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COULD ERECTILE DYSFUNCTION IN TYPE 2 DIABETES CHANGE THE PRESUMPTION OF NORMATIVE TOTAL BLOOD SERUM TESTOSTERONE?


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МОЖЕТ ЛИ ЭРЕКТИЛЬНАЯ ДИСФУНКЦИЯ У БОЛЬНЫХ С САХАРНЫМ ДИАБЕТОМ 2ТИПА ИЗМЕНИТЬ ПРЕДСТАВЛЕНИЕ О НОРМАТИВНОМ УРОВНЕ ОБЩЕГО ТЕСТОСТЕРОНА СЫВОРОТКИ КРОВИ?

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According to research data, the ED is detected in 50–75 % of men with T2DM. During the last decade, the problem of ED in the presence of late onset hypogonadism has been actively studied. There is convincing proof that total serum testosterone (T) deficit influences the development and severity of ED, including in T2DM. The principal aim of the current study was to evaluate ED in males with T2DM at low and middle-to-high normative levels of T.

We have performed a prospective randomized simple comparative study of 86 male patients with T2DM and T level higher than 12.0 nmol/l. The patients were divided into two groups, with low normative level of T and with middle – to high normative T levels. Standard methods of objective evaluation did not permit discrimination in the T2DM compensation. At the same time the diseases based on vascular pathology, dyslipidemia and vascular endothelial dysfunctions were more frequently found in patients with middle-to-high normal T levels. In the two groups of patients the severity of androgen deficiency symptoms was found out to be unequal. The IIEF-5 questionnaire showed significant difference in frequency and severity of ED and significant relation to T levels. Males with T2DM and normotestosteronemia at 12–15 mmol/l are at higher risks of dyslipidemia, endothelium disorders and progress of T2DM as compared to males with blood T of >15 mmol/l.

Key words: erectile dysfunction, testosterone, type 2 diabetes mellitus

По данным исследователей, ЭД выявляется у 50–75 % мужчин с СД 2 типа. Получены убедительные доказательства влиянии дефицита Тобз на развитие и тяжести эректильных нарушений, в том числе и при СД 2 типа. Основной целью настоящего исследования явилась оценка нарушений эректильной функции у мужчин,
Erectile dysfunction (ED) is not just a common male sexual dysfunction, but the one causing the highest anxiety among all sexual dysfunctions. It is known that as much as 30% males aged from 18 to 59 are diagnosed with ED of various severity [14]. The dominant cause among those dysfunctions is type 2 diabetes mellitus (T2DM). The risk of ED in patients with T2DM is 3 times higher than the risk of general population [9, 13].

According to research data, ED is detected in 50–75% of men with T2DM. For example, an examination of 1460 patients with T2DM showed ED in 34% of patients, periodic sexual function disorders in 24%, and only 42% of patients did not report any sex life-related disorders [18]. An important contribution to ED development may be caused by the concomitant vascular system disorders. It has been established that ED increases the risk of coronary disease in middle-aged male group [19].

Besides, there exists proof of correlating interactions between ED and the number of damaged coronary arteries and the extend of their damage [13]. Also, it has been previously demonstrated that ED is concomitant with T2DM with evident damage to the nervous and vascular systems [8, 16, 17, 19].

During the last decade, the problem of ED in the presence of late onset hypogonadism has been actively studied. There is convincing proof that total serum testosterone (T) deficit influences the development and severity of ED, including in T2DM [7, 17]. At the same time, there exist publications where the authors indicate that clinical androgen deficit symptoms together with ED may exist in patients with normative levels of T [11, 15].

Presently, ED pathogenesis in T2DM in the presence of late onset hypogonadism is only partially understood, the issues of vascular and endocrine systems, age-related disorders, ED and their relation to variation on serum T remain unresolved.

The principal aim of the current study was to evaluate ED in males with T2DM at low and middle-to-high normative levels of T. Secondary research aims were the assessment of T2DM compensation at various levels of normative T, as well as searching for informative markers of endothelial dysfunction and lipid metabolism disorders indicating risks of T2DM progress in normal T levels.

Material and Methods. We have performed a prospective randomized simple comparative study of 86 male patients with T2DM and T level higher than 12.0 nmol/l. The study protocol has been approved by the Local Independent Ethics Committee of the Rostov State medical university. All patients have signed informed consent forms before undergoing the study procedures. The patients were divided into two groups. The Group 1 (n=23) included patients with low normative level of T – from 12.0 to 14.9 nmol/l. The Group 2 (n=63) included patients with middle – to high normative T levels≥15.0 nmol/l.

The clinical parameters of erectile function and general health were evaluated from the results of valid international questionnaires filled by the patients: the International Index of Erectile Function (IIEF-5) and Aging Male Symptoms questionnaire (AMS). The comorbidity has been evaluated from anamnesis.

Blood samples were collected from 8.00 to 9.00 a.m. following 12 hours of fasting. Biochemical analyses were performed using fresh blood serum. For performing immune enzyme analysis, the blood was centrifuged and the serum was frozen at -20°C.

To evaluate the T2DM compensation, the level of glycosylated blood hemoglobin (HbA1c) and index of insulin resistance HOMA (IH) have been examined [10, 20].

The lipid metabolism was evaluated by the levels of total cholesterol (TC, optimal<5.2 mmol/l), triglycerides (TG, optimal<1.7 mmol/l), high-density lipoproteins (HDL, optimal≥1.56 mmol/l), low-density lipoproteins (LDL, optimal<2.6 mmol/l). The judgment on the obtained results was passed in accordance with the accepted norms [6].

For assessment of biochemical markers of endothelial function, nitric oxide (NO), endothelin NO synthase type 3 (NOS-3) and endothelin were evaluated using immune enzyme analysis «Biobioscience» (Austria) lab kits.

The detection of NO concentration in the blood serum was performed by the computational method, by calculation the level of final metabolites (nitrites NO2/ nitrates NO3) as products of NO metabolism in accordance with the recommendations of the manufacturer («Bayer»). The normal parameters were defined as: NO level of 37.2 to 87.2 µM, endothelin level of 0.2 to 0.7 fmol/ml [2, 3, 4].

The function of vascular endothelium was examined using the Doppler ultrasound, by measuring endothelin-dependent vasodilation (EDV) of the brachial artery during the test with reactive hyperemia and endothelin-independent vasodilation caused by sublingual nitroglycerine intake according to the Zateischikov D. D. (2008) method. Vessel diameter change by more than 10% of the initial was considered normal [5].

Beside that, in accordance with standardized method of P. Pignoli (1986), the thickness of intima-media complex (TIM) of the lateral wall of common carotid...
arteries was measured, accepting as normal the value of TIM ≤ 0.9 mm [1, 16].

Statistical analysis of the data was performed by non-parametric methods using STATISTICA software package (StatSoft 8.1). The data are presented as median (Me), lower (LQ) and upper (UQ) quartiles. The evaluation of statistical significance of differences in values between two independent groups was performed using the Mann-Whitney U-test. The correlative analysis was estimated by the Spearman rank correlation method. The results were considered statistically significant at a value of p<0.05.

Results and Discussion. The patients in both groups were similar by age (p>0.23), height (p>0.63), glucose level (p>0.75) and duration of T2DM (p>0.44). By body mass and body mass index (BMI) there have been found significant differences with p<0.04 and p<0.02 correspondingly. At the same time, the correlations between those parameters and levels of T were weak and not significant (0.126<|r|<0.132, p>0.05).

Despite the fact that duration of T2DM and glucose levels in groups were comparable, the value of HbA1c correlated to concentration of T. For instance, parameters of HbA1c and IH median analysis were comparable and had no significant differences between patients of both groups. At the same time, the proportion of patients with HbA1c level>7 % prevailed in Group 1 as compared to Group 2 by 12.8 %.

The results above have been confirmed by statistically significant correlation of the insulin resistance expression by HOMA index value with the T level.

The significant differences in groups by body mass and BMI, as well as the results of HbA1C, IH evaluation and correlations detected between them demonstrate that the extent of T2DM compensation is influenced by various T levels, that is, T2DM compensation is the worst at low-normal levels of T (Table 2).

It is known that T2DM is frequently accompanied by comorbidity, predominantly of the cardiovascular system. Overall, comorbidity has been observed in 77.9 % of our patient. The most numerous diseases were those frequently associated with endothelial dysfunction and arterial vessel involvement. Thus, the amanesis of ischemic heart disease and arterial hypertension were found in 22.4 % and 38.8 % of cases correspondingly. At the same time, in Group 1 the total frequency of comorbid pathologies was 18.3 % higher than in Group 2. In inter-group comorbidity comparison, the frequency of ischemic heart disease was comparable in groups, but cases of obesity were 21.8 % higher in Group 1 compared to Group 2. Despite the fact that presence of arterial hypertension was more frequently reported by patients of Group 2, the parameters of systolic (SAP), diastolic (DAP) arterial blood pressure and heartbeat rate (HBR) showed no statistically significant differences between groups (p=0.07 – 0.25) and were (SAP/DAP/HBR) for Group 1 – 140 (130; 160) mm Hg, / 90 (84; 92) mm Hg, / 77 (71; 80) beats per minute; for Group 2 – 138 (130; 149) mm Hg, / 84 (80; 91) mm Hg, / 76 (70; 79) beats per minute. It objectively indicates equal frequency and severity of arterial hypertension in the groups.

Analysis of non-specific symptoms of the androgen deficit (AMS questionnaire) allowed to detect insignificant differences between the total sum of the questionnaire evaluation score: 38.5 (25.8; 46.0) points for Group 1 and 36.5 (28.0; 47.5) points for Group 2 (p>0.05). At the same time the structure of symptoms’ severity in the groups was significantly differ. It has been found that the sum of the severe and moderate symptoms is most frequently encountered in Group 1 patients compared to the Group 2, 60 % compared to 50 % correspondingly. Beside that, the dependence of clinical androgen deficit manifestations on the T levels in T2DM is demonstrated by significant moderate correlation in group 1 and non-significant weak correlation in Group 2 (Fig.).

It has been found that T2DM patients with normal T levels had ED in 80.0 % of cases. The most frequent ED (93.8 %) was in the Group 1. In the same group, the larger number of sexual inactivity cases was found, 31.3 % vs. 20.5 % in the Group 2. The severity of ED was also markedly different: in group 1 the IIEF index was lower and number of patients with severe ED higher than in Group 2 (Table 1). There have been found mild correlations between T levels and presence of ED: significant in group 1 (|r|= 0.261, p<0.05) and non-significant in group 2 (|r|= 0.148, p>0.05).

<table>
<thead>
<tr>
<th>Erectile dysfunction intensity by results of IIEF-5 evaluation</th>
<th>Group 1</th>
<th>Group 2</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ED, %</td>
<td>93.8</td>
<td>75.0</td>
<td>80.0</td>
</tr>
<tr>
<td>No sexual activity, %</td>
<td>31.3</td>
<td>20.5</td>
<td>23.3</td>
</tr>
<tr>
<td>Overall ED, grade</td>
<td>13.5</td>
<td>16.0</td>
<td>16.0</td>
</tr>
<tr>
<td>[11.3; 16.8]</td>
<td>[11.5; 18.5]</td>
<td>[11.3; 18.0]</td>
<td></td>
</tr>
<tr>
<td>ED1 (5-7 points), %</td>
<td>0.0</td>
<td>4.5</td>
<td>3.3</td>
</tr>
<tr>
<td>[0.0; 16.8]</td>
<td>[0.0; 8.9]</td>
<td>[0.0; 11.7]</td>
<td></td>
</tr>
<tr>
<td>ED2 (8-11 points), %</td>
<td>18.8</td>
<td>9.1</td>
<td>11.7</td>
</tr>
<tr>
<td>[18.0]</td>
<td>[9.7; 19.0]</td>
<td>[9.0; 20.0]</td>
<td></td>
</tr>
<tr>
<td>ED3 (12-16 points), %</td>
<td>25.0</td>
<td>18.2</td>
<td>20.0</td>
</tr>
<tr>
<td>[22.0; 27.5]</td>
<td>[17.0; 23.0]</td>
<td>[16.5; 23.5]</td>
<td></td>
</tr>
<tr>
<td>ED4 (17-21 points), %</td>
<td>18.8</td>
<td>22.7</td>
<td>21.7</td>
</tr>
<tr>
<td>[18.0]</td>
<td>[21.0; 24.5]</td>
<td>[20.5; 23.0]</td>
<td></td>
</tr>
</tbody>
</table>

ED – erectile dysfunction. ED1 – severe erectile dysfunction, ED2 – moderate erectile dysfunction; ED3 – mild erectile dysfunction; ED4 – no erectile dysfunction. Significance by total ED score: between groups 1 and 2 p=0.04.

We didn’t find correlations between parameters evaluated by IIEF-5 and AMS questionnaires (0.001<|r|<0.021, p>0.05) and T. At the same time, we detected significant moderate correlations between severity of ED and T2DM compensation, increasing as the T level decreases, which explains a significant growth of ED development risk at low-normal levels of T (Table 2).
A study of lipid metabolism showed that hypercholesterolemia occurred in patients of both groups (p = 0.68 – 0.74), but the percentage of those patients was higher in Group 1 compared to Group 2, 38.1% and 27.6% correspondingly. Increased concentrations of TG were much more frequent at low-normal T levels compared to high-normal, 40.0% against 24.1% correspondingly, and the frequency of borderline LDL values was significantly higher in Group 1. Thus, it has been shown that most frequently disorders of lipid metabolism were found in patients with T levels lower than 15.0 nmol/l.

It is well known that the T2DM is associated with dysfunctions of blood vessel endothelium, and some pathological mechanisms of diabetes development are directly defined by endothelial dysfunction. In this regard assessment of carotid arteries TIM indicated that as much as 50.0% of all subjects had thickening of the arterial wall, although the number of patients with pathologic TIM parameters is comparable between the groups (p = 0.95). This value had a non-significant weak correlation to the T level, for Group 1 |r| = 0.097, p>0.05; for Group 2 |r| = 0.106, p>0.05. At the same time, results of reactive hyperemia test had established that vascular endothelial dysfunctions were more frequently found in patients of group 1 compared to group 2, 55.6% vs. 23.8%. There have been defined more frequently found in patients of group 1 compared to Group 2, 55.6% vs. 23.8%. There have been defined moderate correlations between biochemical markers of endothelial function biochemical markers, confirming significant increase in endothelin concentration and decrease in NOS-3 level, as well as elevated NO concentration as low-normal T levels. At the same time, patients with various normal T levels displayed similar TIM but profoundly different EDV values, thus reflecting the vascular endothelial dysfunctions.

Measurement of the blood serum lipids demonstrated a larger percentage of patients with hypercholesterolemia, borderline and high values of TG and borderline values of LDL at low-normal T levels. At the same time, patients with various normal T levels displayed similar TIM but profoundly different EDV values, thus reflecting the vascular endothelial dysfunctions. Special attention was paid to patients with T2DM, since this disease involves vascular pathology, dyslipidemia and vascular endothelial dysfunctions were more frequently found in patients with middle-to-high normal T levels. Thus, the patients with low-normal and middle-to-high normal T levels displayed no significant differences in glucose levels and duration of T2DM. There was no significant correlation between those parameters and T level. Thus, standardized clinical evaluation of the frequency of borderline LDL values was significantly higher in Group 1. At the same time, questionnaires (AMS and IIEF-5) filled by the patients showed there exist clinical differences in T2DM at different levels of normal T range. For example, in the two groups of patients the severity of androgen deficiency symptoms was not found to be unequal. The IIEF-5 questionnaire showed significant difference in frequency and severity of ED and significant relation to T levels. Those findings were confirmed by evaluation of endothelium function biochemical markers, confirming significant increase in endothelin concentration and decrease in NOS-3 level, as well as elevated NO concentration as low-normal T level compared to middle-to-high normal T. Those results, together with the results of reactive hyperemia test, signify higher frequency and severity of endothelial dysfunction, causing vasodilation disorders at low-normal T levels and allow us to conjecture that the biochemical markers of atherosclerosis are more frequently found in low-normal T levels. Thus, as T level decreases from normal to middle-to-high normal to low-normal, in males with T2DM the frequency and severity of ED increases. This process takes place in presence of the diseases based on vascular pathology, dyslipidemia and vascular endothelial disorders.

Conclusions. For the first time it has become possible to judge the relation of ED symptoms with the T2DM compensation in normal range of T levels. It turns out that males with T2DM and normotestosteronemia at 12–15 mmol/l are at higher risks of dyslipidemia, endothelial disorders of T2DM and ED in comparison to males with blood T of>15 mmol/l. Consequently, it makes sense to continue study of relations between T2DM, ED and normotestosteronemia for understanding both the specifics of their pathophysiological interaction and gaining a new understanding of the testosterone normal range.

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ОПТИМАЛЬНАЯ ТЕРАПИЯ ПАЦИЕНТОВ С УПРУГИМ ИЗМЕРЕНИЕМ СОЕДИНЕНИЙ ВЕРШИН КАПИЛЛЯРНОЙ СЕТИ ЧЕРЕЗ РАЗЛИЧНОГО ГЕНЕЗА

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The treatment challenges in patients with obstructive jaundice is one of the most pressing issues in abdominal surgery. Mechanical jaundice, as a complication of underlying disease and decompensation of intercurrent somatic illness – all this has an adverse impact on the overall condition of the patient. The treatment analysis of 150 patients.