortality may be 20% or higher. Treatment consists of administration of thyroid hormone and correction of the associated physiologic disturbances.^{54 55 56}

Administration of levothyroxine as a single intravenous dose of 500 to 800µg serves to replete the peripheral hormone pool and may cause improvement within hours. Daily doses of intravenous levothyroxine, 100 µg, are given thereafter. Hydrocortisone (5 to 10 mg/hr) should also be given because of the possibility of relative adrenocortical insufficiency as the metabolic rate increases. Hypertonic saline and glucose may be required to alleviate severe dilutional hyponatremia and the occasional hypoglycemia.

A critical element in therapy is support of respiratory function by means of assisted ventilation and controlled oxygen administration. Internal warming by gastric perfusion may be useful. Further heat loss can be prevented with blankets. An increase in temperature may be seen within 24 hours in response to levothyroxine. Finally, the physician should assess the patient for the presence of coexisting disease, such as infection and cardiac or cerebrovascular disease. In particular, the myxedematous patient may be afebrile despite a significant infection. As soon as the patient is able to take medication by mouth, treatment with oral levothyroxine should be instituted.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is defined as an isolated elevated serum thyrotropin level in the setting of normal serum thyroid hormone levels, in the presence or absence of symptoms.⁵⁷

The findings of slightly elevated TSH and normal thyroid hormone levels do not necessarily imply the presence of subclinical hypothyroidism. Several medications and conditions are known to cause an elevation in TSH. Some drugs such as lithium, sulfonylureas, amiodarone, ethionamide, phenylbutazone, aminoglutethimide and iodine can interfere with thyroid hormone production or release and secondarily result in slight elevation of

TSH. In addition, dopamine antagonists such as metoclopramide and domperidone may cause exaggerated TSH response to TRH stimulation by altering the inhibitory effect of dopamine on TSH secretion. Furosemide has also been shown to increase levels of TSH, especially in recovering critically ill patients. Other conditions that cause elevated TSH include thyroid hormone resistance, thyroid hormone secreting tumors(both should be associated with high free thyroxine levels),psychiatric illness, adrenal insufficiency, renal failure, hyperprolactinemias and systemic illness. ⁶⁰

PREVALENCE AND NATURAL HISTORY

Hypothyroidism is much higher in women than men and increases with age. In the Wickham survey TSH levels above 6mIU/L were approximately three times more common in females (7.5%) than in males (2.8%) and occurred more frequently in females over 45 years of age . TSH levels also showed progressive increase with age in women but not in men. ⁶¹

The overall prevalence have been reported to range from 4-10% in large population screening surveys and from 7-26% in studies of elderly. Most studies have shown that subclinical hypothyroidism is more frequent in female sex. Another study demonstrated a prevalence of elevated TSH in 16% men and 21% women over age of 74 years. ^{1, 61, 63}

In patients found to have elevated TSH levels approximately 75% have values lower than 10mIU/L.⁶² Of patients with subclinical hypothyroidism approximately 2%to5% per year will progress to overt hypothyroidism. The rate of progression is proportional to the baseline serum TSH concentration and is higher in individuals with antithyroid antibodies.⁵⁸ There is also a strong association between positive antithyroid antibodies and elevated TSH. Generally the prevalence of elevated TSH levels parallels that of antibody positivity.⁶¹ A high prevalence of antibodies was found in a UK study where antibodies was present in 81% of those with TSH concentration over 10mU/L, 46% of those with TSH over 5 mU/L and less than or equal to 10mU/L and only in 5.7% of those whose TSH concentration was less than 5mU/L.⁴ Interestingly the NHANES 111 survey found a significant association between anti-thyroid peroxidase antibody with hypo- or hyperthyroidism but not with thyroglobulin antibody.

After 20 years of follow up of subjects in the Wickham Survey, the risk of overt hypothyroidism was found to be 4.3% per year in women with elevated TSH and antithyroid antibodies at baseline. This is a 38 times increased risk over normal women. Moreover an isolated elevation in TSH or presence of antithyroid antibodies alone at baseline conferred an increased risk of overt hypothyroidism (2.6% per year and 2.1% per year respectively).⁵⁸ Progression

to hypothyroidism was noted to be more common in those with initial TSH value greater than 10mU/L and in those with positive anti-thyroid antibodies.⁴ Huber et al found that basal TSH , thyroid reserve(increase in T3 after TRH stimulation) and the presence of antimicrosomal antibodies are important prognostic factors in the development of overt hypothyroidism .Interestingly antibodies against thyroglobulin did not have a predictive value

Effects on serum lipid levels

Several cross sectional studies show that serum cholesterol levels are elevated in individuals with mild thyroid failure when compared with euthyroid controls.⁶⁴ In other studies however the observed differences between euthyroid and mild hypothyroid individuals have not been significant.⁶⁵

The Colorado study which screened 25862 subjects found that mean total cholesterol and low density lipoprotein cholesterol progressively increased with increasing TSH levels.⁶² A reanalysis by Tanis et al in 1996 found that subclinical hypothyroidism was 2 to 3 times more frequent in people with elevated total plasma cholesterol levels.

Thyroid substitution therapy replacing the TSH levels to normal decreased total cholesterol by 0.2 to 0.4 mmol/L and mean LDL cholesterol by 0.26 mmol/L and increased HDL cholesterol by 0.08 mmol/L while triglyceride and lipoprotein A1 levels remain unchanged. In another study total

cholesterol and LDL cholesterol level decreased only in patients with pretreatment TSH values $>10\text{mU/L}$.⁶⁶ The decrease in total cholesterol and LDL levels with pretreatment values greater than 40mU/L was greater than those between 10mU/L and 40mU/L .

CARDIAC EFFECTS

Cardiac changes are evident in subclinical hypothyroidism. These include impairment of left ventricular diastolic function at rest (affecting the relaxation of left ventricle and hence filling), reduced left ventricular systolic function, prolongation of pre-ejection time and lastly impaired intrinsic myocardial contractility. There is evidence that these abnormalities improve with levothyroxine, demonstrating that adequate thyroid replacement improves cardiac output accompanied by substantial decrease in systemic vascular resistance, a reversal of diastolic function, and importantly an improvement in left ventricular ejection fraction during exercise. It has been demonstrated in Rotterdam study that subclinical hypothyroidism is a strong indicator risk for atherosclerosis and myocardial infarction.¹⁴

Inadequately treated hypothyroidism has also been demonstrated to have angiographic evidence of coronary atherosclerosis progression. Impairment of endothelium-dependent vasodilatation, a harbinger of atherosclerosis has also

been detected in patients with subclinical hypothyroidism which can be reversed by levothyroxine supplementation.

SOMATIC AND NEUROMUSCULAR EFFECTS

Patients with subclinical hypothyroidism can have subtle clinical manifestations and non-specific symptomatology such as dry skin, cold intolerance, constipation and easy fatigability. In addition, patients with muscular symptoms have mitochondrial oxidative dysfunction with significant lactate increment during exercise. Misuna et al also demonstrated the presence of subclinical polyneuropathy of probable axonal origin in patients with subclinical hypothyroidism.⁶⁷

Subclinical hypothyroidism patients reported significantly more total symptoms than euthyroid individuals in Colorado study⁶² and these symptoms do improve with Levothyroxine therapy. The greatest improvement is seen in patients with baseline TSH of > 12 mU/L. Kong et al observed no improvement in symptoms score after trial of thyroxine for six months in patients with TSH level between 5 and 10mU/L.⁶⁷

Prospective studies suggest that patients with mild thyroid failure have a higher prevalence of somatic symptoms, mood disorders, cognitive dysfunction, and atypical responses to standard psychiatric therapeutic

interventions.⁵⁷ Subclinical hypothyroidism lowers the threshold of depression.

TREATMENT

Risk and benefits of treatment

Among patients with untreated subclinical hypothyroidism there is no single level of serum TSH at which clinical action is always either indicated or contraindicated. As the serum TSH concentration increases above 10mU/L however, the basis for initiating treatment is more compelling. Clinical context is particularly important. This opinion reflects clinical experience and judgment as well as literature that suggest improvement in symptoms and possible lowering of LDL cholesterol. There are no studies that demonstrate decreased morbidity or mortality with treatment. The potential risk of therapy are limited to the development of subclinical hyperthyroidism, which may occur in 14% to 21% of individuals treated with levothyroxine.

Subclinical hypothyroidism with serum TSH of 4.5-10mU/L

Although some studies suggest an association between subclinical hypothyroidism and systemic hypothyroid symptoms⁶² or cardiac dysfunction¹¹ others do not. The available data does not confirm clear cut

benefits for early therapy compared with treatment when symptoms of overt hypothyroidism develop.⁶⁷

Therefore routine levothyroxine treatment for patients with TSH levels between 4.5 and 10 mU/L is not recommended but thyroid function tests should be repeated at 6-12 month intervals to monitor improvement or worsening in TSH level

Subclinical hypothyroidism with serum TSH higher than 10 mU/L

Levothyroxine therapy is reasonable for patients with subclinical hypothyroidism and serum TSH higher than 10 mU/L. The rate of progression is 5% in comparison with lower levels of TSH and treatment may potentially prevent the manifestations and consequences of hypothyroidism in those patients who do progress. Still, the evidence that therapy will reduce total and LDL cholesterol levels and improve symptoms in these patients is inconclusive.

Subclinical hypothyroidism during pregnancy

Pregnant women or women of child bearing potential planning to become pregnant who are found to have elevated TSH should be treated with levothyroxine to restore the serum TSH concentration to reference range .

This recommendation is based on the possible association between high TSH and either increased fetal wastage or subsequent neuropsychological complications occurring in the offspring due to thyroid insufficiency. Although there are no published intervention trials assessing the benefits of thyroid hormone replacement in this special population, the potential benefit-risk ratio of levothyroxine therapy justifies its use. It is important to note that the requirement for levothyroxine in treated hypothyroid women frequently increases in pregnancy, therefore serum TSH concentration should be monitored every 6 to 8 weeks during pregnancy and the levothyroxine dose modified as needed. The risks of appropriately managed levothyroxine therapy are minimal.

Subclinical hypothyroidism in treated overt hypothyroid individuals

When subclinical hypothyroidism is noted in levothyroxine treated patients with overt hypothyroidism, the dosage of levothyroxine should be adjusted to bring serum TSH into reference range. Whether the target TSH level should be in the lower half of reference range is controversial because there are no data demonstrating improved clinical outcomes with this strategy. Nevertheless, when serum TSH is in the upper half of reference range and levothyroxine treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase levothyroxine dosage to bring

serum TSH into lower portion of reference range. The rapidity of dosage adjustment depends on patient's age and medical comorbidities. Minimal TSH elevations may not require dosage adjustment in patients who feel well, particularly those with arrhythmias or other cardiac disorders.

To conclude, the patients with TSH levels greater than 10mU/L should be treated with thyroxine .The AACE has recommended treatment in patients with TSH levels between 5 and 10 m U/L in conjunction with goiter or positive anti-thyroid, peroxidase antibodies or both and also in the presence of symptoms. If the patients are antibody negative and TSH levels are between 5 and 10 mU/L, then an annual check of serum TSH is recommended with commencement of T4 once serum TSH rises above 10mU/L

Arguments against treatment

The arguments against treatment are its expense and the likelihood that some or even most patients will not benefit. There is also a danger of over treatment, which could cause iatrogenic hypothyroidism and ultimately lead to more serious abnormalities (eg; osteopenia and atrial fibrillation) than leaving the subclinical hypothyroidism untreated. Indeed in one large study, suppressed serum TSH consistent with the occurrence of over treatment were found in 21 % of patients taking thyroid hormones.

THYROXINE THERAPY

Given the high rate of conversion of subclinical hypothyroidism to overt hypothyroidism in the presence of circulating antithyroid antibodies, it makes sense to treat asymptomatic patients with positive antibody tests even if they have normal serum lipid levels. However, because an elevated serum thyrotropin level is associated with an increased risk of overt hypothyroidism even in the absence of antithyroid antibodies, positive antithyroid antibody titers should not be the sole criterion for therapy. It is also reasonable to treat subclinical hypothyroidism in pregnant women and women who have ovulatory dysfunction with infertility.

A therapeutic trial for subclinical hypothyroidism is warranted if patients have symptoms consistent with the presence of mild hypothyroidism, hypercholesterolemia, or goiter. Although the overlap in symptoms between patients with subclinical hypothyroidism and euthyroid patients make it difficult to predict who will have response to treatment, some patients have a remarkable improvement in their symptoms with thyroxine therapy. The positive findings in some small clinical trials^{3 68} also support the use of therapy in symptomatic patients and thyroid replacement can always be discontinued if there is no apparent benefit.

An initial dose of thyroxine of 0.05 to 0.075 mg per day is usually sufficient to normalize the serum TSH level. Patients with coronary artery disease should receive lower initial doses (eg: 0.0125 to 0.025 mg). Serum TSH level should be measured 4 to 6 weeks after therapy is begun and after any change in dose and then annually once levels becomes stable. Without treatment only 5% of elevated serum TSH levels will return to normal values in one year in older patients.

The evidence supports the use of treatment for most patients, as long as therapy is monitored with the use of annual measurement of serum TSH.

MATERIALS AND METHODS

Case selection

Women above the age of 50 years attending Medical out patient clinic of Kilpauk Medical College and Hospital , Chennai from January 2008 to June 2008 were studied. A sample of 100 women was randomly selected. Informed consent was obtained from all participants. All the participants were examined for thyroid function. Women with subclinical hypothyroidism (defined as TSH > 5.5 μ IU/ml with normal free T4 and free T3) were considered as cases, and women without subclinical hypothyroidism were considered as controls. Laboratory measurements and clinical assessment was carried out in all the participants.

Exclusion criteria

Those with

Known thyroid disease

History of neck irradiation

Chronic renal failure

Severe illness (such as infections , recent myocardial infarctions, severe heart failure or recent intensive care admission)

Taking drugs such as beta-blockers, amiodarone, interferon $-\alpha$

were excluded

Measurements

Thyroid function test- Free T4, Free T3 and TSH levels were measured. Thyroid function test is done using the electro chemiluminescence method. The normal range for TSH is 0.30-5.50 μ IU/ml, for Free T4 the normal range is 0.70-1.80 ng/dl, and for Free T3 it is 1.70-4.20 pg/ml.

Clinical Assessments

Participants were examined for the presence of goiter and symptoms of hypothyroidism.

Analytical methods

The following data were collected from the entire study group

- Age
- Presence of Hypertension (defined as BP > 140/90 mm Hg on more than one occasion or the patient is known to be hypertensive)
- Diabetes mellitus (defined as fasting blood sugar >126 mg% on two consecutive readings one month apart or the patient is known to be diabetic)
- Ischemic heart disease (defined as angina or myocardial infarction by self report or by analysis of standard 12 lead ECG for ischemic heart disease changes)

- Comparison between cases (subclinical hypothyroidism) and normal control subjects of similar age and ethnic group was done with regard to presence of IHD ,Hypertension and Diabetes mellitus

Statistical Analysis

Statistical analysis was done using the statistical package for social sciences (SPSS). Different statistical methods were used as appropriate. Mean \pm SD was determined for quantitative data and frequency for categorical variables. The independent t- test was performed on all continuous variables. The normal distribution data was checked before any t-test. The Chi-Square test was used to analyze group difference for categorical variables. In logistic regression models, age was adjusted for estimation of each or all the independent effects of hypertension, ischemic heart disease and diabetes mellitus . A p- value < 0.05 was considered significant.

RESULTS

100 women above the age of 50 years who visited the medical outpatient clinic during the study period were studied

23 women were found to have the criteria set for the definition of subclinical hypothyroidism which meant a rate of 23%. Patients with subclinical hypothyroidism were regarded as cases and remaining 77 patients were the control group.

There were differences in the mean age distribution among cases and controls are shown in table 1 and fig 1

Table 1

Age in years	Patients with SH	Patients without SH
50-59	7	36
60-69	9	24
70 and above	7	17

There were 43 patients in the age group 50-59 of which 7 (19.44%) were having subclinical hypothyroidism .

In the 60-69 age group there were 33 patients of which 9 (27.27%) were having subclinical hypothyroidism.

In the 70 and above age group there were 24 patients of which 7 (29.17%) were having subclinical hypothyroidism.

The mean TSH level in patients with subclinical hypothyroidism was 12.11 μ IU/mL. For FT4 it was 1.03ng/dl and for FT3 it was 2.76pg/ml . There were differences in FT4, FT3, TSH distribution in cases and control as shown in Table 2

Table 2

Mean	Patients with SH	Patients without TSH
FT3 (pg/ml)	2.76	3.01
FT4 (ng/dl)	1.03	1.14
TSH (μ IU/ml)	12.11	3.75

There were 23 patients with TSH level more than 5.5 μ IU/ml, the upper level of normal range (0.30-5.5 μ IU/ml). They are the subclinical hypothyroid patients in this study. Of those 23 patients 15(65.2%) had TSH level between 5.5 to 10 μ IU/ml. The remaining 8 (34.8%) patients had TSH levels more than 10 μ IU/ml as shown in the following Table 3

Table 3

TSH levels in patients with SH

TSH level in μ IU/ml	No. of patients(%)
	Total no = 23
5.5 – 10	15 (65.2%)
> 10	8 (34.8%)

Hypothyroid symptoms were reported in 7 out of 23 (30.43%) patients with subclinical hypothyroidism. Fatigability and constipation were the most common complaint, followed by weight gain .The frequency of hypothyroid symptoms in the subclinical hypothyroid patients are as shown in the table 4

Table 4

Frequency of hypothyroid symptoms in patients with SH

Fatigability	6 (26.1%)
Constipation	6 (26.1%)
Weight gain	4 (17.4%)
Goiter	2 (8.7%)
Others(cold intolerance, infertility etc)	2 (8.7%)

Goiter was present in 2 out of 23 patients with subclinical hypothyroidism (8.7%) and 5 out of 77 patients without subclinical hypothyroidism (6.5%).

Other symptoms like cold intolerance infertility were present in 2 of the 23 patients (8.7%) with subclinical hypothyroidism and 1 of the 77 patients (1.3%) without subclinical hypothyroidism

The incidence of risk factors like hypertension diabetes and ischemic heart disease were compared between patients with subclinical hypothyroidism and control.

They were analyzed independently with Chi-Square test. The p- value showed that patients with subclinical hypothyroidism were significantly associated with ischemic heart disease compared to controls. The p- value is not significant for hypertension and diabetes. This is shown in table 5

Table 5

	Patients with SH	Patients without SH	p- value
IHD	5 (21.71%)	5 (6.5%)	0.047
DM	4 (17.4%)	16 (20.1%)	0.490
HT	6 (26.1%)	21 (27.3%)	0.570

DISCUSSION

Sub clinical hypothyroidism is highly prevalent in elderly women. A prevalence of 11 – 26 % had been reported in previous studies,^{4,8,23,62} our study shows a prevalence of 23 % in concordance with the other studies.

Surveys that stratified TSH levels indicate a predominance of TSH < 10 μ IU/ml , which accounts for about 55-85% of cases.^{5,58,69} Almost 65% of our patients with subclinical hypothyroidism had TSH levels < 10 μ IU/ml. Studies that have reported thyroid antibody test on subjects with elevated TSH demonstrated seropositivity rates from 20-78%.^{1,4,59,70}

Several studies have suggested that mild symptoms of hypothyroidism are more prevalent in patients with subclinical hypothyroidism than in age matched controls.^{62,70} Fatigability and weight gain were the most frequent symptoms,⁶⁷ but not all studies have found this to be true.⁷¹ 30% of our patients with subclinical hypothyroidism had symptoms of which fatigability (26%) and constipation (26%) were the most common

There have been three published randomized prospective placebo controlled trials for the therapy of symptoms in patients with subclinical hypothyroidism.^{21,68,72}

Two trials reported significant improvement in symptoms of hypothyroidism, whereas the third found no benefit of therapy.^{21,68,72} The benefit of therapy

was related to TSH level, being more in those who have mean TSH level greater than or equal to 12.7 μ IU/ml at baseline.⁷¹ In women with SH and ovulatory dysfunction, thyroxine therapy may restore fertility.⁷³

Case control and cross-sectional studies on association between subclinical hypothyroidism and cardiovascular disease have been done, but results were controversial.^{1,8,15,16,17,74} A 20 year follow up study of the original Whickham survey⁷⁵ showed no association between elevated TSH and increased risk of IHD, while a report of 1149 women from Rotterdam showed increases atherosclerotic vascular disease and myocardial infarction in patients with subclinical hypothyroidism.⁸ The present study showed a significant increase in IHD in patients with subclinical hypothyroidism compared with controls (p value of 0.047). Several studies on association between subclinical hypothyroidism and dyslipidemia have been done. The initial Whickham study observed that lipid levels were not associated with TSH elevation after age adjustment.¹ The Colorado study and others noted a significantly elevated LDL cholesterol in subjects with subclinical hypothyroidism.^{12,62} A report from Rotterdam noted that with subclinical hypothyroidism subjects actually had lower total cholesterol⁸

Women with subclinical hypothyroidism did not differ from controls with regard to hypertension and diabetes in previous studies.^{8,71} The present study also showed it to be true.

There is documented evidence that many (but not all) effects are improved or corrected when L-thyroxine replacement is instituted. L- thyroxine treatment was recommended for majority of patients with mild thyroid failure, particularly those with symptoms, goiter, positive thyroid antibodies and those who are pregnant. However, despite these positive indications that treatment carries some benefits, the benefits risk ratio of treatment remains to be determined, given the lack of outcome data and the considerable risk of TSH suppression in patients on L-thyroxine replacement.

Conclusion

- Subclinical hypothyroidism is highly prevalent in elderly women above the age of 50 years
- Most of those with subclinical hypothyroidism have TSH level below 10 μ IU/ml
- Hypothyroid symptoms are prevalent in patients with subclinical hypothyroidism. (30% of patients in this study) Fatigability and Constipation being the most common symptoms
- Patients with subclinical hypothyroidism are more prone to develop ischemic heart disease
- There is no increased risk for developing hypertension and diabetes mellitus in patients with subclinical hypothyroidism

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APPENDIX

1	BMI	Body Mass Index	21	rT3	Reverse T3
2	D1	Type 1 deiodinase	22	RAIU	Radio Active Iodine Uptake
3	D2	Type 2 deiodinase	23	RXR	Retinoid X Receptor
4	DIT	Diiodothyronine	24	SH	Subclinical Hypothyroidism
5	DUOX	Dual Oxidase	25	SLC5A	Solute Carrier Family 5A
6	E	Embryonic Day	26	T3	Triiodothyronine
7	FSH	Follicle Stimulating Hormone	27	T4	Tetraiodothyronine
8	FT3I	Free T3 Index	28	TBAb	Thyroid Blocking Antibody
9	FT4I	Free T4 Index	29	TBG	Thyroid Binding Globulin
10	hCG	Human chorionic gonadotropin	30	TgAb	Thyroglobulin Auto antibody
11	HDL	High Density Lipoprotein	31	THBR	Thyroid Hormone Binding Ratio
12	I	Iodine	32	THOX	Thyroid Hormone Oxidase
13	IHD	Ischemic Heart Disease	33	TPO	Thyroid Peroxidase
14	LDL	Low Density Lipoprotein	34	TPOAb	Thyroid Peroxidase Antibody
15	LH	Luteinizing Hormone	35	TR	Thyroid hormone Receptor
16	MCR	Metabolic Clearance Rate	36	TRH	Thyroid Releasing Hormone
17	MCT	Mono Carboxylate Anion Transporter	37	TSAb	Thyroid Stimulating Antibody
18	MIT	Mono Iodo Thyronine	38	TSH	Thyroid Stimulating Hormone
19	NIS	Sodium Iodide Symporter	39	TSHR	TSH Receptor
20	PVN	Para Ventricular Nucleus	40	TTR	Transthyretin

PROFORMA

NAME:

IP NO:

AGE:

ADDRESS:

SEX:

OCCUPATION:

HISTORY OF

- Fatigability
- Weight gain
- Constipation
- Cold tolerance
- Other symptoms: specified

PAST HISTORY:

- Hypertension
- Diabetes Mellitus
- Coronary heart disease
- Hypothyroidism
- Drug intake
- Exposure to irradiation
- Thyroid surgery

PERSONAL HISTORY

- Menstrual history
- Obstetric history

CLINICAL EXAMINATION

Pulse rate: Blood pressure: Temperature: Goiter:

CVS:

RS:

ABDOMEN:

CNS:

INVESTIGATION

- FT3, FT4, TSH
- Fasting blood sugar
- ECG

Figure 1

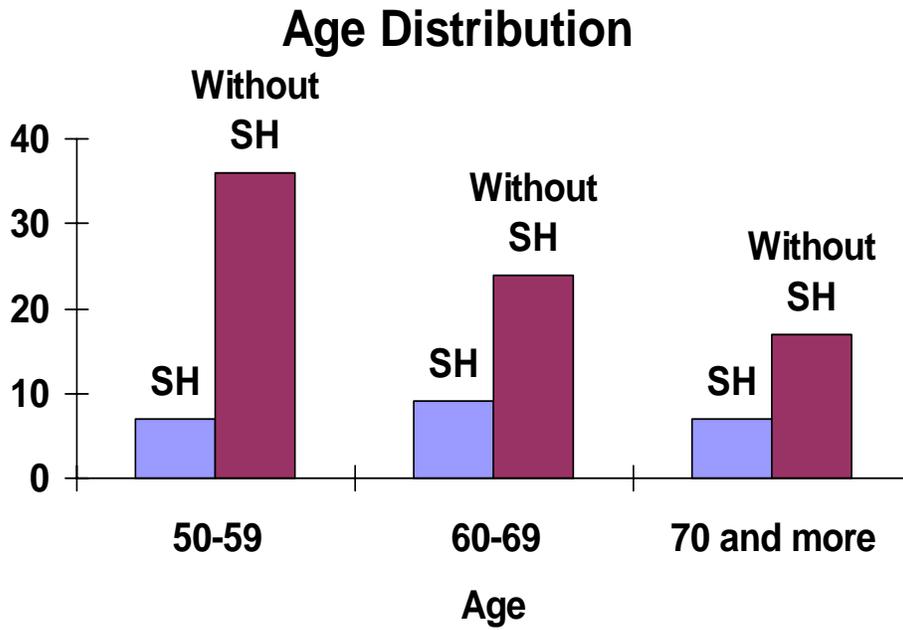


Figure2

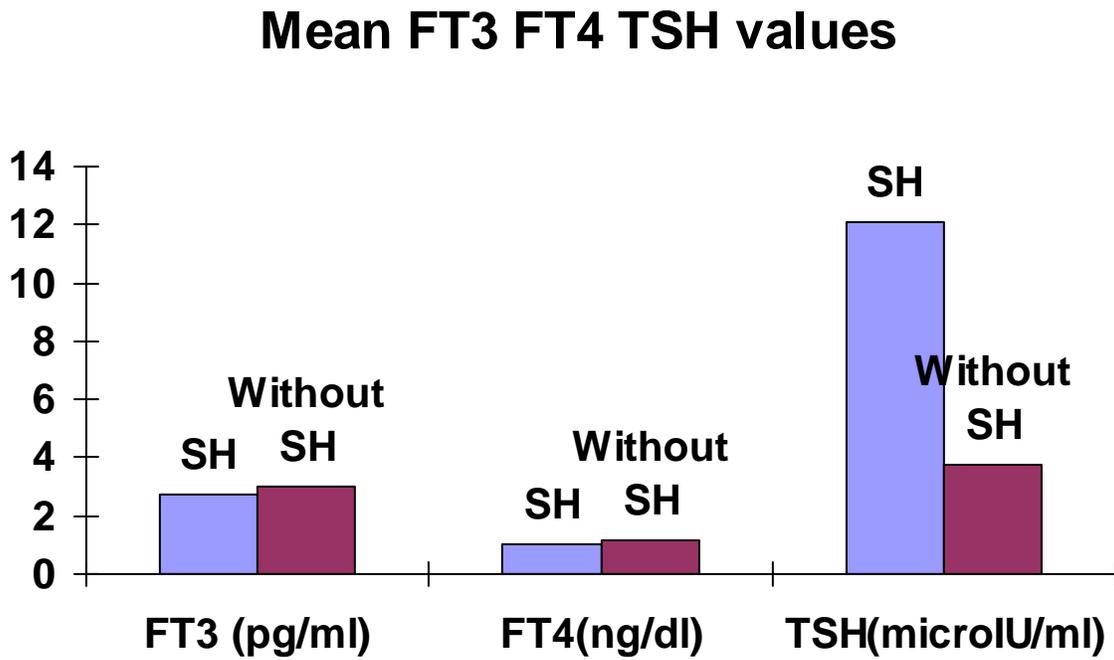


Figure 3

TSH levels in SH

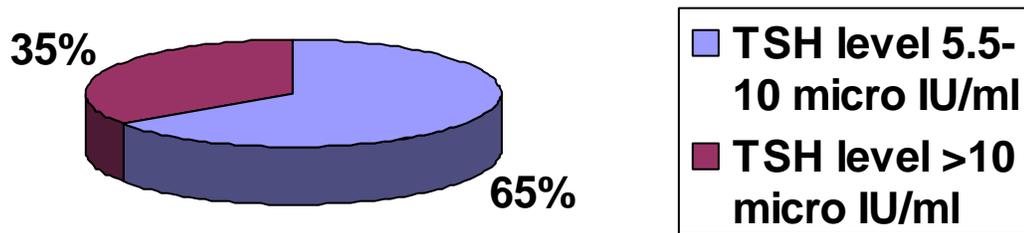


Figure 4

Frequency of hypothyroid symptom in SH patients

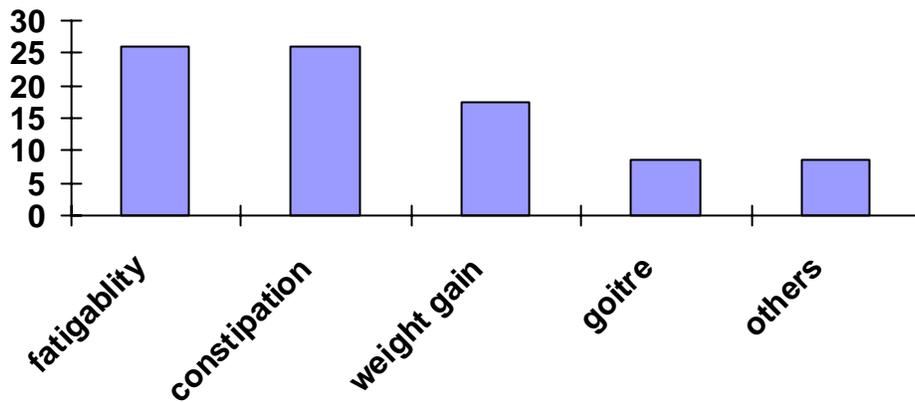


Figure 5

