PECULIARITIES OF INDICES OF THYROID HOMEOSTASIS IN PATIENTS WITH METABOLIC SYNDROME DEPENDING ON BODY MASS INDEX

Summary. Introduction. Nonthyroidal illness syndrome develops in patients against the background of chronic comorbidity as a result of impaired peripheral conversion of thyroid hormones and is characterized by low levels of triiodothyronine (T3).

Objective of the study: to find out the features of thyroid homeostasis in patients with metabolic syndrome (MS).

Materials and methods. 64 patients with MS and 20 healthy individuals were involved in the investigation. We determined the level of thyroid stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3). To study the functional status of the pituitary-thyroid axis, we calculated fT3/fT4 ratio and thyroid index (TI). Peripheral activity of thyroid hormones was estimated by total thyroid index (TTI).

Results. In the course of our study, lower fT3 levels and increased levels of TSH and fT4 was revealed in patients with MS compared with the group of healthy subjects (p < 0.05). We found a reduction of fT3/fT4 ratio (p < 0.05) compared to the control group (p< 0.05). TTI was lower in the examined patients compared with the group of healthy individuals (p < 0.05).

As a result of correlation analysis, it was established that body mass index negatively correlated with the level of fT3 (r = –0.341, p < 0.05), fT3/fT4 index (r = –0.458, p < 0.05), TI (r = –0.415, p < 0.05) and TTI (r = –0.335, p < 0.05) and positively — with levels of fT4 (r = 0.405, p < 0.05) and TSH (r = 0.327, p < 0.05).

Conclusion. The obtained data suggests the development of nonthyroidal illness syndrome in patients with metabolic syndrome as a result of impaired peripheral conversion of thyroid hormones, which deepens with body mass index growth, i.e. the class of obesity.

Key words: obesity, hypertension, metabolic syndrome, thyroid homeostasis, nonthyroidal illness syndrome.

Nonthyroidal illness syndrome (NTI), also known as syndrome of low triiodothyronine (T3), occurs against a background of chronic concomitant diseases and is characterized by reduction of triiodothyronine due to inhibition of deiodinases — enzymes which catalyze peripheral conversion of thyroxine (T4) to its active metabolite (T3). These changes are typical for 75 % of hospitalized patients [10, 11]. About 80 % of thyroid hormones are produced in peripheral tissues through the activity of deiodinases [5, 13].

Three types of deiodinases has been identified: deiodinase I-type (D1) was found in the liver and kidneys; type II deiodynase (D2) — in heart, coronary arteries, smooth muscles of arteries, skeletal muscles, nervous system, adipose tissue and thyroid gland; type III deiodinase (D3) — in embryonic tissues, placenta, liver and skin [6]. D1 and D2 are involved in the conversion of T4 to T3 (its active metabolite) by deiodination in following positions: 5'-D1, and 5'-D1 and D2. D2 regulates local T3 activity and its accessibility to nuclear receptors [13].

D3 inactivates thyroid hormones by formation of reverse triiodothyronine (rT3) from T4 and diiodothyronine from T3 and rT3 [9]. Changes in the organs in which they function (damage of liver, kidney, brain) cause reduction of these enzymes production and development of NTI.

It is known that the highest level of D2 and the lowest levels of D1 and D3 was revealed in the pituitary gland [7]. Under conditions such as stress, obesity, insulin resistance, liver diseases, kidney diseases and other comorbidities the activity of D1 decreases whilst that of D2 and D3 activity increases [7, 10]. These changes help to...
maintain T3 levels in the pituitary gland within the normal ranges thanks to its D2-mediated conversion from T4, which is why thyroid-stimulating hormone (TSH) level is also within normal limits. Thus, TSH is an unreliable indicator of thyroid hormones metabolism in peripheral tissues against the background of diseases that cause NTI development.

Despite the existence of preconditions for the development of NTI in patients with metabolic syndrome (MS), there exists only sporadic and somewhat conflicting data regarding the development of thyreopathies in these patients. It was found that the incidence of hypothyroidism and nodular goiter significantly increased in patients with MS [7, 8, 10, 12]. However, features of peripheral metabolism of thyroid hormones against the background of MS require further research.

The aim of the study: to find out the features of thyroid homeostasis in patients with metabolic syndrome.

**Material and methods**

The study involved 64 patients with MS who were hospitalized in the Chernivtsi regional endocrinology center and 20 healthy people.

Patients were divided into groups as follows: Group I — 20 patients with MS and a body mass index (BMI) within 25–29.9 kg/m² (overweight); Group II — 15 patient with MS and a body mass index within 30–34.9 kg/m² (class I obesity); Group III — 9 patients with MS and a body mass index within 35–39.9 kg/m² (obesity class II and class III); Group IV — 20 patients with MS and a body mass index within 18–25 kg/m² (normal weight).

The diagnosis of MS was established according to the International Diabetes Federation (IDF) criteria on the basis of anthropometric, clinical and laboratory data [1].

Patients with MS had a body mass index (BMI) within 30–34.9 kg/m² (class I obesity); Group III — 9 patients with MS and a body mass index within 35–39.9 kg/m² (obesity class II and class III); Group IV — 20 patients with MS and a body mass index within 18–25 kg/m² (normal weight).

The diagnosis of MS was established according to the International Diabetes Federation (IDF) criteria on the basis of anthropometric, clinical and laboratory data [1]. The levels of thyroid stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) were determined. To study the functional state of the pituitary-thyroid axis, fT3/fT4 ratio and thyroid index (TI) were calculated [2].

Peripheral activity of thyroid hormones was assessed using total thyroid index (TTI) [3].

Statistical analysis of the obtained data was carried out using the Student’s t-test and Pearson’s rank correlation coefficient by means of the software package Statistica 6.0 for Windows. The result was considered reliable at p < 0.05.

**Results**

Investigation of thyroid homeostasis established significant reduction of fT4 in all groups of patients with MS compared to the group of healthy individuals (table 1). The lowest level of fT4 was determined in group II and III — it was respectively 80.2 and 76.8 % lower than in the group of healthy individuals (p < 0.05). Also fT3 level was respectively 55.8 and 34.7 % lower in groups I and IV compared with the healthy individuals (p < 0.05). The level of fT3 in group I was respectively 13.5 and 17.7 % higher when compared with groups II and III (p < 0.05) and was 19.8 % lower than in group IV (p < 0.05).

fT3 level was significantly 31.3 and 33.8 % lower in groups II and III compared to group IV (p < 0.05).

Against this background, a significant elevation of fT3 levels by 22.9 and 30.1 % in groups II and III respectively has been found compared to the group of healthy individuals and group IV respectively (p < 0.05).

fT4/fT3 ratio underwent the most significant changes and was respectively 2.27 and 2.5 times lower in groups II and III compared with the control group (p < 0.05) and respectively 45.5 and 60.0 % lower — compared with group IV (p < 0.05).

fT3/fT4 ratio in group I was respectively 18.2 and 30.0 % higher compared to groups II and III (p < 0.05) and 23.07 and 92.3 % lower in relation to groups IV and the group of healthy individuals respectively (p < 0.05).

Reduction of fT3, and elevation of fT4 proportional to the growth of BMI may indicate a violation of peripheral conversion as a result of inhibition of D1 and activation of D3 which is in turn due to increased leptin content in blood that is typical for people with MS on the background of resistance to leptin.

Patients from groups I and II had respectively 80.3 and 51.9 % (p < 0.05) higher TSH content compared with the group of healthy individuals. Also in group I TSH level was 51.2 % higher than that in group IV (p < 0.05). The highest TSH content in blood serum was revealed in group I.

Noteworthy is the fact that this index had a tendency to decrease in groups with elevated BMI.

This gives a line of empirical evidence that increased leptin level, which is typical for obese patients on a background of MS, leads to stimulation of D2 activity in pituitary tissue, accompanied by local formation of a sufficient amount of T3 and due to this an inhibition of TSH production by the pituitary gland occurs despite the peripheral deficiency of T4 [4].

**Discussion**

TI was 1.89, 2.49, 1.96 and 2.67 times higher in groups I, II, III and IV respectively compared with the group of healthy subjects (p < 0.05). TI in group IV exceeded the corresponding figure in group I by 40.8 % (p < 0.05). TTI in groups I, II, III and IV was respectively 62.6, 83.5, 85.5 and 40.7 %, lower compared with the control group (p < 0.05). TTI was respectively 20.6, 30.5 and 31.9 % lower in groups I, II, III in relation to group IV (p < 0.05). TTI decreased in patients with the highest BMI values, testifying the violation of peripheral conversion of thyroid hormones which leads to NTI development.

Correlation analysis showed that BMI negatively correlated with fT3 (r = −0.341, p < 0.05), fT3/fT4 index (r = −0.458, p < 0.05), TII (r = −0.415, p < 0.05) and TTI (r = −0.335, p < 0.05) and positively correlated with fT3 (r = 0.405, p < 0.05) and TSH (r = 0.327, p < 0.05).

Data, obtained as a result of correlation analysis, indicate the dependence of thyroid supply of organism on components of MS, in particular the degree of obesity.

It is known that patients with MS have resistance to leptin which is accompanied by its increased production by adipose tissue. Revealed changes may be caused by a depression of D1 activity by leptin and as a result, decreased fT3 levels.
Mechanism of negative feedback is impaired in patients with MS (i.e. TSH is not produced in necessary amount because of sufficient formation of T3 in pituitary tissue due to the activation of D2 in the pituitary gland). This makes TSH an unreliable indicator of disorders of thyroid homeostasis in patients with MS [4]. In healthy individuals, leptin stimulates production of TSH by the pituitary gland, but against the background of resistance of receptors to leptin, this process is inhibited [6].

Author declares that there are no conflicts of interest.

Conclusions

1. Impairment of peripheral conversion of thyroid hormones has been revealed in patients with metabolic syndrome which manifests itself by the reduction of free triiodothyronine content, free thyroxine level elevation, lower free triiodothyronine/free thyroxine ratio and lower total thyroid index.

2. Level of thyroid stimulating hormone increased in patients with metabolic syndrome compared with the group of healthy individuals, but in groups with increased BMI more than 35 kg/m² its level was reduced, so this index may not be a reliable indicator of thyroid hormones metabolism against the background of obesity.

3. Changes in thyroid homeostasis parameters in patients with metabolic syndrome aggravate with body mass index growth and were estimated as nonthyroidal illness syndrome.

References


Table 1. Indicators of thyroid homeostasis in patients with metabolic syndrome according to body mass index

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Patients with MS</th>
<th>Healthy individuals, n = 20</th>
</tr>
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<tbody>
<tr>
<td>TSH, mIU/l</td>
<td>3.750 ± 0.458***</td>
<td>2.080 ± 0.152</td>
</tr>
<tr>
<td>fT4, pmol/l</td>
<td>18.590 ± 1.167</td>
<td>16.020 ± 1.451</td>
</tr>
<tr>
<td>T3, pmol/l</td>
<td>4.790 ± 0.237***</td>
<td>7.460 ± 0.172</td>
</tr>
<tr>
<td>fT₃/fT₄</td>
<td>0.260 ± 0.200 ± 0.034*</td>
<td>0.500 ± 0.043</td>
</tr>
<tr>
<td>TTI</td>
<td>24.850 ± 0.235*</td>
<td>13.080 ± 0.521</td>
</tr>
<tr>
<td>TTI</td>
<td>195.30 ± 9.15*</td>
<td>331.30 ± 18.36</td>
</tr>
</tbody>
</table>

Notes: * — p < 0.05 in relation to the group of healthy individuals; ** — p < 0.05 in relation to the group of individuals with a BMI 18–24.9; *** — p < 0.05 in relation to the group of individuals with a BMI 35–39.9; **** — p < 0.05 in relation to those with a BMI of 30–34.9.
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ОСОБЕННОСТИ ПОКАЗАТЕЛЕЙ ТИРЕОИДНОГО ГОМЕОСТАЗА У БОЛЬНЫХ С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ В ЗАВИСИМОСТИ ОТ ИНДЕКСА МАССЫ ТЕЛА

Резюме. Актуальность. Синдром нетиреоидной патологии развивается у больных на фоне хронической сопутствующей патологии в результате нарушенной периферической конверсии тиреоидных гормонов и характеризуется низким уровнем трийодтиронина (Т₃).

Цель исследования: установить особенности тиреоидного гомеостаза у пациентов с метаболическим синдромом (МС).

Материалы и методы. Обследовано 64 пациента с МС и 20 здоровых лиц. Определен уровень тиреотропного гормона (ТТГ), свободного тироксина (сТ₄) и свободного трийодтирионина (сТ₃). Для изучения функционального состояния гипофизарно-тиреоидной оси вычислялось соотношение сТ₃/сТ₄ (ТИ). Периферическую активность тиреоидных гормонов оценивали посредством определения суммарного тиреоидного индекса (СТИ).

Результаты. В ходе нашего исследования более низкие уровни сТ₃ и повышенное содержание ТТГ и сТ₄ выявлено у пациентов с МС по сравнению с группой здоровых лиц (р < 0,05). Обнаружено уменьшение коэффициента сТ₃/сТ₄ (р < 0,05) в сопоставлении с группой контроля (р < 0,05). СТИ был ниже у обследованных больных с МС, чем в группе здоровых лиц (р < 0,05).

В результате корреляционного анализа установлено, что индекс массы тела отрицательно коррелирует с уровнем сТ₃ (r = -0,341, p < 0,05), соотношением сТ₃/сТ₄ (r = -0,458, p < 0,05), ТИ (r = -0,415, p < 0,05) и СТИ (r = -0,335, p < 0,05) и положительно — с содержанием сТ₄ (r = 0,405, p < 0,05) и ТГГ (r = 0,327, p < 0,05).

Вывод. Полученные данные свидетельствуют о развитии синдрома нетиреоидной патологии у пациентов с метаболическим синдромом в результате нарушенной периферической конверсии тиреоидных гормонов, который усугубляется с увеличением индекса массы тела, то есть степени ожирения.

Ключевые слова: ожирение, артериальная гипертензия, метаболический синдром, тиреоидный гомеостаз, синдром нетиреоидной патологии.