

Original article

Reprint

## Testosterone deficiency in type 2 diabetes mellitus with varying degrees of carbohydrate metabolic compensation

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**Abstract:** Objective: to evaluate total testosterone level in men with type 2 diabetes mellitus (DM) and varying degrees of carbohydrate metabolic compensation.

Materials and Methods. The continuous cross-sectional non-interventional screening study included 100 men 45 [43; 48] years of age with newly diagnosed type 2 DM. The study continued from February through May of 2021. The level of glycated hemoglobin (HbA1c) and total blood testosterone were determined. Group comparisons were performed via Mann–Whitney U test, Kruskal–Wallis test and Fisher’s exact test. The differences were assumed statistically significant at  $p < 0.05$ .

Results. When comparing patients with different HbA1c content, we discovered that in patients with HbA1c from less than 6.5 to 9.9%, total testosterone levels as well as testosterone deficiency prevalence did not differ statistically significantly. At HbA1c  $> 12\%$ , the prevalence of testosterone deficiency increased statistically significantly ( $p < 0.001$ ), and testosterone levels decreased ( $p < 0.001$ ). Comparison of patient groups with HbA1c levels from less than 6.5 to 9.9% and from 10 to 11.9% did not yield statistically significant differences in the testosterone deficiency prevalence and testosterone content. However, there was a trend towards worse parameter values in the latter group, especially because patients with HbA1c levels from less than 6.5 to 9.9% were older.

Conclusion. Total testosterone levels in type 2 DM patients are associated with carbohydrate metabolic compensation. Negative impact on testosterone production was detected in patients with HbA1c content of  $\geq 10\%$ .

**Keywords:** hypogonadism, testosterone deficiency, diabetes mellitus.

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### Introduction

Hypogonadism remains one of the most common complications of type II diabetes mellitus (DM) [1]. In patients with type II DM, compared with healthy men, there is a reduction in testosterone levels by 2.5 nmol/L, and the prevalence of hypogonadism syndrome is higher than the population average and may occur in every other patient [2–4]. At the same time, unsatisfactory carbohydrate metabolic compensation per se is associated with a reduced level of testosterone [5, 6]. However, there are no published studies demonstrating a specific level of HbA1c, at which it is necessary to start correcting carbohydrate metabolism, and only when its target level is reached, to assess the androgenic status of a man. Lacking evidence base for identifying this level substantiates the scientific interest in this problem and, accordingly, the relevance of our study.

Objective – to assess total testosterone level in men with varying degrees of carbohydrate metabolic compensation and type II DM.

### Materials and Methods

Our research design is a continuous cross-sectional non-interventional screening study.

The inclusion criteria for the study were male gender, newly diagnosed type II DM, and patient age of 40–50 years.

The exclusion criteria were as follows. First, taking any medicines that could affect the androgenic status. Second, since age-related hypogonadism is not a separate nosological form of hypogonadism, and a gradual decline in the total testosterone level is typical for all men after 30 years of age, this type of hypogonadism was not an exclusion criterion. Finally, since obesity is an independent risk factor for reduced testosterone production, obese patients were not included in the study, but excess body weight was allowed.

The period for collecting study material lasted from February through May of 2021. The sample was formed from patients observed at the medical center; therefore, the prevalence of testosterone deficiency in the population of men with type II DM, who were not under medical supervision or had other values of carbohydrate metabolic compensation, could have been different.

The study included 100 men. The characteristics of the sample are presented in *Table 1*.

Blood sampling for the study was performed from the cubital vein in the mornings (between 7 and 11 am) strictly on an empty stomach.

The main expected outcome of the study was the establishment of the testosterone deficiency prevalence and testosterone content at different glycosylated hemoglobin (HbA1c) values.

Patient groups were compared according to HbA1c levels: <6.5% in Group 1, 6.5–7.9% in Group 2, 8–9.9% in Group 3, 10–11.9% in Group 4, ≥12% in Group 5. In addition, a comparison was made between the groups with HbA1c levels from less than 6.5 to 9.9% and from 10 to 11.9%.

An anamnesis was taken, sexological questionnaires were not used. Total testosterone levels were determined on an Architect i2000 analyzer (Abbot, USA) by chemiluminescence immunoassay on microparticles, while HbA1c content was identified on a CAPILLARYS-2 analyzer (Sebia, USA) by capillary electrophoresis. Testosterone deficiency was diagnosed when total testosterone level was under 12.1 nmol/L [1].

Statistical data processing. The sample size was calculated from an expected prevalence of hypogonadism of 30% and 95% confidence interval width of 10%. The choice of these values was based on the results of the study with a similar design albeit with a larger sample [7]. Statistical processing of collected obtained data was carried out using Statistica software package (StatSoft Inc. USA, version 8.0). Quantitative data are presented as medians and interquartile range. Comparison of groups was performed by a nonparametric method using Fisher's exact test for categorical variables, while Mann-Whitney U test and Kruskal-Wallis method were employed for quantitative variables. Differences were assumed statistically significant at  $p < 0.05$ .

## Results

Testosterone deficiency was detected in 41 men; therefore, its prevalence in the sample was 41%. The studied groups of patients were comparable in terms of their age and body mass index (*Table 2*).

Comparing patients with different levels of HbA1c, we discovered that both total testosterone levels and the prevalence of its deficiency did not differ significantly between the patients of the first three groups (*Table 3*). Herewith, a comparison of each of these groups with Group 5 yielded statistically significant differences: the level of total testosterone in Group 5 was lower, while the incidence of hypogonadism syndrome was higher in the groups 1–3. When comparing the values established in groups 4 and 5, we detected statistically significant differences in total testosterone, but not in the prevalence of hypogonadism, even though it was higher in Group 5.

When comparing the values detected in the first three groups with values in Group 4, statistically significant differences were revealed only for total testosterone, when compared with the Group 1. Thus, the results of comparisons with Group 4 turned were the most controversial. In this regard, an additional intergroup analysis was carried out

(*Table 4*). When comparing groups of patients with HbA1c levels from less than 6.5 to 9.9% (groups 1–3 combined), and from 10 to 11.9% (Group 4), no statistically significant differences were detected in the prevalence of hypogonadism and testosterone levels. However, there was a trend towards worse indicators in Group 4, especially since statistically significant differences in age were shown: the patients of the combined groups 1–3 were older than in Group 4.

Hence, our study revealed an association between severe decompensation of carbohydrate metabolism with HbA1c levels of 12% or more, along with a reduced production of total testosterone. Also, our data allow assuming the presence of a negative effect at lower levels of HbA1c (starting from 10% on).

## Discussion

Studies by foreign authors demonstrated a high prevalence of testosterone deficiency in type II DM, ranging from 15 to 50% [3, 4, 8]. In one of the few studies conducted in the Russian Federation, a higher frequency of concomitant testosterone deficiency was discovered: from 68 to 83%. Although in accordance with employed diagnostic method, participation in the study was restricted solely to inpatients with multiple comorbidities and a more severe course of DM, which could have led to higher values of this indicator [8]. Accordingly, it could be assumed that decompensation of carbohydrate metabolism had a negative effect on testosterone production, but the specific level of HbA1c was unclear [1]. To identify this level, we formed a sample of men with newly diagnosed type II DM in order to exclude the influence of disease therapy and long history of DM, when complications may develop. In addition, in order to minimize the influence of the patient age on the study results, all patients were in the same age group, rather too young for the development of type II DM. Besides, patients diagnosed with obesity were excluded. Groups did not differ in the severity of excess body weight, since both age and obesity per se affect testosterone production [10].

The results of statistical analysis indicated that the level of HbA1c up to 9.9% was not associated with a reduction in the total testosterone level, whereas its level exceeding 12% was associated with decreased testosterone. Regarding the level of HbA1c ranging 10–11.9%, our data were not unambiguous. Still, they more likely implied the presence of such association rather than the fact that statistically significant difference was achieved due to a small number of study subjects in Group 4.

## Conclusion

In men with type II DM, the prevalence of testosterone deficiency is associated with decompensated carbohydrate metabolism. A decrease in testosterone production is observed from the HbA1c level of ≥10%.

**Conflict of interest:** None declared.

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**Table 1. Sample characteristics**

Parameter	Value
Age, years	45 [43; 48]
Body mass index, kg/m <sup>2</sup>	27.3 [26.0; 28.7]
HbA1c, %	8.7 [6.9; 11.6]
Total testosterone, nmol/L	12.8 [7.8; 15.0]
Prevalence of hypogonadism	41%

Data are presented as medians and interquartile range.

**Table 2. Group comparability assessment**

Parameter	HbA1c					p*
	<6.5% (n=20)	6.5–7.9% (n=20)	8.0–9.9% (n=20)	10–11.9% (n=20)	≥12% (n=20)	
Age, years	46 [43; 48]	46 [42; 48]	46 [45; 49]	43 [42; 46]	45 [42; 48]	0.128
Body mass index, kg/m <sup>2</sup>	27.1 [26.2; 28.5]	27.6 [25.9; 28.8]	27.7 [26.2; 29.2]	27.6 [26.1; 28.4]	26.8 [25.7; 28.3]	0.735
HbA1c, %	6.1 [5.8; 6.3]	7.3 [6.9; 7.6]	8.7 [8.3; 9.2]	11.2 [10.4; 11.6]	13 [12.5; 14]	<0.001

\* Kruskal–Wallis method; data are presented as medians and interquartile range.

**Table 3. Results of intergroup analysis**

Parameter	HbA1c					Group comparisons, p									
	<6.5% (n=20)	6.5–7.9% (n=20)	8.0–9.9% (n=20)	10–11.9% (n=20)	≥12% (n=20)	1 vs. 2	1 vs. 3	1 vs. 4	1 vs. 5	2 vs. 3	2 vs. 4	2 vs. 5	3 vs. 4	3 vs. 5	4 vs. 5
Total testosterone, nmol/L *	15.0 [12.6; 19.5]	12.9 [8.7; 15.5]	13.3 [10.1; 14.6]	11.6 [8.1; 14.2]	7.2 [5.8; 8.5]	0.096	0.288	<b>0.013</b>	<b>&lt;0.001</b>	0.799	0.327	<b>0.001</b>	0.264	<b>0.001</b>	<b>0.006</b>
Prevalence of testosterone deficiency, % **	20	30	25	50	80	0.716	1.0	0.095	<b>&lt;0.001</b>	1.0	0.333	<b>0.003</b>	0.190	<b>0.001</b>	0.095

Here and in Table 4: \* Mann–Whitney U test; \*\* Fisher's exact test; data are presented as medians, interquartile range and percent.

**Table 4. Results of intergroup comparison by glycosylated hemoglobin content <10% vs. 10–11.9%**

Parameter	HbA1c		p
	From <6.5 to 9.9% (n=60)	10–11.9% (n=20)	
Age, years	46 [43; 48]	43 [42; 46]	<b>0.016</b>
Body mass index, kg/m <sup>2</sup>	27.3 [26.0; 28.7]	27.6 [26.1; 28.4]	0.951
HbA1c, %	7.3 [6.3; 8.3]	11.2 [10.4; 11.6]	<b>&lt;0.001</b>
Total testosterone, nmol/L	13.4 [11.0; 16.5]	11.6 [8.1; 14.2]	0.059
Prevalence of testosterone deficiency, %	25	50	0.051

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