Factors of variation and reference values for TSH in 45-70 year old women

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The prevalence of thyroid diseases is difficult to assess because of the differences between measurement methods and heterogeneity in population origin. For example, in the GA-ZEL cohort, 3.4 % of French women and 0.6 % of men had thyroid disorders with geographical variations [24]. Hypothyroidism is the most common thyroid disease, more frequent in women over 40 years [27]. Its prevalence is probably underestimated due to existence of subclinical hypothyroidism. This subclinical pathology, characterized by an elevated thyroid-stimulating hormone (TSH) level and by a normal free thyroxin (FT4) [15], was found in 7.5 % of women in the Whickam Survey [27].

Despite this high frequency, screening for subclinical hypothyroidism in a general population is discussed and not recommended, due to evolution of the pathology, adverse effects of medication, specially on risk of osteoporosis, expected benefits and requisite strategy for follow-up [1, 6, 14, 22, 29, 30].

Screening for subclinical hypothyroidism by measurement of TSH at periodic health examinations must be based on epidemiological arguments. In this context, a study was
performed in 11 Centers for health screening to estimate the frequency of this pathology in a sample of French women 45-70 years old and to study its prognostic value by a follow-up survey.

In this work, we describe the characteristics of the target population, clinical signs and medical history linked to TSH variations. Distribution of TSH values in the total sample and reference limits in a selected sample are presented.

POPULATION AND METHODS

Population

A sample of 4,403 volunteer women aged 45 to 70 years (mean: 55.2 ± 6.9 years), attending a routine health examination in one of the 11 participating centers were included between October 1997 and June 1998. They were fasting, non-treated by thyroid hormone therapy and gave written informed consent for participating in this study which was approved by the French National Committee on Informatics and Freedom (CNIL).

Collected data

The following information was recorded by questionnaire: birthday, birthplace of parents, socio-demographic characteristics, socioprofessional status (following INSEE classification), number of children born alive. Medical history of the subject and of her mother was collected concerning thyroid and autoimmune diseases. For the subject herself, medical history of X-ray examination, symptoms of thyroid diseases, menopausal status, hormonal replacement therapy and drug consumption were recorded. A physical examination was performed to search for thyroid enlargement following OMS classification and to note cardiac pulse frequency, cardiothoracic indice (cardiomegaly) and electrocardiogram (ECG) conclusions: normal, minor abnormalities or pathological ECG (ventricular hypertrophy, conduction or rhythm disorders). Cholesterol and triglycerides were measured by enzymatic methods following recommendations for Centres for health screening.

Serum TSH was determined on fresh sera by a third-generation microparticle enzyme immunoassay (Abbott hTSH Ultrasensitive) on Imx or AxSYM [3]. The determination of precision and accuracy was monitored using control sera. The coefficient of variation from day to day was below 7% on 6 months for a mean value of 6 mU/l and the bias was below 4%, corresponding to recommendations [28]. The measurement of FT4 was performed on the same systems with a microparticle enzyme immunoassay (Abbott). The CV was below 7% (mean value = 7 ng/l). Antithyroperoxidase antibodies (TPO Ab) were purchased from BMD on frozen sera in two laboratories using identical reagents. The cut-off was 64 UI/ml. T4L and TPO Ab were measured only on subjects with TSH level between 4 and 12 mU/l.

Statistical analyses

The data collected in each center were sent for statistical analysis to Cetaf (Centre technique d’appui et de formation des Centres d’examen de santé) (CNIL N° 997016).

Analyses were performed using BMDP statistical software (Ltd Cork, Ireland). The mean values of TSH after log-transformation were compared between groups using the Fisher-Snedecor test.

RESULTS

Description of the population

The studied sample included 2,168 women from 45 to 54 years and 2,235 from 55 to 70 years, 469 were 65 to 70 years of age. In these groups, 611 women...
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(14.5 %) stated they had a maternal medical history of thyroid disorders and goiter for more than half of them (376 cases), hyperthyroidism (88 cases, 14.4 %) or hypothyroidism (72 cases, 11.6 %). Maternal history of autoimmune diseases was mentioned by 246 subjects (5.9 %), particularly type 1 diabetes mellitus for 69.1 % among them.

Personal medical history of thyroid diseases were found in 8.1 % of the women. Most of them were goiters (65.8 %). The number of hypothyroidism or hyperthyroidism cases was low, respectively 28 (8.3 %) and 41 cases (12.1 %). Twelve subjects reported a history of pituitary disease and 80 an autoimmune disease.

Signs suggestive of thyroid dysfunction are presented in Table I. The most frequent were dry skin, cold intolerance, muscle cramps, recent weight gain. Some symptoms were more frequently reported by younger women: weight gain or cold intolerance, others by older women: dry skin or cramps.

The presence of a palpable or visible thyroid enlargement was found in 10.4 % of subjects and the clinician indicated presence of nodulars in 29.4 % of them. Frequency of pathological ECG was 5.9 % and increased with age while frequency of minor disorders was 9.8 %.

The cardiothoracic index over 50 % was observed in 8.7 % of the cases when it had been measured.

Finally, 66 % of the subjects were menopausal and 42.1 % of them were on post-menopausal hormone therapy (58.8 % between 45-54 years and 36.6 % between 55 and 70 years).

Table I
Frequency of symptoms of thyroid diseases.

<table>
<thead>
<tr>
<th>Age</th>
<th>45-54 years</th>
<th></th>
<th>55-70 years</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Dry skin</td>
<td>481</td>
<td>23.5</td>
<td>619</td>
<td>29.2</td>
<td>1000</td>
<td>26.4</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>581</td>
<td>28.2</td>
<td>501</td>
<td>23.5</td>
<td>1082</td>
<td>25.8</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>422</td>
<td>20.5</td>
<td>519</td>
<td>24.4</td>
<td>941</td>
<td>22.5</td>
</tr>
<tr>
<td>Recent weight gain</td>
<td>485</td>
<td>23.6</td>
<td>431</td>
<td>20.3</td>
<td>916</td>
<td>21.9</td>
</tr>
<tr>
<td>Chronic tiredness</td>
<td>444</td>
<td>21.6</td>
<td>384</td>
<td>18.1</td>
<td>828</td>
<td>19.8</td>
</tr>
<tr>
<td>Hair loss</td>
<td>246</td>
<td>12.0</td>
<td>251</td>
<td>11.8</td>
<td>497</td>
<td>11.9</td>
</tr>
<tr>
<td>Eyelid oedema</td>
<td>216</td>
<td>10.5</td>
<td>207</td>
<td>9.7</td>
<td>423</td>
<td>10.1</td>
</tr>
<tr>
<td>Face swelling</td>
<td>119</td>
<td>5.8</td>
<td>127</td>
<td>6.0</td>
<td>246</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Table II
Distribution of TSH values (mU/L) according to age in a female sample.

<table>
<thead>
<tr>
<th>Age</th>
<th>45-49 years</th>
<th>50-54 years</th>
<th>55-59 years</th>
<th>60-64 years</th>
<th>65-70 years</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1.260</td>
<td>907</td>
<td>858</td>
<td>879</td>
<td>499</td>
<td>4.403</td>
</tr>
<tr>
<td>Percentile 5</td>
<td>0.60</td>
<td>0.55</td>
<td>0.55</td>
<td>0.50</td>
<td>0.43</td>
<td>0.55</td>
</tr>
<tr>
<td>Percentile 50</td>
<td>1.41</td>
<td>1.45</td>
<td>1.49</td>
<td>1.50</td>
<td>1.41</td>
<td>1.46</td>
</tr>
<tr>
<td>Percentile 95</td>
<td>3.30</td>
<td>3.65</td>
<td>3.64</td>
<td>3.80</td>
<td>3.68</td>
<td>3.65</td>
</tr>
<tr>
<td>&lt; 0.30 mU/L</td>
<td>0.9 %</td>
<td>0.9 %</td>
<td>1.3 %</td>
<td>0.9 %</td>
<td>1.8 %</td>
<td>1 %</td>
</tr>
<tr>
<td>≥ 4.00 mU/L</td>
<td>2.3 %</td>
<td>3.9 %</td>
<td>4.1 %</td>
<td>4.7 %</td>
<td>4 %</td>
<td>3.8 %</td>
</tr>
</tbody>
</table>
Factors of TSH variation

Factors that significantly modified serum TSH are presented in Table IV. Compared to subjects without any thyroid enlargement, TSH mean value was significantly lower when subjects stated they had goiter or when a goiter was observed at clinical examination. Differences vary from 0.20 to 0.40 mU/l, i.e. a decrease of 10 to 23%.

Inversely, presence of the following symptoms: muscle cramps, tiredness, weight gain, morning eyelid edema, corresponded to a weak but significant increase of TSH from 0.10 to 0.20 mU/l. Finally, abnormal ECG was associated with higher mean TSH value (+0.27 mU/l) than in controls.

Reference limits

The factors that significantly influenced TSH values were used as exclusion criteria to select a reference sample. In addition, we excluded subjects consuming drugs known to modify thyroid function (psychotropic drugs, hypnotics, sedatives, diuretics, antiparkinson agents, hypolipemics, or drugs for gastrointestinal diseases).

The reference group included 1,348 women from 45 to 70 years of age. The reference limits for TSH concentration were 0.43-3.71 mU/l for 2.5 and 97.5 percentiles respectively (Table V).

DISCUSSION

Determination of TSH concentration plays a key role in the evaluation of thyroid function. A method with a functional sensitivity of at least 0.1 mU/l provides the most reliable single test for the assessment of thyroid status. In the present multicentric study, third generation assay was used and, in order to control for analytical variations, measurements of TSH and FT4 were performed with the same reagents on homogeneous systems.

TSH measurement allows to distinguish euthyroidism when TSH is normal, hyperthyroidism when TSH is low and hypothyroidism when TSH is high. There are some situations in which TSH results alone may be misleading. A TSH between 4 and 10 or 12, depending on studies [8, 21], with FT4 higher than 8 ng/l, characterizes subclinical hypothyroidism. The presence of TPO-Ab reflects a risk for development of thyroid dysfunction [8, 18, 26].

Hypothyroidism is the most common thyroid disorder. The incidence in a sample of 2,779 adults that closely matched the British population was 3.5% in women and 0.6% in men [26]. The frequency of elevated TSH over 10mU/l in a 79 year old population was 5% in women and 1% in men [7]. In this population, signs and symptoms usually regarded as related to hypothyroidism were as common in subjects with high TSH concentration as in the remaining population and occurred in 10 to 50% of the subjects [7].

Frequency of subclinical hypothyroidism reaches 2.5% to 10% depending on the studied population [15, 24, 27] but seems underestimated. It is twice to three times more frequent in the female population than in males and its prevalence increases clearly after menopause. Measurement of TSH seems especially adapted for women older than 40 [11].

Following these results, the present study was performed in 11 Centers for health screening in 45-70 year old healthy women. Frequency of subclinical hypothyroidism defined by a TSH value between 4-12 mU/l and FT4 higher than 8 ng/l was close to 3%. Hypothyroidism frequency was 0.4% while hyperthyroidism is observed in 1% of the population. These results are consistent with those observed elsewhere [24].

Metabolic consequences of subclinical hypothyroidism are difficult to determine. It could be at the origin of dyslipemia and HDL-C decrease, which constitutes an atherogenic profile and a reason to systematically measure TSH. However, in spite of these biological
In hypothyroidism, some clinical signs are frequent but non-specific: tiredness, cold intolerance, muscle cramps, decreased cognitive functions [25]. Among those used in this study, four are associated with a significant but weak increase (below 12 %) of TSH in general population: tiredness, muscle cramps, recent weight gain, and morning eyelid edema. The cardiac effects of thyroid hormones are also well known: rhythm disorders, heart

\[ \begin{array}{|l|c|c|c|}
\hline
\text{Factors of variation of TSH.} & \text{Number} & \text{Mean} & \text{Standard deviation} \\
\hline
\text{Goiter medical history ***} & & & \\
\text{yes} & 223 & 1.45 & 1.09 \\
\text{no} & 4,172 & 1.75 & 1.28 \\
\hline
\text{Thyroid size ***} & & & \\
\text{nonpalpable} & 3,436 & 1.75 & 1.24 \\
\text{palpable} & 271 & 1.57 & 1.17 \\
\text{visible} & 127 & 1.38 & 1.57 \\
\hline
\text{Thyroid volume **} & & & \\
\text{normal} & 3,436 & 1.75 & 1.24 \\
\text{diffuse goiter} & 195 & 1.56 & 1.48 \\
\text{nodular goiter} & 85 & 1.35 & 1.38 \\
\hline
\text{Symptoms} & & & \\
\text{Muscle cramps *} & & & \\
\text{yes} & 940 & 1.82 & 1.38 \\
\text{no} & 3,239 & 1.71 & 1.24 \\
\text{Recent weight gain **} & & & \\
\text{yes} & 916 & 1.85 & 1.47 \\
\text{no} & 3,268 & 1.70 & 1.21 \\
\text{Eyelid oedema ***} & & & \\
\text{yes} & 423 & 1.91 & 1.40 \\
\text{no} & 3,758 & 1.71 & 1.25 \\
\text{Chronic tiredness *} & & & \\
\text{yes} & 828 & 1.82 & 1.35 \\
\text{no} & 3,351 & 1.72 & 1.25 \\
\text{ECG ***} & & & \\
\text{normal} & 3,687 & 1.70 & 1.20 \\
\text{minor abnormalities} & 428 & 1.97 & 1.61 \\
\text{pathologic} & 258 & 1.84 & 1.50 \\
\hline
\end{array} \]

* : p < 0.05 ; ** : p < 0.01 ; *** : p < 0.001 after logarithmic transformation and adjustment on age.

\[ \begin{array}{|l|c|c|c|c|c|c|c|}
\hline
\text{Percentiles} & 1 & 2.5 & 5 & 50 & 95 & 97.5 & 99 \\
\hline
\text{percentile} & 0.30 & 0.43 & 0.59 & 1.43 & 3.23 & 3.71 & 4.94 \\
\hline
\end{array} \]
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REFERENCES


failure with ECG disorders [21, 25]. In our sample, only ECGs presenting minor abnormalities were associated with a significant increase of TSH. We did not observe any significant link with other examinations of the cardiac system: cardiac pulse frequency and cardiothoracic index. It must be noticed that the studied population is a general population, supposedly healthy, without thyroid hormone drugs. So, effects of hyper and hypothyroidism are assumed to counterbalance each other.

Concerning personal medical history, existence of clinical goiter was significantly associated with a 10 % to 23 % decrease of TSH. None of the other personal or familial medical histories concerning thyroid disorders or autoimmune diseases were associated with variation of TSH. The collection of these data by questionnaire is perhaps not relevant enough to give valid information.

The usual biological factors of variation do not influence TSH value which is a relatively stable constituent. In our population, neither age, nor menopausal status nor postmenopausal hormone treatment influenced median value. These results are in agreement with those obtained in other populations [5, 12, 18, 23]. However, the range of TSH distribution increased with age and may explain the rise in dysthyroidism frequency.

A bibliographic review did not reveal any differences between males and females over 40 years old [12], and increase during pregnancy remained between reference limits [9, 20]. Inversely, physical exercise leads to a 15 % decrease TSH after 30 minutes and an increase of FT4 and total T4 after 10 minutes, due to metabolic modification rather than hemocoencentration [17]. Female smokers would have an increased risk to develop hypothyroidism [19].

Some drugs are well known to modify thyroid function: dopamine agonists, neuroleptics, lithium, corticoids or interferon as well as numerous drugs with iodine even in local treatment [2, 21]. Neck irradiation can also provoke hypothyroidism [10, 13].

Factors and drugs able to modify TSH results were used as exclusion criteria to obtain the reference sample. Reference limits are 0.40-3.7 mU/l, narrower than usual. It seems judicious to follow up women when TSH is over 4 mU/l in order to determine their risk to develop clinical hypothyroidism. In addition, the measurement of serum TSH each five years, especially in cases of hypercholesterolemia induced by dysthyroidism, could have an economic interest in decreasing medical cost [4, 16].
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