Androgen deficiency in men with type 2 diabetes mellitus

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Introduction.

The issue of the impact of disturbances of functional status of gonads in men on the development of type 2 diabetes mellitus (T2DM) has been studied for a long time. However, the results obtained appear to be ambiguous. A number of studies conclude that blood levels of testosterone (T) in men with DM are within the normal range of fluctuations and do not play a pathogenetic role. At the same time, recent epidemiological studies demonstrate a high prevalence of low T levels in the blood of men with T2DM [1–4]. In most of them, symptomatic hypogonadism is diagnosed, and this is often attributed to a low level of sex-steroid-binding globulin (SSBG).

Population studies have demonstrated a relationship between diabetes mellitus and metabolic syndrome (MS) in men with androgen deficiency. Hypogonadism is diagnosed in 20 to 64% of men with T2DM, being more common among elderly men. Hypogonadism is considered to be a possible risk factor of development of T2DM and metabolic syndrome under the influence of different mechanisms: polymorphism of androgen receptors, glucose transfer, decreased antioxydant activity, etc. At the same time, T2DM and MS may represent by themselves risk factors of development of hypogonadism under the effect of such mechanisms as increased body mass, decreased level of sex-steroid-binding globulin, inhibition of gonadotropin secretion or testosterone synthesis in testes, being mediated by cytokines of inhibition of testosterone synthesis, increase in aromatase activity, and subsequent excess of estrogens [5].

Massachusetts Man Aging Study (MMAS) [6] was one of the first important studies which confirm androgen deficiency in men aged 39 to 70 years with one or several chronic diseases. In men with T2DM, levels of T, SSBG, and androgen metabolites decreased with age as in the group of men without onerous chronic diseases, but T levels in the study group were lower by 10 - 15% and developed several years earlier. Average levels of total and free T, SSBG were also significantly lower in men who further developed T2DM.

Blood concentrations of total testosterone (tT) decreased by 0.8 %, free T (fT) by 2% per year beginning from the age of 35 years. Aging of men is associated with an increase in T2DM and HG frequency. Concentrations of estrogens and cortisol did not significantly change for this age period and did not differ between the groups, and FSH, LH and PRL contents were increasing with no differences between both groups.

A follow-up to 985 men from the town of Rancho Bernando, aged 40 to 79 years, showed in 110 subjects with diabetes much lower average levels of T and SSBG in blood plasma [7]. Average levels of androstenediol, estrone, and estradiol did not differ significantly after correction taking into account the age and body mass index (BMI). Decreased T levels in blood were noted in 21% of men with T2DM and in 13% of men without diabetes. In all subjects there was an inversely proportional relationship between the T indices under study and degree of glycemia, since in the whole range of blood plasma levels of glucose a gradual decrease was reported in average T levels in the presence of an obvious increase in fasting levels of glucose in blood plasma. A similar pattern was reported both in T2DM patients and healthy subjects.

Changes in blood concentration of free testosterone are considered to be much more common compared to total T. A follow-up to 55 men with T2DM (aged 63.6$\pm$7.9 years) has shown decreased levels of total T (<3,4 ng/ml) in 20%, and low levels of free T (<11 ng/ml) in 54,5% [8]. The proportion of men with T2DM with subnormal T levels increased with age: total T 50-59 yrs: 11,2% ; 60-69 yrs: 17.4% ; >70 yrs: 36% ; and, similarly, free T: 38.0%, 69.6%, 54.5%, respectively. However, no linear correlation has been found between the levels of total and free T and fasting indices of glucose, insulin, C-peptide, fructosamine. There was a positive correlation between the level of total T and HbA1c index (r-0,322, p=0,01).

At the same time, recent studies suggest that androgen deficiency plays a certain role in the mechanisms of T2DM development. T, ЕД, and HG are associated in men with such diseases of elderly men, as DM, cardiovascular, depression, and MS. Blood levels of free and total T were decreased in 46% and 34% of patients with DM and in 24% and 23% of non-diabetics, respectively. [9]. There was a strong correlation of subnormal T levels with T2DM, but not with an increased BMI, and subnormal levels of total T with increased indices of

BMI ratio, but not with DM. Levels of free and total blood T were subnormal in 46% and 34% of men with DM and in 24% and 23% without DM.

In order to ascertain the role of HG in the pathogenesis of MS and T2DM in men, 702 middle-aged men in Finland have been followed up for a period of 11 years [10]. 11 years after, MS developed in 147 and T2DM in 57 men. Men with a marked decrease in total and free T, SSBG levels have a several-fold increased risk of MS development (by 2.3, 1.7, and 2.8 times, respectively) and T2DM (by 2.3, 1.7, and 4.3 times, respectively). A regression analysis suggests that cardiovascular diseases, smoking, alcohol consumption do not cancel these associations. The results of our studies confirmed that lower levels of total T and SSBG are independent predictors of MS and T2DM development in middle-aged men.

Other authors [1, 11] have come to similar conclusions, confirming that low levels of total T and SSBG are independent predictors of MS and T2DM development in men, and hypoandrogenism is an early marker of disturbances of insulin and glucose metabolism, contributing to MS and T2DM pathogenesis. A low blood level of total T in men correlates with mortality from cardiovascular diseases [1]. Dihydrotestosterone (DHT) and dihydroepiandrosterone-C (DHEA-C**)** levels were also decreased. A correlation analysis suggested that hormonal disturbances were not due to obesity, alcohol abuse, and smoking. There was a positive correlation of total T level, but not free T with and a negative correlation with triglyceride (TG) levels. A similar association was also noted in men without DM. A low level of endogenous androgens is considered to occur in aged men with DM, and they appear to correlate with a diabetic dyslipidemia.

Tsai E.C. et al. have carried out a glucose tolerance test (GTT) (75.0 glucose per os) to 110 men and assessed BMI, visceral obesity (intraabdominal adipose zone using CT), tested insulin, C-peptide, total T levels. The level of T significantly correlated with changes in intraabdominal adipose zone, but not with changes in the common zone of subcutaneous adipose tissue, BMI, common fat. Using the model of linear regression, a significant correlation has been shown between the changes in intraabdominal adipose zone and basal T level [12]. Thus, a decrease in total T level is an independent predictor of an increase in intraabdominal adipose zone, and this provides for a rise in visceral obesity. Low T levels may increase the risk of T2DM.

However, a follow-up to 990 men with **ED** (of these, 229 had DM) has shown that HG frequency in T2DM did not differ significantly from the general population [13].

Aim of the work: analyze the functional status of hypophyseal-gonadal system in men with type 2 diabetes mellitus in order to assess their androgen status.

Material and methods of study

To assess the androgen status of patients, the functional status of hypophyseal-gonadal system has been assessed. 147 men aged from 35 to 65 years with type 2 diabetes mellitus and 82 virtually healthy men who constituted the control group, have received follow-up. Using an immunoenzymic method, blood concentrations of the following hormones were tested: follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (tT), free testosterone (fT), bioavailable testosterone (bT), estradiol (E_2), prolactin (PRL), dihydroepiandrosterone-sulphate (DHEA-s), and sex-steroid-binding globulin (SSBG). Fasting blood collection was performed from 08 to 10 hours a.m. According to tT levels in study patients, we considered hormone concentrations below 8.0 nmol/L to be a sign of total hypogonadism, 8.0 to 12.0 nmol/L a sign of partial androgen deficiency. All surveyed men had a general clinical examination with anthropometry measurements and body mass index (BMI) assessment. An excess of BMI > 30 kg/m^2 was considered a criterion of obesity. The stage of compensation and severity of T2DM was determined at examination by the endocrinologist.

Results and discussion

The average blood level of tT in study patients was significantly decreased (Table1). Marked fluctuations of hormone concentrations from 2.3 nmol/L to 29.9 nmol/L were noted. An analysis of individual indices in certain patients showed a decreased hormone level (less than 11.7 nmol/L) in 64 out of 147 surveyed men with T2DM, which represents 43.5 % of patients. It has been established that in 28 patients with T2DM (19.0%) tT level was below 8.0 nmol/L, and in 50 men (34.0%) was within the range 8.0 to 12.0 nmol/L. That is, one fifth of men with type 2 diabetes mellitus showed a clinical pattern of

total hypogonadism, and in one third a partial androgen deficiency. Overall, the percentage of such patients constituted 53.0% of study patients. However, it should be stressed that the lower limit of tT level range in blood plasma of healthy men in our study was 11.7 nmol/L, i.e. less than 12.0 nmol/L.

Blood concentrations of free testosterone were determined in 88 men with T2DM. The average level of hormone in patients was significantly decreased (Table1). At the same time, an analysis of individual indices in men with T2DM showed a considerable polymorphism of fT values in blood: from 8.1 to 78.3 pmol/L. Blood concentration of fT was below the lower limit of normal hormone range in healthy men in 52 out of 88 study subjects, which made up 59.1%. Thus, we may see that at testing free testosterone the frequency of laboratory hypogonadism in men with type 2 diabetes mellitus is higher than at testing total T concentrations in blood.

Testosterone is known to circulate in blood as three main fractions: free T - 2-3%; fT bound with albumin - 20-40%; fT strongly bound with SSBG - 60-80 % (G.Hackett, 2009). Free testosterone and albumin-bound T belong to a biologically active fragment, constitute bioavailable T. Blood concentrations of bioavailable testosterone in men with T2DM have been tested in 33 patients with T2DM. The average level of bT in men with T2DM was significantly decreased (Table1) as well. Moreover, this index was below the lower limit of fluctuations in 23 out of 33 surveyed men, which made up 69.6%. Thus, testing of blood testosterone concentration in men with T2DM allowed to establish decreased average levels of total, free, and bioavailable testosterone, which suggests development of androgen deficiency. The index of bioavailable testosterone appears to be the most informative one, being decreased in two thirds of surveyed patients, while total T level was decreased in 43.5 % of men with T2DM.

SSBG concentration was tested in 76 men with T2DM. Its average level was significantly decreased (Table 1). Fluctuations of blood levels of SSBG in healthy men were within the range 26.4 to 60.8 nmol/L. An analysis of individual indices in surveyed patients showed decreased levels of SSBG in 36, normal levels in 38 (being within the lower limit in 16 men), and increased levels in 2 patients. The data obtained suggested that in type 2 diabetes mellitus SSBG blood levels were decreased or within the lower limit of normal range in two thirds of study patients.

Indices of total T levels in blood were analyzed depending on the compensation status of metabolic disturbances, and only in patients with a diabetes duration up to 5 years (39 patients). Patients with decompensation of diabetes had a significantly decreased average hormone level, and in patients with compensation it did not differ from the index for healthy men (Table 2). At the same time, there was no significant difference between both indices, which may be due to important fluctuations of tT concentrations and a small number of observations in the group of patients with compensation of T2DM. The average tT level was significantly increased in men with severe form and middle severity form of T2DM (Table 2), being somewhat lower in patients with severe form of DM, though insignificantly.

In men with T2DM, decreased blood levels of tT were noted both in case of stable and labile course of diabetes. There were no significant differences between average T levels in blood depending on the course of DM. Blood tT concentrations have been analyzed in men with T2DM depending on diabetes duration, since diabetes duration and blood levels of testosterone are considered to correlate with one another [18]. The results obtained showed decreased average tT levels in all groups of patients (Table 3).

According to literature, abdominal obesity represents an important risk factor of androgen deficiency development [5, 19]. We have conducted an analysis of blood levels of tT in patients with T2DM depending on the presence of obesity. Average levels of blood plasma testosterone in patients of both groups were decreased compared to control group (Table 4). Lower hormone levels were noted in patients of group 1 (with T2DM and obesity); however, there was no significant difference between the average levels in both groups.

Dihydrotestosterone (DHT) is a hormone derived from testosterone convertation, mainly in peripheral “target” reproductive organs, and has a higher biological activity.

Average blood levels of DHT were decreased in men with T2DM (Table 1). Average values of DHT in blood were significantly decreased in patients with T2DM irrespective of diabetes severity and compensation of metabolic disturbances of diabetes (Table 2), DM course, and diabetes duration (Table 3). It should be stressed that in men with a diabetes duration above 5 years DHT blood concentrations were lower than in the group of patients with a diabetes

duration up to 5 years, the difference being insignificant - perhaps due to a small number of surveyed subjects.

Thus, a study of dihydrotestosterone blood concentrations in patients with T2DM suggested decreased DHT levels irrespective of DM type, severity, compensation of metabolic disturbances, diabetes course and duration.

In order to assess the functional status of central link of regulation of the status of reproductive system in T2DM patients, basal blood levels of lutropin were tested.

There were no significant difference between average blood concentration of LH and the same index in T2DM patients (Table 1). An analysis of individual indices of LH content suggested that normal indices of the hormone were reported in 69, decreased ones in 26, and increased indices in 19 patients with T2DM. It should be stressed that in the group with normal LH blood content 27 patients had hormone's levels within the lower limit of normal range. That is, blood levels of LH were decreased or within the lower limit of normal range in nearly the half of surveyed patients. An analysis of LH blood levels depending on the severity of diabetes suggested that average hormone levels did not differ significantly from the same index in the control group and in patients with a moderate degree of DM severity, and between one another (Table 2) as well. Compensation status of metabolic disturbances of DM had no considerable effect on LH blood indices in T2DM patients (Table 2) either. Interestingly, average LH blood indices were somewhat higher at decompensation stage compared to compensation stage in different types of DM, though with an insignificant difference.

Average blood concentration of LH was significantly increased in men with a T2DM duration less than 5 years and did not differ significantly from the same index in the control group of men with a duration of diabetes more than 5 years (Table 3).

We have determined the indices of T/LH ratio which suggests to some extent the status of realization of endogenous lutropin effect on the hormonal testicular function. T/LH ratio was shown to be significantly decreased in men with T2DM (Table 5). An analysis of individual indices of T/LH ratio showed a decreased index in 27, a normal one in 18, and an increased index in men with T2DM. The results obtained suggest a combined lesion of central and peripheral links of hypothalamo-hypophyseal-gonadal [HHG] system and a decrease in its

functional activity in part of study patients, which is evidenced by decreased average concentrations of testosterone and absence of any response to this decrease from LH and FSH.

Aging in men is associated with a rise in T2DM and hypogonadal state frequency. The study “Baltimore Longitudinal Study of Aging” has established that total T level is gradually decreasing beginning from the age of 30, and the frequency of hypogonadism increases from 12% in men aged 50 years to 19%, 28%, and 49% in men aged 60, 70, and 80 years, respectively [14]. When using free testosterone index (FTI), the above percentage correlations were even higher (34, 64, and 91%, respectively). SSBG levels are increasing with years.

Moreover, there are data suggesting that 85% of healthy elderly men have a level of total T below the normal levels, which may be estimated as bordering on hypogonadism [15]. These changes were even more notable when testing the indices of free and bioavailable testosterone [16], since the content of bioavailable T begins to decrease earlier than that of total T. That is why disturbances of steroid hormone balance in elderly subjects may be considered one of the main risk factors of development of a number of chronic diseases.

Epidemiological studies demonstrate a higher prevalence of low blood levels of T in men with T2DM [17, 18], and also a significantly higher probability of development of hypogonadism, which emphasizes its clinical significance [19]. However, the results of a study of HG frequency in men with T2DM appeared to be ambiguous. Different studies have established that from 20% to 64% of men with T2DM had hypogonadism [7, 8, 9]. A follow-up to 355 men in Barnsley (Sheffield) where DM frequency constitutes 6%, showed that 52% of men with DM aged about 70 years have a level of T $\leq$ 12 nmol/L and symptoms of HG. In 17.8% of men with T2DM the level of total T was under 8.0 nmol/L, and in 42.5 % below 12.0 nmol/L; bioavailable T in 40.37% was below 2.5 nmol/L, and in 43.6 % under 4.0 nmol/L [20]. Primary HG was diagnosed in 26 %, and secondary HG in 10 % of surveyed men. LH and FSH levels in most subjects with mixed HG were normal [21]. There was an age-related dependence: the percentage of men with decreased blood levels of T increased with age, the number of subjects with decreased level of free T increasing to a greater extent. A similar relationship was noted between BMI indices and blood levels of total T: the highest indices of BMI were reported in

men with diabetes and levels of T below 8 nmol/L. Similar results were obtained by other authors [2, 9, 22, 23, 24].

Thus, based on most of publications, metabolic disturbances in DM seem to have a notable impact on the hypothalamo-hypophyseal-gonadal system whose functional status changes during a long period of the disease. The most notable changes occur in patients with poor glycemic control, however disease duration and presence of chronic complications are essential as well. At the same time, adult and elderly patients with T2DM show, already at detection of the disease, a decreased T level in blood. A follow-up to 1419 men aged 25 to 84 years has established a negative correlation of Hba1c with levels of total T and SSBG, and a positive correlation with BMI and WS (Svartberg et al., 2004). A multiple regression analysis has shown that levels of total T and SSBG, the number of cigarettes, BMI, and independently correlated with HbA1c. Men with a history of DM had lower levels of total T and SSBG. The authors conclude that lower blood levels of total T and SSBG are associated with increased levels of HbA1c and DM irrespective of the degree of obesity and distribution of adipose tissue. However, according to literature (Corona J., et al. 2007), at examination of men with erectile dysfunction HG have been detected in 41% of those with MS and T2DM, and in 29% of those with MS without T2DM according to tT level, and 77.1% and 58% according to fT level [3].

Visceral obesity is a component of MS, and is also common for T2DM, and represents the main independent risk factor of development of coronary vessel diseases, and is also associated with IR that is a predictor of T2DM development [8]. Recent literature reviews suggest that hypogonadism is associated with obesity and increases the risk of cardiovascular diseases [25]. Certain researchers affirm that a lower level of total T in blood predicts the development of central obesity and accumulation of intraabdominal fat [26]. In men with DM blood T levels are decreasing proportionally to obesity degree, and leptin that is produced by adipose tissue inhibits T secretion and represents a causal factor of LOH in men with obesity, being the best predictor of T deficiency in ageing men [27].

In our study the average blood level of T in patients with T2DM was decreased in patients with diabetes and obesity and in patients with diabetes without obesity. Lower levels of hormone were reported in patients with obesity, though no significant difference between average levels in both groups was

noted. Lower T levels were found in men with DM without obesity compared to control group [**were]** reported in the work of Selvin E. et al., 2007 [28]. Therefore, it may be assumed that not only obesity plays a determining role in the subsequent development of disturbances of carbohydrate metabolism. At the same time, a number of authors assume that adipose mass and insulin resistance (IR) are associated with primary hypogonadism, and that just adipose mass, leptin, and possibly adipokines have a predominant effect. Lower T levels may have independently an effect on IR through increasing the adipose mass and decreasing muscular mass [29]. The hypothesis "Hypogonadal-Obesity-Adipocytokine Cycle" determines the stimulatory effect of obesity on T metabolism and weakened capacity of hypothalamo-hypophyseal-gonadal system [30]. SSBG levels inversely correlate with obesity and, therefore, the velocity of decrease in total T levels is considered to be higher in men with obesity compared with lean men, because of a lower velocity of SSBG rise [18, 22, 26, 27, 28]. Obesity and SSBG represent important injury factors in interelatioships between T and T2DM. However, the predictor role of free T in T2DM development has not been confirmed by long-term studies, and there was no significant association between total T + SSBG and diabetes after correction of central obesity indices [31], though a lower SSBG was confirmed to be a strict independent predictor of T2DM [32]. When discussing the role of obesity in sequence of events which eventually lead to the development of IR and vascular endothelial dysfunction that represent potential causal factors of CVD and ED, we recalled the hypothesis of "Hypogonadal-Obesity-Adipocytokine Cycle": an interaction between a lower T and visceral obesity, which acts through proinflammatory agents, determines the stimulatory effect of obesity on T metabolism and the weakened capacity of hypothalamo-hypophyseal-gonadal system [30]. In this context, we can assume the presence of combined effects of T deficiency and visceral obesity.

The question remains open whether HG y men with T2DM develops as a consequence or as a pathogenetic factor? The results of a number of works strongly suggest the predictory role of low blood levels of T and SSBG in T2DM development [33]. HIM Study (Hypogonadism and Metabolic Syndrome Study) has established that HG relationship with T2DM made up 50% (range 45.5-54.5); chances being equal to 2.09 [34]. In men with DM blood T levels are decreasing proportionally to the degree of obesity, and leptin that is produced by

adipose tissue inhibits T secretion and represents a causal factor of LOH in men with obesity, being the best predictor of T deficiency in ageing men [35]. At the same time, our data and the results of a great number of works suggest a notable influence of metabolic disturbances and chronic complications of diabetes on the hypothalamo-hypophyseal-gonadal system. These data allow to assume that a lower testosterone blood level is a predictor of T2DM development in men; however, after manifestation of diabetes symptoms, over time, it occurs a further decrease in blood concentrations of T and a worsening of HG symptoms.

Андрогендефицитное состояние у мужчин, больных сахарным диабетом 2-го типа

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Резюме.

Ряд исследований отрицает взаимосвязь СД 2 типа с уровнем тестостерона в крови у мужчин, в то время как другие авторы указывают на наличие абсолютного или относительного андрогенодефицита у мужчин с СД 2 типу. Обследовано 147 мужчин в возрасте от 35 до 65 лет с сахарным диабетом 2 типа и 82 практически здоровых мужчины, которые составили контрольную группу. Установлено снижение среднего уровня общего тестостерона в крови у 53,0% пациентов: у 1/5 мужчин, больных, сахарным диабетом 2 типа отмечался абсолютній гипогонадизм, а у 1/3 – относительній андрогенодефицит. Концентрация тестостерона в крови была ниже от показателя нижней границі нормальных колебаний гормона в 59,1% случаев. Остается открытым вопрос - андрогенодефицит у мужчин с СД 2 типа является следствием или патогенетитическим фактором?

Ключевые слова: *гипогонадизм, сахарный диабет 2 типа, возраст, тестостерон, мужчина*.

Androgendefisiensy in males with type 2 diabetes mellitus

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Resume

Some of researches denie interlinks between type 2 diabetes (T2DM) and low testosterone levels in men, while other authors specify the presence of absolute or relative androgendefisiency in males with T2DM. 147 men were obserwed in age from 35 to 65 years with T2DM and 82 practically healthy men which made a control group. The decline of middle level of general testosterone was set r 53,0% patients: for 1/5 men, patients with T2DM absolute hypogonadysm was marked, and at 1/3 it was ralative androgendefisiency/ The concentration of testosteron in blood was below from the index of lower limit of normal hormone levels in 59,1% cases. It is a question: androgenodeficiensy for men with T2DM is a complication or pathogenic factor?

Key words: *hypogonadism, type 2 diabetes mellitus, age, testosterone, man.*

Table 1. Pituitary and sex hormones in T2DM male patients

		Показник							
		T com	T free	T bioavai.	LHH	**FSH**	SSBH	**PRL**	**DEAS-s**
		nmol/l	pmol/l	nmol/l	IU/l	IU/l	nmol/l	IU/l	nmol/l
T2DM	M	11,9	20,8	7,7	4,5	4,4	36,3	342	11,6
	m	0,5	1,6	0,7	0,3	0,9	1,3	33,6	1,4
	n	147	88	33	114	57	76	30	28
	p	<0,001	<0,001	<0,001	>0,5	>0,5	<0,01	0,1<0,05	<0,001
Controlles	M	20,1	45,7	13,4	4,2	4,4	43,1	254,4	19,1
	m	0,8	2,7	1,1	0,3	0,6	2,3	27,6	1,8
	n	82	33	15	55	24	40	16	10

Table 2. Pituitary-sex hormones concrentration in males with T2DM depended on sevetetydiabetes

		Концентрація гормонів							
		T total nmol/l	**E_2** nmol/l	LH IU/l	**FSH IU/L**	**PRL IU/L**	DHT nmol/l	**SSBH** nmol/l	DHEA-s Mkmol/l
T2DM decompensation	M m n P	11,3 1,2 30 <0,001	0,18 0,02 22 >0,2	4,9 0,8 24 <0,02	5,8 1,1 9 >0,2	178,9 21,517 >0,2	2,1 0,3 15 <0,02	57,6 4,4 19 >0,1	3,7 0,4 17 <0,05
T2DN compensation	M m n P P_1	15,0 3,6 9 >0,5 >0,2	0,15 0,02 7 >0,5 >0,5	5,1 1,5 8 >0,5 >0,5	8,2 1,8 3 0,05<0,1 >0,2	236,2 22,65 >0,2 >0,2	1,9 0,7 4 <0,05 >0,5	78,7 12,06 <0,05 >0,5	2,1 1,8 3 0,05<0,1 >0,2
T2DM middle severity	M m	12,6 1,6	0,21 0,03	5,1 1,3	4,7 1,2	229,9	2,2 0,4	65,1 5,5	3,4 0,6

	n P	22 <0,01	14 >0,5	16 >0,2	7 >0,2	32,9 12 >0,5	12 <0,01	14 <0,0 2	12 <0,05
T2DM strong severity	M m n P P_1	10,8 1,8 21 <0,00 1 >0,2	0,23 0,02 16 <0,0 2 >0,2	4,0 0,6 17 >0,5 >0,2	6,2 0,9 9 >0,1 >0,2	198, 6 22,9 14 >0,5 >0,2	1,5 0,3 9 <0,01 >0,1	57,3 5,3 14 >0,1 >0,5	3,4 0,6 12 <0,05 >0,2
Controlles	M m n	19,7 1,4 24	0,15 0,02 11	4,2 0,3 55	4,5 0,6 10	207, 3 33,4 10	4,5 0,8 10	45,3 5,7 10	6,6 1,2 10

Table 3. Pituitary-sex hormones depends on term of T2DM

		Концентрація гормонів						
		T total nmol/l	**E_2** nmol/l	LH IU/l	**FSH** **IU/L**	**PRL** **IU/L**	DHT nmol/l	**SSBH** nmol/l
T2DM<years	M m n P	13,1 1,3 34 <0,01	0,15 0,02 14 >0,5	5,8 0,5 11 <0,05	3,2 1,5 6 >0,2	137,4 32,2 11 >0,1	2,1 0,4 10 <0,02	74,7 14,7 12 0,05<0,
T2DM>years	M m n P_1 P	10,4 1,2 46 <0,001 >0,2	0,2 0,02 16 0,05< 0,1 >0,2	4,9 0,8 22 >0,2 >0,2	5,3 1,0 10 >0,2 >0,2	235,8 24,2 15 >0,2 <0,05	1,8 0,4 11 <0,01 >0,5	52,6 5,6 16 >0,2 >0,1
Controlles	M m n	20,1 0,8 82	0,15 0,02 11	4,2 0,5 21	4,5 0,6 10	207,3 33,4 10	4,5 0,8 10	45,3 5,7 11

Table 4. Pituitary and sex hormones concentration in depend of obesity

Концентрація гормонів гіпофізу та

		T tot	T free	**E_2**	LH	FSH	SSBH	**PRL**	DHEA -s
		nmol/l	pmol/l	pmol	nmol/l	IU/l	nmol/l	**IU/l**	nmol/l

				/l					
T2DM witt obesity	M	11,6	17,3	0,18	4,28	4,15	40,6	342	7,6
	m	0,52	2,1	0,03	0,62	0,56	4,8	33,6	1,4
	n	38	38	22	30	30	30	30	16
	p	<0,001	<0,001	>0,2	>0,5	>0,5	>0,2	0,1<0,05	<0,001
T2DM without obesity	M	12,18	23,5	0,12	4,05	3,12	38,1	339	6,8
	m	0,9	2,4	0,03	0,49	1,3	9,7	42,5	1,3
	n	18	18	13	13	11	13	11	13
	p	<0,001	<0,001	>0,2	>0,5	>0,2	>0,5	>0,1	<0,001
Controlles	M	20,1	45,7	0,14	4,2	4,4	43,1	254,4	19,1
	m	0,8	2,7	0,02	0,3	0,6	2,3	27,6	1,8
	n	82	33	28	55	24	40	16	10

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