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Approach to Subclinical Thyroid Disease

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Summary:
Subclinical thyroid dysfunction is defined as an abnormal serum thyroid-stimulating hormone level and free thyroxine and triiodothyronine levels within their reference ranges. The prevalence of subclinical hyperthyroidism is about 2 percent. Subclinical hypothyroidism is found in approximately 4 to 8.5 percent of the population. Most national organizations recommend against routine screening of asymptomatic patients, but screening is recommended for high risk populations. The management of subclinical thyroid dysfunction is controversial. There is good evidence that subclinical hypothyroidism is associated with progression to overt disease. Patients with a serum thyroid-stimulating hormone level greater than 10 mIU/L have a higher incidence of elevated serum low density lipoprotein cholesterol concentrations; however, evidence is lacking for other associations. There is insufficient evidence that treatment of subclinical hypothyroidism is beneficial. A serum thyroid stimulating hormone level of less than 0.1 mIU/L is associated with progression to overt hyperthyroidism, atrial fibrillation, reduced bone mineral density, and cardiac dysfunction. There is little evidence that early treatment alters the clinical course.

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Introduction:

Subclinical thyroid disease is, by its very nature, a laboratory diagnosis. Patients with subclinical disease have few or no definitive clinical signs or symptom

It is a common clinical problem. Some patients will progress to overt disease, and in some patients, the serum thyroid- stimulating hormone (TSH) concentration will remain stable over time or will spontaneously return to the reference range.[1,2]

There are many controversial issues regarding screening, evaluation and management.

In 2002, a consensus committee was formed with representatives from the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society. The committee makes recommendations about the controversial issues.[3]

Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free thyroxine (FT_4) concentration is within its reference range.[4] The panel defined the reference range of normal serum TSH concentration as 0.45 to 4.5 mIU/L[3]

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Subclinical hyperthyroidism is defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT_4 and triiodothyronine (T_3) concentrations are within their reference ranges.[4]

Epidemiology of Subclinical Thyroid Disease:

The prevalence of subclinical hypothyroidism in the US adult population is about 4% to 8.5% in those without known thyroid disease.[5,6] The prevalence increases with age, and in women older than 60 years, subclinical hypothyroidism is present in up to 20%.[6]

Subclinical hyperthyroidism is much less common than subclinical hypothyroidism. When the lower limit of TSH is less than 0.4 mIU/L, 3.2% of the population is defined as having subclinical hyperthyroidism.[5] If patients with known thyroid disease are excluded, the prevalence decreases to 2%. Subclinical hyperthyroid disease is more common in women than men, in blacks than whites, in the elderly, and in patients with low iodine intake.[7]

Screening for Thyroid Disease:

In January 2004, the U.S. Preventive Services Task Force concludes that "the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults."[1]

The 2002 consensus group's expert panel recommended against population-based screening but recommends "screening asymptomatic person for

Although the primary mechanism of action of methotrexate in JIA or adult RA is not clearly known, recent reviews suggest that the anti-inflammatory effects of methotrexate seems to be related to the extra cellular adenosine release and its interaction with specific cell surface receptor[44].

Dose & route of administration:
In general, children with JIA, methotrexate therapy started at a dose of 10 to 15 mg/m^2/week or 0.3-0.6 mg/kg/week. However children seem to tolerate much higher dose than adult and some series describe using up to 20-25 mg/m^2/week in children with refractory cases, with relative safety in the short term. At doses more than 15 mg/m^2/week the parental route may be preferred.

A recent multinational, randomized controlled study by Pediatric Rheumatology International Trials Organization (PRINTO) compared 30mg/m^2/week in children with polyarticular JIA who failed to improve with 8-12.5 mg/m^2/week. Maximum response was found with 15 mg/m^2/week and there was no added benefit of the 30mg/m^2/week dose over 15mg/m^2/week[47].

Folic acid supplementation:
A recent multi center randomized double blinded placebo controlled trail showed that 2.5-5mg folic acid supplementation 2 days after methotrexate reduced the incidence of increased liver enzyme but had no effect on the incidence of other gastrointestinal and mucosal side effects[26].

Side effects:
Nausea is infrequent and can be lessened by use of antiemetics like Ondansetron, consideration needs to be given to be psychological support of children in methotrexate, in whom habitual nausea may sometimes occur[48, 49].

Sulphasalazine:
Three recent studies have confirmed earlier reports that Sulphasalazine is effective in oligoarticular & polyarticular varieties of JIA. Usual doses are 40-50 mg/kg of body wt/day (maximum 2gm/day). In a placebo controlled study 10 of 69 patients withdrew due to side effects, which were reversible[31, 32, 33].

Leflunomide:
Leflunomide, an orally administrated inhibitor of pyrimidine synthesis has been shown to be safe and effective long term therapy for adult with rheumatoid arthritis. In a pilot open-label study of children with polyarticular course JIA, 52% of those receiving leflunomide had a response even though all patients either had no response to or were intolerant to methotrexate. To confirm this a total 48 weeks randomized control multicentre (32 centres in 12 countries from march 2002-jan 2003) study was conducted to compare leflunomide with methotrexate in children (3-17 yrs), with active polyarticular JIA. Of 94 patients, randomized response rate was 89% and 68% in methotrexate and leflunomide respectively at 16 weeks and improvement was maintained at 48 weeks. Methotrexate was used in a dose of 0.5 mg/kg/week (25 mg/week) and leflunomide 10-20 mg/day according to body wt. following a bolus dose of 100 mg/day (for l-3 days according to body wt). Methotrexate & leflunomide both resulted in high rate of improvment in JIA patient (polyarticular type) but at doses used in that study methotrexate was more effective than leflunomide[62-66].

Monitoring Methotrexate and other DMRD therapy:
Before commencing DMARD therapy baseline information regarding CBC, Liver function, renal function should be obtained. Full blood count and liver and renal function monitoring is required fortnightly until a stable dose is achieved. Thereafter monthly monitoring for 6 months, increasing to 6 weekly is the usual practice[28-30].

TNF α blocker (Etanercept):

Tumor necrosis factor was identified in synovial fluid in 45% patient of JIA & found to play a proinflammatory role in pathogenesis.

In a randomize double blind multi-centre study, TNF α blocker was found safe, effective in children with poly articular JIA who did not tolerate or had an inadequate response to methotrexate. At the end of open study 74% of patient had a 30% improvement, 64% had a 50% improvement & 36% had a 70% improvement[43].

Refractory JIA:
Refractory juvenile idiopathic arthritis should be considered when the disease does not respond to

high dose of Methotrexate (1 mg/Kg/week, subcutaneously)[23, 56]. Combination of methotrexate with other DMRDS e.g. sulphasalazine, leflunomide are required in such cases and in some JIA subtypes such as ehthesitis related and systemic onset JIA[69-73]. Eternercept as monotherapy or in combination with methotrexate resulted in signifixcant improvement in sign and symptom of JIA. More aggressive therapies like IV methylprednisolone & cyclophosphamide can be considered in some cases of refractory JIA, since the biological agents is not possible for most patients[23, 37, 39, 42].

General aspects of management:

Nutrition:

All children with chronic rheumatic disease are susceptible to both growth retardation and malnutrition[7, 8]. Fatigue, non-specific abdominal pain, or worry about poor body image may all cause anorexia, limiting dietary intake. Ensuring an adequate protein, calorie and calcium intake is important but supplements including iron, folic acid, and vitamin D may also be indicated[58-60].

Physiotherapy and splints:

Physiotherapists ensure that both passive and active exercise schedules are implemented to maintain joint movement and improve muscle function.

Compliance:

Education of children with chronic disease and their parents about the need to take medication according to prescribed regimens is essential. Parents may be wary about giving children about the multiple medications, which are often necessary. In a useful review of factors affecting compliance it was noted that between 55-95% of medication (including self-administered or by parents for younger children) is taken correctly, but adhere with physiotherapy regimens is lower at 46-86%. Where there is suspected lack of compliance with oral therapy, perhaps with adverse social factors, in association with poor disease control, the administration of methotrexate sub-cutaneously by home care team may be useful.

Written information about arthritis, treatment and support groups should be offered to children, adolescents and parents.

Remission rate or when to discontinue the therapy:

The question of when, how and by what criteria, attempt should be made to withdraw methotrexate therapy in JIA is still more a clinical art than a science. “Remission” is a controversial concept in JIA. The criteria for “remission” or “relapse” have never been operationally defined and prospectively tested in JIA. In literature on JIA, the cited criteria for remission are often subjective and have not included long-term physical and functional outcomes.

However, methotrexate withdrawal may result in disease flare in more than 50% of patients as shown by Ravelli et al, a feature also noted by others[26]. The ease with which remission is achieved when methotrexate is re-established is still unclear. Reported rates of “remission” in JIA treated with methotrexate vary from 6.9% to 45%; the average duration of methotrexate treatment until “remission” is around one year at a weekly dose 10-15 mg/m^2.

The first phase of remission is the achievement of inactive disease which is defined as: no joints with active arthritis; no fever, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR or CRP; and a physician’s global assessment of disease activity indicating no disease activity. Clinical remission on medication is defined as inactive disease on medication for a full six months, and clinical remission off medication is achieved when there is inactive disease off of medications for a full 12 months. Although many children can achieve clinical remission on medications, most will have a flare of their arthritis within three years of discontinuing medications.

Once there is complete remission, effective medications are continued for 6 to 12 months before tapering[45].

Complications of JIA:

Complication may be local or systemic, disease related or as a consequence of treatment.

Localized joint problems can be minimized by good, early control of inflammatory process. Children with inflamed joints will rapidly develop flexion deformities which may become fixed if inadequately managed. Drug treatment is combined with

physiotherapy and the judicious use of splinting to maintain correct joint position and function. Persistent inflammation in a joint may lead to bony overgrowth at that joint. This is seen particularly in children with oligoarthritis and involvement of one knee. If not controlled this may lead to overgrowth of that knee and a leg length discrepancy. Undergrowth of the mandible as a consequence of temporomandibular joint involvement may lead to significant functional and cosmetic problems.

Disturbance of overall growth is well recognized in children with JIA. Many children with JIA develop marked osteopenia. Poor diet, inactivity and steroids may contribute but other factors more directly related to disease process are clearly involved.

Anemia in severe JIA may be a significant problem and detract from the well being of child[60].

Oligoarticular arthritis is associated with chronic uveitis which is asymptomatic and may therefore go undetected for considerable time unless screened for.

Amyloidosis is well described in this condition and was previously reported to occur in around 10% of European cases[36].

Prognosis:

JIA is a chronic disease with perhaps 50% of patients will have active arthritis in adult years. JIA impacts the life style of not only the child but also the whole family. There is still very little published data to predict which patients will have a prolonged disease course & which medications are likely to be effective in which type of patients. In general those with involvement of few joints do better than those with systemic disease or RA factor positive JIA. Fifteen year follow up studies from USA & Italy of 227 patients from all subgroups of JIA show that frequently the long-term outcome is good, the worst prognostic factors were identified as the severe type of arthritis score at onset; early hand involvement & symmetrical arthritis with suggestion that ESR may have some predictive value related to quality of life[15, 16, 61].

Future developments in JIA

The aetiology of JIA remains elusive. It is hoped that an improved classification system will facilitate further research by identifying more homogeneous patient groups for study. As our understanding of these conditions improves, so the search for a 'cure' should prove more fruitful.

New developments in the field of antirheumatic therapy include biologic agents (such as anti-cytokine drugs) and new immunosuppressive agents with improved toxicity profiles. Stem cell transplantation is being increasingly used in the field of autoimmune disease and several children with severe JIA have been successfully transplanted.

Conclusion:

JIA is the most common group of rheumatic disease in childhood. Diagnosis is made on the basis of clinical criteria. The effective treatment needs multidisciplinary approach. Awareness amongst general pediatricians/ rheumatologist/ physicians, early recognition, prompt introduction of specific DMARD (e.g. methotrexate, Sulphasalazine) therapy either singly or as a combination at appropriate doses, in addition to other supportive therapies (NSAIDs, Intra articular Steroid etc.) are measures that will improve outcome and quality of life for these children. Nowadays, parents are more likely to request for newer therapies & adequate time is needed to address their concerns about the disease and the drugs.

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thyroid disease should be considered, specially for those older than 60 years or with risk factors such as women with a family history of thyroid disease, prior thyroid dysfunction, symptoms suggestive of hyperthyroidism or hypothyroidism, abnormal thyroid gland on examination, type 1 diabetes, or a personal history of autoimmune disorder.[3]

The panel found insufficient evidence to recommend for or against screening pregnant women or women planning a pregnancy.[3]

The American College of Physicians (1998), recommends screening for women older than 50 years who have symptoms consistent with thyroid disease.[8]

Subclinical Hypothyroidism:

Etiology

Hashimoto's thyroiditis , protracted recovery from acute thyroiditis, early hypothalamic disorder, inadequate levothyroxine replacement therapy in a patient with known hypothyroidism.'[3]

Consequences of Untreated Subclinical Hypothyroidism:

Serum lipid levels in subclinical hypothyroidism (SCH) have been reported as either normal [9] or elevated [10] . In the Tromso study, low density lipoprotein – cholesterol (LDL-C) levels were significantly higher.[10] In Suita study, no significant association was observed between sub clinical thyroid dysfunction and lipid metabolism. The suita study reported that SCH was associated with lower fasting blood glucose (FBG).[11]

SCH patients have impaired endothelial function, normal / depressed systolic function, left ventricular diastolic dysfunction at rest, and systolic and diastolic dysfunction on effort.[12] In two studies, positive association between arterial stiffness & SCH has been reported.[12, 13] But no significant association between SCH and intima-media thickness(IMT) was observed in Suita study[11], which suggests that SCH might not be related to an increased risk of atherosclerosis.

Patient may exhibit the feature of systemic hypothyroid symptoms[6,14], neuropsychiatric symptoms[6,14] and may progress to overt, symptomatic hypothyroidism.[15]

Evaluation of Subclinical Hypothyroidism :

The TSH measurement should be repeated along with an FT_4 measurement at a minimum of 2 weeks, but no longer than 3 months, after the initial assessment.

If a high serum TSH concentration is confirmed on repeat testing and serum FT_4 is within the reference range, the patient should be evaluated for signs and symptoms of hypothyroidism, previous treatment for hypothyroidism, thyroid gland enlargement, or family history of thyroid disease. Lipid profiles should be reviewed. Women who are pregnant or hope to become pregnant in the near future deserve special consideration.

Anti-thyroid peroxidase(Anti-TPO) antibodies are to be measured because the presence of anti-TPO antibodies predicts a higher risk of developing overt hypothyroidism (4.3% per year vs 2.6% per year in antibody-negative individuals).[16]

Risks of Treating Subclinical Hypothyroidism:

The potential risks of therapy are limited to the development of subclinical hyperthyroidism, which may occur in 14% to 21% of individuals treated with levothyroxine.[17]

Treatment:

Subclinical Hypothyroidism With Serum TSH of 4.5 to 10 mIU/L.

- Routine levothyroxine treatment is not recommended for patients with TSH levels between 4.5 and 10 mIU/L, but thyroid function tests should be repeated at 6- to 12-month intervals to monitor for improvement or worsening in TSH level.[3] Very recently a study showed that patient with subclinical hypothyroidism with TSH > 4 mIU and FT_4 in normal range obtained improvement in their cardiovascular rick factor profile and reduced tiredness after treatment with Levothyroxine. [18] Thyroxin therapy for TSH level between 4.5- 10 mIU/L should be reserved for patients who have goitre, women that are anticipating pregnancy or are pregnant, patient with depression or dipolar disorder or TPO antibody positive. Thyroxine therapy may be considered in patients with symptoms of hypothyroidism who have TSH level between 4.5-10 mIU/L and continued only if there is clear symptomatic benefit.

Subclinical Hypothyroidism With Serum TSH Higher Than 10 mIU/L

Levothyroxine therapy is reasonable. The rate of progression is 5% in comparison with patients with lower levels of TSH. [3]

Subclinical Hypothyroidism During Pregnancy. A TSH level might be obtained in pregnant women and women who wish to become pregnant if they have a family or personal history of thyroid disease, physical findings or symptoms suggestive of goiter or hypothyroidism, type 1 diabetes mellitus, or a personal history of autoimmune disorders. Pregnant women or women of childbearing potential planning to become pregnant who are found to have elevated serum TSH should be treated with levothyroxine to restore the serum TSH concentration to the reference range. [3] The requirement for Levothyroxine in treated hypothyroid women frequently increases during pregnancy. Therefore, the serum TSH concentration should be monitored every 6 to 8 weeks during pregnancy.

Subclinical Hypothyroidism in Treated Overt Hypothyroid Individuals.

When the serum TSH is in the upper half of the reference range and levothyroxine-treated patients continue to note symptoms suggestive of hypothyroidism, it is reasonable to increase the levothyroxine dosage to bring the serum TSH into the lower portion of the reference range. Minimal TSH elevations may not require dosage adjustment in patients who feel well.

Subclinical Hyperthyroidism

Etiology

It may be transient or persistent

Persistent

- Exogenous
  - Iatrogenic- excessive thyroxine replacement
  - Intentional suppression
  - Surreptitious
- Endogenous
  - Early graves' disease
  - Toxic multi nodular goiter
  - Autonomous functioning nodules

Transient

- De Quervain's thyroiditis
- Postpartum thyroiditis

Differential diagnosis of low TSH

Hyperthyroidism

- Over
- Subclinical

Secondary

- pituitary insufficiency

Euthyroidism

- Physiological (Near end of first trimester)
- Elderly patients

Non thyroidal illness

Interpretation of Thyroid laboratory test

FT4 level	Normal TSH	Increased TSH	Decreased TSH
Normal	Normal, euthyroid sick syndrome.	Subclinical hypothyroidism	Subclinical hyperthyroidism
Increased	Early thyroitites	Hyperthyroidism (Pituitary adenoma)	Hyperthyroidism (Graves' disease, toxic nodule)
Decreased	Late thyroidites	Hypothyroidism (Primary thyroid failure)	Hypothyroidism (Primary pituitary failure)

Consequences of Untreated Subclinical Hyperthyroidism:

The potential adverse outcomes would be related to the degree of TSH suppression. Patients with serum TSH levels < 0.1 mIU / L are at higher risk than those patients with TSH levels between 0.1 & 0.45 mIU/L.[3]

Some studies noted, subclinical hyperthyroid patients have an increase in heart rate[19], increase in the frequency of atrial & ventricular premature beats[20] & an increase in left ventricular mass.[19, 21] However, a recent study noted, sub clinical hyperthyroidism was not associated with left ventricular hypertrophy.[22]

Two studies found minimal or no effect on systolic function [19, 20] and one showed slightly enhanced systolic function [23]. Biondi et al. [23] also reported a statistically significant impairment in diastolic function with decreased transmitral blood flow due to slowed left ventricular relaxation, but significant changes were not observed in two other study. [19, 20] Gussekloo et at. [24] found individuals over age 85 years with low serum TSH values had the highest rates of mortality. In contrast, two studies found no increased frequency of coronary artery disease or cardiovascular mortality. [25, 26]

Bone mineral density is lower at all sites in post menopausal women [27], in contrast, in premanopausal women it appears to be normal. [28]

In one report, the risk of vertebral fracture was elevated 4- fold and hip fracture was elevated 3- fold in women of 65 years of age or older with serum TSH values 0.1 mIU / L or less compared with control. [29]

Recently, two studies described an increase in typical hyperthyroid symptoms (Palpitation, tremor, heat sensitivity, sweating, and nervousness) in young & middle aged patients with sub clinical hypothyroidism. [19, 23]

In a community- based study of persons age 65 years & older, there were no significant differences in mood, anxiety or cognition between sub clinical hyperthyroid persons & those who were euthyroid [30].

One study showed an increased basal oxygen consumption that decreased to normal after treatment with methimazole. [31] In another study, patients with sub clinical hyperthyroidism were found to have decreased muscle strength compared with control.[32]

The risk of progression of overt hyperthyroidism varies. The etiology plays a role in this regard. Woeber[33] observed that serum TSH values normalized in five of seven patients with Graves' disease and subclinical hyperthyroidism followed for 3-19 months, whereas it remained subnormal in patients with multinodular goiters followed for 11-36 months.

Evaluation of Subclinical Hyperthyroidism :

Individuals With Serum TSH 0.1 to 0.45 mIU/L Not Treated With Levothyroxine. Measurement should be repeated by measuring FT_4 and either total T_3 or FT_3 levels. Repeat testing within 2 weeks is prudent for patient with atrial fibrillation, cardiac disease, or other serious medical conditions. Repeat testing within 3 months is recommended, when these factors are absent.[3]

If the repeat serum TSH concentration remains higher than 0.1 but lower than 0.45 mIU/L, with normal FT_4 and T_3 concentrations, and the patient has no signs or symptoms of cardiac disease, atrial fibrillation, or other arrhythmias, retesting should occur at 3- to 12-month intervals, until either serum TSH level normalizes or the clinician & patient are confident that the condition is stable. [3]

Individuals With a Serum TSH Lower Than 0.1 mIU/L. The measurement is repeated along with an FT_4 and a total T_3 or FT_3 within 4 weeks if the patient has no signs or symptoms of cardiac disease, atrial fibrillation or other arrhythmia but within a shorter interval if signs or symptoms of hyperthyroidism are present.[3]

The panel recommendts further evaluation to establish the etiology of the low serum TSH.[3]

A radio-active iodine uptake & Thyroid scan can distinguish between destructive thyroiditis & hyperthyroidism due to Graves' disease or nodular Goiter.

Risks of Treatment of Subclinical Hyperthyroidism:

The risks of treatment with antithyroid drugs are potential allergic reactions including agranulocytosis. Radioactive iodine therapy commonly causes hypothyroidism & may cause exacerbation of hyperthyroidism or Graves' eye disease.[34]

Treatment:

Exogenous Subclinical Hyperthyroidism With TSH 0.1 to 0.45 mIU/L.

The indication of thyroid hormone therapy should be reviewed. Many patients with thyroid cancer & some patients with thyroid nodules required TSH suppression and target TSH level should be reviewed by the treating physician. When prescribed for other causes the dosage of levothyroxine is decreased to allow serum TSH to increase toward the reference range.[3]

Exogenous Subclinical Hyperthyroidism With TSH Lower Than 0.1 mIU/L.

The indication for thyroid hormone therapy should be reviewed. For patients with thyroid cancer and thyroid nodules, the target serum TSH value should be reviewed by the physician. When levothyroxine is prescribed for hypothyroidism in the absence of thyroid nodules or thyroid cancer, the panel recommends decreasing the dosage of levothyroxine to allow serum TSH to increase toward the reference range.[3]

Endogenous Subclinical Hyperthyroidism (Serum TSH 0.1-0.45 mIU/L)

The panel[3] recommends against routine treatment for all patients whose TSH is mildly decreased (0.1-0.45 mIU/L). Because of a possible association with

increased cardiovascular mortality,[35] clinicians might consider treatment of elderly individuals and for those with or at increased risk for heart disease, osteopenia, or osteoporosis (including estrogen-deficient women), or for those with symptoms suggestive of hyperthyroidism, despite the absence of supportive data from intervention trials and no therapy is required for younger patient .

Endogenous Subclinical Hyperthyroidism (Serum TSH Lower Than 0.1 mIU/L)

The panel[3] recommends that treatment be considered for subclinical hyperthyroidism (TSH <0.1 mIU/L) due to Graves or nodular thyroid disease. Treatment should be considered for patients who are older than 60 years and for those with or at increased risk for heart disease, osteopenia, or osteoporosis (including estrogen-deficient women), or for those with symptoms suggestive of hyperthyroidism. Younger individuals with subclinical hyperthyroidism and serum TSH persistently (months) lower than 0.1 mIU/L may be offered therapy or follow-up depending on individual considerations.

Conclusions:

There are many controversies regarding the management of subclinical thyroid disease.Until data of well conceived and executed intervention trials are available, following may be recommended: If TSH > 10 mIU/L, thyroxine therapy is to be given. If TSH 4.5- 10 mIU/L, thyroxine therapy may be given for goitrous patients, women who are pregnant or anticipating pregnancy, or patient with depression or TPO antibody positive. Postmenopausal women or patient older then 60 years or with heart disease or osteoporosis or symptoms of hyperthyroidism should be treated if TSH <0.1 mIU/L and considered for treatment if TSH 0.1 to 0.45 mIU/L. Premenopausal women or patient <60 years, or no heart disease or osteoporosis or symptoms of hyperthyroidism therapy is optional if TSH <0.1 mIU/L and no therapy is required if TSH 0.1 to 4.5 mIU/L

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