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Prevalence and causes of undiagnosed hyperthyroidism in an adult healthy population. The Tromsø study

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ABSTRACT. ***Background:*** **The causes of subclinical hyperthyroidism have only been reported from clinical studies.** ***Aim:*** **To determine the prevalence and pathological causes of reduced serum TSH levels in subjects recruited from an epidemiological survey.** ***Material/subjects and methods:*** **Serum TSH was measured in 7954 subjects in the 5th Tromsø study. Subjects with serum TSH<0.50 mIU/l, not using T_4, without a previous diagnosis of thyroid disease, without serious concomitant disease, and younger than 80 yr, were invited for a re-examination. If low serum TSH was persistent, thyroid scintigraphy was performed.** ***Results:*** **Among the 4962 subjects that met the inclusion criteria, serum TSH was <0.50 mIU/l in 105 subjects. Twelve subjects had a suppressed serum TSH level (<0.05 mIU/l). Two of these were lost to follow-up, 4 had Graves' disease, 4 had adenoma, and 2 had multinodular goiter. In the 93 subjects with serum TSH 0.05-0.5 mIU/l, 55 were re-examined, of whom 35 had normalized their serum TSH level. In the remaining 20 subjects, 1 had Graves' disease, 6 had adenoma (of which 2 were toxic adenomas), 7 had multinodular goiter, and 6 were considered normal. Among the 521 subjects using T_4, 70 (13.4%) had a suppressed serum TSH level.** ***Conclusions:*** **Most of the subjects with a suppressed serum TSH level will be on T_4 medication. Otherwise, if the suppressed serum TSH level is found by chance, this probably represents a clinically important thyroid pathology. Also, in subjects with a persistently low serum TSH level (0.05-0.5 mIU/l) most will have a pathological thyroid scan.**

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INTRODUCTION

Overt hyperthyroidism has several well-known harmful effects on health. It can cause atrial fibrillation, systolic hypertension, cardiac failure, tremor, myopathy, reduced fertility, and demineralisation of the skeleton (1). Because of the seriousness of the disease, the incidence of hyperthyroidism and its causes have been thoroughly studied. Depending on the population in question, the most common causes of hyperthyroidism are Graves' disease, multinodular goiter, autonomously functioning thyroid nodule, and thyroiditis (1).

Similarly, subclinical hyperthyroidism, defined as serum TSH below the reference range with free T_4 and free T_3 within the normal range (2), also appears to be of potential harm with an increased risk of atrial fibrillation (3), development of dementia (4), impaired quality of life (5), and an increased mortality (6). However, the prevalence and causes of subclinical hyperthyroidism have not been investigated to the same extent, and even less is known about subjects with serum TSH that is not suppressed, but below the normal range. Most studies published so far have included subjects mainly recruited from clinical practice and therefore highly selected. To determine the true prevalence and pathological causes of reduced serum TSH levels, subjects should be recruited from an epidemiological survey.

We recently had the opportunity to address this issue. In the Tromsø study (7), which was performed for the fifth time in 2001 (8), serum TSH was measured in nearly 8000 subjects. From this cohort the subjects with subnormal TSH levels (<0.5 mIU/l) were retested approximately 1 year after the initial measurement. If the low serum TSH levels were persistent, further examinations including thyroid scintigraphy were performed to establish the causes.

MATERIALS AND METHODS

Subjects

The Tromsø study is a general health survey, which was performed for the first time in 1974 in the Tromsø municipality in Northern Norway (7). Originally, the study focused on heart and vascular diseases, but it has gradually expanded to include other disorders. In the 5th Tromsø study in 2001, all subjects that participated in the second and more extensive phase of the 4th Tromsø study (8) or who became 30, 40, 45, 60 or 75 yr old during 2001, were invited to participate.

All subjects filled in a questionnaire that included previous diseases and use of thyroid medication. Blood samples were drawn in the non-fasting state for serum TSH analysis.

Subjects with a serum TSH value below the 2.5 percentile (which was found to be ~0.5 mIU/l in those without serious disease, below the age of 80 yr, and not using T_4 medication) were considered for re-examination 1 year later. Subjects on T_4 medication, those with previously diagnosed thyroid disorder, and those older than 80 yr in 2002 were not invited. Furthermore, the management of the 5th Tromsø study did not allow us to re-examine those who reported serious disease in the questionnaire (cancer, angina pectoris, previous myocardial infarctions, stroke or diabetes), and those participating in other follow-up studies. Before invitation to the re-examination, the hospital records were also reviewed for diseases not reported in the questionnaires, and to identify those diagnosed and treated for hyperthyroidism after the 5th Tromsø study.

Key-words: Hyperthyroidism, thyroid scintigraphy, T_4, TSH.

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The remaining eligible subjects were invited to the outpatient clinic at the University Hospital of Northern Norway for a clinical examination and a repeated blood testing including serum TSH, free T_4, and free T_3.
In those with a persistent serum TSH level below 0.6 mIU/l (a higher cut-off value than the original 0.5 mIU/l because of a change of the TSH assay, see below) a thyroid scintigram was performed, and anti-TSH receptor antibody (TRAb) and antibodies towards thyroid peroxidase (TPO Ab) were measured.
The thyroid scintigrams were initially assessed by a specialist in nuclear medicine unaware of their thyroid status. A final diagnosis was made based on this report together with the respective serum TSH, free T_4 and free T_3, and TPO Ab and TRAb-values.

Analytical methods

In the 5th Tromsø study, serum TSH was measured with the Modular E instrument (Hoffmann-La Roche, Basel, Switzerland) with a reference range of 0.2-4.0 mIU/l. At the time of the re-examination 1 year later, the Department of Medical Biochemistry had changed to the AxSYM instrument (Abbott, IL) with reference range 0.20-4.20 mIU/l. This assay gave slightly higher serum TSH values than the first assay, and a value of 0.6 mIU/l with the AxSYM instrument was equivalent to 0.5 mIU/l by the Modular E instrument. Serum free T_4 and free T_3 were analysed on the AxSYM instrument with reference ranges of 9-22 pmol/l and 2.8-7.1 pmol/l, respectively.
Serum TRAb was analysed with the kit TRAK human (BRAHMS aktiengellschaft, Henningsdorf; Germany) with a reference range of <2 IU/l. Serum TPO Ab was measured with the Immulite® 2000 automated analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA) with an immunometric assay based on chemiluminescence with a reference value of <50.0 IU/ml.
All data are given as mean±SD unless otherwise stated.

Scintigraphic method and diagnostic criteria

^{99m}Tc-pertechnetat was injected intravenously, and a thyroid scintigram was made after approximately 20 min. The patient was subjected to 100 MBq of radiation. The gamma (γ) camera used was the DST XLi (Sopha Medical Vision, Buc Cedex, France) with a pinhole collimator. The exposure time varied from 1 to 10 min.
Based on the scintigraphic and laboratory findings the following diagnoses were applied:
- The thyroid gland was considered normal if the uptake of isotope was uniform and symmetrical and serum TSH, free T_4, free T_3, TRAb, and TPO Ab were within the laboratory's reference range.
- An adenoma was diagnosed if the scintigram showed a hot nodule without suppression of the serum TSH level.
- A toxic adenoma (an autonomously functioning nodule) was diagnosed if the scintigram showed a hot nodule with suppression of the surrounding thyroid tissue and with a suppressed serum TSH level (9).
- A multinodular goiter was diagnosed if the scintigram showed a non-uniform uptake with two or more hot nodules in a thyroid gland with reduced uptake (9).
- Graves' disease was diagnosed if the TRAb concentration was above the reference range and the scintigram showed a uniformly increased uptake of isotope (9).
- If the scintigram showed a markedly reduced uptake the patient was considered to have some form of thyroiditis, assuming no other clear cause of the condition was present, such as exogenous thyroid hormone ingestion, recent iodine intake, or *struma ovarii* (10).

Ethics

The study was approved by the Regional Committee for Medical Research Ethics in Northern Norway, and all subjects gave their written informed consent to participate.

RESULTS

Ten thousand, three hundred fifty-three subjects (4636 men, 5717 women) were invited to participate in the 5th Tromsø study and 8130 attended (3511 men, 4619 women). Serum TSH was successfully measured in 7954 (3447 males and 4507 females). Information on use of T_4 was lacking in 1220 subjects, 521 subjects reported use of T_4 [of whom 70 subjects (13.4%) had a suppressed serum TSH value (<0.05 mIU/l)], 90 subjects had previously diagnosed thyroid disease, 212 subjects were older than 80 yr, and 750 subjects were not eligible because of restrictions set by the management of the 5th Tromsø study (past or current serious illness reported in the questionnaire). Thus, 4962 subjects (2167 males, 2795 females) fulfilled the inclusion criteria. In this "healthy" cohort, the mean ages were 56.9±13.7 yr in the males and 55.8±13.7 yr in the females, and the corresponding serum TSH levels 1.91±2.30 mIU/l and 1.85±2.44 mIU/l. The 2.5 percentile for serum TSH was 0.57 mIU/l in the males and 0.50 mIU/l in the females.
A cut-off value for serum TSH of 0.50 mIU/l was applied when re-examining subjects for causes of possible hyperthyroidism.
Among these 4962 subjects, 105 had a serum level <0.51 mIU/l (2.1%), 22 subjects (0.44%) had a serum level <0.20 mIU/l, and 12 subjects (0.24%) had a serum TSH value <0.05 mIU/l). One subject had moved out of the Tromsø area, two subjects were participating in other studies, and 20 subjects were considered too ill (based on restrictions by the management of the 5th Tromsø study) for a recall after examining their hospital records.
Seven subjects were diagnosed with a thyroid disorder between the 5th Tromsø study and the time of re-examination. One of these subjects had a toxic adenoma (serum TSH in the 5th Tromsø study <0.05 mIU/l), 2 had a multinodular goiter (serum TSH 0.06 and 0.10 mIU/l, respectively), and 4 had Graves' disease (3 subjects with serum TSH <0.05 mIU/l and 1 with a value of 0.25 mIU/l in the 5th Tromsø study).

Table 1 - *Number of subjects in the different serum TSH ranges at the screening in the 5th Tromsø study and at re-examination 1 year later.*

		Serum TSH (mIU/l) at re-examination (new assay)			
		<0.05	0.05-0.20	0.21-0.60	>0.60
Serum TSH (mIU/l) at	<0.05	3	3		
screening in the 5th	0.05-0.20	1		1	3
Tromsø study (old assay)	0.21-0.50		1	11	32

Table 2 - *Characteristics of the 20 subjects examined with thyroid scintigraphy at re-examination.*

Gender	At 5th Tromsø study		At re-examination					Final diagnosis
	Age (yr)	Serum TSH (mIU/l)	Serum TSH (mIU/l)	Free T_4 (nmol/l)	Free T_3 (pmol/l)	TPO Ab (IU/ml)	TRAb (IU/l)	
Female	42	<0.05	<0.05	14	4.2	<10	3	Graves in multinodular goiter
Male	55	<0.05	0.11	20	5.0	<10	<1	Adenoma
Female	74	<0.05	0.16	16	4.8	<10	<1	Multinodular goiter
Female	42	<0.05	<0.05	15	4.8	<10	<1	Toxic adenoma
Female	60	<0.05	<0.05	16	6.8	<10	<1	Toxic adenoma
Male	62	<0.05	0.15	13	4.3	<10	<1	Multinodular goiter
Male	73	0.05	<0.05	19	5.2	<10	<1	Multinodular goiter
Male	69	0.17	0.27	15	4.2	<10	<1	Multinodular goiter
Female	61	0.28	0.48	18	4.7	<10	<1	Adenoma
Male	57	0.29	0.13	13	4.2	<10	<1	Multinodular goiter
Male	68	0.30	0.48	15	4.8	<10	<1	Normal
Female	65	0.33	0.39	18	3.4	<10	<1	Normal
Male	32	0.34	0.45	17	4.1	<10	<1	Normal
Female	55	0.34	0.46	11	4.9	<10	<1	Multinodular goiter
Female	43	0.39	0.48	17	4.4	<10	<1	Multinodular goiter
Male	32	0.41	0.57	17	4.3	13	<1	Adenoma
Male	60	0.42	0.51	17	3.8	<10	<1	Adenoma
Female	47	0.43	0.55	18	5.3	<10	<1	Normal
Female	47	0.43	0.47	19	4.4	<10	<1	Normal
Female	32	0.45	0.56	17	3.8	<10	<1	Normal

TRAb: anti-TSH receptor antibody; TPO Ab: antibodies towards thyroid peroxidase.

The remaining 75 subjects were invited to participate in the re-examination, and 55 subjects (16 males, 39 females) attended. Their serum TSH values in relation to those in the 5th Tromsø study are shown in Table 1. Thirty-five subjects had serum TSH-values >0.6 mIU/l and were not further examined. All these 35 subjects had normal free T_4 and free T_3 values at re-examination. The final 20 subjects (9 males, 11 females) had a thyroid scintigram and TPO Ab and TRAb analyses performed, and the results are shown in Table 2. Six subjects were found to have a normal thyroid gland, 6 had a solitary adenoma (of which 2 were toxic adenomas), 7 had multinodular goiter, and 1 had a combination of Graves' disease and a multinodular goiter. A flow chart of the subjects participating in the study is shown in Figure 1.

DISCUSSION

In the present healthy population of middle-aged subjects not using T_4, we have found the prevalence of serum TSH below 0.51 mIU/l, 0.20 mIU/l, and 0.05 mIU/l to be 2.1%, 0.44%, and 0.24%, respectively.

The prevalence of low serum TSH values in similar populations has been reported from several large epidemiological studies. Thus, in the HUNT study from Nord-Trøndelag, Mid-Norway including 30,297 subjects, 0.59% and 0.33% had serum TSH below 0.20 mIU/l and 0.05 mIU/l, respectively (11), in the Colorado thyroid disease prevention study including 24,337 subjects, 0.99% and 0.09% had serum TSH levels below 0.3 mIU/l and 0.01 mIU/l, respectively (12), and in the NHANES III study including 16,533 subjects, 0.4% had a serum TSH below 0.1 mIU/l (13).

These differences in prevalence of low serum TSH levels can be explained not only by the different cut-off values for serum TSH used, but also by differences in TSH assays, populations studied, and intake of iodine (14).

Presumably, subclinical hyperthyroidism is caused by the same thyroid disorders that result in clinical hyperthyroidism (15). However, to our knowledge, the causes of the subclinical hyperthyroidism (or a low serum TSH level) have not been investigated in depth in any of the larger epidemiological studies. On the other hand, there are several clinical studies on the etiology of subclinical hyperthyroidism where thyroid nuclear imaging has been included. Thus, in a retrospective study by Tollin et al. from USA that included 50 patients seen during a 4-yr period, toxic multinodular goiter was found in 50%, autoimmune thyroid disease in 18%, solitary toxic adenoma in 8%, silent thyroiditis in 2%, and an apparently normal gland in 22% (10). A similar finding was reported from Turkey by Canbaz et al. who prospectively examined 52 patients with subclinical hyperthyroidism and found multinodular goiter in 65% of the subjects (16). However, these and other studies published on etiology of subclinical hyperthyroidism (17-19) have been performed in subjects referred to specialist centers because of clinical symptoms and may therefore not be representative of truly subclinical disease.

Among the 105 subjects from our "healthy cohort" with a serum TSH value below 0.51 mIU/l at the initial screening, 12 subjects had a serum TSH value below 0.05 mIU/l. Ten of these subjects were available for further diagnosis, and thyroid pathology (pathological thyroid scan and serum TSH below 0.20 mIU/l) was confirmed in all (4 with Graves' disease, 4 with adenoma, and 2 with multinodu-

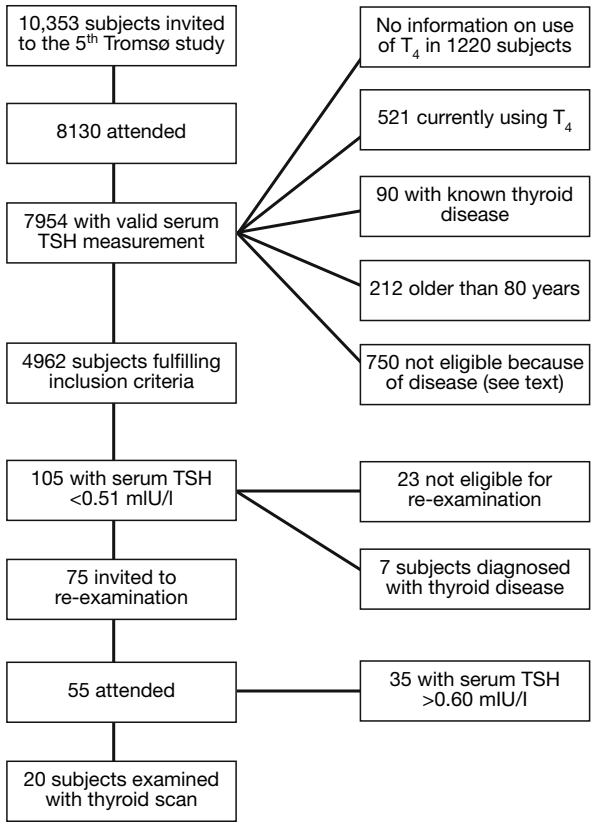

Fig. 1 - *Flow chart of the subjects included in the study.*

lar goiter). On the other hand, in subjects with serum TSH in the range 0.05-0.50 mIU/l at the screening, 71% of those re-examined normalized their serum TSH value. This could represent the well-known phenomenon of regression-towards-the-mean, but also transient conditions like thyroiditis, non-thyroidal illness, and short-term use of a number of medications that could decrease the serum TSH level (15). However, in the 14 subjects with a persistently reduced serum TSH level (0.05-0.60 mIU/l with the new assay), a pathological scan was found in 8 subjects (5 with multinodular goiter and 3 with adenoma). Accordingly, a suppressed serum TSH value discovered by chance will in most cases represent clinically important thyroid pathology, whereas this is not the case in most of the subjects with a low, but not suppressed, serum TSH value, except if the low serum TSH value is persistent over time.

In our study no cases with thyroiditis were diagnosed. This was not unexpected as most cases of thyroiditis are of self-limiting nature, and the re-examination was performed 1 year after the initial screening. We may also have excluded subjects with drug-induced thyroiditis and individuals with suppressed serum TSH due to non-thyroidal illness as those with serious diseases were not included in the study.

Although it was not our main focus, it is noteworthy that among the 82 subjects with suppressed serum TSH levels presented in our study, 70 were on T_4 medication. Thus, 13% of the 521 subjects using T_4 were overdosed (with a possible exception of subjects using suppressive doses of T_4 because of thyroid cancer). Even higher figures have been reported from other studies such as the Colorado Thyroid Disease Prevention Study, where 1/5 of the subjects using T_4 had a suppressed serum TSH level (12). Accordingly, to avoid the potential harmful effects of hyperthyroidism (3-6), it is probably more cost-effective to focus on correct T_4 medication than on finding subclinical cases of hyperthyroidism.

Our study has several shortcomings. First of all, we did not measure free T_4 and free T_3 at the screening which would have characterized the cohort better. There was also a change in the serum TSH assay between the initial screening and the follow-up, and the lag between the two examinations was approximately 1 year. Therefore, we probably missed several cases with transient conditions like thyroiditis. We did not have a proper control group, and can therefore not exclude that we would have found similar thyroid scans in those with normal serum TSH levels. Furthermore, there were only 20 subjects in the final group that were examined with thyroid scintigraphy, and the prevalence of thyroid pathology found must therefore be viewed with caution. However, it should be recalled that to find these 20 subjects, we had to screen almost 8000.

Our study also has considerable strengths. We screened a large group of subjects, and used strict inclusion criteria. The lag time between the two examinations could also be of value, as persistently low serum TSH values are likely to be clinically more important than a transiently low serum TSH value.

In conclusion, we have found that in a healthy cohort where the subjects are not using T_4, a suppressed serum TSH value in most, if not all cases, represents clinically important thyroid pathology. In most subjects where a low serum TSH value (0.05-0.50 mIU/l) is persistent over a 1-year period, thyroid pathology will be found by nuclear imaging. This could be of potential importance, as these subjects have been reported to have increased over-all mortality (6).

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