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Characteristics of depression treatment in men with testosterone deficiency

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ABSTRACT

BACKGROUND: Treatment of depression in men with testosterone deficiency is particularly challenging because of the overlap between the symptoms of depression itself and those associated with testosterone deficiency, which requires the development of additional diagnostic and therapeutic approaches.

AIM: To enhance the effectiveness of comprehensive treatment of depression in men with testosterone deficiency.

MATERIALS AND METHODS: The study involved 140 male participants (aged 18–65 years) diagnosed with depressive episodes and recurrent depressive disorder according to the International Classification of Diseases, 10th revision. Patients were divided into the main group (testosterone levels below 12.1 nmol/l) and the control group (normal testosterone levels). The main group (*n*=90) was further divided into three therapeutic subgroups of 30 patients each: receiving sertraline monotherapy, testosterone monotherapy, and combined sertraline and testosterone treatment. The control group included men with depression and normal testosterone levels (*n*=50), who received sertraline only.

RESULTS: Depression in men in the context of testosterone deficiency has distinct clinical features, both phenomenologically and syndromally. The severity of the depressive syndrome in men with testosterone deficiency is lower (17.0 [16.0; 18.75] points on the HDRS scale) than in patients with normal testosterone levels (19.0 [18.0; 22.0] points on the HDRS scale), and the depressive episode tends to occur later in life (47.0 [42.0; 55.0] years) compared to those with normal levels of testosterone (29.5 [24.25; 40.0] years) and is less likely to be recurrent than in those with normal testosterone levels (29.5 [24.25; 40.0] years). The study of the efficacy and safety of depression therapy in the context of testosterone deficiency shows that a combined approach to the treatment of depression in men with testosterone deficiency has both advantages (considering the specifics of patients by normalizing testosterone levels and erectile function) and disadvantages (relatively higher risk of adverse events) compared to sertraline monotherapy.

CONCLUSION: The identified characteristics of the course and treatment of depression in the context of reduced testosterone levels allowed for the development of a more effective therapeutic and diagnostic algorithm.

Keywords: depression; testosterone; men; testosterone deficiency; treatment.

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Особенности терапии депрессии у мужчин с дефицитом тестостерона

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АННОТАЦИЯ

Обоснование. Лечение депрессии у мужчин с дефицитом тестостерона имеет определённые трудности в связи с пересечением симптомов как самой депрессии, так и связанных с недостатком данного гормона, что требует разработки дополнительных диагностических и терапевтических подходов.

Цель. Повышение эффективности комплексной терапии депрессии у мужчин с дефицитом тестостерона.

Материалы и методы. В исследовании приняли участие 140 мужчин (возраст 18–65 лет) с установленными диагнозами депрессивного эпизода и рекуррентного депрессивного расстройства. Пациенты были распределены в основную группу (концентрация тестостерона менее 12,1 нмоль/л) и контрольную (нормативные показатели тестостерона). Основная группа (n=90) была поровну разделена на три терапевтические подгруппы: получавшие монотерапию сертралином, монотерапию тестостероном, комбинированное лечение сертралином и тестостероном. В контрольной группе были мужчины с депрессией и нормальным уровнем тестостерона (n=50), которые получали только сертралин.

Результаты. Депрессия у мужчин, развившаяся на фоне гипотестостеронемии, имеет отличительные особенности клинической картины. Выраженность депрессивного синдрома у мужчин с дефицитом тестостерона ниже (17,0 [16,0; 18,75] баллов по шкале HDRS), чем у пациентов с нормальным уровнем тестостерона (19,0 [18,0; 22,0] баллов по шкале HDRS), а сам депрессивный эпизод при дефиците тестостерона развивается сравнительно позже (47,0 [42,0; 55,0] лет) чем при нормальном уровне тестостерона (29,5 [24,25; 40,0] года), реже депрессивное расстройство имеет рекуррентный характер. Результаты работы позволяют сказать, что комбинированный подход к лечению депрессии у мужчин на фоне дефицита тестостерона учитывает специфику пациентов, нормализуя уровень тестостерона и эректильную функцию, однако существует сравнительно больший риск нежелательных явлений по сравнению с монотерапией сертралином.

Вывод. Депрессия с мужчин с дефицитом тестостерона имеет клинические и терапевтические особенности, требующие учёта и анализа для повышения эффективности терапии.

Ключевые слова: депрессия; тестостерон; мужчины; дефицит тестостерона; лечение.

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Тестостерон кытлыгы күзәтелгән ир-атларда депрессияне дәвалау үзенчәлекләре

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АННОТАЦИЯ

Нигезләмә. Тестостерон кытлыгы күзәтелгән ир-атларда депрессияне дәвалауда депрессиянең үз билгеләре белән әлеге гормон җитешмәү билгеләре үзара кисешү аркасында билгеле бер кыенлыклар булу өстәмә диагностика һәм дәвалау алымнарын булдыруны таләп итә.

Максат. Тестостерон кытлыгы күзәтелгән ир-атларда депрессияне комплексны дәвалауның нәтиҗәлелеген арттыру.

Материалы һәм ысуллар. Тикшеренүдә депрессия эпизоды һәм рекуррент депрессия тайпылышы диагнозы куелган 140 ир-ат (18–65 яшь) катнаша. Пациентлар төп төркемгә (тестостерон концентрациясе 12,1 нмоль/л дән кимрәк) һәм контроль төркемгә (тестостеронның норматив күрсәткечләре) бүленгән. Төп төркем (*n*=90) өч терапевтик төркемгә тигезләп бүленгән: сертралин белән монотерапия узучылар, тестостерон белән монотерапия узучылар, сертралин белән тестостерон комбинациясе белән дәваланучылар. Контроль төркемгә депрессия билгеләре күзәтелгән, тестостерон дәрәҗәләре нормада булган ир-атлар кертелгән (*n*=50), алар бары тик сертралин белән генә дәвалану узганнар.

Нәтиҗәләр. Ир-атларда гипотестостеронемия фонында барлыкка килгән депрессиянең клиник картинасы аерым үзенчәлекләргә ия. Тестостерон дефициты булган ир-атларда депрессия синдромы нормаль тестостерон дәрәҗәсе булган пациентларга караганда түбәнрәк (HDRS шкаласы буенча 17,0 [16,0; 18,75] балл), тестостерон дефициты булганда, депрессия эпизоды чагыштырмача соңрак (47,0 [42,0; 55,0] яшь) (нормаль тестостерон дәрәҗәсе булган очрак белән чагыштырганда) (29,5 [24,25; 40,0] яшь) күзәтелә; сирәк очракларда депрессия тайпылышы рекуррент характерда була. Тикшеренү нәтиҗәләре шуны күрсәтә: ир-атларда тестостерон кытлыгы фонындагы депрессияне комбинацияле дәвалау пациентларның үзенчәлекләрен исәпкә ала, тестостерон дәрәҗәсен һәм эректиль функциясен нормальләштерә, әмма бу дәвалау алымының, сертралин монотерапиясе белән чагыштырганда, тискәре нәтиҗәләргә китерү куркынычы чагыштырмача зуррак.

Йомгак. Ир-атларда тестостерон кытлыгына бәйле депрессиясенең клиник һәм дәвалау үзенчәлекләре бар. Дәвалауның нәтиҗәлелеген арттыру максатларында, аларны исәпкә алу һәм анализлау гаять мөһим.

Төп төшенчәләр: депрессия; тестостерон; ир-атлар; тестостерон кытлыгы; дәвалау.

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BACKGROUND

Recently, several factors have been identified that influence the course and clinical presentation of depression [1–3]. One of these factors is a patient's sex. Although some authors have emphasized the need to consider the patient's sex when diagnosing depression [4], international classifiers of diseases [Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases (ICD)] do not include sex-specific symptoms in the diagnostic criteria.

Depression is more common in women [5, 6] than in men. This has led to studies focusing on identifying the cause of such a prevalence of depression [7, 8]. Thus, men and the characteristics of their physiological and psychological processes, which can affect the clinical presentation of the disease, are not considered [9, 10]. Depression in men can be masked by atypical symptoms and may not diagnosed within the standard depressive syndrome [11, 12]. Furthermore, the results of several studies indicate an increased risk of depression in patients with reduced testosterone levels [13].

Despite the decades of research on sex-based differences in antidepressant therapy, the existence of such a difference remains a debate [14]. Some studies have indicated a positive effect of testosterone replacement therapy on depressive symptoms [15]. However, it seems premature to unambiguously evaluate such reports because the design of most of these studies has significant limitations and deficiencies [16].

Thus, the study of depression in men and its association with testosterone deficiency remains a topic of interest. In this study, we aimed to increase the effectiveness of a complex therapy for depression in men with testosterone deficiency by developing a treatment and diagnostic algorithm.

The results of this study may help reduce the patients' social and personal issues, which may contribute to the greater efficiency of the therapeutic and rehabilitation processes.

Furthermore, during our analysis of the depression in men with low testosterone levels, the relevance of the issue, its priority, and the unresolved nature of the tasks were highlighted.

MATERIALS AND METHODS

The main research methods used in the study were clinico-psychopathological, psychometric, and mathematical statistical methods. The main tool used in this study was the Examination Record of a Patient with Depression and Concomitant Testosterone Deficiency. This record included socio-demographic data and the mental status assessment results that were obtained during a clinical interview. Furthermore, the quantitative indicators of the severity of the identified symptoms were recorded. The Hamilton depression rating scale (HDRS) and the Hamilton anxiety rating scale (HARS) were used to quantitatively assess the severity of depressive and anxiety disorders, respectively [17, 18]. The indicators of these scales were the main measures of treatment efficiency. The Gotland Depression Scale was used to determine the characteristics of depression in men [19].

This study was conducted in several stages, namely the formation of a control and three therapeutic groups (Fig. 1), the selection and application of examination and treatment methods, and assessment of the efficacy of the chosen methods using the appropriate psychometric scales and tools. The study was approved by the ethics committee of the Rostov State Medical University of the Ministry of Health of the Russian Federation (No. 15/18; dated 10/11/2018).

The following were the inclusion criteria: male sex, age from 18 to 65 years, clinical presentation consistent with a depressive episode (single or part of a recurrent depressive disorder according to the ICD-10 criteria), and consent to participate in the study. The selection of patients with a depressive episode or recurrent depressive disorder was determined by the study objective to focus on distinct depressive states, as opposed to other disorders that may be associated with stressful situations and for which psychotherapeutic interventions are preferred.

The following were the exclusion criteria: female sex, age over 65 years, congenital hypogonadism, prostate cancer, significant somatic diseases in the acute stage, psychopathological productive symptoms of a psychotic level, other mental illnesses such as bipolar affective disorder, and depressive reactions caused by adjustment disorder.

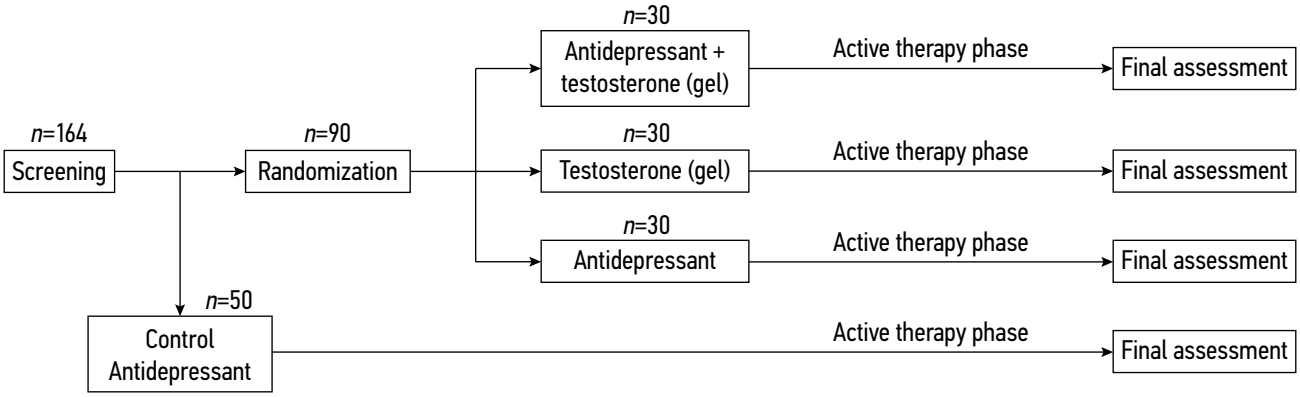

Fig. 1. Study design.

The blood level of total testosterone in all the study participants was determined using enzyme immunoassay. If the level was <12.1 nmol/l, the patient was referred to an endocrinologist and urologist. This total testosterone level cut-off was based on the international clinical guidelines of the European Association of Urologists, American Society of Endocrinology, International Society of Male Aging, and Canadian Foundation for Men's Health [20].

The consultant identified cases of testosterone deficiency (E29) due to age-related and metabolic changes; other forms were excluded. If both consultants approved the patient's participation in the study, he was included in the main group. If the total testosterone level in the blood was > 12.1 nmol/L, the patient was included in the control group.

Once enrolled in the study, the patients were excluded in the following conditions: non-compliance with the study protocol, intolerance to or serious side effects of the treatment, deterioration of the patient's condition, detection of alcohol or psychoactive substance dependence syndrome, detection of a new concomitant pathology, and termination of the patient's participation without permission. The investigator could also exclude patients at their discretion for reasons related to ethics, safety, or other circumstances that may affect the study results.

The minimum sample size of the study was calculated using to the following equation:

$$n = (A + B)^2 \times \frac{p_1 \times (1 - p_1) + (p_2 \times (1 - p_2))}{(p_1 - p_2)^2},$$

where n is the sample size for each group, p_1 is the frequency 1 (0.50 in the current calculation), p_2 is the frequency 2 (0.20 in the current calculation; the upper and lower frequency limits were determined according to the step-by-step data processing as information was received and groups were formed); p_1–p_2 are clinically significant differences that were determined by step-by-step data processing (0.30 in this case); A is the dependence on the significance level (1.96 in this calculation at a significance level of 0.05); and B is the dependence on the power (1.28 in this case at a study power of 90%).

Based on the above calculation, it was determined that at least 30 patients (n >30) had to be included in each subgroup. Thus, 90 men with established depression and reduced testosterone levels were randomly and evenly distributed among three therapeutic subgroups. A comparable control group was formed disproportionately (there was no continuous screening) to allow for comparisons and analyses. The control group included 50 patients who underwent the same number of test and visits as the patients in the main groups.

The mean age of the participants in the therapeutic groups was 50.58±8.43 years, which is higher than the mean age of the control group participants (41.16±10.35 years). The nosological composition of the study patients is included in Table 1.

Table 1. Distribution of the study patients according to the nosological characteristics

ICD-10	Main group	Control group	*p*
Depressive episode	56.7% (*n*=51)	36% (*n*=18)	0.03
Recurrent depressive disorder	43.3% (*n*=39)	64% (*n*=32)	

The therapeutic stage of the study lasted 10 weeks. During this time, the patients were followed-up six times. During these visits, the intermediate effectiveness of the therapy used and the severity of the associated side effects were assessed. Furthermore, the characteristics of the occurrence of side effects during the treatment were studied.

The main criterion indicative of an effective therapy was the change in the HDRS and HARS scores. An international index of erectile function (IIEF) score of 5 was also an indicator of effective therapy.

Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line treatment for depression due to their effectiveness and safety ratio [21]. Sertraline, which is a classic SSRI with one of the most studied efficacy and safety profiles [22], does not interact with testosterone. Thus, it was chosen as the therapeutic drug in our study. Furthermore, the selection of a single SSRI enables us to standardize the results obtained for subsequent meta-analyses.

The initial dosage of sertraline was 50 mg/day. If the efficacy was insufficient, the dosage was increased by 25 mg every week, as required, up to a maximum daily dosage of 200 mg. The average daily dosage of sertraline was 87.5±32 mg/day in subgroup 1, 85±30.51 mg/day in the combination treatment subgroup, and 107±33.52 mg/day in the control group. Testosterone was prescribed in the form of a gel at a dosage of 50 mg once a day (in the morning). During each visit, the level of depression was quantitatively assessed using two scales, and any adverse reactions were recorded.

RESULTS

During the study, we discovered several characteristic symptoms of depression in men with testosterone deficiency (Table 2). Furthermore, decreased libido was observed in all the patients (*n*=90, 100%). Another observed symptom, which was relatively less common than decreased libido, was irritability (63.3%, *n*=57). The other common complaints were daytime sleepiness (47.8%, *n*=43), emotional lability (44.4%, *n*=40), and superficial and light sleep (37.8%, *n*=34).

In addition to sleep disorders, some patients experienced nightmares (23.3%, *n*=21). However, men with depression and normal testosterone levels experienced melancholy (78.0%, *n*=39) more often than nightmares. Decreased libido, irritability and aggression, hypesthesia, daytime sleepiness, superficial and light sleep, confusion, and nightmares were recorded in 54% (*n*=27), 40% (*n*=20), 36% (*n*=18), 24% (*n*=12), 20% (*n*=10), 18% (*n*=9), and 8% (*n*=4) of the patients, respectively.

Table 2. Symptoms that exhibited statistically significantly different frequencies between the study groups

Symptom	Main group (*n*=90)	Control group (*n*=50)	Empirical φ
Hypesthesia	15.6% (*n*=14)	36.0% (*n*=18)	3.054* (*p*=0.011)
Daytime sleepiness	47.8% (*n*=43)	24.0% (*n*=12)	0.345* (*p*=0.007)
Nightmares	23.3% (*n*=21)	8.0% (*n*=4)	0.286* (*p*=0.036)
Superficial and light sleep	37.8% (*n*=34)	20.0% (*n*=10)	0.412* (*p*=0.037)
Irritability and aggression	63.3% (*n*=57)	40.0% (*n*=20)	0.386* (*p*=0.013)
Confusion	2.2% (*n*=2)	18.0% (*n*=9)	9.659* (*p*=0.002)
Decreased libido	100.0% (*n*=90)	54.0% (*n*=27)	0.000* (*p* ⩽0.001)
Melancholy	46.7% (*n*=42)	78.0% (*n*=39)	4.052* (*p* ⩽0.001)
Emotional lability	44.4% (*n*=40)	26.0% (*n*=13)	0.439* (*p*=0.045)

Note. *statistically significant differences; *p* — level of statistical significance of differences.

The depressive syndrome in men with testosterone deficiency was predominantly an asthenodepressive variant (46.7%, *n*=42). Normal hormone levels were recorded in only 22% of the patients (*n*=11). The remaining variants of depressive syndromes were distributed evenly in the main and control groups. Furthermore, the testosterone deficiency was associated with a lower severity of depressive symptoms according to the HDRS score (Fig. 2).

In this study, the depression in patients with testosterone deficiency were treated using the following three approaches: monotherapy with an antidepressant (sertraline), monotherapy with testosterone, and a combined approach of administering both drugs (sertraline and testosterone).

The thymoanaleptic effect of the combined therapy did not demonstrate and advantages over monotherapy with an antidepressant (Fig. 3). Although the effectiveness of monotherapy with sertraline was comparable to that of combined therapy, its use does not account for the specific needs of patients with testosterone deficiency. The thymoanaleptic effect of testosterone monotherapy did not demonstrate any advantages over the other treatment regimens. However, testosterone administration increased the level of this hormone, which may have been critically important for this group of patients. The combination therapy exhibited an anxiolytic effect that was comparable to that of sertraline monotherapy (Fig. 4).

Analysis of the side effects (Table 3) of the SSRI regimens confirmed the existing data on the possible side effects of these drugs. In the group receiving only antidepressants, 26.67% and 16.67% of the patients experienced nausea and headache, respectively, which corresponds to the available data on the side effects of SSRIs. The increase in blood pressure (13.33%) and diarrhea (10.0%) recorded in patients being administered testosterone may be attributable to the physiological action of this hormone.

The testosterone level was significantly higher in the control group than in the three main subgroups at the beginning of the study (18.15 [interquartile range (IQR), 16.57–20.78] nmol/l) as well as at the end of the study (18.30 [IQR, 17.10–21.2] nmol/l) (Fig. 5). To determine the efficiency of the studied therapeutic regimens, the change in testosterone

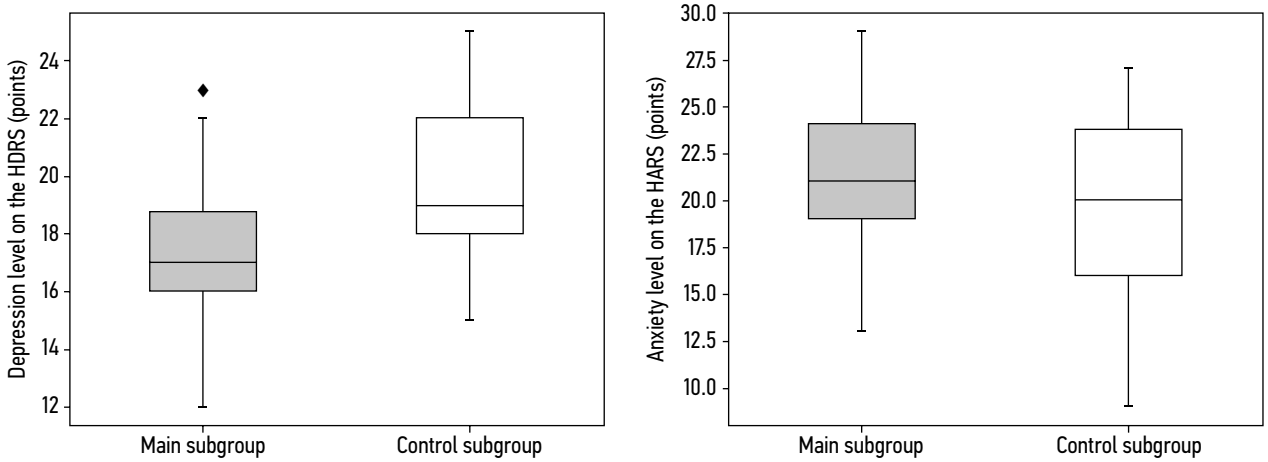

Fig. 2. Differences in the levels of depression (p <0.001) and anxiety (p=0.082) in depressed patients against the background of reduced (main subgroup) and normal (control subgroup) testosterone levels; HDRS — Hamilton Depression Rating Scale; HARS — Hamilton Anxiety Rating Scale.

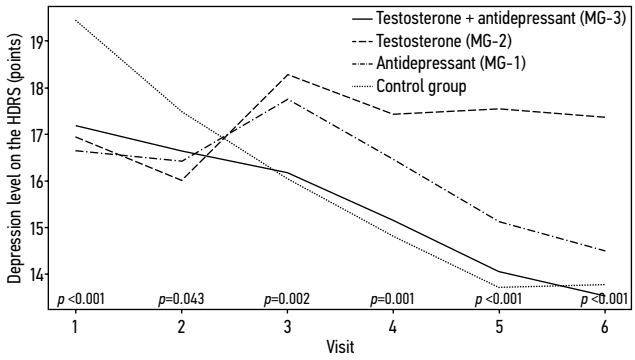

Fig. 3. Dynamics of depression level according to the Hamilton Depression Rating Scale (HDRS) against the background of treatment with different schemes in patients with depression on the background of reduced testosterone level (MG-1 — the first experimental subgroup, MG-2 — the second experimental subgroup, MG-3 — the third experimental subgroup) and control group; *p* — statistical significance of differences in all subgroups on the day of the visit according to the Kraskell–Wallis test.

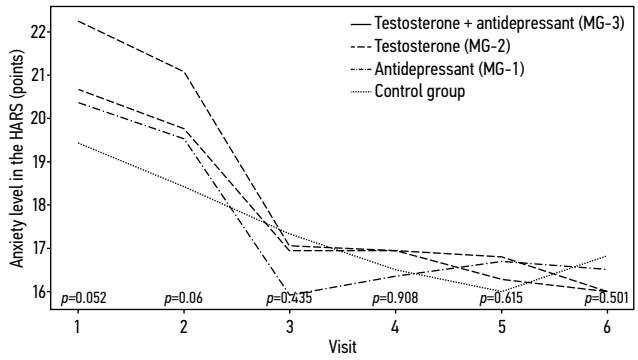

Fig. 4. Dynamics of anxiety level in depressed patients with testosterone deficiency according to Hamilton Anxiety Rating Scale (HARS) on the background of treatment with different schemes (MG-1 — the first experimental subgroup, MG-2 — the second experimental subgroup, MG-3 — the third experimental subgroup) and in control group patients; *p* — statistical significance of differences in all subgroups on the day of the visit according to the Kraskell–Wallis criterion.

levels in the three main subgroups were assessed. At the beginning of the study, the testosterone level was 7.05 [IQR, 5.8–8.9] nmol/l, 6.9 [IQR, 6.1–8.95] nmol/l, and 7.35 [IQR, 5.8–8.45] nmol/l in subgroups 1, 2, and 3, respectively.

Pairwise comparisons of the listed parameters exhibited no statistically significant differences between the groups. Furthermore, in the control group, the testosterone level at the end of the study was comparable to that at the beginning of the study.

DISCUSSION

In this study, we identified several statistically significant factors of the clinical and dynamic presentation in patients with depression and testosterone deficiency in relation to the age of disease onset (47.0 [IQR, 42.0–55.0] years), number of depressive episodes (1.0 [IQR, 1.0–2.0] episode), and functional decline. These factors were absent in most of the study participants (87.8%, *n*=79). These data emphasize

Table 3. Distribution of the side effects in the therapeutic subgroups and control group

Side effects	MG-1 (*n*=30)		MG-2 (*n*=30)		MG-3 (*n*=30)		Control group (*n*=50)		χ^2	*p*
	%	(*n*)	%	(*n*)	%	(*n*)	%	(*n*)		
Anxiety	0		0		0		2.0	1	1.5	0.682
Increased blood pressure	6.67	2	13.33	4	0		0		17.778	0.006*
Decreased libido	13.33	4	0		0		10.0	5	7.317	0.109
Increased anxiety	0		0		0		4.0	2	3.028	0.451
Nausea	26.67	8	0		20.0	6	20.0	(10)	8.687	0.078
Headache	16.67	5	0		20.0	6	4.0	(2)	13.838	0.020*
Diarrhea	0		10.0	3	3.33	1	0		13.160	0.020*
Anorgasmia	0		0		0		10.0	5	7.790	0.101
Acne	0		6.67	2	6.67	2	0		8.687	0.048*
Nightmares	0		0		0		4.0	2	4.584	0.318
Numbness in arms	0		0		0		2.0	1	1.5	0.682
Insomnia	0		0		0		12.0	6	9.442	0.067
Weight gain	0		0		0		4.0	2	3.028	0.452
Tachycardia	0		0		0		4.0	2	3.028	0.452

Note. MG-1, subgroup 1 of the main group that was administered antidepressant monotherapy. MG-2, subgroup 2 of the main group that was administered testosterone monotherapy. MG-3, subgroup 3 of the main group that was administered a combination of antidepressant and testosterone. χ^2 is the χ^2 value determined using Monte Carlo simulations. *p*, statistically significant difference; and *, statistically significant difference level.

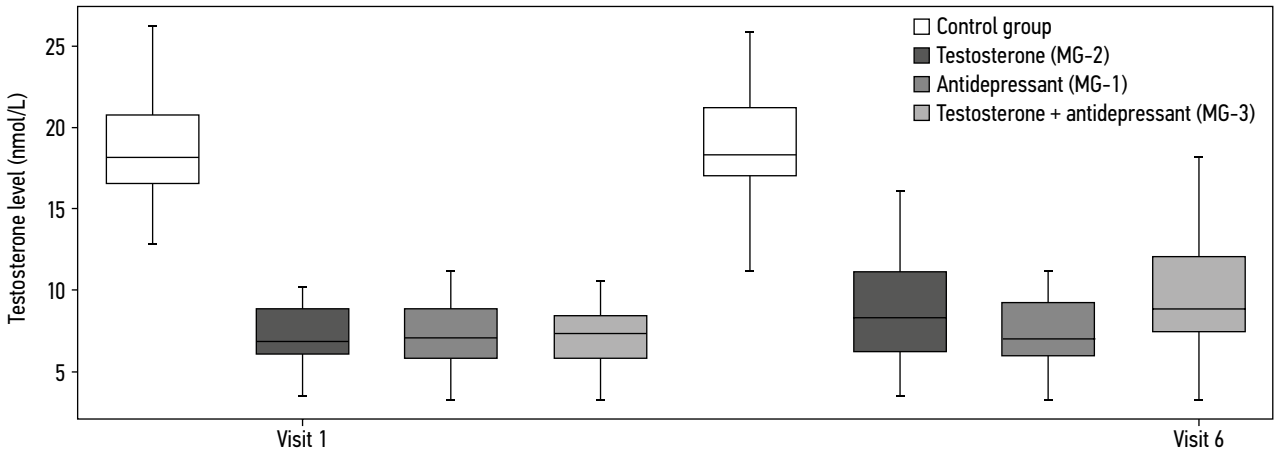

Fig. 5. Testosterone level control in depressed patients with testosterone deficiency in control group patients during the first and last visits. In pairwise comparison of testosterone levels, statistically significant differences were found between the subgroup of patients treated with the combination treatment and the subgroup treated with antidepressant alone (p=0.036) by the 6th visit; MG-1 — first experimental subgroup; MG-2 — second experimental subgroup; MG-3 — third experimental subgroup.

the importance of considering the testosterone level when assessing patients with depression. Furthermore, these results could aid in developing more individualized approaches for the treatment and rehabilitation of such patients.

In our therapeutic group, the role of the endogenous factor in the development of depression was less and the role of testosterone deficiency as a provoking or catalytic factor for clinical manifestation was more significant. This indicates that depression may present later and occur less frequently in the therapeutic group. This was confirmed by the predominance of the asthenodepressive variant in the therapeutic group, which can be characterized as a secondary disorder that does not lead to severe damage in the affective sphere.

The late onset and less frequent depressive episodes in the therapeutic group is also confirmed by the less severe depressive symptoms in patients with reduced testosterone levels. This finding is consistent with that of previous studies [23, 24]. However, the use of the Gotland scale did not reveal any statistically significant differences between the groups. This indicates that the Hamilton scale and Gotland scale may exhibit differences when assessing male depression symptoms. This finding emphasizes the importance of choosing an appropriate diagnostic tool, suggests the potential directions for further research in this area, and confirms the need to create a valid scale for assessing depression symptoms that consider sex characteristics [25].

A study of the distribution of symptoms accompanying depression between patients with low and normal testosterone levels revealed that sexual dysfunction was recorded in all patients with low testosterone levels in the main group. This was the main reason for seeking help. This emphasizes the significance of sexual dysfunction in the identification of a differential path and the need for a clearer position regarding additional diagnostic procedures in men with depression and severe sexual dysfunction. The very presence of sexual dysfunction as one of the pathognomonic symptoms of decreased testosterone may be a significant factor that aggravates depression in men [24]. Other symptoms such as confusion, melancholy, and hypoesthesia were more typical in patients in the control group than in the therapeutic group. Thus, the depressive syndrome in the control group was more endogenous and exhibited more pronounced symptoms.

The constitutional and biological characteristics of the patients in the therapeutic and control groups were different. The body weight and waist circumference were significantly different between the two groups. Furthermore, a decrease in erectile function was noted in the therapeutic group. These findings are typical for patients with reduced testosterone levels, which may present a possible pathogenic mechanism for the development of depression in such patients. Excess body weight and visceral obesity are reportedly significantly more common in patients with depression than in those without depression [26]. Despite the statistically significant differences in these indicators, there were no statistically significant differences between the groups during the vector assessment of the sexual constitution. This highlights the complexity and multifaceted impact of testosterone deficiency on the sexual constitution and general phenotype of patients.

Assessment of the therapeutic approaches revealed some peculiarities. Although sertraline monotherapy was effective against symptoms of depression, its use does not consider the specific needs of patients with testosterone deficiency. In contrast, testosterone monotherapy was less effective in the treatment of depression. However, it helped restore the testosterone levels and prevented specific depression symptoms in patients with a low testosterone level (Fig. 5). Thus, testosterone therapy may have been critically important in the patients with low testosterone level. Furthermore, testosterone monotherapy exhibited a good anxiolytic effect and improved erectile function. However, side effects were recorded in group that received testosterone monotherapy.

Monotherapy with the antidepressant sertraline exhibited a pronounced thymoanaleptic effect. However, it did not affect the testosterone levels, which did not improve erectile function. This may have negatively affected the quality of life of the patients.

Combination therapy with sertraline and testosterone was comparable to antidepressant monotherapy in terms of thymoanaleptic and anxiolytic effects (Fig. 4). Furthermore, it significantly improved the erectile function. However, an increased incidence in certain side effects that were associated with both the antidepressant and testosterone were noted in the combined therapy group. Our finding of the effect of the combination therapy is a significant contribution to understanding the interaction of pharmacological drugs when treating depressive disorders in patients with testosterone deficiency.

Our study findings indicate that the combination therapy is most appropriate for patients with depression and hypotestosteronemia. The efficacy is comparable to that of antidepressant monotherapy, and it considers the specific needs of these patients who require testosterone level correction and erectile function improvement. These findings are consistent with those of previous studies that emphasize the importance of testosterone replacement therapy in patients with depression and hypotestosteronemia [27].

Although the combination therapy increased the diversity of side effects, including those that are characteristic of both SSRI use and testosterone replacement therapy, it did not significantly increase the number of withdrawals from the study due to adverse events. This indicates that the safety of the combination therapy was comparable to that of monotherapy.

Based on the study findings, we have created an algorithm for managing patients with depression and testosterone deficiency (Fig. 6). The diagnostic algorithm includes a comprehensive assessment of the clinical presentation and biochemical parameters of the patient as well as a psychometric assessment of the patient's condition. The therapeutic algorithm combines methods for dietary correction, physical rehabilitation, and psychological support as well as pharmacological treatments. Together these algorithms may comprehensively impact several factors affecting the condition of patients. Furthermore, this approach may help restore hormonal balance, improve the patient's psycho-emotional state, and increase their overall quality of life.

An individual approach and constant monitoring of the patient's condition are imperative to correct the treatment methods being used. The proposed algorithm serves as a base plan that can be adapted to each specific patient. In the future, new models may be developed on the basis of this approach to more effectively assist patients with depression and testosterone deficiency.

CONCLUSIONS

Depression in men with testosterone deficiency exhibits distinctive clinical features. Phenomenologically, depression in men with testosterone deficiency is characterized by decreased libido (100%), emotional lability (44.4%), irritability (63.3%), and superficial and light sleep (37.8%). However, the characteristic complaints in patients with depression but normal testosterone levels are hypesthesia (36.0%), confusion (18.2%), and melancholy (78%). The depressive syndrome in men with testosterone deficiency is typically of the asthenodepressive variant (46.7%). Furthermore, the depressive syndrome is less severe in men with testosterone deficiency (HDRS score, 17.0 [IQR, 16.0–18.75]) than in men with normal testosterone levels (19.0 [IQR, 18.0–22.0]). Moreover, the depressive disorder develops later (47.0 [IQR, 42.0–55.0] years vs. 29.5 [IQR, 24.25–40.0] years) and is not as recurrent in men with testosterone deficiency than in those with normal testosterone levels.

The thymoanaleptic effect of testosterone monotherapy is insufficient and does provide relief in a depressive episode. However, the thymoanaleptic effect of the combined therapy is comparable to that of sertraline monotherapy. The combined therapy is more advantageous than sertraline monotherapy in terms of restoring the erectile function level and blood levels of testosterone. Furthermore, it exhibits an anxiolytic effect comparable to that of sertraline monotherapy. Finally, there was no significant difference in the adverse reaction profile between the combined treatment and monotherapy groups. The most common adverse reactions of sertraline monotherapy were nausea (26.67%), headache (16.67%), decreased libido (13.33%), and increased blood pressure (6.67%). The most common adverse reactions of testosterone monotherapy were increased blood pressure (13.33%), diarrhea (10.0%), and acne (6.67%). The most common adverse reactions of the combination therapy were nausea (20.00%), headache (20.00%), acne (6.67%), and diarrhea (3.33%).

Our study findings indicate that the choice of therapeutic approach for patients with depression and testosterone deficiency should consider the need to correct the mental state as well as the somatic state. Furthermore, a comprehensive therapeutic care plan should include a psychopharmacological approach (antidepressant + testosterone) as well as regular monitoring of adverse events.

ADDITIONAL INFORMATION

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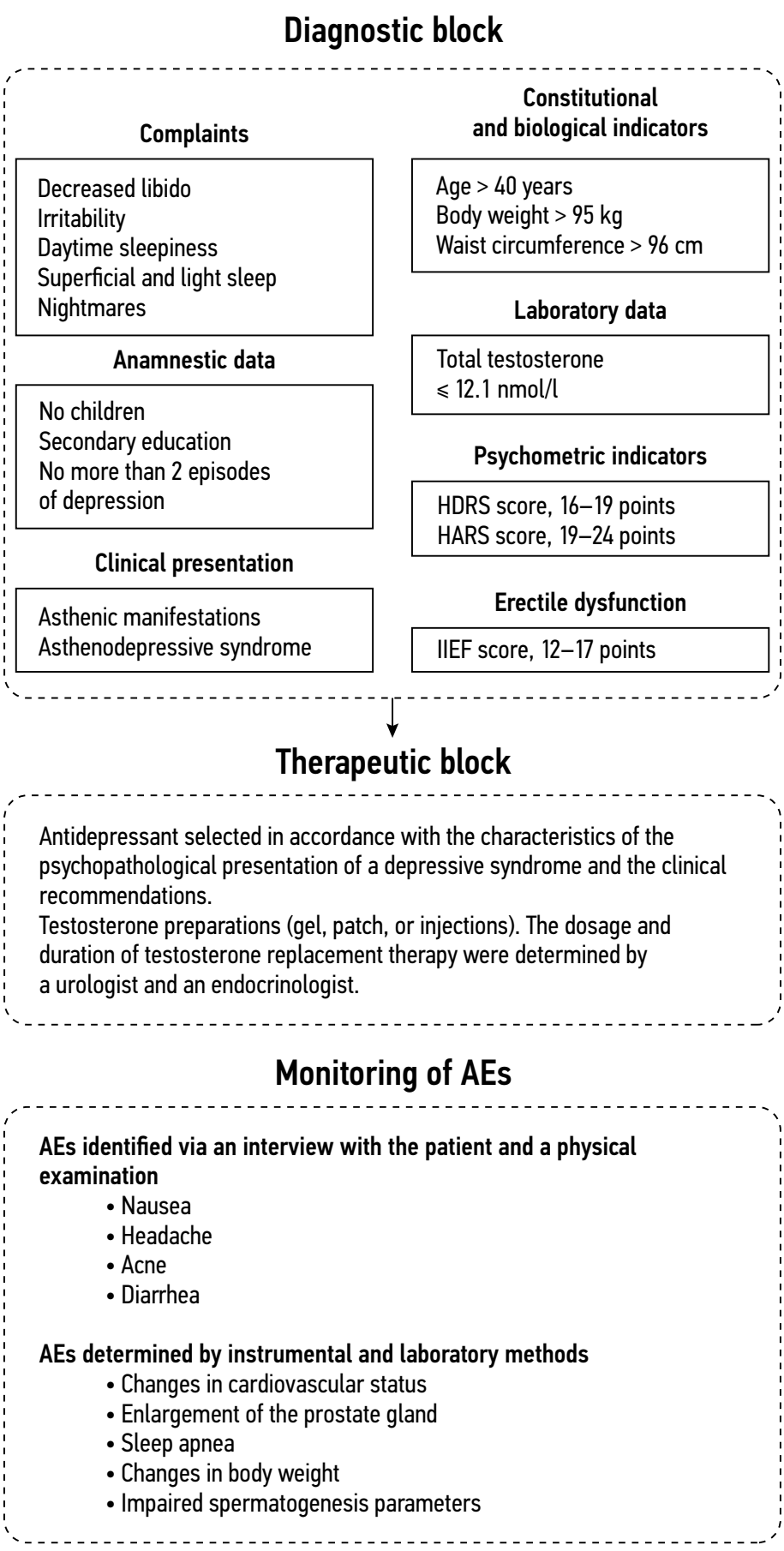

Fig. 6. Algorithm of work with patients suffering from depression on the background of testosterone deficiency; AEs — adverse events; HDRS — Hamilton Depression Scale; HARS — Hamilton Anxiety Scale; IIEF — International Index of Erectile Function.

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