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METABOLIC DISORDERS: A PROSPECTIVE TARGET IN THE PROSTATE CANCER TREATMENT COMPLEX

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Abstract

Prostate cancer (PC) is currently one of the most socially significant world oncological diseases. In many regions PC ranks first in the structure of oncological diseases and leading position in elderly men mortality structure. Taking into account the great importance of metabolic disorders in the carcinogenesis and the aggressive course of PC, the diseases with metabolic component (cardio-vascular, obesity, diabetes mellitus) are activiely studied. Their common feature is metabolic dyslipidemia. While the feasibility and effectiveness of metabolic disorders correction in PC is the object of close attention of many researchers the results of studies are very contradictory - from a negative impact or complete absence of any effect to a significant improvement in survival rates. Correction of metabolic disorders is currently achieved by metabolic drugs, in particular, statins and metformin. Some studies have established a positive effect of this therapy on the course of PC. This indicates its prospects as an additional method in the complex therapy of PC.

Key words: **prostate cancer; diabetes mellitus; obesity; metabolic dyslipidemia; metabolic syndrome; statins; metformin**.

Relevance of the problem

Prostate cancer (PC) is currently one of the most socially significant oncological diseases all over the world. In its many regions PC ranks first in the structure of oncological diseases and occupies leading positions in the mortality of elderly men [16; 62]. In Ukraine in recent years there has been an increase in the incidence and mortality because of PC [5; 6; 60], the ratio between morbidity and mortality is 37.1%, which is twice as bad as in developed countries (17.8%) [2].

Taking into account the great importance of metabolic disorders in the carcinogenesis of PC [50; 51; 63; 70; 74], diseases with a metabolic component are actively studied as risk factors for aggressive course of PCA, in particular, cardiovascular diseases (CVD), obesity, diabetes mellitus (DM) and metabolic syndrome (MS). Their common feature is metabolic dyslipidemia [11; 32; 52]. The feasibility and effectiveness of correction of metabolic disorders in PC, in particular, with statins and/or metformin, is actively studied, but the results of the studies are very contradictory - from a negative impact or complete absence of any effect [12; 43] to a significant improvement in survival rates [34; 45; 73; 75].

The purpose: to review publications devoted to metabolic disorders and the feasibility and effectiveness of their correction in PC patients.

Materials and methods. A search and analysis of publications with the results of metabolic disorders studies, their role in pathogenesis and correction of PC has been made. The data base of the US National Institutes of Health *MedLine* was used. Key words "prostate cancer" , “diabetes mellitus", "obesity", "metabolic dyslipidemia", "metabolic syndrome", "statins", "metformin" were considered; search depth was 10 years.

Results. *Metabolic disorders as PC and its aggressive course risk factor*.

The past decades progress of medicine and related sciences has ensured the invention and widespread implementation of revolutionary pharmacotherapeutic and invasive treatment methods, which has significantly increased human life expectancy. At the global level, the largest increase in average life expectancy has been observed since 2000 [22]. This definitely positive trend in the life of mankind has led to a significant increase in the proportion of people over 60 years of age, which currently reaches 24% compared to 16.9% in 1990 [54]. In Ukraine in 2022, persons of 60 y.o. and over composed 24.8% [3].

At the same time, the frequency of “age-related diseases” associated with aging is increasing.

This is characterized by oxidative damage to cellular structures, disruption of all types of metabolism, functional and structural changes in all organs and systems of the human body

[7; 35]. To some extent, age-related diseases include prostate cancer, which has the highest incidence in men aged 75-79 years [6], CVD, obesity, diabetes mellitus and other diseases that arise against the background of dysepidemics [11; 23; 32]. A common feature of these diseases is an increase in morbidity and mortality with age and the presence of almost the same type of metabolic disorders, mainly lipid metabolism disorders [26; 64].

In addition, at the end of the last century, researchers drew attention to the frequent combination of obesity, diabetes and arterial hypertension (AH) in one patient. The common feature of these conditions is insulin resistance (IR) and associated hyperinsulinemia, impaired glucose tolerance, increased triglyceride (TG) concentration and decreased high-density lipoprotein (HDL) concentration in blood plasma. These metabolic changes were defined as "syndrome X" and were considered as etiological factors and risk factors for diabetes, AH and coronary heart disease (CHD) [56]. Almost simultaneously, a significant role in these processes was established by upper body obesity [38]. It has been proven that the disproportionate accumulation of visceral fat compared to subcutaneous fat mass, which occurs with increasing age, leads to an increase in gene expression and secretory profiles of adipokines and pro-inflammatory factors, enhances the release of fatty acids and contributes to the development of IR and cancer [14; 52]. IR is associated with pro-inflammatory cytokine-mediated mechanisms that affect insulin signaling, glucose transport, lipid synthesis and metabolism, as well as pro-oxidant and cytotoxic processes [1], which determine the close relationship between obesity and diabetes [44; 59]. At the same time, many studies have found an association of CVD, obesity and diabetes with prostate carcinogenesis [40; 52; 66].

The set of diseases with similar etiopathogenesis, the leading mechanism of which is IR, is currently defined as the "metabolic syndrome" (MS) [11]. Although MS is recognized as a separate pathology, there is still no generally accepted definition of it. In particular, in addition to dyslipidemia, WHO experts include IR separately in MS, define central obesity by BMI (more than 30 kg/m2) or waist-to-hip ratio (more than 0.9 in men), define hypertension as blood pressure (BP) from 140/90 mm Hg. and add microalbuminuria [10]. National Cholesterol Education Program (NCEP) and IDF experts assess the presence of obesity by waist circumference (NCEP – more than 102 cm, IDF – more than 94 cm in men), and hypertension – from 130/85 mm Hg. [42; 49]. Experts from Polish medical societies define MS as obesity and two of the following three criteria : high blood pressure, impaired glucose metabolism, elevated low-density lipoprotein (non-HDL) cholesterol (atherogenic dyslipidemia), without mentioning triglyceridemia [25].

Regardless, MS is recognized as a risk factor for aggressive PC (APC). It has been found that MS has been associated with positive surgical margins, increased PC grade, overall mortality rate, postoperative complications, and biochemical recurrence [4; 20; 39; 47; 57]. There are reports of an association of MS with high-grade PC without an association with low-grade PC [68]. It has been found that individual components of MS were not associated with PC, but an increase in its components was associated with an increase in PC aggressiveness [17]. J. Feunteun et al. (2022) found an age-dependent association between PC and MS. No association was found in men aged 20-39 years; in men aged 40-64 years and aged 65 years and older, MS and its components were associated with an increased prevalence of PC [27]. Aggressive PC was associated with arterial hypertension and type 2 diabetes and an increased risk of fatal PC in the presence of more than three MS components [24].

Metabolic disorders play a significant role in the pathogenesis of the above-mentioned diseases and in PC carcinogenesis, which can potentially be corrected, which creates new promising targets for therapeutic influence.

Promising additional methods of treating prostate cancer in patients with metabolic disorders

Currently, it has been established that the course of tumors of various localization is improved when adding physical exercises, stress reduction, sleep improvement, diet, food supplements, green tea, vitamin D, metformin, statins, cimetidine, spironolactone, etc. to the main course of treatment, which affect various metabolic pathways of tumor cells [31]. Measures aimed at weight loss are considered promising [52]. According to the results of a meta-analysis of 28 studies, it was found that in PC patients who received androgen-depressant therapy (ADT), physical exercises and nutrition optimization can improve body composition and metabolic status [23]. At the same time, there is evidence that demonstrate improved PC survival, quality of life, improved psychological and physical outcomes, and reduced fatigue even in patients over 65 years of age who exercise regularly. In addition, regular physical activity may counteract the adverse effects of ADT associated with secondary hypogonadism [18]. According to Japanese researchers, the risk of localized and progressive PC can be reduced by quitting smoking and alcohol consumption, and the positive effect of the Japanese diet and green tea consumption has been established [61]. In a clinical trial involving 82 healthy overweight and obese subjects, an isocaloric Mediterranean diet was found to reduce plasma cholesterol levels and alter the microbiome and metabolome [46].

Physical activity has been shown to affect all stages of prostate carcinogenesis through its effects on circulating levels of insulin-like growth factor-1 (IGF-1), oxidative stress, systemic inflammation, sex hormones, and myokines [71].

Among pharmacological agents, statins are the most frequently mentioned. Statins are inhibitors of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, thereby inhibiting cholesterol synthesis in the mevalonate pathway [33]. In addition, statins induce overexpression of LLD receptors on the surface of hepatocytes, which increases their uptake and reduces the level of lipoproteins in the blood [13]. In preclinical studies, atorvastatin has been shown to inhibit the uptake of the adrenal androgen dehydroepiandrosterone sulfate, which stimulates the proliferation of pancreatic cells [33]. The beneficial effects of statins include cholesterol levels lowering, which are important for supporting tumor cell proliferation; anti-inflammatory and antiangiogenic effects; inhibition of invasion and metastasis; induction of apoptosis and autophagy; and reduction of testosterone levels due to the reduction of cholesterol, which is a precursor of androgens [15; 33; 41; 45]. In addition, statins are candidates for drugs that target cells in the process of endothelial - mesenchymal transformation, i.e. have a greater antimetastatic focus with a potential effect on dormant metastases [15]. The direct antitumor effect of statins at doses 100-500 times higher than the dose required for cholesterol reduction is also discussed [41].

The antitumor effects of statins are confirmed by preclinical studies, but to a lesser extent by clinical studies, the results of which are contradictory [19]. Simvastatin treatment has been shown to reduce tumor cell viability and migration [37]. In a population-based study of nearly 12,000 men with newly diagnosed PC, statin use prior to PC diagnosis was associated with a reduced risk of cancer-related mortality (hazard ratio (HR), 0.55; 95% CI, 0.41–0.74) and all-cause mortality (HR, 0.66; 95% CI, 0.53–0.81). Patients who started statin therapy after PC diagnosis also had a reduced risk of mortality, but to a lesser extent (HR, 0.82; 95% CI, 0.71–0.96; and HR, 0.91; 95% CI, 0.82–1.01, respectively). [73] By a prospective cohort study (more than 2579 cases of PC, of which 316 were progressive) had been proved that statin use did not affect the overall risk of PC, but reduced the relative risk of its progression (OR 0.51 (95% CI: 0.30 to 0.86) and metastasis development (OR 0.39 (95% CI: 0.19 to 0.77). This effect was more pronounced with long-term use of statins (more than 5 years) [55].

A systematic review and meta-analysis of 27 randomized trials found that statin treatment reduced the risk of all-cause mortality and survival in cancer, including PC, and mortality in patients with advanced cancer. [75]. A meta-analysis of 12 trials found that statin

use during ADT for PC reduced the risk of all-cause mortality (HR = 0.73, 95% CI: 0.64–0.84, p< 0.0001) and cancer mortality (HR = 0.61, 95% CI: 0.49–0.77, p< 0.0001). This effect was not observed in patients with progression of PC or in patients who started statin therapy before ADT [34]. Similar results were obtained in another meta-analysis, which showed that the use of statins both before and after PC diagnosis was associated with a reduced risk of all-cause mortality in patients who received local therapy alone and cancer mortality in patients who received ADT. In the meta-analysis by P. Tan et al. (2016) it was found that the use of statins was associated with a reduced risk of high-grade PC (relative risk (RR) 0.83; 95% CI 0.66–0.99) and the risk of progressive PC (RR = 0,87, 95% CI: 0,82-0,91) [65].

According to the results of the meta-analysis by P. Yin et al. (2022) only a trend towards increased biochemical relapse-free survival in patients with PC after radical prostatectomy (RPE) and radial therapy (PT) was found, but the use of statins improved survival in patients with high-risk PC [72]. In a double-blind randomized clinical trial, RPEs found that the administration of atorvastatin (80 mg per day) before RPE did not reduce the proliferative activity index (Ki-67) and prostat-specific antigen (PSA**)** levels, but when atorvastatin was used for at least 28 days, Ki - 67 was 14.1% lower compared to placebo (p=0.056), and PSA levels were reduced by 0.6 ng/ml in high-grade ISUP PC. The authors concluded that atorvastatin may be effective if used for at least 28 days [48].

In some studies, no effect of statin use was found [21], and in the study by A. Aminsharifi et al. (2019) it was found that preoperative use of statins alone increased the risk of biochemical recurrence compared with patients who did not receive statins or metformin (HR 1.84; 95% CI, 1.28-2.64). This effect being greater in men with a BMI greater than 30 kg/m2 (HR 3.12; 95% CI, 1.70-5.72) [12]. An earlier study it was found that patients who used statins before RPE had lower preoperative PSA concentrations and more often Gleason's score from 7 points. In multivariate analysis, statin use was an independent predictor of biochemical recurrence and a lower 5-year recurrence-free survival. The authors suggest that this risk is related to delayed diagnosis and masking of aggressive disease due to decreased PSA [58].

Another drug which efficacy is being actively studied in patients with PC is metformin. Metformin is a first-line drug in type 2 diabbbetes patients aand has antiproliferative effects in solid tumors. These effects are associated with direct mechanisms that reduce protein synthesis and proliferation of cancer cells, affecting cellular oxygen consumption and ATP production, as well as by activating proliferation inhibitors. The indirect mechanism is associated with the effect on the transcription of genes that regulate

glycogenesis in liver cells, leading to a decrease in serum glucose and insulin levels and glucose uptake by cancer cells. Metformin also inhibits the activity of the androgenic receptor (AR). The authors believe that, given the potential link between MS and PC, metformin may be an effective adjunct treatment as monotherapy or in combination with others drugs [9].

In a study of human androgen-dependent and androgen-independent PC cell lines, metformin was found to inhibit tumor cell viability and enhance apoptosis by down regulating AR mRNA in both lines, especially in combination with another anti-AR agent, bicalutamide. The authors believe that this combination is a particularly promising, highly effective and low-toxic treatment for castrate-resistant PC [69].

The results of clinical trials are less demonstrative. A review of publications on the effects of metformin on prostate function and its pathology, PSA and prostatic gland benigh hyperplasia (PGBH) decrease and an unclear effect on the PC risk is reported. According to some data, metformin use has no effect, while others show a decrease of PC risk, metastases, and disease recurrence. [67]. In particular, in cases of concomitant type 2 diabetes mellitus, metformin was not found to have an effect on PC risk (HR = 0.96, 95% CI = 0.77–1.19), while the use of insulin or sulfonylurea significantly reduced it (HR = 0.73, 95% CI = 0.55–0.98) compared with subjects without antidiabetic therapy [30]. There was also no clinical effect of metformin use on PSA levels and the risk of MS at the background of ADT [43].

Encouraging results have been obtained when metformin and statins are used in combination with other drugs compared to monotherapy [19]. Thus, in the study by J.M. Jiménez-Vacas et al. (2021) it was found that the simultaneous use of metformin and statins in patients with PC contributed to an increase in survival without biochemical recurrences, as well as a decrease in the aggressiveness of PC (according to Gleason's score). In addition, an *in vitro* study was conducted in which it was found that metformin in combination with simvostatin reduced the proliferation rate, migration ability and tumor sphere formation, which may be the result of a decrease in the expression of ARs and their activity, and through different oncogenic and metabolic signaling pathways [36]. In the study by Danzig MR et al. (2015) diabetes persons after RPE were examined, 9.9% of them received statins, 7.3% - metformin, and 5.5% - statins and metformin. It was found that patients who took metformin and statins had a lower probability of Gleason scores of 8 – 10 points, a lower incidence of pT3-4, and better 2-year and 5-year biochemical recurrence-free survival. The use of statins or metformin alone had no such effect [21]. A. Aminsharifi et al. (2019) did not find an effect of metformin alone or in combination with statins on the risk of biochemical recurrence of PC [12].

Conclusions

Thus, among the known risk factors for prostate cancer occurrence and aggressive course, cardiovascular diseases, obesity, diabetes mellitus, and metabolic syndrome occupy an important place.

Metabolic disorders is an important mechanism of pathogenesis of these diseases and prostate cancer, in particular, metabolic dyslipidemia.

Correction of metabolic disorders is currently achieved by metabolic drugs, e.g. statins and metformin. Some studies have established a positive effect of this therapy on prostate cancer course, which indicates its prospects as an additional method in the complex therapy of prostate cancer.

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