THYROID DISEASE, TSH SCREENING, AND COMORBIDITY

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ABSTRACT

Objective: *Although thyroid disease is frequent in the population, it is not clearly established who should be screened for TSH. The aim of this study was to investigate the comorbidities related to thyroid disease and the value of screening TSH.*

Material and Method: *The study included 796 consecutive patients. Age, sex, diagnoses of the patients were recorded, and TSH levels were measured. When they were outside the reference values, measurement was repeated; free T3 and T4 levels were also measured.*

Results: *Of the 796 patients, 37 had known thyroid disease. 10 patients were hyperthyroid, 10 patients were hypothyroid and, 17 had euthyroidism. New diagnoses of overt thyroid disease were made in 4 patients. Subclinical thyroid disease was present in 13.5% and overt thyroid disease was present in 0.5% of the patients. While subclinical hypothyroidism was observed in more women than men (68% vs. 32%, p= 0.001), there was no significant difference in subclinical hyperthyroidism between the men and women (p= 0.919). There was no correlation between TSH and age. No significant differences were found between those with and without subclinical thyroid disease, in terms of coexisting cardiovascular disease.*

The frequency of diabetes mellitus was slightly higher in patients with subclinical hyperthyroidism (p=0.048) than in those with subclinical hypothyroidism (p=0.367).

Conclusion: *When the high cost of thyroid disease is considered, we think that TSH screening may be useful in patients with diabetes and cardiovascular disease, particularly women, although this is not strongly supported by our study.*

Key Words: *TSH screening, thyroid diseases, comorbidity*

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TSH TARAMASI ve TİROİD HASTALIKLARININ KOMORBİDİTESİ

ÖZET

Amaç: Toplumda tiroid hastalıkları sık görülmekle birlikte kimlerin TSH taraması açısından değerlendirilmesi gerektiği konusu açık değildir. Biz bu çalışmada TSH taramasının değerini ve troid hastalıklarının komorbiditesini araştırmayı amaçladık

Materyal ve Metod: İstanbul Eğitim ve Araştırma Hastanesi İç Hastalıkları Polikliniklerine 1-31 Ocak 2007 tarihlerinde başvuran ardışık 796 hasta çalışmaya alındı. Hastaların yaş, cins ve tanıları kaydedildi. TSH düzeyleri ölçüldü. Referans aralığı dışında bulunduğunda TSH tekrarlandı, FT_3 ve FT_4 düzeyleri de ölçüldü.

Bulgular: 796 hastanın verileri toplandı. 37 hastada daha önceden bilinen tiroid hastalığı mevcuttu. Bunlardan 10 tanesi hipertiroid, 10'u hipotiroid ve 17'si ötiroid idi. 4 hastada yeni tanı konmuş belirgin tiroid hastalığı mevcuttu. Hastaların %13,5'inde subklinik tiroid hastalığı, %0,5'inde aşikar tiroid hastalığı saptandı. Subklinik hipotiroidi kadınlarda daha fazla (%68'e %32, p=0,001)) iken subklinik hipertiroidi için ilişki saptanmadı (p=0,919). TSH ve yaş arasında ilişki saptanmadı. Subklinik tiroid hastalıkları bulunanlarda kardiyovasküler sistem hastalığı veya hipertansiyon birlikteliği açısından anlamlı fark yoktu. Subklinik hipertiroidizmi olanlarda (p=0,048) diabetes mellitus, hipotiroidi olanlara göre (p=0,367) hafif anlamlı bir artış göstermekteydi.

Tiroid hastalığı nedeniyle tedavi görenlerin yeterli ölçüde kontrol altında olmadığı gözlendi.

Sonuç: Her ne kadar çalışmamızda tümüyle desteklenmemiş olsa da tiroid hastalıklarının maliyeti göz önüne alınınca TSH taramasının diyabeti ve kardiyovasküler hastalığı olanlarda ve özellikle kadınlarda yararlı olduğunu düşünüyoruz.

Anahtar Kelimeler: TSH taraması, tiroid hastalıkları, komorbidite. **Nobel Med 2011; 7(1): 88-93**

INTRODUCTION

Subclinical thyroid disease is characterized by normal serum thyroid hormone levels, even if TSH levels are outside the reference range. Subclinical hyperthyroidism and hypothyroidism represent the early stages of thyroid dysfunction; thus, there are no symptoms or signs in most patients. There is no consensus on how to determine who should be screened for TSH and who requires treatment.[1] TSH screening may help in the diagnosis of symptomatic cases and it is reported to be beneficial, especially in women over 50 years of age. The ability of treatment to improve the quality of life in these individuals is not clear.[2] Subclinical hypothyroidism is a risk factor for dyslipidemia and coronary artery disease. There is also an association between subclinical hyperthyroidism and atrial fibrillation. Although the physiopathological consequences of mild thyroid dysfunction are not fully understood, mortality due to all causes has been demonstrated to increase in patients > 60 years old with low TSH levels.[3] Subclinical hyperthyroidism may transform into overt hyperthyroidism, leading to atrial fibrillation, cardiac dysfunction, and increased risk of bone fracture due to a reduction in bone mineral density. Since there is currently no consensus on the necessity of treatment, many national health organizations do not recommend TSH screening.[4]

The aim of the present study was to investigate the comorbidities related to thyroid disease as well as the value of TSH screening in the inpatient and outpatient clinics of our internal diseases department.

MATERIAL and METHOD

The study included 796 consecutive patients that presented to the Department of Internal Medicine at Istanbul Education and Research Hospital between January 1 and 31, 2007. Age, sex, and diagnoses of the patients were recorded.

In addition to routine biochemical evaluations, TSH levels were measured by the electrochemiluminescence method (Roche Diagnostics GmbH, Mannheim, Germany). Linearity (measurement range) was between 0.005 and 100.0 µIU/mL, and functional sensitivity was 0.014 µIU/mL. Intra-study reproducibility was 3.0% and total reproducibility was 7.2% with a serum TSH level of 0.040 µIU/mL and they were 1.1% and 3.3% with a serum TSH level of 9.37 µIU/mL, as stated in the prospectus. When TSH levels were outside the reference range, TSH measurements were repeated 15 days later, using the same method, and beside this free T4 (FT_4) and free T3 (FT_3) levels were also measured. Adult reference ranges determined by the manufacturer are as follows: TSH: 0.27-4.2 µIU/mL; FT_4: 0.82-1.77 ng/dL; FT_3: 2.0-4.4 pg/mL. The study protocol was approved by our local institutional ethics committee. →

Table 1: Age and TSH levels (patients with TSH< 10 IU/ml)

Age group	<45 (n: 130)	45-65 (n: 256)	>65 (n: 398)	Total (n: 784)
Female	65	120	208	393
Euthyroid	55	98	178	
Hypothyroid	5	16	15	
Hyperthyroid	5	6	15	
Male	65	136	190	391
Euthyroid	64	128	176	
Hypothyroid	1	3	1	
Hyperthyroid	0	5	13	
TSH	1.61±1.14	1.84±1.60	1.52±1.28	1.64±1.34

Statistical analysis was performed using Primer of Bioistatistics v.3.01 software (Stanton A. Glantz, McGraw-Hill, Inc.). Percent ratios were compared, means and standard deviations were calculated, and t-test was used for comparing means.

RESULTS

Data for 796 consecutive patients that presented during a 1-month period were recorded. The study population consisted of 393 (49%) men and 403 (51%) women who lived in Istanbul. Among the patients, 37 were under treatment for thyroid disease. Of the 796 patients in the study, 759 had no previous symptoms or records suggesting thyroid disease. TSH values were > 10 µIU/mL in only 12 patients, which resulted in a high standard deviation value due very high levels of up to 100 µIU/mL. Therefore, statistical analysis was repeated for 784 patients after exclusion of these 12 patients' data. Age distribution, mean age, sex distribution, and TSH levels of the patients are presented in (Table 1). No significant correlation was found between age and TSH values (r=0.016, p= 0.668).

Of the 759 patients without a previous diagnosis of thyroid disease, overt thyroid dysfunction was detected according to TSH and thyroid hormone levels in 4 patients (0.52%); hypertension, cardiac and renal failure, and hypothyroidism were present in 2 of these patients, lung cancer and hyperthyroidism were present in 1 patient, and primary hypothyroidism was present in 1 patient who had dyspeptic complaints without a comorbid condition.

Of the 759 patients without a previous diagnosis of thyroid disease, subclinical hyperthyroidism (mean TSH: 0.12±0.08 µIU/mL) was present in 55 (7.2%) and subclinical hypothyroidism (mean TSH: 6.24±2.76 µIU/mL) was present in 48 (6.3%). The prevalence of subclinical thyroid disease was 13.5%.

Among the subclinical hypothyroidism cases, 68% were women and 32% were men; the difference between them was not statistically significant (p= 0.001). Women constituted 52.7% of the cases with subclinical hyperthyroidism, which was not significant (p= 0.819).

Mean age of the patients with subclinical hypothyroidism was 57.93±16.25 years among the women and 59.73±12.46 among the men, whereas mean age of the patients with subclinical hyperthyroidism was 63.06±19.69 years among the women and 65.88±10.65 years among the men. Although female cases of subclinical hyperthyroidism and hypothyroidism were about 2 years younger than the male cases, there was no significant difference between mean ages according to gender (p=0.35 and p=0.54, respectively).

Comorbid diseases are presented in (Table 2). When the cases with subclinical hyperthyroidism and hypothyroidism were compared to the entire study population, no significant difference was found in terms of the presence of cardiovascular disease (p=0.986 and p=0.774, respectively). No significant difference was found in the prevalence of hypertension between the cases of subclinical hyperthyroidism and hypothyroidism (p=0.203). No significant difference was found between the subclinical hyperthyroidism and hypothyroidism cases (p=0.76 and p= 0.66, respectively) with respect to the presence of cardiac disease. When they were compared in terms of comorbid diabetes, there was a significant increase in diabetes comorbidity among the subclinical hyperthyroidism (p=0.048) cases, but no significant relationship was observed between diabetes and subclinical hypothyroidism (p=0.367).

DISCUSSION

The prevalence of subclinical hypothyroidism is between 4% and 10% in the general population, which increases to 20% in women older than 60 years of age. Similar to overt hypothyroidism, cardiac dysfunction manifests as diastolic dysfunction, diastolic hypertension, and increased systemic resistance in subclinical hypothyroidism patients. Increased lipoprotein (a) and cholesterol levels, in addition to a low-grade systemic inflammatory activity, enhance ischemic cardiovascular risk; however, careful consideration of the risk-benefit ratio is essential when administrating levothyroxine, especially in elderly patients.[5]

Symptoms and signs of overt hyperthyroidism are absent in subclinical hyperthyroidism. Excessive levels of thyroid hormones may have detrimental →

results, such as cardiovascular events and bone loss on target-organs, especially in high-risk populations.[6] Yet, whether or not these patients require treatment should be considered on a case-by-case basis, without generalization. Circumstances such as persistent low-level TSH, the presence of a multinodular goiter, elevated FT_3, and the occurrence of symptoms require treatment.[7]

Subclinical hypothyroidism is more common in regions with high iodine intake. Hypothyroidism is mostly due to autoimmune destruction; however, it can also result from surgery, exposure to radioactive iodine, or treatment with such drugs as amiadaron, lithium, and interferon,[1, 6] which none of our patients experienced.

Among 759 patients, only 4 new cases of overt thyroid disease were detected by TSH screening. The presence of serious comorbidities might have resulted in the under diagnosis of thyroid disease in these patients. The symptoms and signs of thyroid disease might have overlapped with the signs of the observed comorbidities. Among the patients without a previous diagnosis of thyroid disease, 2 had hypothyroidism with concomitant hypertension, and cardiac and renal failure. Overt hypothyroidism was diagnosed based on TSH screening in patient with dyspeptic complaints. The case with hyperthyroidism was followed-up for lung cancer. In the present study the prevalence of overt thyroid disease was as low as 0.52% based on TSH screening. The subclinical thyroid disease rate was 13.5%. Various results have been reported in trials from different countries. While the average prevalence of subclinical hypothyroidism is between 4% and 8.5%, it is about 2% for subclinical hyperthyroidism.[4] In one study in which 422,242 patients were screened, TSH levels were low in 1.2% and high in 3.7% of the subjects. At the 5-year follow-up, pathological values were observed in 2% of the individuals that previously had normal results. Furthermore, when measurements were repeated in patients with TSH values outside the reference range, they were found to be within normal limits in 50% of the cases.[8]

In a Japanese study conducted with 3607 subjects, subclinical hypothyroidism was detected in 14.6% of those 70-80 years of age, and in 20.1% of those over 80 years old. While subclinical thyroid disease was correlated with high fasting blood sugar, no correlations were observed with other metabolic parameters, pulse rate, blood pressure, or intima media thickness.[9] In a US study, 3233 individuals over 65 years of age were evaluated in terms of thyroid function and incidental cardiovascular disease. Among them, 82% were euthyroid, 15% had subclinical hypothyroidism, 1.6% had overt hypothyroidism, and 1.5% had subclinical hyperthyroidism. While subclinical hyperthyroidism was correlated with the risk of atrial fibrillation, no correlations between subclinical thyroid dysfunction and other cardiovascular events were observed.[10] In another study that included 2730 patients, significantly more cardiovascular events were noted in patients over 70 years of age with subclinical hypothyroidism and TSH levels > 7 mIU/L, as compared to those that were euthyroid.[11] In the present study, when the subclinical hyper-hypothyroidism cases were compared to the entire study population, no significant differences were found in terms of the presence of cardiovascular disease (p= 0.986 and p= 0.774, respectively). Cardiovascular system diseases and diabetes, being the most frequent comorbidities among our 103 cases with subclinical hyperthyroidism and hypothyroidism, were evaluated and no significant differences concerning the presence of cardiac disease were found between the patients with subclinical hyperthyroidism and subclinical hypothyroidism (p= 0.76 and p= 0.66, respectively), whereas there was a significant increase in diabetes comorbidity among the subclinical hyperthyroidism cases (p= 0.048). In a Danish study of 480 patients >60 years of age without a history of thyroid disease, overt hypothyroidism was found in only 3 (0.6%), subclinical hypothyroidism in 23 (4.8%), subclinical hyperthyroidism in 49 (10.2%), and overt hyperthyroidism in 4 (0.8%) patients. Thus, the percentage of patients requiring treatment was less then 1%. Treatment had to be readjusted for one third of the patients treated for thyroid dysfunction. Although TSH screening is not recommended for the elderly population, it has been reported that individuals with a known thyroid disease should be carefully monitored.[12] In 8 out of 16 patients with a previous diagnosis of thyroid disease and comorbid cardiovascular system disease, treatment dose adjustments were needed →

Table 2: Comorbidities of patients

	Thyroid disease known	Thyroid disease unknown	Subclinical hypothyroidism	Subclinical hyperthyroidism
Comorbidity	37	759	48	55
Cardiovascular	16	429	32	42
DM*	6	213	10	22
CRF**	3	130	13	4
COPD***	6	59	1	7
Cancer	4	45	2	10
Other	14	291		

*Diabetes mellitus, **Chronic renal failure, ***Chronic obstructive pulmonary disease

in order to establish euthyroid state. Since thyroid dysfunction has significant detrimental effects on the cardiovascular system, thyroid function should be evaluated in the presence of cardiac disease.[13]

In a study involving 25,862 subjects, total cholesterol and LDL-cholesterol levels were significantly higher in individuals with TSH levels between 5.1 and 10 mIU/L than in euthyroid subjects. Since this has a negative impact on the cardiovascular system, hyperlipemic individuals need to be evaluated for thyroid dysfunction as well.[14] An Australian study involving 2033 subjects found that comorbid hypertension was more common in subclinical hyperthyroidism than in subclinical hypothyroidism.[15] No significant difference was found in the prevalence of hypertension between cases of subclinical hyperthyroidism and those with subclinical hypothyroidism in our study (p= 0.203). In a British study involving 555,960 subjects over 65 years of age, excluding those with known thyroid disease or a history of surgery, the prevalence of overt hyper- and hypothyroidism was 0.3% and 0.4%, respectively. The prevalence of subclinical hypothyroidism and hyperthyroidism was 2.9% and 2.1%, respectively; and both were more commonly seen in women and by increasing age.[16] In the present study, 68% of subclinical hypothyroidism cases were women and 32% were men, and the difference was statistically significant (p= 0.001). Women constituted 52.7% of the cases with subclinical hyperthyroidism, though this percentage was not significantly more than what was observed in the men (p= 0.819). Mean age of the patients with subclinical hypothyroidism was 57.93 ± 16.25 years among the women and 59.73 ± 12.46 years among the men, whereas mean age of the patients with subclinical hyperthyroidism was 63.06 ± 19.69 years among the women and 65.88 ± 10.65 years among the men. Although female cases of subclinical hyperthyroidism and hypothyroidism were on average 2 years younger than men, the difference between the mean age of women and men was not significant (p= 0.35 and p= 0.54, respectively).

Among the patients with normal hypothalamus and hypophysis functions, doubling of the FT_4 level reflected a 10-20-fold increase in TSH level; however, pre-analytic variability due to factors such as age, pregnancy, hepatic and renal dysfunction, as well as drug effects and systemic diseases may have impaired the relationship between TSH and FT_4. TSH measurement is recommended as the first step in most diagnostic guidelines for thyroid diseases; nevertheless, in many of North American programs, FT_4 measurement is performed as a first step, and TSH is measured only if a low FT_4 level is detected. During a 1-week assessment period, coefficient of variation (CV%) within individual biological variability was 3.5 for FT_4 and 19.3 for TSH, and between individuals it was 10.8 for FT_4 and 19.7 for TSH. Thus, FT_4 seems to be more advantageous as a screening test. Moreover, TSH serum levels exhibit intra-day variability, reaching a maximal level between 02.00 am and 04.00 am and a minimal level between 06.00 pm and 08.00 pm.[17-19]

Due to advances in methodology and autoantibody detection, reference values for thyroid hormones have been reevaluated; in particular, the upper reference values of TSH are controversial[20-22] and have been published as 2.5-3.0 µIU/mL in the most recent guideline (20). Selection of reference populations is important since autoantibody positivity at subclinical levels is common. In our study, TSH values were between 3.0 and 4.2 µIU/mL in 57 patients (38 women, 19 men); these patients may need further investigation. It should not be forgotten that it is more appropriate to identify subclinical hypothyroidism cases with ultrasonographic evaluation together with autoantibodies and periodic long-term follow-up.

Another important issue is that false high TSH values can be obtained in the presence of heterophil antibodies. Antiserums of animal origin that are used in immunological methods may cause interference. For instance, antibodies that were developed against rats were utilized in our methods and products. Heterophil antibodies may be present in blood samples of individuals who have previously been exposed to these animal proteins, which may interact with the antiserum used in the immunological method. In addition to the immune response against exogenous proteins, autoantibodies against various chemicals and proteins can be formed in autoimmune diseases. It would be useful for each laboratory to contact other laboratories that use different methods or analyzers. If this were to occur, measurements could be repeated for samples with discordant results employing an alternative method and substrate, and then it could be determined whether the result was in fact due to a measurement error or due to a disease process.

Study limitations

There are several limitations of our study. First the group is small which, may lead to inadequate assessment. Second we did not investigate the thyroid hormone levels and thyroid ultrasonography that are being evaluated as the second part of the study. Comorbidities were restricted to the previously diagnosed disease. Because of the study included various diseases, some may have low T_3 syndrome whom we did not deal with them. Some of our →

patients might have subclinical cardiovascular, autoimmune or other diseases that were not recorded; they might also have been previously exposed to some animal proteins which could affect the laboratory methods. These may be investigated in a more detailed study. But our aim was only to see how much valuable to screen for TSH was.

CONCLUSION

When all of our patients are taken into account, the number of overt or subclinical thyroid disease cases are not sufficient to recommend routine TSH screening of general and elderly (> 65 years old) populations. Instead, measurement of FT_4, together with TSH is recommended for detecting thyroid dysfunction in high-risk populations (diabetes, hyperlipidemia, and cardiovascular disease), particularly among women, following an extensive medical history (family history of thyroid disease, history of autoimmune disease) and thorough physical examination.

Moreover, patients with a known thyroid disease need to be monitored more carefully.

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