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Hormone Replacement Therapy in Patients with Type 2 Diabetes Mellitus and Androgen Deficiency in the Aging Male

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Abstract

The aim of the study was to investigate the influence of lifestyle changes and the use of testosterone undecanoate and mixtures of testosterone esters on the course of diabetes mellitus, erectile function, and blood lipid profile in aging male diabetic patients during the treatment of androgen deficiency. Every six weeks, two injections of testosterone undecanoate 1,000 mg were administered intramuscularly to 32 T2DM patients suffering from androgen deficiency in the aging male, then the procedure was repeated every three months. Testosterone esters preparation was used in 47 patients with androgen deficiency in the aging male in the dose of 250 mg every 21 days. We used the International Index of Erectile Function score in order to assess erectile function. The levels of total testosterone and sex hormone-binding globulin were determined by radioimmunoassay. The level of free testosterone was assessed by an electronic calculator-converter. The results showed that during the treatment by testosterone undecanoate in most cases the blood level of testosterone remained stable, and insulin sensitivity increased. This created an opportunity for full or partial normalization of metabolic processes, and led to the creation of long-term compensation of diabetes mellitus. During the treatment by testosterone preparations, there were no considerable changes in the volume of enlarged prostate. Thus, changes in the lifestyle and adequate administration of androgens against this background, particularly testosterone undecanoate preparation (depot testosterone formulation), were accompanied by complete or partial normalization of erectile function and blood lipid profile, increased exercise tolerance, decreased depression, and improved cognitive function.

Keywords

Type 2 diabetes mellitus; Androgen deficiency in the aging male; Hormone replacement therapy; Erectile dysfunction

Introduction

Androgen deficiency in the aging male (ADAM) or adult hypogonadism develops in men after normal completion of puberty and the formation of secondary sexual characteristics [1]. A decrease in blood testosterone levels of patients with type 2 diabetes mellitus (T2DM) does not develop after 30 yrs but at the earlier age [2]. In 50% of T2DM patients, there are signs of ADAM and erectile dysfunction (ED). ADAM, along with the ED, is accompanied by abdominal obesity, depression, dyslipidemia, increase in the rate of heart disease and other metabolic disorders [3,4]. In this regard, the treatment of ADAM includes hormone replacement therapy (HRT) with androgens. Recent studies show that high levels of testosterone stimulate the ability of insulin to utilize glucose and reduce the risk of metabolic syndrome development [5]. Changing the lifestyle by T2DM patients and the use of adequate doses of testosterone in ADAM patients are accompanied by an improvement in metabolic parameters including erectile function. In order to perform HRT with androgens, there are several forms of testosterone. Testosterone undecanoate which is the last generation testosterone differs from the previous preparations by its advantages [6]. In addition to the above, we found it useful to study the influence of lifestyle changes and the use of testosterone undecanoate against this background as well as mixtures of testosterone esters on the course of diabetes mellitus, erectile function, and blood lipid profile in T2DM patients on the treatment of ADAM.

Materials and Methods

Nonrandomized controlled study included 79 T2DM male subjects living in the Sheki-Zagatal'sky and Balakan-Gabalinsky regions of Azerbaijan with diagnosis of ADAM confirmed both clinically and in a laboratory. The study was conducted in 2008-2014. During the

study, we have used individual medical records of the World Health Organization (WHO) used in clinical studies. We used International Index of Erectile Function (IIEF) score in order to assess erectile function. 22-25 points by IIEF score referred as normal erectile function, 17-21 points referred as a mild ED, 8-11 points as moderate ED, and 5-7 points as severe ED [7]. Given the fact that depression is a risk factor in the development of ED in patients according to the stationary Anxiety and Depression Scale (The Hospital Anxiety and Depression Scale (HADS), we ruled out the presence of depression [8]. For the diagnosis of ED, we performed routine (history, general examination, common blood count, and biochemical analysis of blood and urine), and special procedures (rectal manual examination and color Doppler ultrasonography of the prostate, evaluation of prostate specific antigen (PSA), densitometry). We have measured anthropometric indicators: waist circumference (cm), height (cm), weight (kg), and assessed body mass index (BMI). Glycohemoglobin concentration was determined by Nycocard Reader II apparatus. Normal HbA_{1c} level referred as <6.5%. We also estimated blood glucose level in order to assess the glycemic profile during the whole day: fasting, 2 h after meal, after dinner and supper, and at the bedtime. To examine an androgen status, we used international standard questionnaire "Symptoms in adult men" (AMS – Aging Males Symptoms). According to this questionnaire, we evaluated 17 answers by a 5-point scale [9]. The state

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of androgen deficiency or hypogonadism was evaluated against the following criteria: clinical signs of hypogonadism, total testosterone level <12 nmol/l or free testosterone level <0.225 nmol/l, 37 points by AMS questionnaire. In order to determine the level of testosterone in the blood, we collected venous blood samples at least two times in the morning from 7 a.m. to 10 a.m. with a break of 30 min. The levels of total testosterone and sex hormone binding globulin (SHBG) were determined by radioimmunoassay analyzer Strategy Electronic SR 300 (Germany) using "Berkman Coulter" reagents (USA). Free testosterone level was assessed by an electronic calculator-converter.

Statistical analysis

The obtained quantitative indicators are arranged in a variation row. We calculated the mean value (M), standard deviations (σ), and standard error of the mean ($\pm m$). We defined asymmetry and excess indicators as well as representative errors to test for normality of the distribution. Asymmetry and excess indicators did not exceed their representative error by more than two times. From these considerations, we accepted the hypothesis of normal distribution of variation rows and used Student's *t*-test for quantitative analysis. For qualitative data, we determined the frequency of sampling factors (P%) and calculated their standard errors ($\pm mp\%$). Statistical significance of qualitative data differences was determined by Pearson χ^2 criterion.

Results and Discussion

Age of patients – 79 T2DM men residing in Sheki-Zagatala, Balakan-Gabalala regions of Azerbaijan, in whom the diagnosis of ADAM was confirmed both clinically and laboratory based at the age from 30 to 60 yrs (51.7 \pm 8.5 yrs). A history of diabetes mellitus ranged from 6 months to 30 yrs (17.4 \pm 7.5 yrs). Patients were divided into two groups: 47 subjects were included in group 1 and 32 subjects in group 2.

We made the first injection of Nebido ("Bayer health Care Pharmaceuticals") which is an oil depot of testosterone undecanoate at the dose of 1,000 mg intramuscularly to 32 patients with type 2 diabetes mellitus with ADAM symptom. Six weeks later we performed the second injection, then the procedure was repeated every three months. Omnadren preparation, being a mixture of testosterone esters, was used in 47 patients suffering from ADAM symptom in the dose of 250 mg every 21 days.

Patients were excluded from the study according to the following criteria: prostate cancer, breast carcinoma, polycythemia (hematocrit >50%), intravesical obstruction on the background of benign prostatic hypertrophy (IPSS >19), PSA >3 ng/ml, patients with grade 3-4 heart failure as well as men that did not need any reproductive activity.

As a result of lifestyle changes and instruction in the "School of diabetes," subjects of both groups demonstrated positive dynamics and effective changes. Changing of lifestyles in group I led to a decrease in BMI by 12.8%, changes in lifestyles in group II, along with testosterone treatment, led to a decrease in BMI by 18.3%; waist circumference decreased in group I by 4.6% and in group II by 10.2%; HbA_{1c} in group I decreased by 15.1% and in group II by 16% indicating a positive trend. Changing lifestyles in subjects of group I led to lower levels of total cholesterol by 17.9%. Changing of lifestyles along with the HRT by androgens contributed to the reduction of the total cholesterol level by 24.6%. Although triglyceride levels before the study in group I was 2.5 \pm 0.5 nmol/l, we observed its reduction down to 2.1 \pm 0.2 nmol/l (16%). Due to changes in a lifestyle as a result of co-administration of HRT with testosterone and lifestyle changes, triglycerides level in subjects of group II decreased down to 34.5%. Along with improvement of blood lipid profile total testosterone level in subjects of group I increased from 9.8 \pm 0.6 nmol/l to 12.6 \pm 0.9 nmol/l; in group II this parameter also increased from 10.07 \pm 0.7 nmol/l to 18.7 \pm 1.5 nmol/l. SHBG level decreased in both groups. Also in both groups we noted a positive dynamics of erectile function. In subjects of group I IIEF score at the baseline was 9.2 \pm 0.6 points, 12 months after changing the lifestyle this indicator increased to 15.1 \pm 0.9 points; in subjects of group II at the baseline the score was 9.4 \pm 0.8 points, 12 months after changing the lifestyle along with the treatment by testosterone undecanoate IIEF index increased up to 19.1 \pm 1.7 points. Hence, changing the lifestyle as well as an adequate therapy by testosterone undecanoate led to positive changes in the form of transition of severe ED form to the mild. Changing the lifestyle reduced the level of AMS parameters in group I from 39.1 \pm 1.2 points to 35.0 \pm 1.5 points. In group II on the same background the use of adequate doses of testosterone undecanoate AMS indicators decreased from 40.08 \pm 1.4 points to 23.3 \pm 1.1 points. There was a marked statistical significance with indicators at the baseline (Table 1).

The study conducted showed the presence of an inverse relationship between the levels of both free and total testosterone levels and ADAM symptoms (AMS indicators). In the course of the conducted treatment

Parameter	Group I (n = 47)		Group II (n = 32)	
	Changing lifestyles		Changing lifestyles + testosterone	
	Before study	After 12 months	Before study	After 12 months
BMI (kg/m ²)	32.7 \pm 0.47	28.5 \pm 0.46***	33.4 \pm 0.5	27.3 \pm 0.41***
Waist circumference (cm)	106.3 \pm 1.44	101.4 \pm 1.12**	108.3 \pm 1.5	96.8 \pm 1.1***
HbA _{1c} (%)	7.9 \pm 1.3	6.71 \pm 1.1	7.5 \pm 1.2	6.3 \pm 0.8
Total cholesterol (nmol/l)	6.7 \pm 0.5	5.5 \pm 0.7	6.9 \pm 0.4	5.2 \pm 0.5***
Triglycerides (mmol/l)	2.5 \pm 0.15	2.1 \pm 0.2	2.9 \pm 0.2	1.9 \pm 0.1***
Total testosterone (nmol/l)	9.8 \pm 0.6	12.6 \pm 0.9*	10.0 \pm 0.7	18.7 \pm 1.5***
Free testosterone (nmol/l)	0.19 \pm 0.02	0.21 \pm 0.01	0.21 \pm 0.02	0.35 \pm 0.03***
SHBG (nmol/l)	55.7 \pm 3.9	47.8 \pm 3.7	57.4 \pm 4.4	32.9 \pm 3.2 ***
PSA(nmol/L)	2.37 \pm 0.13	2.6 \pm 0.12	2.05 \pm 0.12	2.75 \pm 0.13 ***
IIEF (points)	9.2 \pm 0.6	15.1 \pm 0.9***	9.41 \pm 0.8	19.1 \pm 0.7***
AMS (points)	39.1 \pm 1.2	35.0 \pm 1.5*	40.1 \pm 1.4	23.3 \pm 1.1***

Note: Statistically significant difference before the study: **P* < 0.05; ***P* < 0.01; ****P* < 0.001.

Table 1: Lifestyle changes in patients with diabetes and effectiveness of HRT with testosterone

with testosterone the increased PSA levels above the normal range were observed only in one case, and in this patient the treatment was terminated.

In 17 (36.1%) out of 47 men with hypogonadism and T2DM treated by a mixture of testosterone esters (Omnadren) there was an improvement of erectile function. The reduction of ADAM symptoms was determined with the help of AMS-map (Table 2). During the first week of injections of a mixture of testosterone esters these patients had positive changes, both regarding erectile function, and optimization of the libido. In the period of 7-10 days after the injection until the next injection there was poor libido and poor erectile function or its complete absence, as well as cases of depression. In patients of groups I subsequently after Omnadren injection, i.e., during the first week there was nocturnal and day tumescence, during the weeks 2 and 3 there was neither libido nor nocturnal tumescence. This once again proves the fact that the concentration of a mixture of testosterone esters in the blood is accompanied by abrupt changes adversely affecting the psycho-emotional sphere.

Nebido, being the last depot preparation of testosterone undecanoate, had a positive effect on erectile function in 19 (59.4%) of 32 hypogonadal men with diabetes.

After 12 weeks of treatment the level of total testosterone increased up to 18.1 ± 2.1 nmol/l and the free testosterone up to 0.39 ± 0.4 nmol/l. This increase was accompanied by an improvement of libido and erectile function IIEF scores up to 21.5 ± 1.0 points and a decrease in AMS indicators from 34.0 ± 1.5 points to 23.3 ± 1.1 points. No dramatic changes in the level of total and free testosterone were observed during administration of testosterone undecanoate (Nebido) within 2 to 12 weeks, and up to 12 months. On the contrary, taking Nebido helped to stabilize the level of testosterone in almost all patients. During the treatment nocturnal and morning tumescence and libido remained stable, and in some cases there were cases of depression due to family and living conditions.

In patients receiving treatment with testosterone, there was a reduction or absence of angina attacks, increased exercise tolerance. On the ECG, there was a decrease in the period of ST segment depression by 1 mm. When analyzing the results of HRT with 2 testosterone preparations by the questionnaire, we revealed that among 47 patients treated with the drug Omnadren the results of the treatment were evaluated as good in 15 (31.9%) subjects, as satisfactory in 6 (12.8%) subjects, and as unsatisfactory in 26 (55.3%) subjects; from the 32 patients treated with Nebido the results of treatment were evaluated as good in 19 (59.4%) patients, satisfactory in 8 (25%) patients and unsatisfactory in 5 (15.6%) patients (Table 3).

There is a sufficient evidence base indicating Nebido formulation advantages as compared to other testosterone preparations. Our results are consistent with the results obtained by Dedov *et al.* [10]. There were only the results of Nebido treatment in their study. Performing a comparative description of the treatment of both testosterone preparations (Omnadren and Nebido), we attempted to evaluate their effectiveness. In the treatment of Nebido in most cases the level of testosterone in blood remained stable, while insulin sensitivity was increased. This created an opportunity for full or partial normalization of metabolic processes, and led to the creation of long-term compensation of diabetes mellitus [11]. Despite the fact that during the treatment of several patients by both drugs, there was an increase in the testosterone level from 10% to 15%, PSA – from 9% to 10%, the results were not clinically significant.

There were no considerable changes in the size of enlarged prostate gland during the treatment with both testosterone preparations. Although there were cases of spermatogenesis depression, patients enrolled in the study did not pay attention to this adverse event.

Wang *et al.* noted that younger men suffering from type 2 diabetes mellitus and ADAM, having the regular sex life, prefer treatment with testosterone preparations. However, middle-aged and elderly men favored treatment by PDE-5 inhibitors during the treatment of

Parameter	Omnadren (n = 47)			Nebido (n = 32)		
	Week 2	Week 4	Week 12	Week 2	Week 4	Week 12
Total testosterone (nmol/l)	$12.8 \pm 0.9^{**}$	$13.2 \pm 0.9^{**}$	$13.9 \pm 0.9^{***}$	$13.7 \pm 1.6^*$	$15.9 \pm 1.7^{**}$	$18.1 \pm 2.1^{***}$
Free testosterone (nmol/l)	0.22 ± 0.02	$0.25 \pm 0.02^*$	$0.27 \pm 0.03^*$	$0.31 \pm 0.03^{**}$	$0.37 \pm 0.03^{***}$	$0.39 \pm 0.04^{***}$
SHBG (nmol/l)	47.8 ± 3.7	45.5 ± 3.6	$44.6 \pm 3.4^*$	$45.5 \pm 3.2^*$	$35.1 \pm 3.0^{***}$	$32.4 \pm 3.2^{***}$
PSA (nmol/l)	2.41 ± 0.13	2.54 ± 0.12	2.66 ± 0.13	2.49 ± 0.12	2.59 ± 0.12	$2.73 \pm 0.12^*$
IIEF (points)	$15.0 \pm 0.9^{***}$	$16.8 \pm 1.0^{***}$	$17.1 \pm 1.1^{***}$	$17.0 \pm 0.9^{***}$	$19.2 \pm 1.0^{***}$	$21.5 \pm 1.0^{***}$
AMS (points)	$35.0 \pm 1.5^*$	$30.2 \pm 1.4^{***}$	$25.7 \pm 1.2^{***}$	$34.0 \pm 1.5^*$	$27.1 \pm 1.2^{***}$	$23.3 \pm 1.1^{***}$

Note: Statistically significant difference before the study: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 2: Dynamics of the hormone replacement therapy with androgen drugs

Parameter	Level	Omnadren (n = 47)		Nebido (n = 32)	
		Before treatment	After treatment	Before treatment	After treatment
Evaluation of erection	M ± m	9.2 ± 0.6	17.1 ± 1.1	9.41 ± 0.8	21.5 ± 1.0
	Min-max	5-9	9-21	5-10	11-22.0
	P		$P < 0.001$		$P < 0.001$
	Good	–	15 (31.9%)	–	19 (59.4%)
	Satisfactory	–	6 (12.8%)	–	8 (25%)
	Bad	47	26 (55.3%)	32	5 (15.6%)
		$\chi^2 = 27.7; P < 0.001$		$\chi^2 = 46.7; P < 0.001$	

Table 3: Evaluation of HRT with androgens according to IIEF

ED. If monotherapy by PDE-5 inhibitors had not given the desired effect during the treatment of men with hypogonadism, the addition of testosterone preparations in therapy led to a considerable positive effect [12].

Thus, changes in the lifestyle (diet, physical activity, insulin, antidiabetic hypoglycemic agents) and the appropriate use of androgens on this background, in particular Nebido, the latest generation drug (generational testosterone preparation) were accompanied by full or partial normalization of erectile function and blood lipid profile, increased exercise tolerance, decreased depression, improved cognitive function.

Conclusions

Thus, on the basis of the obtained results the following can be stated:

1. Changing lifestyles in patients with type 2 diabetes mellitus is accompanied by a decrease in ADAM (AMS) symptoms in 10.26% of cases. The use of testosterone preparations on this background reduces symptoms of ADAM in 24.65% of cases. There was an inverse proportional relationship between the ADAM symptoms and testosterone levels.
2. Despite the fact that the effect achieved on the background of treatment by a mixture of testosterone esters was equal to 36.1% by IIEF score, the cause of testosterone unstable level in the blood is the lack of long-term compensation of diabetes and cases of depression in patients with type 2 diabetes mellitus.
3. We obtained an effect of 59.4% by IIEF score in the treatment by testosterone undecanoate. We also reached a state of prolonged diabetes compensation, complete or partial normalization of lipid profile, and improved cognitive function.

After the analysis of the results, we concluded that on the background of lifestyle changes the use of hormone replacement therapy of various testosterone preparations in T2DM patients with age-related androgen deficiency leads to considerable compensation of diabetes along with

improved erectile dysfunction. The best result was obtained when using undecanoate which leads to the recovery of erectile function by maintaining stable testosterone blood levels, improved glucose and lipid metabolism, and restoration of cognitive impairment.

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