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Evaluation of sub-clinical thyroid disease in adult patients

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Abstract: Sub-clinical or "Mild" thyroid disease is a common disorder, particularly in middle-aged and elderly individuals. Both sub-clinical hypothyroidism and hyperthyroidism are diagnosed, based on laboratory evaluation with mild if any clinical signs or symptoms. Sub-clinical hypothyroidism is defined as an elevation in serum TSH above upper limit of the reference range with normal serum Free T4 concentration; sub-clinical hyperthyroidism is defined as a decrease in serum TSH below the reference range with normal serum Free T3 and T3 concentration. It is reported that most patients who found to have sub-clinical thyroid disease have TSH values between 4.5 and 10 □IU/L (reference range 0.45□IU/L – 4.5□IU/L). We present here studies carried out during Dec 2002-Dec 2006 in 202 patients (80 males, 122 females) regarding evaluation of sub-clinical thyroid disease. Their TSH, T3 T4, FT3 and FT4 levels were also determined and data is cumulated and presented as percent occurrence. In female groups of 122 patients, 21 (17.21%) exhibited sub-clinical thyroid disorders [n=13; 10.65% Sub-clinical hypothyroidism, n=8; 6.55% sub-clinical hyperthyroidism], whereas 43 (35.24%) exhibited true-thyroid disorder. In male group of 80 patients; 9 patients (11.25%) showed sub-clinical thyroid disorders [n=8; 10% sub-clinical hypothyroidism; n=1; 1.2% sub-clinical hyperthyroidism], whereas 18 (22.5%) exhibited true thyroid disorder. It is concluded that sub-clinical thyroid dysfunction predicts future progression to overt disease. It is also advisable that routine screening for thyroid disease through clinical investigations aided with lab findings be promoted, especially in pregnant women.

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INTRODUCTION

Sub-clinical thyroid disease or disorder, more specifically, hypothyroidism and hyperthyroidism represent the earliest stages of thyroid dysfunction. Sub-clinical hypothyroidism is defined as an elevation in serum thyroid stimulating hormone (TSH) above upper limit of the reference range with normal serum free tetra-iodo-thyronine (free thyroxine, FT4) concentration; sub-clinical hyperthyroidism is defined as a decrease in serum TSH below the reference range with normal serum free tri-iodo-thyronine (FT3) and tri-iodo thyronine (T3) concentration[1,3]. Most patients have mild, if any, signs and symptoms of thyroid dysfunction; therefore, it is a diagnosis based on laboratory evaluation[1,4,5]. Because the risk for sub-clinical thyroid dysfunction, particularly sub-clinical hypothyroidism, increases with age, the number of cases may increase as the population ages[6-8]. It is reported that sub-clinical hypothyroidism is much more common than hyperthyroidism[2,6]. Nonetheless, early detection and treatment of sub-clinical thyroid dysfunction is potentially beneficial, especially in children and pregnant women[9-11]. In addition, routine screening of TSH, FT3, T3, FT4, T4 for such patients is recommended. It is also agreeable to process a strong case finding approach towards patients presented with signs and symptoms that suggests the possibility of thyroid dysfunction[1].

Because of the significance of this particular clinical anomaly regarding patients' care and treatments, we evaluated sub-clinical thyroid dysfunction status of several patients in our setting, both males and females. The study will provide a base-line data in our setup and assist in future investigation, analysis and strategic planning of treatment and management of sub-clinical thyroid dysfunctions.

MATERIALS AND METHODS

Patients

Total 202 patients (80 males, 122 females) were selected from Medical, Endocrinology and General OPDs of Liaquat National Hospital, and their clinical investigations, initial diagnosis and related lab investigations were collected. The study period was Dec 2002 to Dec 2006. Inclusion criteria were patients with suspicion or diagnosed with sub-clinical thyroid disease between the age group of 17 to 66 years. Exclusion criteria were patients with ischemic heart disease, cerebrovascular and neurological diseases, diabetes mellitus, chronic renal impairment, known psychological illnesses, previous history of thyroid disease or previous thyroxin therapy, asthma and pregnancy. The patients were grouped in each gender according to age; for females age groups were = 17-30 yrs, 31-45 yrs, 46-59 yrs and 60-66 yrs. In Males, age groups were = 18-30 yrs, 31-45 yrs and 45-58 yrs. The patients were further classified according to the presence of sub-clinical dysfunction or true thyroid disorders. The subgroups were also abbreviated as,

male sub-clinical thyroid disease (MSCTD) and female sub-clinical thyroid disease (FSCTD). Patients' subgroups and their respective patients were, for females = 17-30 yrs (n=30), 31-45 yrs (n=20), 46-59 yrs (n=43) and 60-66 yrs (n=29) and for males, 18-30 yrs (n=32), 31-45 yrs (n=30) and 45-58 yrs (n=18). The patients diagnosed with subclinical thyroid dysfunction (SCTD) were; Females (Table I); 17-30 yrs (n=3), 31-45 yrs (n=3), 46-59 yrs (n=5) and 60-66 yrs (n=10).

Analysis

Six ml blood samples were collected from each patients, serum was separated and stored at -20^{o}C until analyzed. TSH, T3 T4, FT3 and FT4 levels were measured on automated immunoassay analyzers (Elecsys 2010, Roche Diagnostics, Basel) using Electro-chemiluminescence technology. Reference ranges are provided in result tables.

Data presentations

The results are presented in tabulated as well percent occurrence forms for clarity. Where necessary comparable thyroid hormone and TSH data are presented in groups for conclusion. Statistical calculation was performed using Microsoft SPSS ver 15 (USA).

RESULTS

Results are summarized in tables 1-4. A total of 202 patients, (male n=80, females n=122) were included in the study, presented with suspicion and/or confirmed diagnoses of thyroid dysfunction. Table 1 shows FSCTD and are expressed in each column as total number in that group and relative percentage w.r.t. main or preceding group. 21 (17.21%) [n=13; 10.65% Sub-clinical hypothyroidism, n=8; 6.55% sub-clinical hyperthyroidism] out of 122 showed sub-clinical thyroid disorders, whereas 43 (35.24%) exhibited true-form. Moreover, 58 (47.54%) subjects out of 122 exhibited normal thyroid hormone and TSH levels and devoid of any sub-clinical or true thyroid disorders.

In Males n=3 (18-30 yrs), n=4 (31-45 yrs) and n=2 (45-58 yrs) were diagnosed with SCTD (Table 2). Results are expressed in each column as total number in that group and relative percentage w.r.t. main or preceding group. 9 patients (11.25%) n=8; 10% sub-clinical hypothyroidism; n=1; 1.2% sub-clinical hyperthyroidism] out of 80 showed sub-clinical thyroid disorders, whereas 18 (22.5%) exhibited true-form. Moreover, 53 (66.25%) subjects out of 80 exhibited normal thyroid hormone and TSH levels and devoid of any sub-clinical or true thyroid disorders.

The patients diagnosed, which have true thyroid disorders were; females (Table 1); n=12 (17-30 yrs), n=7 (31-45 yrs), n=13 (46-59 yrs) and n=11 (60-66 yrs). Males of age group (Table 2); n=7 (18-30 yrs), n=5 (31-45 yrs) and n=6 (45-58 yrs) were diagnosed with true thyroid disorders. Percent occurrence of sub-clinical thyroid dysfunction with respect to age-subgroups were found to be; Females; n=3; 10% (17-30 yrs), n=3; 15% (31-45 yrs), n=5; 11.6% (46-59 yrs) and n=10; 34.5% (60-66 yrs). In Males; n=3; 9.3% (18-30 yrs), n=4; 13.3% (31-45 yrs) and n=2; 11.1% (45-58 yrs). Overall occurrence of SCTD in females was 10.39% and males 4.45%.

Table 1: Female subjects (n=122)♦ tested for sub-clinical and true thyroid disorders (Hyperthyroidism; Hypothyroidism).

Groups w.r.t. age ranges 17 to 66 yrs	Number of subjects screened	Sub clinical thyroid disorders	Sub-clinical Hypothyroid	Sub-clinical Hyperthyroid	True Thyroid disorders	True Hypothyroid	True Hyperthyroid
17 to 30 yrs	30	3 (10%)	2	1	12 (40%)	12	---
31 to 45 yrs	20	3 (15%)	3	---	7 (35%)	4	3
46 to 59 yrs	43	5 (11.6%)	2	3	13 (30.23%)	9	4
60 to 66 yrs	29	10 (34.5%)	6	4	11 (38%)	10	1
Total	122	21 (17.21%)	13	8	43 (35.24%)	35	8

♦Results are expressed in each column as total number in that group and relative percentage w.r.t. main or preceding group. 21 (17.21%) [n=13; 10.65% Sub-clinical hypothyroidism, n=8; 6.55% sub-clinical hyperthyroidism] out of 122 showed sub-clinical thyroid disorders, whereas 43 (35.24%) exhibited true-form. Moreover, 58 (47.54%) subjects out of 122 exhibited normal thyroid hormone and TSH levels and devoid of any sub-clinical or true thyroid disorders.

Thyroid hormone levels analyzed in female patient groups and subgroups are presented in Table III. No significant variation was found in the levels of T3, T4, FT3 and FT4 levels in sub clinical thyroid hypo and hyperthyroidism, whereas high concentration w.r.t. normal reference range was found in sub clinical hypothyroidism and slightly lower concentration was noted in sub-clinical hyperthyroidism. In groups of true hypothyroidism, TSH levels were analyzed to be significantly high ($P>0.01$) where as that of FT4 moderately significant ($P<0.05$) (Table 3). Furthermore patients in subgroups of true hyperthyroidism exhibited significantly ($P<0.01$) altered TSH, FT3 and T3 levels as compared to normal reference ranges.

Analysis of thyroid hormones in groups and subgroups of male patients are summarized in Table 4. TSH level evaluated in subgroup-sub clinical hypothyroidism exhibited significantly high levels ($P<0.01$) where as mildly low levels were noted in sub-clinical hyperthyroidism. Moreover, significantly elevated levels of TSH ($P< 0.001$) were noted in true hypothyroidism patients with low concentration of FT4 as compared to reference values (Table 4). However in sub group of true hyperthyroidism, TSH, FT3 and T3 were significantly ($P<0.05$) altered w.r.t. normal reference range.

DISCUSSION

It is reported that sub-clinical hypothyroidism occurs in 4% to 10% of the general population, and is especially prevalent in elderly women6-8. The definition of sub-clinical thyroid dysfunction is based on serum TSH determination. There is substantial uncertainty concerning the consequences of untreated subclinical hypothyroidism and hyperthyroidism, as well as the benefit of initiating treatment1. Potential risks of sub-clinical hypothyroidism include progression to overt hypothyroidism, dyslipidemia, cardiovascular complications, and neurological and neuropsychiatric effects12. In turn, sub-clinical hyperthyroidism represents a considerable risk factor for atrial fibrillation in the elderly patients and for postmenopausal osteoporosis12. A study evaluating the prevalence of thyroid diseases and their relationship to autoimmunity in a population of Khulna district where goitre is not endemic, exhibited that female outnumbered male, the ratio being 2.5:1 with preponderance of female subjects in all disease groups8. In our study also derangement of TSH levels related to sub-clinical thyroid disease/disorder was more profound in female (10.39%) than in males (4.45%). A survey was performed among citizens of a union of selected population of Khulna district.

Table 2: Male subjects (n=80)♦ tested for sub-clinical and true thyroid disorders (Hyperthyroidism; Hypothyroidism).

Groups w.r.t. age ranges 18 to 58 yrs	Number of subjects screened	Sub clinical thyroid disorders	Sub-clinical Hypothyroid	Sub-clinical Hyperthyroid	True Thyroid disorders	True Hypothyroid	True Hyperthyroid
18 to 30 yrs	32	3 (9.3%)	3	---	7 (21.8%)	6	1
31 to 45 yrs	30	4 (13.3%)	3	1	5 (16.6%)	5	---
45 to 58 yrs	18	2 (11.1%)	2	---	6 (33.3%)	4	2
Total	80	9 (11.25%)	8	1	18 (22.5%)	15	3

♦Results are expressed in each column as total number in that group and relative percentage w.r.t. main or preceding group. 9 (11.25%) %) [n=8; 10% sub-clinical hypothyroidism; n=1; 1.2% sub-clinical hyperthyroidism] out of 80 showed sub-clinical thyroid disorders, whereas 18 (22.5%) exhibited true-form. Moreover, 53 (66.25%) subjects out of 80 exhibited normal thyroid hormone and TSH levels and devoid of any sub-clinical or true thyroid disorders.

Table 3: Thyroid hormone (T3, FT3, FT4) and TSH levels♦ in Female Patients tested for sub-clinical and true thyroid disorders (Hyperthyroidism; Hypothyroidism).

Groups w.r.t. age ranges 17 to 66 yrs	Sub-clinical Hypothyroid TSH; *FT4*	Sub-clinical Hyperthyroid TSH; *FT3*; T3	True Hypothyroid TSH; *FT4*	True Hyperthyroid TSH; *FT3*; T3
17 to 30 yrs	7.66; 1.1	0.38; 2.8; 1.2	17.65; 0.45	---
31 to 45 yrs	7.83; 1.4	---	21.43; 0.34	0.02; 6.21; 3.45
46 to 59 yrs	8.98; 1.8	0.33; 3.01; 1.8	18.01; 0.67	0.18; 5.98; 3.89
60 to 66 yrs	10.09; 1.7	0.11; 2.99; 1.4	24.55; 0.22	0.01; 7.45; 4.01

♦Results are expressed as mean value of each sample tested for required parameter. **Units:** TSH = 0.45 to 4.5 μIU/L; FT4 = 0.9 to 1.9 μg/dl; FT3 = 2.6 to 5.1 pg/ml; T3 = 0.8 to 2.0 ng/ml; T4 = 5.1 to 14.10μg/dl.

Of the total 925 individual studied; 527 were females and 398 were males with age ranges from 2-62 years (mean 19.86 +/- 13.62 years). The spectrum of thyroid disorders showed highest incidence of diffuse goiter (7.35%), followed by sub-clinical hypothyroidism (6.59%), hypothyroidism (4.97%), hyperthyroidism (0.86%) and sub-clinical hyperthyroidism (0.65%)[8]. The incidence of thyroid disorders was observed to be highest in the 11-45 years age group (79.89%)[8]. Although treatment may be beneficial in individuals with serum TSH lower than 0.1 μIU/L or higher than 10μIU/L, most persons found to have sub clinical thyroid dysfunction have values between 4.5 and 10μIU/L, for which the benefits of treatment are not clearly established[1]. It was suggested that until clear therapeutic benefits were established for treating sub-clinical thyroid dysfunction, general population screening for these conditions is not recommended[1]. However, the benefits of TSH determination to detect occult thyroid dysfunction were greater among those populations at higher risk for developing overt disease, including women, older persons, and individuals with previous or family history of thyroid disease, type 1 diabetes mellitus, radioactive iodine treatment for hyperthyroidism, recurrent miscarriages, or administration of medications that may affect thyroid function, such as lithium carbonate or interferon[1].

In this study, 21 female patients (17.21%) out of 122 showed sub-clinical thyroid disorders, whereas 43 (35.24%) exhibited true-form. Moreover, 58 (47.54%) female subjects out of 122 exhibited normal thyroid hormone and TSH levels and devoid of any sub-clinical or true thyroid disorders. Furthermore, in male group of patients, 9 (11.25%) out of 80 showed sub-clinical thyroid disorders, whereas 18 (22.5%) exhibited true-form. Moreover, 53 (66.25%) male patients out of 80 exhibited normal thyroid hormone and TSH levels and devoid of any sub-clinical or true thyroid disorders.

It is reported that the etiology of sub-clinical hypothyroidism is the same as the etiology of overt hypothyroidism[13-15]. It is most often caused by chronic lymphocytic thyroiditis (goitrous Hashimoto's thyroiditis and atrophic thyroiditis), an autoimmune disorder of the thyroid gland that is the most common cause of decreased thyroid hormone production in patients with acquired mild, sub-clinical, or overt hypothyroidism[15, 16-18]. Other causes of primary hypothyroidism may result from therapies that destroy thyroid tissue such as radioactive iodine treatment or external radiation therapy. Mild and overt hypothyroidism is common after external radiotherapy of the head and neck area and develops gradually within the first year with a risk that appears to be dose-dependent[13, 19].

Moreover, the most common cause of sub-clinical hyperthyroidism is exogenous due to unintentional excessive replacement therapy in hypothyroid patients or to intentional TSH suppressive therapy for benign or malignant thyroid disease[13,20-26]. Endogenous sub–clinical hyperthyroidism (SHyper) is commonly associated with autonomous thyroid function as occurs in Graves' disease, multinodular goiter, and solitary autonomously functioning thyroid nodules (AFTN)[17,21-26]. In Graves' disease, SHyper may resolve spontaneously without treatment. Alternatively, it may be transitory during treatment with antithyroid drugs or after radioiodine therapy (because of delayed recovery of the suppressed pituitary thyrotrophic cells)[25], or it may be persistent because of the continued thyroidal autonomy. Long-standing SHyper with a progressive increase in thyroid hormone levels, sometimes preceding the onset of overt hyperthyroidism, is frequent in patients with multinodular goiter and autonomously functioning thyroid adenoma[17, 27].

It remains a dilemma, whether to treat sub-clinical hypothyroidism (SHypo) or not? [13,28,29]. It was observed that most clinicians treat SHypo patients who have a serum TSH concentration above 10μIU/L, whereas opinions differ about the management of mild disease in which TSH ranges between 4.5 and 10μIU/L, especially in elderly asymptomatic patients. International evaluation studies reports that, some endocrinologists support

Table 4: Thyroid hormone (T3, FT3, FT4) and TSH levels♠ in Male Patients tested for sub-clinical and true thyroid disorders (Hyperthyroidism; Hypothyroidism).

Groups w.r.t. age ranges 18 to 58 yrs	Sub-clinical Hypothyroid TSH; *FT4*	Sub-clinical Hyperthyroid TSH; *FT3*; T3	True Hypothyroid TSH; *FT4*	True Hyperthyroid TSH; *FT3*; T3
18 to 30 yrs	8.15; 1.6	---------	18.19; 0.56	0.09; 7.33; 3.01
31 to 45 yrs	6.75; 1.5	0.32; 3.6; 1.7	19.66; 0.47	------
45 to 58 yrs	7.76; 1.2	--------	20.22; 0.51	0.07; 6.01; 4.22

♠Results are expressed as mean value of each sample tested for required parameter. **Units:** TSH = 0.45 to 4.5 μIU/L; FT4 = 0.9 to 1.9 μg/dl; FT3 = 2.6 to 5.1 pg/ml; T3 = 0.8 to 2.0 ng/ml; T4 = 5.1 to 14.10μg/dl.

the idea that treatment is indicated in patients with SHypo, even those with a mild TSH increase, in the presence of risk factors[14,30,31], whereas others believe that treatment is seldom necessary[32-34]. L-thyroxine is the drug of choice for the treatment of SHypo. It is inexpensive and it stabilizes thyroid hormone levels. There is no reason to use T3, and there is no evidence of benefit from combined T3 and T4 therapy[13,35,36]. It is suggested that small doses, i.e., 25-75µg/day are often adequate to normalize serum TSH levels in SHypo13. However, opinions differ about the treatment of endogenous SHyper[37,38]. According to the American College of Physicians' guidelines, the potential benefits of treating patients with SHyper are only theoretical, and the management of patients without clinical findings is not clear[37]. Recommendation by a panel of experts suggested against routine treatment for those patients whose TSH is mildly decreased; treatment was recommended only for those with serum TSH levels<0.1 mIU/L who were older than 60 years and for those with or at increased risk of heart disease, osteopenia or osteoporosis, or those with symptoms of hyperthyroidism[32]. Individual assessment for treatment or follow-up is recommended for younger individuals with SHyper and serum TSH persistently below 0.1µIU/L. Similar recommendation were made by American Association of Clinical Endocrinologists, ATA and the Endocrine Society[13,39]. A case-based mail survey of ATA members on the management of patients with SHyper showed that most recommended observation alone for young patients with a low but detectable serum TSH (84%) or an undetectable TSH (58%)[40]. However, 66% favored treating older patients who had an undetectable serum TSH. Radioactive iodine was considered the treatment of choice for toxic multinodular goiter. There are no controlled studies comparing the efficacy of different therapies (antithyroid drugs, radioiodine or surgery) in patients with SHyper. The options for definitive therapy are based on the considerations recommended for overt disease[13,25,41].

CONCLUSIONS

It is concluded that management of patients with sub-clinical thyroid dysfunction remains undecided because of the limited scientific evidence available to guide clinical decisions. Fundamental questions such as whom to screen and when to initiate treatment remains largely unresolved. It is suggested that individuals with serum TSH levels lower than 0.1 or higher than 10µIU/L are more likely to benefit from treatment. Nonetheless, sub-clinical thyroid dysfunction predicts future progression to overt disease; however, TSH levels in some individuals with sub-clinical hypothyroidism and hyperthyroidism returns to reference ranges. It is cautiously recommended that, if evidence backed the diagnoses, initiating treatment for sub-clinical hypothyroidism although doesnot alter the natural history of the disease but may prevent symptoms and signs of overt disease. It is also advisable that routine screening for thyroid disease through clinical investigations aided with lab findings be promoted, especially in pregnant women. Moreover, in our study, which is in its progression stage, it is premature to ascertain exact and a final percentage of sub-clinical thyroid dysfunction patients in our population. The study is in progress to evaluate sub-clinical thyroid dysfunction in lager groups including children and pregnant women.

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REFERENCES

1. Col NF, Surks MI, Daniels GH. Sub Clinical Thyroid Disease. *JAMA;* 2004; 291: 239-243.
2. Wilson GR, Curry RW Jr. 2005. Subclinical thyroid disease. *Am. Fam. Physician.*2005; 72**:** 1517-1524.
3. Stöckli R. Subclinical thyroid disease. *Praxis (Bern).* 2007; 19**:** 2047-2050.
4. Krysiak R, Okopień B and Herman ZS. Subclinical thyroid disorders. *Pol. Merkur. Lekarski.,* 2006; 21: 573-578.
5. Gaby AR. Sub-laboratory hypothyroidism and the empirical use of Armour thyroid. *Altern. Med. Rev.,* 2004; 9**:** 157-179.
6. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. *Arch. Intern. Med*., 2000; 160: 526-534.
7. Vanderpump MP, Tunbridge WM and French JM. 1995. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin. Endocrinol. (Oxf)*., 1995; 43: 55-68.
8. Paul AK, Miah SR, Mamun AA and Islam S. Thyroid disorders in Khulna district: a community based study. *Bangladesh Med. Res. Counc. Bull*., 2006; 32: 66-71.
9. Lerch M, Meier C and Staub JJ. Is there a need for treatment in subclinical hypo- and hyperthyroidism?. *Ther. Umsch.,* 1999; 56**:** 369-373.
10. Schlienger JL, Goichot B, Vinzio S, Perrin AE, Grunenberger F and Sapin R. Sub-clinical hypothyroidism, towards the end of a controversy? *Presse. Med*., 2003; 32: 1760-1765.
11. Sheth JJ, Thakore PB, Trivedi BB, Shah NN and Vaidya RA. Sub-biochemical hypothyroidism: an exaggerated thyroid stimulating hormone response to thyrotrophin releasing hormone. *J. Assoc. Physicians. India.,* 1999; 47: 275-279.
12. Krysiak R, Okopień B and Herman ZS. Subclinical thyroid disorders. *Pol. Merkur. Lekarski.,* 2000; 21**:** 573-578.

13. Biondi B and Cooper DS. The Clinical Significance of Subclinical Thyroid Dysfunction. *Endocr. Rev.,* 2000; 29**:** 76-131.
14. Roos A, Bakker SJ, Links TP, Gans RO and Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. *J. Clin. Endocrinol. Metab.,* 2007; 92**:** 491-496.
15. Krysiak R, Marek B and Okopień B. Subclinical hyperthyroidism. *Endokrynol. Pol.,* 58**:** 536-542.
16. Roberts CG and Ladenson PW. Hypothyroidism. *Lancet,* 2004; 363: 793-803.
17. Ross D. Subclinical hypothyroidism In Braverman LE, Utiger RD (eds) Werner & Ingbar's The Thyroid: *a fundamental and clinical text.* 8th ed**.** 2005; Philadelphia Lippincott Williams & Wilkins. pp 1070-10785.
18. Surks M and Ocampo E. Subclinical Thyroid disease. *Am. J. Med.,* 1996; 100: 217-223.
19. Singer P. Primary hypothyroidism due to other causes. In Braverman LE, Utiger RD, (eds) Werner & Ingbar's The Thyroid: *a fundamental and clinical text.*8th ed. 2005; Philadelphia, Lippincott Williams & Wilkins. pp745-754.
20. Anker GB, Lonning PE, Aakvaag A and Lien EA. Thyroid function in postmenopausal breast cancer patients treated with tamoxifen. *Scand. J. Clin. Lab. Invest.,* 1995; 58: 103-107.
21. Ross DS. Subclinical thyrotoxicosis. In: Braverman LE, Utiger RD, eds.Werner and Ingbar's. The Thyroid: *a Fundamental and Clinical Text.* 8th ed. 2000; Philadelphia:Lippincott Williams and Wilkins. pp 1016-1020.
22. Papi G, Pearce EN, Braverman LE, Betterle C and Roti E. A clinical and therapeutic approach to thyrotoxicosis with thyroid-stimulating hormone suppression only. *Am. J. Med*., 2000; 118: 349-361.
23. Biondi B, Filetti S and Schlumberger M. Thyroid hormone therapy and thyroid cancer: a reassessment. *Nat. Clin. Pract. Endocrinol. Metab.,* 2005; 1: 32-40.
24. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI and Tuttle RM. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid,* 2006; 16**:** 109-142.
25. Cooper DS. Hyperthyroidism. *Lancet,* 2003 362: 459-468.
26. Toft AD. Clinical practice. Subclinical hyperthyroidism. *N. Engl. J. Med.,* 2001; 345: 512-516.
27. Pearce CJ and Himsworth RL. Total serum thyroxine and triiodothyronine: a comparison between Graves' disease and hyperthyroxinaemia due to thyroxine replacement. *Acta Endocrinol. (Copenh),* 1984; 107: 213-217.
28. Ringel MD and Mazzaferri EL. Subclinical thyroid dysfunction–can there be a consensus about the consensus? *J. Clin. Endocrinol. Metab.,* 2005; 90: 588-590.
29. Cooper DS. Subclinical thyroid disease: consensus or conundrum? *Clin. Endocrinol. (Oxf).,* 2004; 60: 410-412.
30. Wilson GR and Curry RW Jr. Subclinical thyroid disease. *Am. Fam. Physician*., 72**:** 1517-1524.
31. Biondi B, Lombardi G and Palmieri EA. Screening and treatment for subclinical thyroid disease. *JAMA* , 2004; 291: 1562-1563.
32. Rossi M, Galetta F, Franzoni F, Antonelli A and Santoro G. Cardiovascular remodelling in patients with sub-clinical hypothyroidism. *Minerva. Cardioangiol.,* 2006; 54**:** 807-810.
33. Cooper DS. Combined T4 and T3 therapy-back to the drawing board. *JAMA,* 2003; 290: 3002-3004.
34. Helfand M. U.S. Preventive Services Task Force Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S.Preventive Services Task Force. *Ann. Intern. Med.,* 2004; 140: 128-141.
35. Escobar-Morreale HF, Botella-Carretero JI, Escobar del Rey F and Morreale de Escobar G. Treatment of hypothyroidism with combinations of levothyroxine plus liothyronine. *J. Clin. Endocrinol. Metab.,* 2005; 90: 4946-4954.
36. Mariotti S. Thyroid function and aging: do serum 3,5,3'-triiodothyronine and thyroid-stimulating hormone concentrations give the Janus response? *J. Clin. Endocrinol. Metab.,* 2005; 90: 6735-6737.
37. Clinical guideline, part 1. Screening for thyroid disease. American College of Physicians. *Ann. Intern. Med.,* 1998; 129**:** 141-143.
38. Cooper DS. Subclinical thyroid disease: a clinician's perspective. *Ann. Intern. Med.,* 1998; 15**;**129: 135-138.
39. Bonnema SJ, Bennedbaek FN, Ladenson PW and Hegedus L. Management of the nontoxic multinodular goiter: a North American survey. *J. Clin. Endocrinol. Metab.,* 2002; 87**:** 112-117.
40. McDermott MT, Woodmansee WW, Haugen BR, Smart A and Ridgway EC. The management of subclinical hyperthyroidism by thyroid specialists. *Thyroid,* 2003; 13**:** 1133-1139.
41. Cooper DS. Antithyroid drugs. *N. Engl. J. Med.,* 2004; 352**:** 905-917.