Research Results in Pharmacology

Research Results in Pharmacology 5(4): 57–67
UDC: 615.331
DOI 10.3897/rrpharmacology.5.49414

Research Article

# Optimization of pharmacotherapy of patients with prostate adenoma with hormonal and metabolic disordes: correction of vitamin D deficiency with “Aquadetrim”

Oleg I. Bratchikov[1], Igor A. Tyuzikov[2], Sergey O. Artishchev[1]

1 *Urology Department, Kursk State Medical University, 3 Karl Marx St., Kursk 305041, Russian Federation*

2 *Tandem-Plus Medical Center, 3V Pervomayskiy Lane, Yaroslavl 150000, Russian Federation*

Corresponding author: *Oleg I. Bratchikov* (bratov45@mail.ru)

**Academic editor:** *Oleg Gudyrev* ♦ **Received** 14 October 2019 ♦ **Accepted** 20 November 2019 ♦ **Published** 30 December 2019

**Citation:** Bratchikov OI, Tyuzikov IA, Artishchev SO (2019) Optimization of diagnostics and management of patients with prostate adenoma with hormonal and metabolic disorders on the basis of integrative approach. Research Results in Pharmacology 5(4): 57–67. https://doi.org/10.3897/rrpharmacology.5.49414

## Abstract

**Introduction:** Modern studies demonstrate an epidemiological and pathogenetic role of systemic hormonal and metabolic disorders in men with prostate adenoma (PA), so it is obvious that a pharmacotherapeutic correction of these disorders can increase the efficacy of the traditional therapy of the disease.

**Aim of study:** To investigate the frequency, relationships among themselves and with PA local parameters of key systemic hormonal and metabolic disorders (obesity, insulin resistance, testosterone deficiency, vitamin D deficiency) and to develop practical algorithms for optimizing diagnosis and management based on an integrative approach.

**Material and Methods:** The results of a comprehensive examination of 160 patients with PA (main group; average age 62.3 ± 4.2 years) and 30 healthy men without PA of the same age (control group), including: collection of anamnesis and complaints; questionnaires; physical, hormonal and sonographic studies, – are presented. Pharmacotherapeutic correction methods were tested in some patients of the main group. The data was processed using descriptive and comparative statistics.

**Results and Discussion:** In the patients with PA, a significantly higher frequency of concomitant systemic hormonal and metabolic disorders formed at a younger age was established, compared to the men without PA, and significantly worse local characteristics of PA compared to the patients with PA without such ($p < 0.05$). Reliable connections of some studied systemic hormonal and metabolic disorders with one another and with local parameters of PA ($p < 0.05$) were revealed. A more severe vitamin D deficiency in the patients with PA compared to the control group was revealed, and the safety and a significant positive effect of its drug compensation on the parameters of hormonal and metabolic status and PA in D-deficient men with PA were shown ($p < 0.05$).

**Conclusion:** The results of the study confirm an important role of the studied systemic hormonal and metabolic disorders in the pathogenesis of PA and the need for their diagnosis and pharmacotherapeutic correction in all patients with PA on the basis of an integrative approach, according to the proposed algorithms.

## Keywords

prostate adenoma, lower urinary tract symptoms (LUTS), nocturia, metabolic syndrome, obesity, insulin resistance, testosterone deficiency, vitamin D deficiency, diagnosis, pharmacotherapy, optimization, integrative approach.

## Introduction

Prostate adenoma (PA) is one of the most common diseases of aging men, negatively affecting their life quality (Lopatkin 2009; Alyaev 2016).

However, the revolutionary breakthrough of modern pharmacology gave clinicians effective drugs for drug correction of the symptoms of the disease, which led to a significant reduction in the need for its surgical treatment, and the basis of modern traditional pharmacotherapy of PA are drugs affecting directly and/or predominantly the vesico-urethro-prostatic segment of the urogenital tract (α-1-blockers, M-cholinolytics, inhibitors of 5-α-reductase, β-3-adrenomimetics, phytopreparations) (Lopatkin 2009; Alyaev 2016).

Nevertheless, the current standard pharmacotherapy of PA is often not effective enough for a number of patients, especially those with systemic hormonal and metabolic disorders (obesity, insulin resistance, testosterone deficiency, vitamin D deficiency), which tends to increase in frequency in the male population and significantly reliably correlate with one another, as well as with the frequency and severity of PA (Park et al. 2008; Gorbachinsky et al. 2010; Vignozzi et al. 2012; Espinosa 2013; Tyuzikov and Kalinichenko 2016; Udensi and Tchounwou 2016; Wang et al. 2016; Zou et al. 2016; Ngai et al. 2017).

In this regard, new concepts of PA etiopathogenesis are being formed today from the standpoint of an integrative approach, which implies the most important role of the above-mentioned systemic disorders in the pathogenesis of hormonal and metabolic imbalance in the prostate gland, leading to PA and its further independent progression (the theory of cholesterol imbalance, the theory of subclinical chronic inflammation, the theory of oxidative stress, etc.), which reflects the modern evolution of classical theories of PA etiopathogenesis, many of which are also hormonal by nature (the theory of androgen-estrogen imbalance, dihydrotestosterone theory, the theory of stromal-epithelial relationships) (Ruan et al. 2011; Gacci et al. 2015; Russo et al. 2015; Tyuzikov et al. 2015; Fu et al. 2016; Zhao et al. 2016a, b). The available data from foreign literature allow us to conclude that integrative assessment of a hormonal and metabolic status and subsequent pharmacotherapeutic correction of the identified systemic hormonal and metabolic disorders in patients with PA can be considered as a more effective therapeutic option than the current strategy of standard pharmacotherapy; besides, it can have potential preventive effects in this disease. In the Russian scientific literature, there is a clear shortage of scientific publications on this topic, which makes the relevance of this study obvious.

## Aim of study

To investigate the frequency, relationships among themselves and with local parameters of PA of the key systemic hormonal and metabolic disorders (obesity, insulin resistance, testosterone deficiency, vitamin D deficiency) and to develop practical algorithms for optimizing diagnosis and management based on an integrative approach.

## Material and methods

The work was organized and carried out in accordance with the legal acts and guidelines governing the conduct of clinical trials in the Russian Federation.

All the patients who participated in the study group until the end of the study, as well as the men in the control group, had been pre-informed about the goals and objectives of the study, and each of them had signed an informed consent to participate in the study and to have his personal research results used for a further statistical analysis.

The work is based on the clinical observations, the results of a complex examination and medical treatment of the men with PA and systemic hormonal and metabolic disorders, performed in the period 2016–2018 in the outpatient departments of the Clinic of Urology of Kursk State Medical University. The total number of the examined cohort was 190 men, of which 160 patients with PA made up the main group, and 30 healthy men without PA (control group). The study was on-going, prospective and full-design in nature. The results of a comprehensive survey of the men of the control group were taken as normal reference values of the studied indicators.

Criteria for inclusion in the study:

- The presence of PA in combination with the studied hormonal and metabolic disorders (obesity, insulin resistance, testosterone deficiency, vitamin D deficiency);
- The absence of diabetes mellitus resistant to the standard therapy;
- No history of surgical operations, neurological diseases or injuries (and their consequences) of the pelvic area and perineum.

Criteria for exclusion from the study:

- The presence of the prostate middle lobe (intravesical growth of PA);
- Complicated course of PA, including the presence of acute urinary retention (AUR) in the history,

even though it happened once and/or was stopped by medication;
- The presence of absolute indications for surgical treatment of PA, according to the results of a comprehensive examination of the patient;
- Existing or suspected prostate cancer (total blood PSA > 4 ng/ml);
- Any pharmacotherapy for PA performed at least 6 months before hands.

Statistical processing of the age index of the control group of men without PA (n = 30) rendered an average age of 58.3 ± 3.5 years (confidence interval being 0.95|4869), and for the patients with PA of the main group (n = 160), an average age was 62.3 ± 4.2 years (confidence interval being 0.95|45–75) ($p < 0.05$) (Table 1).

The distribution of patients with PA by the severity of LUTS/PA, quality of life index and assessment of nocturia in them are presented in Tables 2–3.

Complaints and anamnestic data on generally accepted medical techniques were collected from all the patients before the examination and treatment.

To objectify and assess the severity of symptoms of the lower urinary tract associated with PA (LUTS/AP), as well as the quality of life due to them, a questionnaire was conducted according to the scale of the assessment of the symptoms of prostate diseases (IPSS-LQ). To assess the possible symptoms of age-related testosterone deficiency in men, the AMS (Aging Males Symptoms) questionnaire was used. All the men underwent a General physical clinical examination according to the standard method with additional studies (measurement of waist circumference, detection of cutaneous markers of insulin resistance (acanthosis nigricans of large skin folds, recurrent cutaneous papillomatosis)) and testosterone deficiency (gynecomastia). A special urological examination was also performed for all the men included in the study (assessment of pubic hair distribution, examination and palpation of the scrotum and penis, finger rectal examination (FRE) of the prostate gland, according to the generally accepted methodology in urology). Laboratory diagnostics of insulin resistance was carried out on the basis of simultaneous determination of blood plasma levels of glucose (glucose oxidase method) and insulin (by radioimmune analysis, or RIA). Blood sampling for the study was carried out from the peripheral (cubital) vein in the morning on an empty stomach. Laboratory diagnostics of testosterone deficiency was carried out on the basis of simultaneous determination of the total testosterone level in blood plasma (by enhanced chemiluminescence using an automatic analyzer Vitros ECi (Ortho-Clinical Diagnostics, J&J, UK) and the level of globulin binding sex steroids (GBSS) by enzyme immunoassay (EI), using an automatic analyzer Elecsys 2010 (Hoffmann-La Roche)), followed by the calculation of the level of free testosterone using a special calculation formula available through specialized Internet services. Laboratory diagnosis of vitamin D deficiency was carried out in accordance with the Russian clinical recommendations Vitamin D Deficiency in Adults: Diagnosis, Treatment and Prevention on the basis of determination of the concentration of inactive form 25(OH)-vitamin D in serum by enhanced chemiluminescence, as an objective generally accepted indicator of the adequacy of the D-status of the human body. Determination of total PSA level in blood serum was carried out by immunochemical analysis (ICA) through electrochemiluminescence detection (ECLD), using an analyzer and a test system Cobas 6000 (Roche Diagnostics, Switzerland). To test the

**Table 1.** Age Distribution in the Study Groups (n = 190).

| Age (years) | Control group (n = 30) | | Main group (n = 160) | |
|---|---|---|---|---|
| | Absolute number (people) | Percentage (%) | Absolute number (people) | Percentage (%) |
| 45–55 | 9 | 30.0 | 42 | 26.3 |
| 55–65 | 10 | 33.3 | 54 | 33.7 |
| 65–75 | 11 | 36.7 | 64 | 40.0 |
| Total | 30 | 100.0 | 160 | 100.0 |

**Table 2.** Distribution of Patients with PA of the main group by the degree of severity of LUTS/PA and the quality of life index (QL) (M ± m; n = 160).

| Severity of LUTS/PA according to IPSS scale LQ (points) | Life quality index (LQ) (average score and confidence interval 0,95) | Absolute number of patients | Percentage of the total number of patients (%) |
|---|---|---|---|
| 0–7 (slight LUTS) | 1.2 ± 0.6 (1–2) | 78 | 48.8 |
| 8–19 (mild LUTS) | 3.3 ± 0.3 (1–4) | 61 | 38.1 |
| 20–22 (severe LUTS) | 5.1 ± 0.2 (2–6) | 21 | 13.1 |
| Total | 2.9 ± 0.3 (0–5) | 160 | 100.0 |

**Note:** LUTS – lower urinary tract symptoms; PA – prostate adenoma; IPSS – International Prostate Symptoms Score; LQ –Life Quality.

**Table 3.** Frequency of nocturia and severity of LUTS in patients with PA (n = 160).

| Degree of LUTS/PA severity according to IPSS-LQ scale (points) (Absolute number of patients and percentage of total number of patients) | Average frequency of nocturia (Absolute number of patients and percentage of total number of the corresponding group of patients) | Frequency of single nycturia (Absolute number of patients and percentage of number of patients with nycturia in this group) | Frequency of repeated nocturia (Absolute number of patients and percentage of patients with nocturia in this group) |
|---|---|---|---|
| 0–7 (slight LUTS) (n = 78, or 48.8%) | 43 (55.1%) | 43 (55.1%) | – |
| 8–19 (mild LUTS) (n = 61, or 38.1%) | 35 (57.4%) | 20 (57.2%) | 15 (42.8%) |
| 20–35 (severe LUTS CHMII) (n = 21, or 13.1%) | 18 (85.7%) | 10 (55.5%) | 8 (44.5%) |
| Total: (n = 160, or 100.0%) | 96/160 (60.0%) | 73/160 (45.6%) | 23/160 (14.4%) |

**Note:** LUTS – lower urinary tract symptoms; PA – prostate adenoma; IPSS –International Prostate Symptoms Score; LQ – Life Quality.

reference parameters of healthy men (prostate volume, its structure, the amount of residual urine), as well as to assess the initial morphometric parameters of the prostate and bladder and their dynamics during observation and pharmacotherapy, TRU was performed to all the men included in the study of the main and control groups, using a 5.5 to 7 MHz rectal biplane probe (ultrasonic device "Ultramark-9") and an ultrasonic complex Logiq 500 Proseries. As a drug for pharmacological correction of vitamin D deficiency, a drug Aquadetrim, licensed in Russia for the main indications, had been chosen, which was prescribed at the stage of starting the therapy at a daily dose of 10,000 IU once, and after the elimination of laboratory vitamin D deficiency (plasma level of 25(OH)-vitamin D > 75 nmol/l) – at a preventive dose of 3000 IU/day once, in accordance with the Russian clinical recommendations. The total duration of administering vitamin D-containg Aquadetrim to the D-deficient patients with PA was 12 months, during which its efficacy and safety were evaluated on the basis of periodic clinical, laboratory and instrumental monitoring. Statistical processing was performed using Microsoft Excel 2007 and Statistica 6.0. (StatSoft, USA). The data were processed using descriptive and comparative statistics. The results of the study were entered into a personal computer running Microsoft Excel–2007 and Statistica 6.0. The Spearman correlation coefficient (r) was determined to study the relationship of quantitative features among themselves. The Student's criterion was used to estimate the intergroup differences in the feature values with a continuous distribution. To solve the tasks of studying the influence of two or more conditions on a certain random variable, various statistical methods of multivariate analysis were used. The critical level of reliability of the null statistical hypothesis (the absence of significant intergroup differences or factor influences) was assumed to be 0.05. The value of $p < 0.05$ was considered statistically significant for all indicators generally accepted in biomedical studies.

## Results and discussion

The study revealed a statistically significant higher frequency of systemic hormonal and metabolic disorders in patients with PA compared with healthy men without PA. Thus, the incidence of obesity in patients with PA was 42.5% versus 23.3% in healthy men without PA, that is on average 1.8 times more often ($p < 0.05$) (Fig. 1). At the same time, the incidence of obesity and the rate of its progression in patients with PA at a younger age (45–55 years) was 1.8 times (26.5% vs. 14.3%; $p < 0.05$) and 2.7 times, respectively, significantly higher, compared with men of the same age of the control group without PA ($p < 0.05$). Despite the fact that in the main and control groups there were no significant differences between the absolute values of plasma glucose level (glycemia), 30.0% of patients of the main group had a significantly higher average blood insulin level compared to that in the control group ($p < 0.05$), which allowed detecting the laboratory symptom of hyper-insulinemia (insulin resistance) in them, the most common in obesity (Fig. 1.) The frequency of clinical and laboratory signs of testosterone

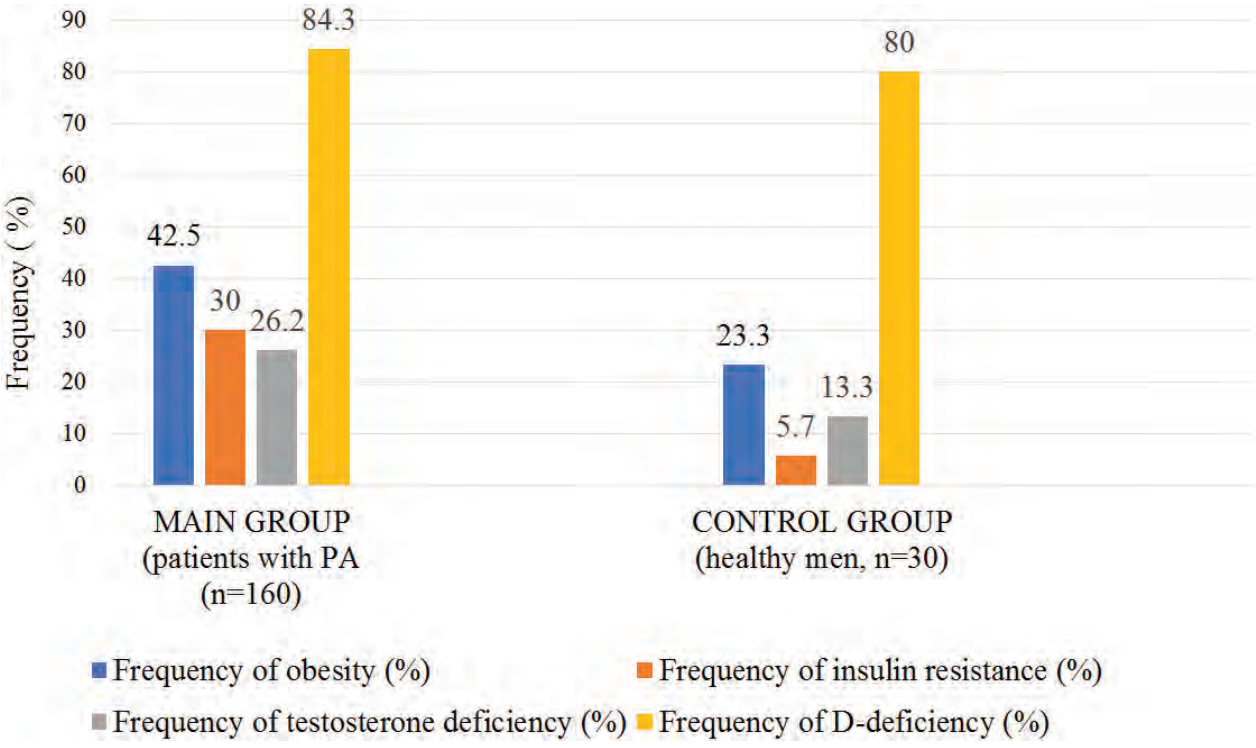


**Figure 1.** Distribution of detected systemic hormonal and metabolic disorders in the main and control groups (frequency %).

deficiency in patients with PA was 2 times significantly higher than that of men in the control group without PA (26.2% vs. 13.3%; $p < 0.05$) (Fig. 1.). As a characteristic feature of testosterone deficiency in PA should be considered its early chronological manifestation in 16.7% of middle-aged men (45–55 years), and the most severe forms of testosterone deficiency in patients with PA were encountered in obese patients. The study also demonstrated an extremely high incidence of vitamin D deficiency in both the control group of men without PA (80.0%) and in the main group of patients with PA (84.3%) ($p<0.1$), which with age in both groups had similar trends to increase in both groups; however, men of the control group without PA had a significantly more compensated D-status (higher (on average 2.2-time) plasma levels of 25(OH)-vitamin D) compared with patients with PA of the main group ($p < 0.05$) (Fig. 1).

In the patients with PA and systemic hormonal and metabolic disorders, a negative relationship between the waist circumference and the free calculated testosterone level was revealed ($n = 68$; $r = -0,265$; $p < 0.05$); a positive relationship between the waist circumference and the blood insulin level ($n = 68$; $r = + 0,312$; $p < 0.05$) and a positive relationship between the level of 25(OH)-vitamin D and the level of total blood testosterone ($n = 135$; $r = +0,356$; $p < 0.05$).

In the patients with PA and systemic hormonal and metabolic disorders (the main group), unlike the patients who did not have them, and the men of the control group as a whole, significantly worse local parameters of PA were revealed ($p < 0.05$). Thus, the total score of clinical symptoms according to the IPSS scale and the frequency of nocturia in patients with PA and systemic hormonal and metabolic disorders were 80.0% and 2.7 times significantly higher, respectively, than in the patients with PA who did not have them ($p < 0.05$), which was accompanied by a lower quality of life. In addition, the established fact of a higher (1.8-time) level of total blood PSA in the patients with PA and hormonal and metabolic disorders compared with the men without PA of the control group and the patients with PA without hormonal and metabolic disorders, which, however, did not exceed the upper value of the reference range of the norm ($p < 0.05$), drew attention to itself. In the patients with PA and systemic hormonal and metabolic disorders, the average volume of the prostate gland was by 38.8%, and the amount of residual urine – by 73%, respectively, significantly higher than in the patients with PA without them, and on average – 2.5 and 6 times more, respectively, than in the control group ($p < 0.05$). The correlation multifactorial analysis in the patients with PA and systemic hormonal and metabolic disorders revealed: a positive relationship between the waist circumference and the prostate volume ($n = 60$; $r = + 0.289$; $p < 0.05$); a positive relationship between the plasma level of insulin and the prostate volume ($n = 60$; $r = + 0.413$; $p < 0.05$); a significant negative relationship between the plasma level of total testosterone and the amount of residual urine ($n = 60$; $r = -0.256$; $p < 0.05$); a significant negative relationship between the plasma level of 25(OH)-vitamin D and the prostate volume ($n = 60$; $r = -0,212$; $p < 0.05$).

A comparative analysis of the impact of drug compensation of vitamin D deficiency on the indicators of hormonal and metabolic status of patients and local parameters of PA was conducted in two groups of D-deficient patients with PA and systemic hormonal and metabolic disorders: Group 1 ($n = 40$) did not receive the vitamin D drug and Group 2 ($n = 40$) received the vitamin D drug in accordance with the previously described design of the pharmacological part of the study. In the Group 1 patients, who were not treated with vitamin D, further progression of vitamin D deficiency was revealed (with a significant decrease in the average value of plasma 25(OH)-vitamin D from $16.3 \pm 0.2$ to $15.6 \pm 0.3$ nmol/L, respectively, or an average of 3.0%; $p < 0.05$) by the 12th month of the monitoring, which was accompanied by a progressive, although statistically insignificant, decrease in the level of total blood testosterone compared to its baseline level (from $13.4 \pm 0.4$ to $13.1 \pm 0.5$ nmol/L, respectively, or an average of 2.2%; $p < 0.1$) and a significant increase in the average level of plasma insulin compared to its baseline level (from $17.4 \pm 0.8$ to $19.6 \pm 0.9$ µed/ml, respectively, or an average of 12.6%; $p < 0.05$), indicating progression of insulin resistance in the D-deficient patients with PA. On the contrary, along with the gradual elimination of vitamin D deficiency (normalization of the plasma level of 25(OH)-vitamin D) in the patients with PA of Group 2, starting with the 6th month of the vitamin D therapy (since the total elimination of laboratory vitamin D deficiency in all the patients), there were positive changes in their hormonal and metabolic status, which by the 12th month of the therapy were in a significant increase in the total blood testosterone level by 15.6% from its initial level before the treatment ($16,0 \pm 0,3$ nmol/L vs. $14.1 \pm 0.6$ nmol/L, respectively) ($p < 0.05$) and in stabilization of the plasma insulin level (stabilization of insulin resistance) ($p < 0.1$). The effect of the vitamin D therapy on the waist circumference in both groups was not statistically significant ($p > 0.1$).

In Group 1, within 12 months, against the background of progression of systemic hormonal and metabolic disorders, PA itself progressed as well (the average annual increase in its volume by transrectal ultrasound was an average of 1.9% (from $40.2 \pm 1.5$ $cm^3$ to $44.9 \pm 1.7$ $cm^3$, respectively) ($p < 0.05$). On the contrary, in Group 2, by the 12th month of the therapy with vitamin D, there was a significant 22.9% decrease in the volume of the prostate gland compared to its initial volume before the treatment ($35.2 \pm 0.9$ $cm^3$ versus $45.7 \pm 1.3$ $cm^3$, respectively) ($p < 0.05$). At the same time, the amount of residual urine in the Group 2 patients by the 12th month of the therapy was on average by 23.3% significantly less than the same indicator of Group 1 without treatment ($29.6 \pm 2.6$ ml vs. $38.6 \pm 2.4$ ml; $p < 0.05$) (Fig. 2).

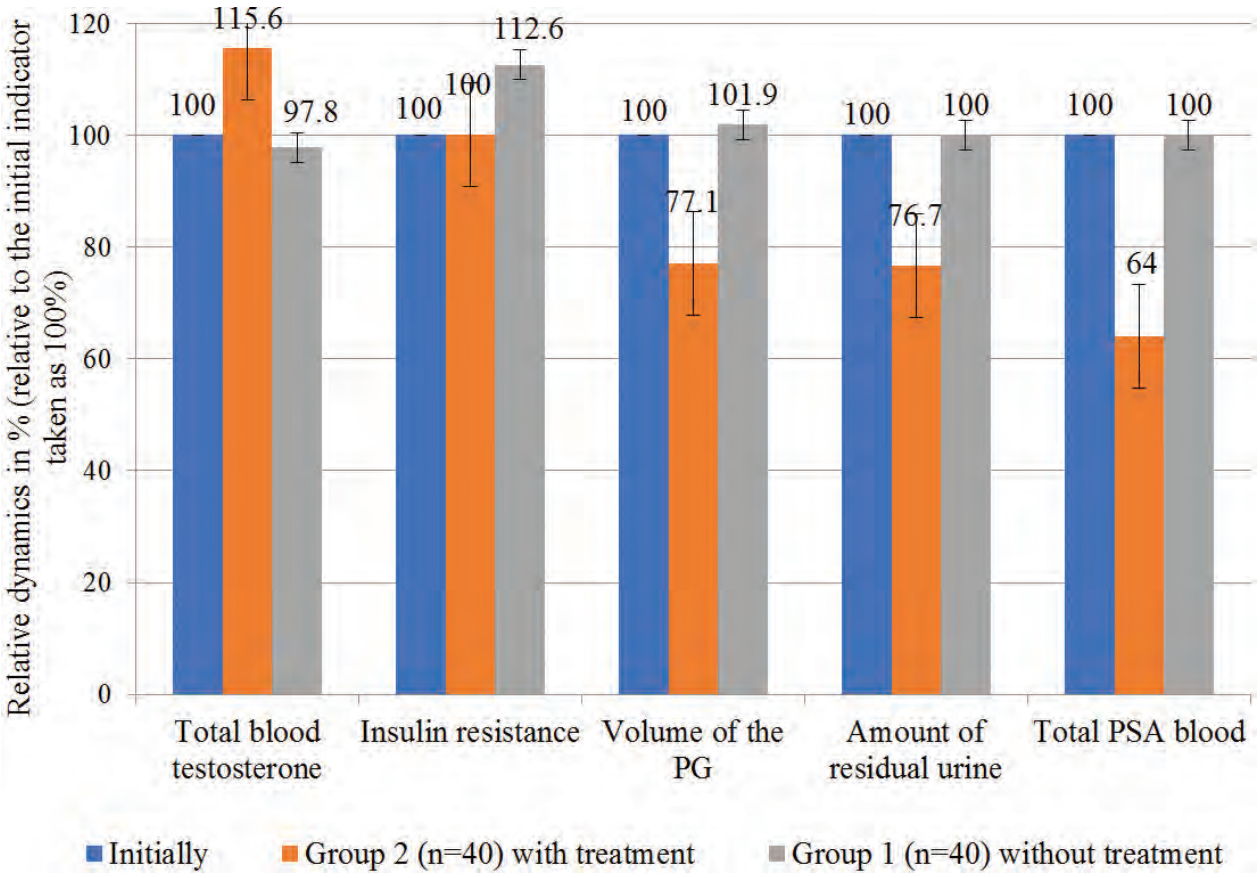


**Figure 2.** Comparative characteristics of the dynamics of hormonal and metabolic status and local parameters of the prostate gland in patients with PA depending on the presence/absence of treatment with vitamin D (n = 80). Note: PG – prostate gland; PSA – prostate-specific antigen.

For 12 months of the therapy, no fluctuations in the level of the total blood PSA suspicious for prostate cancer were observed, while the level of this marker in the patients of Group 2 was on average by 36.0% less than the same indicator in Group 1 (2.0 ± 0.3 ng/ml vs. 2.9 ± 0.4 ng/ml, respectively; $p<0.05$), which indicated a high level of prostatic safety of the treatment with vitamin D.

Improvement of the hormonal and metabolic status and local parameters of PA in the Group 2 patients, when compensating for vitamin D deficiency, 12 months later resulted in the clinically significantly better indicators of the severity of LUTS/PA and the life quality index (LQI) compared with the patients of Subgroup 1, while the frequency of nocturia in Group 2 significantly decreased from 30/40 (75.0%) to 19/40 (47.5%), i.e., on average, by 27.5% from the initial ($p < 0.05$), in contrast to Group 1, where these indicators even further deteriorated ($p < 0.1$) by the 12$^{th}$ month of the dynamic observation (Fig. 3).

Thus, in patients with PA, a significantly higher frequency of concomitant systemic hormonal and metabolic disorders (obesity – 42.5%, insulin resistance – 30.0%, testosterone deficiency – 26.2%, vitamin D deficiency – 84.3%) was established, which are usually formed at a younger age (45–55 years) compared with the men without PA ($p < 0.05$). Significant connections were established between them, which makes it possible to conclude about their close interaction and the ability to influence and aggravate each other. At the same time, in the patients with PA and systemic hormonal and metabolic disorders, significantly worse local PA characteristics (more pronounced LUTS/nocturia, lower quality of life, relatively higher level of total blood PSA, prostate volume and residual urine) were detected, unlike in the patients with PA without hormonal and metabolic discredit and in the healthy men. The presence of significant links between the severity of obesity, insulin resistance, testosterone deficiency and vitamin D deficiency with local parameters of PA (prostate volume and amount of residual urine) allows considering them as the most important modern systemic hormonal and metabolic factors of PA pathogenesis.

A high frequency of vitamin D deficiency, both in the population of men without PA (80.0%) and in the patients with PA (84.3%), as well as the presence of more severe laboratory vitamin D deficiency in the patients with PA justify the pathogenetic feasibility of early detection and drug correction of vitamin D deficiency. According to the results of the present study, pharmacological compensation of vitamin D deficiency in the patients with PA for 12 months allows achieving a significant improvement of the

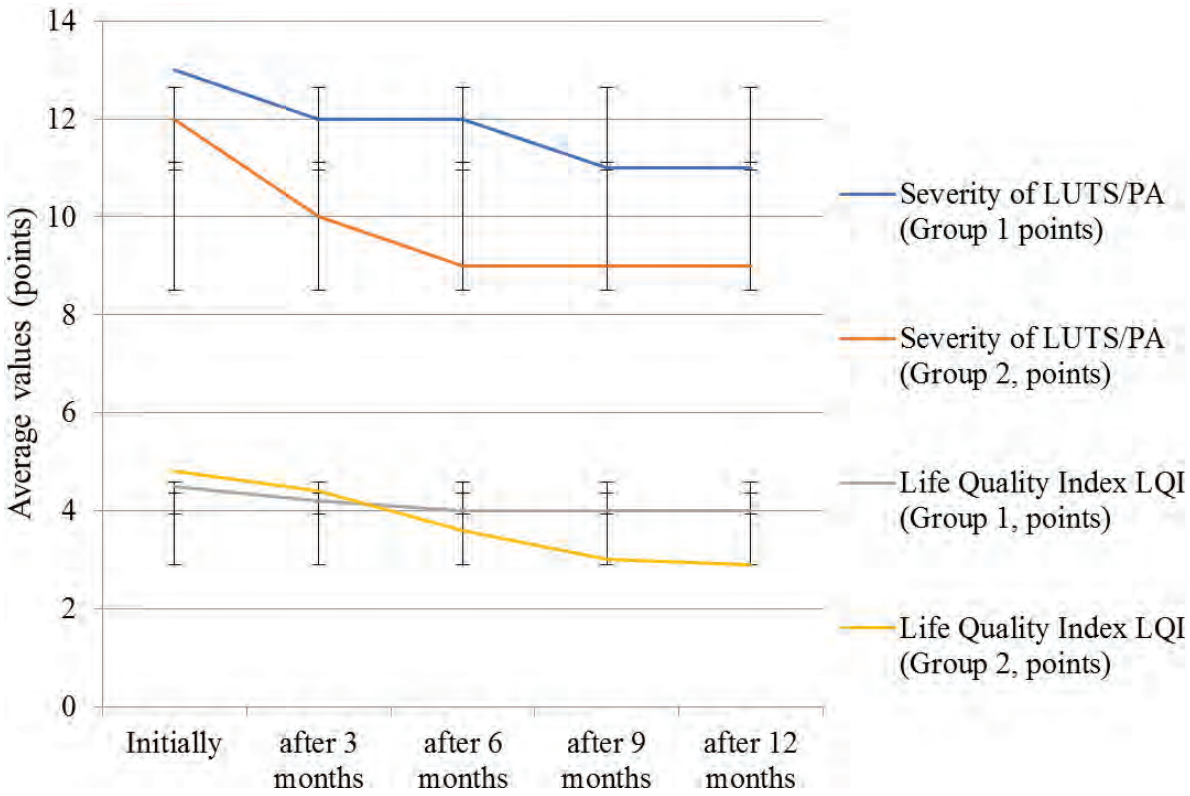


**Figure 3.** Comparative dynamics of LUTS/PA severity (IPSS) and Life Quality Index (LQI) in patients of Groups 1 and 2 for 12 months (n = 80). Note: LUTS – lower urinary tract symptoms; PA – prostate adenoma; IPSS – International Prostate Score Symptom's (international scale assessment of prostatic symptoms); LQ –Life Quality (life quality).

key local parameters of PA (reduce the severity of LUTS/PA, reduce the frequency of nocturia by 27.5%, decrease the prostate volume by 22.9% and the amount of residual urine by 23.3% from the baseline). At the same time, it has a simultaneous positive effect on a systemic hormonal and metabolic status (in particular, on the androgen status (a significant increase in the level of total blood testosterone on average by 15.6% from baseline to the end of the therapy) and carbohydrate metabolism (stabilization of existing insulin resistance) without any side effects, with a high level of compliance and prostatic safety (significant reduction in the total blood PSA level – by 36% from the baseline). All of that results in a significant improvement of life quality for the D-deficient patients with PA on the background of systemic hormonal and metabolic disorders.

Therefore, drug compensation of vitamin D deficiency should be considered as the most important, effective and safe pharmacotherapeutic "first line" option in the treatment of PA, since it predetermines both its independent positive prostatic antiproliferative effects and the effects associated with the improvement of the clinical course of testosterone deficiency and insulin resistance associated with vitamin D deficiency.

Based on the results of the study, an original integrative model of hormonal and metabolic pathogenesis of PA was proposed (Fig. 4).

In this model, black solid arrows of various directions indicate the relationship between obesity, insulin resistance, testosterone deficiency and vitamin D deficiency, which has already been studied in numerous studies. These arrows also show the potential mechanisms of influence that these systemic factors have on the local parameters of the prostate gland in PA, which have also been properly studied in a number of studies. Red dotted lines depict the relationship of systemic and local mechanisms in PA pathogenesis, established in the course of this study. The question marks in some of the mechanisms under consideration refer to the presumptions (since no unambiguously objective and reliable confirmation of them was obtained in the course of this study), or they appeared in the course of this study, but they were not included in either its aims and objectives. It is clear that further evidence-based research is needed to answer these questions. In order to optimize the treatment and diagnostic search in case of PA to the fullest, against the background of systemic hormonal and metabolic disorders and on the basis of the results of the study, a optimized algorithms of the routine clinical practice to diagnose and manage patients with PA with hormonal and metabolic disorders were developed, based on interdisciplinary and integrative principles (Figs 5, 6.).

Thus, the proposed practical algorithms are designed to improve a traditional PA diagnostics carried out in a routine urological practice and to change the approaches

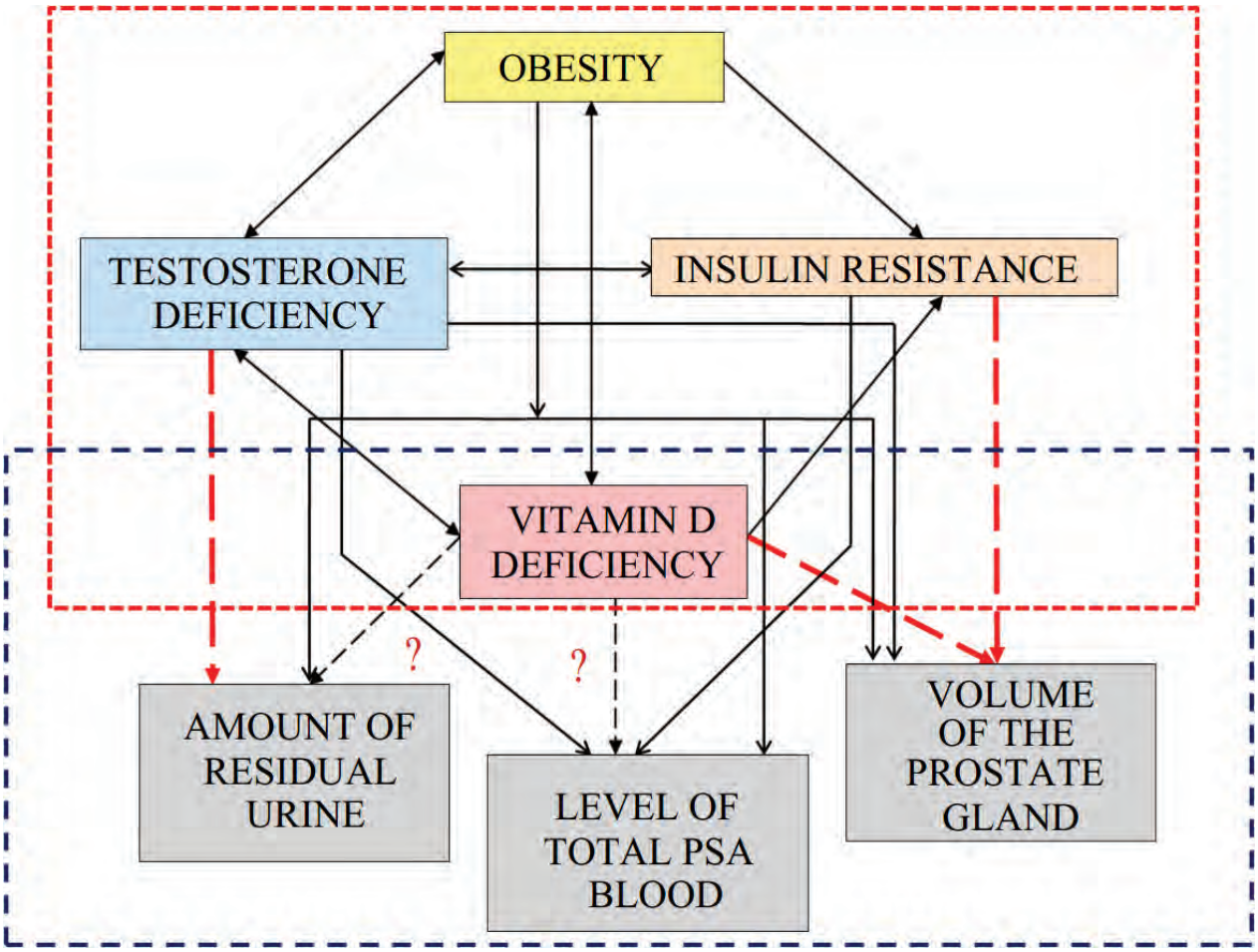


**Figure 4.** Integrative original model of hormonal and metabolic pathogenesis of PA, according to the results of the study.

to the management of patients with the disease in order to improve its pathogenetic diagnostics and treatment and, perhaps, to outline some concrete ways of its prevention through early detection and effective therapy of all systemic hormonal and metabolic factors identified during the examination of the patient with PA, in combination with the standard PA therapy by means of the medicines recommended in urology, mostly having only local effects on the vesico-urethro-prostatic segment of the male urogenital tract.

## Conclusion

The results strongly suggest a significant role of systemic hormonal and metabolic disorders in men (obesity, insulin resistance, testosterone deficiency, vitamin D deficiency) in the multifactorial pathogenesis of PA in them. These findings can be considered as a clinical justification of a new direction in the PA pharmacotherapy, based on an integrative and interdisciplinary approach, namely – on mandatory diagnosis and subsequent correction of systemic hormonal and metabolic disorders in all men with PA, against the background of taking specialized diagnostic and therapeutic measures within the existing standards of providing specialized medical care and clinical recommendations of various levels.

The obvious prospects for subsequent development of an integrative approach to the diagnosis and treatment of PA are believed to be further studies of these and other systemic hormonal and metabolic disorders potentially involved in the complex pathogenesis of PA, as well as a search for new drugs among pharmacological agents with systemic and local effects in this disease in order to further optimize and improve the efficacy of the PA pharmacotherapy.

The promising area is definitely carrying out major evidence-based studies aimed at investigating the prophylactic efficacy of the pharmacological correction of systemic hormonal and metabolic disorders in PA, because an effective pathogenetic pharmacological prevention of the disease at the evidence-based methodological level has not been well developed yet.

## Conflict of interests

The authors declare no conflict of interest.

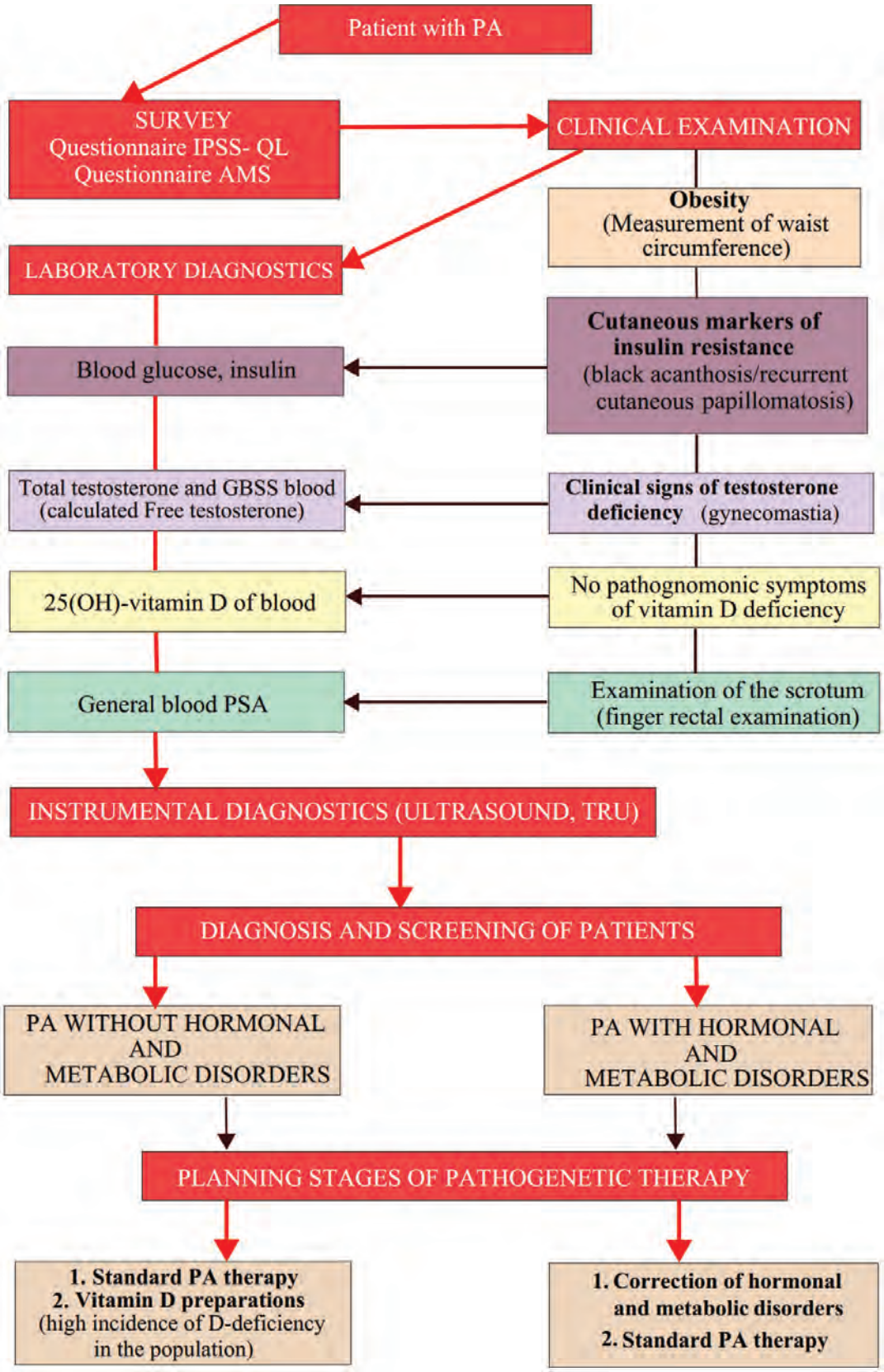


**Figure 5.** Practical algorithm of optimized diagnostics of hormonal and metabolic disorders and screening in patients with PA. Note: PA – prostate adenoma; LUTS – lower urinary tract symptoms; IPSS – International Prostate Score Symptom's (international scale assessment of prostatic symptoms); LQ – Life Quality (quality of life); AMS – Aging Men Score (scale of evaluation of symptoms of aging men); GSPS – globulin binding sex steroids; PSA – prostate-specific antigen; Ultrasound-ultrasound examination; TRU – transrectal ultrasound examination.

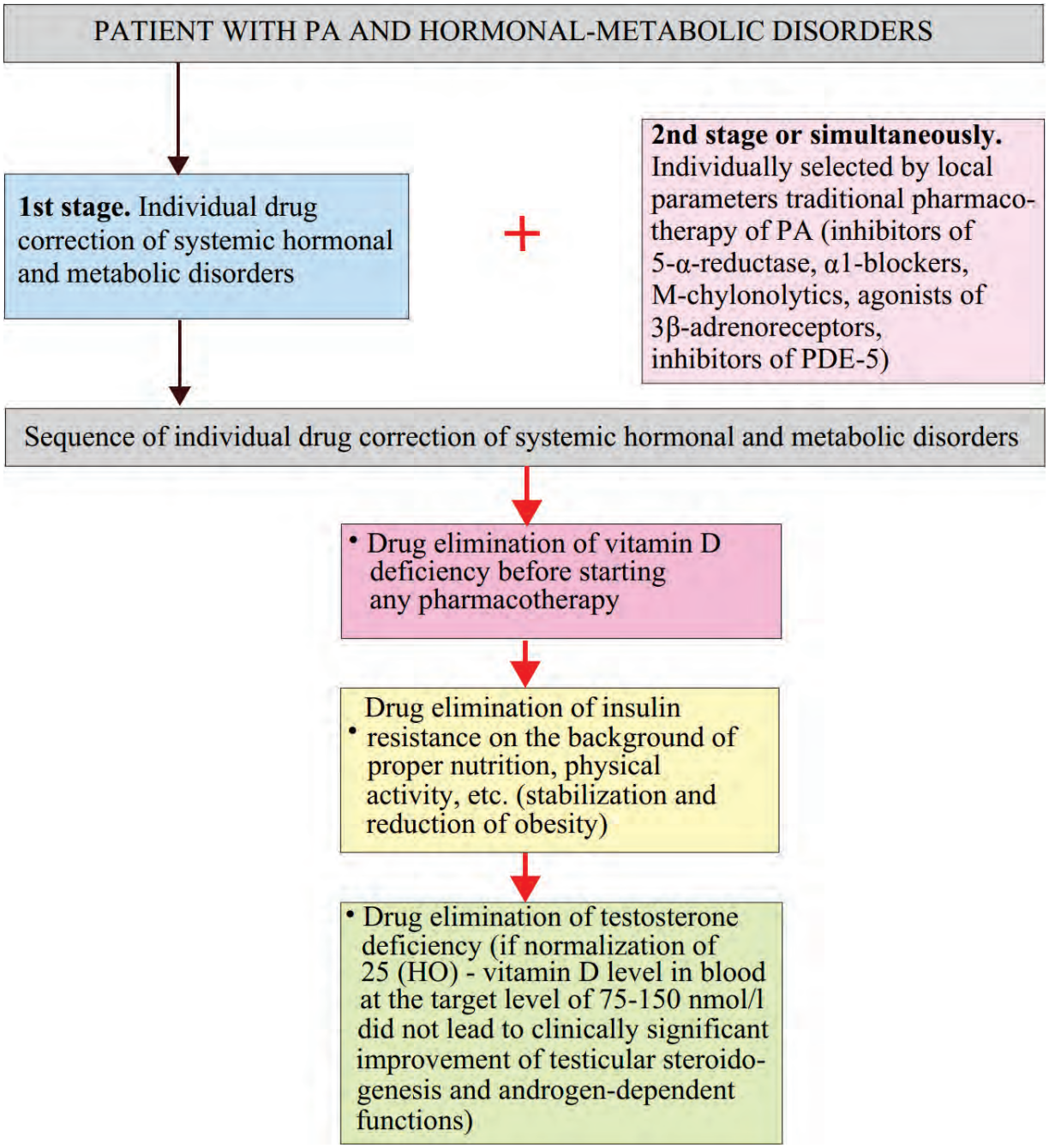


**Figure 6.** Practical algorithm of optimized diagnostics of hormonal and metabolic disorders and screening in patients with PA. Note: PA – prostate adenoma; PDE – 5-phosphodiesterase type 5.

## References


- Alyaev U, Glybochko P, Pushkar D [Ed.] (2016) Urology. Russian Clinical Guidelines. GEOTAR-Media, Moscow, 496 pp. [in Russian]
- Espinosa G (2013) Nutrition and benign prostatic hyperplasia. Current Opinion in Urology 23(1): 38–41. https://doi.org/10.1097/MOU.0b013e32835abd05 [PubMed]
- Fu Y, Zhou Z, Yang B, Zhang K, He L, Zhang X (2016) The relationship between the clinical progression of benign prostatic hyperplasia and metabolic syndrome: a prospective study. Urologia Internationalis 97(3): 330–335. https://doi.org/10.1159/000448484 [PubMed]
- Gacci M, Corona G, Vignozzi L, Salvi M, Serni S, De Nunzio C, Tubaro A, Oelke M, Carini M, Maggi M (2015) Metabolic syndrome and benign prostatic enlargement: a systematic review and meta-analisys. BJU International 115(1): 24–31. https://doi.org/10.1111/bju.12728 [PubMed]
- Gorbachinsky I, Akpinar H, Assimos DG (2010) Metabolic syndrome and urological diseases. Reviews in Urology 12(4): 157–180. [PubMed] [PMC]
- Lopatkin N [Ed.] (2009) Urology. National Guidance. GEOTAR-Media, Moscow, 1024 pp. [in Russian]

- Ngai HY, Yuen KS, Ng CM, Cheng CH, Chu SP (2017) Metabolic syndrome and benign prostatic hyperplasia: an update. Asian Journal of Urology 4(3): 164–173. https://doi.org/10.1016/j.ajur.2017.05.001 [PubMed] [PMC]
- Park HK, Lee HW, Lee KS, Byun SS, Jeong SJ, Hong SK, Lee SE, Park JH, Lee SB, Kim KW (2008) Relationship between lower urinary tract symptoms and metabolic syndrome in a community based elderly population. Urology 72(3): 556–560. https://doi.org/10.1016/j.urology.2008.03.043 [PubMed]
- Ruan L, Zhong WD, Li ZM, Hua X (2011) Relationship between vitamin D receptor gene Fok I polymorphisms and benignprostatic hyperplasia complicated by histological prostatitis. National Journal of Andrology [Zhonghua Nan Ke Xue] 17(10): 880–883. [PubMed]
- Russo GI, Castelli T, Urzì D, Privitera S, La Vignera S, Condorelli RA, Calogero AE, Favilla V, Cimino S, Morgia G (2015) Emerging link between non-neurogenic lower urinary tract symptoms secondary to benign prostatic obstruction, metabolic syndrome and its components: a systematic review. International Journal of Urology 22(11): 982–990. https://doi.org/10.1111/iju.12877 [PubMed]
- Tyuzikov I, Grekov E, Kalinichenko S (2015) Variants of clinical course and morphometric parameters of benign prostatic hyperplasia in men with metabolic syndrome and androgenic deficiency. Urology [Urologiya] 5: 66–69. [in Russian]
- Tyuzikov I, Kalinichenko S (2016) Benign prostatic hyperplasia (BPH) as a systemic hormonal-metabolic disease: time to change the paradigm of pathogenesis and pharmacotherapy. Effective Pharmacotherapy [Effektivnaya Farmakoterapiya] 3: 32–53. [in Russian]
- Udensi UK, Tchounwou PB (2016) Oxidative stress in prostate hyperplasia and carcinogenesis. Journal of Experimental and Clinical Cancer Research: CR 35(1): 1–139. https://doi.org/10.1186/s13046-016-0418-8 [PubMed] [PMC]
- Vignozzi L, Morelli A, Sarchielli E, Comeglio P, Filippi S, Cellai I, Maneschi E, Serni S, Gacci M, Carini M, Piccinni MP, Saad F, Adorini L, Vannelli GB, Maggi M (2012) Testosterone protects from metabolic syndrome-associated prostate inflammation: an experimental study in rabbit. The Journal of Endocrinology 212(1): 71–84. https://doi.org/10.1530/JOE-11-0289 [PubMed]
- Wang JY, Fu YY, Kang DY (2016) The association between metabolic syndrome and characteristics of benign prostatic hyperplasia: A Systematic Review and Meta-Analysis. Medicine (Baltimore) 95(19): e3243. https://doi.org/10.1097/MD.0000000000003243 [PubMed] [PMC]
- Zhao S, Chen C, Chen Z, Xia M, Tang J, Shao S, Yan Y (2016) Relationship between metabolic syndrome and predictors for clinical benign prostatic hyperplasia progression and international prostate symptom score in patients with moderate to severe lower urinary tract symptoms. Urology Journal 13(3): 2717–2726. https://doi.org/10.22037/uj.v13i3.3225 [PubMed]
- Zhao S, Tang J, Shao S, Yan Y (2016a) The relationship between benign prostatic hyperplasia/lower urinary tract symptoms and mean platelet volume: the role of metabolic syndrome. Urologia Internationalis 96(4): 449–458. https://doi.org/10.1159/000443313 [PubMed]
- Zou C, Gong D, Fang N, Fan Y (2016b) Meta-analysis of metabolic syndrome and benign prostatic hyperplasia in Chinese patients. World Journal of Urology 34(2): 281–289. https://doi.org/10.1007/s00345-015-1626-0 [PubMed]


## Author contributions


- **Oleg I. Bratchikov**, Doctor of Medical Sciences, Professor, Head of the Department of Urology, e-mail: bratov45@mail.ru, **ORCID ID** http://orcid.org/0000-0002-0906-9851. The author developed the research design, analyzed the obtained data and was engaged in the article writing.
- **Igor A. Tyuzikov**, Doctor of Medical Sciences, Professor, Urologist, e-mail: phoenix-67@list.ru, **ORCID ID** http://orcid.org/0000-0001-6316-9020. The author obtained the data for analysis, analyzed the obtained data, and was engaged in the article writing.
- **Sergey O. Artishchev,** Postgraduate Student, Department of Urology, e-mail: artishchev_sergey@yandex.ru, **ORCID ID** http://orcid.org/0000-0003-1321-4617. The author reviewed the literature on the topic of the article and analyzed the obtained data.