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THE EFFECTIVENESS OF DIFFERENT REGIMENS OF TESTOSTERONE GEL THERAPY IN MEN WITH ANDROGEN DEFICIENCY

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The results of androgen replacement therapy with the appointment of a transdermal gel with testosterone in patients with androgen deficiency were presented. 90 men with testosterone deficiency (<12 nmol/L) and impaired erectile function were observed. The average age of patients was 58 ± 5.2 years. Patients were divided into 3 groups. Patients of the 1st (control) group underwent basic behavioral therapy, the 2nd group received basic therapy with testosterone gel for a dose of 50 mg, the 3rd group received basic therapy with testosterone gel at a dose of 100 mg. The duration of treatment was 6 months. The use of testosterone in the form of a transdermal gel led to a significant increase in the content of total testosterone in both patients of the 2nd (50 mg) and 3rd groups (100 mg). A dose-dependent effect was noted, in patients of the 3rd group the level of testosterone was significantly higher than in patients 2nd group. An increase in testosterone was accompanied by a decrease in FSH and LH levels.

Keywords: age-related androgen deficiency; replacement therapy; transdermal gel.

ЭФФЕКТИВНОСТЬ РАЗЛИЧНЫХ РЕЖИМОВ ТЕРАПИИ ТЕСТОСТЕРОН-ГЕЛЕМ У МУЖЧИН С АНДРОГЕННЫМ ДЕФИЦИТОМ

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Представлены результаты андроген-заместительной терапии с назначением трансдермального геля с тестостероном пациентам с андрогенным дефицитом. Под наблюдением находились 90 мужчин с дефицитом тестостерона (<12 нмоль/л) и нарушением эректильной функции. Средний возраст больных составил 58 ± 5,2 года. Пациенты были разделены на 3 группы. Пациентам 1-й (контрольной) группы проводили базовую поведенческую терапию, 2-й группы — базовую терапию вместе с тестостерон-гелем в дозе 50 мг, 3-й группы — базовую терапию вместе с тестостерон-гелем в дозе 100 мг. Продолжительность лечения 6 мес. Применение тестостерона в форме трансдермального геля привело к достоверному повышению содержания общего тестостерона как у пациентов 2-й (50 мг), так и 3-й групп (100 мг). Отмечена дозозависимость эффекта — в 3-й группе уровень тестостерона оказался достоверно выше. Увеличение содержания тестостерона сопровождалось снижением уровней фолликулостимулирующего гормона и лютеинизирующего гормона.

Ключевые слова: возрастной андрогенный дефицит; заместительная терапия; трансдермальный гель.

Androgen deficiency in men is an urgent problem encountered by urologists that is characterized by a relative or absolute lack of free testosterone. It manifests as a myriad of urological diseases and metabolic disorders [1]. Low levels of androgens cause impaired sexual function and fertility, changes in the metabolism of bone and muscle tissue, psychoemotional disorders, and problems of social adaptation [2, 3]. Decreased testosterone levels in combination with clinical symptoms of hypogonadism are seen in 2.1%–5.7% of men aged 40–79 years [4, 5]. The incidence of androgen deficiency is estimated as 11.7–12.3 per 1,000 people [6, 7].

According to the Massachusetts Study of Older Men, the level of bioavailable testosterone decreases by the age of 30–35 (by 1%–2% per year); while, the level of total testosterone starts decreasing from the age of 50–55 years (by 0.8%–1.6% per year). This difference can be explained by the age-related increase in the levels of sex-steroid-binding globulin (SSBG) by 1.5% per year that causes a decrease in the blood concentration of testosterone [8].

Diagnosis of androgen deficiency is based on the determination of levels of blood plasma total testosterone (normally >12 nmol/l) and gonadotropins (follicle stimulating hormone, FSH; luteinizing hormone, LH). The concentration of total testosterone <8 nmol/L, decreased or increased levels of gonadotropins in combination with severe clinical symptoms enable the diagnosis of hypogonadotropic or hypergonadotropic hypogonadism. When the clinical symptoms of hypogonadism are pronounced with levels of total testosterone within the range of 8–12 nmol/L, it is essential to determine the levels of SSBG and free testosterone (normally >250 pmol/L) [9].

It should be borne in mind that the blood concentration of testosterone varies according to the circadian rhythm; hence, the peak levels of the hormone are normally registered at 4 am, and they decrease significantly in the evening [10, 11]. Therefore, the evaluation of testosterone levels is performed in the morning and in a state of fasting. The levels of testosterone can be influenced by factors such as emotions, nutrition, level of physical activity; as well as concomitant urological diseases, including inflammatory ones that should be considered when diagnosing the disease [10, 12].

Androgen replacement therapy is recommended for men with persistently low testosterone levels and symptoms of androgen deficiency, in the absence of contraindications, to restore levels within the physiological limits. Results of meta-analyses have demonstrated that testosterone replacement therapy was ineffective when its levels were ≥12 nmol/L (3.5 ng/ml). Conversely, positive treatment results were seen when the testosterone levels were <12 nmol/L, especially in those with severe forms of hypogonadism (<8 nmol/L) [13, 14].

Currently, androgen replacement therapy with testosterone preparations in the form of transdermal gels has become commonplace, and is associated with fewer side effects and ease of use [10, 15]. However, it is associated with certain adverse effects in that it affects spermatogenesis negatively; leading to azoospermia in some patients [16].

The study aimed to determine the effectiveness of various modes of testosterone gel therapy in men with androgen deficiency.

MATERIALS AND METHODS

The study involved 90 men with testosterone deficiency (<12 nmol/L) and erectile dysfunction of varying severity. The average age of the patients was 58 ± 5.2 years, the values of anthropometric parameters were body weight of 92 ± 5 kg and waist circumference of 102 ± 3.6 cm. All patients underwent an examination by a urologist-andrologist, and hematological investigations to determine the levels of total testosterone, SSBG, prolactin, LH, FSH, thyroid stimulating hormone, prostate-specific antigen (PSA), and hematocrit. The study did not include patients with oncological or endocrine diseases, chronic obstructive pulmonary disease, and those with a history of alcohol and/or drugs abuse.

The patients were distributed into 3 groups of 30 people each. Basic behavioral therapy (sports and dieting) were prescribed to the patients of group 1 (control); basic therapy with 50 mg testosterone gel for external use was prescribed to group 2; and group 3 received basic therapy with 100 mg testosterone gel. The data obtained during visit 1 were taken as the baseline values of the blood parameters. The subsequent assessment was performed 6 months later at visit 2.

Statistical analysis was performed on MS Excel 11.0 and IBM SPSS Statistics 21.0; and a parametric (Student's *t*-test) test was used. A p-value of <0.05 was considered to be statistically significant for the observed differences between the mean values of the samples.

STUDY RESULTS

Before the start of the treatment, the level of sex hormones in patients of groups 1, 2, and 3 were practically the same. During visit 2 (6 months after the start of therapy) significant changes in these indicators were noted (see Table 1).

In group 1 patients (control), a significant ($p < 0.05$) decrease in the blood FSH and LH levels by 1.0 mU/L was seen on visit 2 when compared with the values at visit 1. At the end of therapy, the testosterone levels had significantly increased by 0.9 nmol/L. The levels of prolactin, PSA, and SSBG changed insignificantly between the two visits.

The dynamics of the laboratory results in patients of the 1st, 2nd and 3rd groups (n = 90)
Динамика результатов лабораторных исследований у больных 1, 2 и 3-й групп (n = 90)

Indicators	Visit 1			Visit 2		
	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)	Group 1 (n = 30)	Group 2 (n = 30)	Group 3 (n = 30)
Total testosterone, nmol/L	Group	6.5 ± 1.0	6.7 ± 1.2	7.6 ± 1.4#	10.5 ± 1.0*#	14.7 ± 1.2**#
SSBG, nmol/l	53.3 ± 17.5	55.7 ± 18.4	53.6 ± 17.8	53.2 ± 17.7	55.4 ± 17.4	53.5 ± 17.6
FSH, mU/l	5.5 ± 1.0	5.6 ± 1.1	5.9 ± 1.1	4.5 ± 1.0#	4.2 ± 1.0#	4.0 ± 1.0#
LH, mU/l	4.8 ± 1.2	4.9 ± 1.2	5.0 ± 1.3	3.8 ± 1.1#	3.5 ± 1.0#	3.3 ± 1.0#
Prolactin, mU/l	268.1 ± 86.7	268.5 ± 92.4	266.1 ± 86.2	271.2 ± 85.6	267.4 ± 90.2	268.6 ± 88.2
PSA, ng/ml	2.1 ± 0.7	2.2 ± 0.9	2.0 ± 0.7	2.2 ± 0.8	2.1 ± 1.0	1.9 ± 0.8

Note. SSBG – sex-steroid-binding globulin, FSH – follicle stimulating hormone, LH – luteinizing hormone, PSA – prostate-specific antigen. * differences with the group 1 are significant ($p < 0.05$); ** differences with the groups 1 and 2 are significant ($p < 0.05$); # differences with the values at visit 1 are significant ($p < 0.05$).

While evaluating the effectiveness of the therapy in group 2 patients, a significant decrease in the FSH and LH levels by 1.4 mU/L ($p < 0.05$) was observed on visit 2. After the end of treatment, group 3 patients showed a significant increase in total testosterone by 8.0 nmol/L, as well as a decrease in the FSH and LH levels by 1.9 and 1.7 mU/l, respectively.

Based on our findings, the following conclusions can be drawn: testosterone levels increased in all patients; however, this increase was unequal across the groups. In group 1 patients, the treatment was least effective when compared with group 2 and 3 patients (1.3 and almost 2 times lesser than in group 2 and 3, respectively). In group 3, the testosterone levels were higher by 4.2 nmol/L than in group 2 ($p < 0.05$). The FSH levels in group 1 (control) after the treatment were higher by 0.3 and 0.5 mU/L compared with those in groups 2 and 3, respectively that indicated a greater aromatization of testosterone. The differences in the FSH levels in groups 2 and 3 after treatment (0.2 mU/L) were not statistically significant. A similar tendency was noted for the LH levels in the patients under supervision.

During the course of treatment, we did not observe any significant changes in the levels of SSBG, prolactin, and PSA in patients across all the groups.

Thus, the use of testosterone in the form of a transdermal gel significantly increased the levels of total testosterone both in group 2 and 3 patients who received 50 and 100 mg of testosterone, respectively. This effect was found to be dose-dependent, as the testosterone levels in group 3 patients were significantly higher. The increase in testosterone levels was accompanied by a decrease in FSH and LH levels.

CONCLUSION

The results of the study highlight the efficiency of the use of testosterone transdermal gel in doses of 50 and 100 mg. Testosterone gel application for 6 months was accompanied by a dose-dependent increase in the blood levels of total testosterone in patients with androgen deficiency.

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