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Review Article

Nutritional supplementation of the pharmacotherapy of prostate diseases

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Abstract

Introduction: Nutritional supplementation is an integral part of modern pharmacotherapeutic strategies for prostate diseases with different levels of evidence for specific nutrients.

Provitamin A (beta-carotene), vitamin A (retinol) and prostate diseases. Their effects have not been sufficiently studied, and the available data are conflicting to recommend them as a nutritional supplement.

Vitamin E (tocopherol) and prostate diseases. Its effects have not been sufficiently studied, and the available data are conflicting to recommend it as a nutritional supplement.

Vitamin C (ascorbic acid) and prostate diseases. Its effects have not been sufficiently studied, and the available data are conflicted to recommend it as a nutritional supplement.

Vitamin K and prostate diseases. Its effects have not been sufficiently studied, and the available data are conflicted to recommend it as a nutritional supplement.

Vitamin D and prostate diseases. The evidence base of the vitamin D prostatotropic effects has been accumulated, which allows us to consider its deficiency replacement as an effective nutritional supplement in prostate diseases.

Omega-3 PUFAs and prostate diseases. They have universal physiological effects; however, the evidence base for their recommendation as a nutritional supplement for prostate diseases is still insufficient.

Zinc and prostate diseases. Positive effects of zinc on the prostate gland are known for a fact and allow us to recommend it as a nutritional supplement for prostate diseases.

Selenium and prostate diseases. The reliably proven positive effects of selenium on the prostate gland allow us to recommend it as a nutritional supplement for prostate diseases.

Magnesium and prostate diseases. Its effects have not been sufficiently studied, and the available data are conflicting to recommend it as a nutritional supplement.

Keywords

prostate diseases, nutritional supplementation, vitamin A, vitamin C, vitamin E, vitamin K, vitamin D, Omega-3 polyunsaturated fatty acids, zinc, selenium, magnesium.

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Introduction

Prostate diseases are among the most common pathologies in men of various ages, but their modern pharmacotherapy does not always allows to achieve a rapid and complete relief of clinical symptoms and improvesing the quality of a man's life. In addition, nowadays, when most of age-associated diseases (including the prostate diseases) are getting diagnosed at a much younger age, another equally important pharmacotherapeutic problem, related to the possibility of effective early prevention of prostate diseases, is extremely relevant. The solution to the problem of increasing the effectiveness of pharmacotherapy and drug prevention of prostate diseases can be found through rational pharmacological management of prostate metabolism, which is achieved by the intake of various pharmacological agents, in particular vitamins and minerals (nutraceuticals), which have a long history of clinical use in urological practice as oral nutritional supplement (Gorbachev and Gorbacheva 2011; Veselovskiy 2013). It should be noted that the conservative therapy of the prostate diseases today must be performed in complete accordance with the available clinical protocols, based on high-quality recommendations, which, first of all, order the administration of medications of the appropriate groups, but clinical practice shows that the additional administration of nutraceuticals, most of which are deficient in modern people, is not a tactical mistake. Moreover, some vitamins and trace elements necessary for the prostate gland can enter the body exclusively with food or dietary supplements due to their absence in the form of medications. This article provides a brief review of the main vitamins, micro-and macronutrients necessary to maintain metabolic homeostasis in the prostate gland, which can be used as a nutritional supplementation for traditional pharmacotherapy of the prostate diseases.

Provitamin A (beta-carotene), vitamin A (retinol) and prostate diseases

Provitamin A (beta-carotene), as well as carotenoids that are incapable of vitamin A formation, perform important antioxidant functions due to the presence of isoprenoid sites in their srtucture. They are quite effective traps for singlet oxygen, especially at low partial pressure of oxygen. In addition, in this case, they also have another mechanism, acting as antioxidant compounds, breaking the chain of lipid peroxidation. At the same time, with high oxygen content, beta-carotene can show prooxidant activity (Shikh and Makhova 2014). Vitamin A (retinol) together with beta-carotene (provitamin A) is an important component of the natural antioxidant system of cells and has a certain antioxidant effect, which is confirmed mainly in experimental studies in animals. According to the membrane theory of the vitamin A action, retinol is able to penetrate the hydrophobic zone of biological membranes and interact with lecithin-cholesterol monolayers at the interface, causing the rearrangement of cell membranes, lysosomes, and mitochondria (Shikh and Makhova 2014). Vitamin A ensures the integrity of cell membranes, regulates epithelial cell proliferation, and is involved in the regulation of spermatogenesis with various effects on fetal and neonatal Leydig cells, Sertoli cells, and the germinogenic epithelium of the testes, that makes a possibility to suppose the presence of some reproductive effects in vitamin A (Livera et al. 2000; Zhang et al. 2002; Ambrosini et al. 2008; Clagett-Dame et al. 2011).

The role of vitamin A in the pathogenesis of prostate diseases is understudied. At the same time, vitamin A is known to have antitumor activity, such as induction of apoptosis and cell differentiation, as well as inhibition of cell proliferation (Mondul et al. 2017; Surman et al. 2020). However, it has also been shown that vitamin A and its derivatives (retinoids) can promote tumor growth (Peehl and Feldman 2003), possibly acting through the receptor of insulin-like growth factor-1 (IGF-1) or sex steroids, which may affect the risk of prostate cancer (Mondul et al. 2011). Thus, the ATBC study found a 23% higher incidence of prostate cancer in men receiving 20 mg of beta-carotene daily (Alpha-Tocopherol et al. 1994), while other studies did not report the effect of beta-carotene (plus 25,000 IU of retinol palmitate) at the dose of 30 mg daily (Omenn et al. 1996) or 50 mg of beta-carotene once every other day (Cook et al. 2000) on prostate cancer. The results of the ATBS study are confirmed by other recent, larger analyses (Nash et al. 2015). In a placebo-controlled prostate cancer prevention trial (PCPT), men with higher levels of circulating retinol had a significantly increased risk of prostate cancer (OR=1.30, 95% CI 1.00–1.68 for the higher and lower quartiles, n=974). The risk was higher for the well-differentiated form of the disease (OR=1.74, 95% CI 1.14–2.68). The risk also increased in men with higher levels of circulating α-carotene (OR=1.32, 95% CI 1.01–1.73 for the higher and lower quartiles) (Nash et al. 2015). In a large pooled study involving more than 11,000 cases and 18,000 men in control groups, higher retinol levels were associated with an increased risk of prostate cancer (OR=1.13, 95% CI 1.04–1.22 for the highest and lowest quartiles) (Key et al. 2015). There were no associations of a prostate cancer risk with the levels of provitamin A, carotenoids, α-carotene, or β-cryptoxanthine, as confirmed by a recent meta-analysis (Wang et al. 2015). The results of the larger studies suggest inefficiency of the previous studies to detect a 20–30% increased risk associated with higher level of vitamin A. Smoking and prostate cancer screening did not appear to affect the study results either. While GWA study has identified genetic variants associated with higher serum concentrations of carotenoids and retinol, they have not yet been tested for a prostate cancer risk (Mondul et al. 2011).

Vitamin E (tocopherol) and prostate diseases

Vitamin E is a lipid soluble vitamin, naturally occurring in eight forms: four tocopherols and four tocotrienols, which have similar biological activity, however, only α-tocopherol is considered for establishing dietary requirements, since it has the greatest vitamin and direct antioxidant activities, and therefore it is widely used in medicine (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). The mechanism of the antioxidant action of α-tocopherol is the transfer of the hydrogen of the phenyl group to the peroxide radical at the initial interaction with the free radical. The resulting phenoxy radical is quite stable and does not participate in the chain reaction (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). Ascorbic acid (vitamin C) has a synergistic effect, reducing the oxidation product of α–tocopherol, α–tocopheroxide, to α–tocopherol. The total antioxidant effect of α-tocopherol is not pronounced, since neutralization of free radicals with this substance results in compounds with residual radical activity (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). Another disadvantage of α-tocopherol is its lipophilicity, which makes it difficult to create dosage forms for parenteral administration necessary for emergency care. However, it also has advantages, the main of which is its very low toxicity, as in an endogenous compound (Khadang et al. 2018).

Vitamin E is one of the most studied antioxidants in male infertility, which is confirmed by high-quality randomized clinical trials (RCTs) and meta-analyses (Salas-Huetos et al. 2017; Majzoub et al. 2018). Currently, vitamin E is applied in the complex treatment of chronic prostatitis (Bratchikov et al. 2019); however, the immediate and long-term results of such a therapy are still unknown due to the lack of high-quality RCTs (Balercia et al. 2015). The role of vitamin E in prostate cancer is widely discussed in the scientific literature; however, the contradictory data available indicate a possible dose-dependent oncostatic effect of vitamin E in some categories of patients, in particular, in smokers, with various histological variants of prostate cancer, the discussion of which is not the purpose of this review (Alkhenizan et al. 2007; Albanes et al. 2014).

Vitamin C (ascorbic acid) and prostate diseases

Vitamin C in the body is able to form a redox pair "ascorbic acid/dehydroascorbic acid", which acts together with vitamin E (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). At the lipids-water interface, ascorbic acid protects α-tocopherol or restores its oxidized form after the action of free radicals. Vitamin C can prevent or reverse the oxidation of reduced glutathione to its functionally inactive form. Vitamin C has a pronounced antioxidant effect only in the absence of metals of mixed valence (iron and copper ions); in the presence of the active form of iron (Fe^{3+}), it can reduce it to divalent iron (Fe^{2+}), which is able to release a hydroxyl radical by the Fenton reaction and act as prooxidant (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). Most studies of vitamin C are devoted to its effect on male fertility, while data on its antioxidant effects in prostate diseases are still insufficient for any definite evidence-based conclusions (Long et al. 2021). In clinical studies, it has been shown that in patients with chronic bacterial prostatitis, the concentrations of vitamins C, A, and E in the blood plasma are significantly reduced compared to healthy volunteers, against the background of a decrease in the activity of the key enzymes of the antioxidant defense system (superoxide dismutase, catalase, glutathione peroxidase) and increase in the concentration of lipid peroxidation products (in particular, malondialdehyde) and nitric oxide (NO). That justifies the pathogenetic expediency and prospects of the deficit correction of the above-mentioned vitamins-antioxidants in this disease (Zhou et al. 2006; Xiong et al. 2020).

Vitamin K and prostate diseases

Vitamin K is a group name for a number of derivatives of 2-methyl-1,4-naphthoquinone with the similar structure and similar function in the body, which is that vitamin K is a cofactor for γ-glutamyl carboxylase, catalyzing the post-translational conversion of specific glutamyl residues to γ-carboxyglutamyl residues in various vitamin K-dependent proteins involved in blood clotting, bone and cartilage metabolism (calcium, phosphorus and vitamin D metabolisms), signal transduction, and cell proliferation (Simes et al. 2020). Only two K-group vitamins have been found in nature: vitamin K_1 (phylloquinone) isolated from alfalfa and K_2 (menoquinone) isolated from the rotting fish (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). In addition to natural K vitamins, a number of synthetic naphthoquinone derivatives are currently known to have an antihemorrhagic effect. There are the following compounds: vitamin K_3 (2-methyl-1,4-naphthoquinone), vitamin K_4 (2-methyl-1,4-naphthohydroquinone), vitamin K_5 (2-methyl-4-amino-1-naphthohydroquinone), vitamin K_6 (2-methyl-1,4-diaminonaphtoquinone), and vitamin K_7 (3-methyl-4-amino-1-naphthohydroquinone) (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014).

Sometimes vitamin K is called an overlooked vitamin, because it has other important effects besides those described above. Today, there are reliable experimental data suggesting the potential antitumor activity of vitamin K in several types of cancer, including prostate cancer, and ear-

lier *in vitro* and *in vivo* studies showed that the anti-tumor activity of vitamin K is based on its antioxidant effects (Dasari et al. 2017; Luo et al. 2018). Recent studies have found that vitamin K inhibits cancer cell growth through other mechanisms, including regulation of apoptosis, cell cycle arrest, autophagy, and modulation of various transcription factors such as Myc and Fos, and the protective role of vitamin K against progressive and fatal prostate cancer was found in the Heidelberg cohort of the EPIC study (Nimptsch et al. 2010; Kristensen et al. 2019). Donaldson M. S. (2015) proposed a very interesting and original hypothesis, according to which bad prostate health is, in fact, vitamin K deficiency (Donaldson 2015), referring to the results of the recent studies showing that even subclinical varicocele, which is more common than usually believed, causes retrograde blood flow from the testicles past the prostate gland, leading to a more than 130-fold increase in free testosterone in the veins of the periprostatic venous plexus, which is able to activate the prostatic proliferation. In this regard, according to the author of that hypothesis, the periprostatic veins distensibility in varicocele is the direct cause of prostate adenoma, and the embolization of the internal seminal vein can reverse the enlargement of the prostate gland, with appropriate symptomatic relief. On the other hand, recent studies have revealed the role of vitamin K in the calcification of varicose veins, as well as its role in the proliferation of smooth muscle cells in the medial layer of the vein wall. Vitamin K is directly involved in the varicose vein formation. Consumption of vitamin K in the right form and quantity, along with other supporting nutrients and phytochemicals can likely prolong the excellent prostate health and possibly can reverse the bad prostate health (Donaldson 2015). This hypothesis can be further evaluated in future studies of the relationship between vitamin K and varicocele, as well as of the relationship between varicocele and prostatic hyperplasia onset. And if it turns out to be correct, the management of the prostate health can be radically changed: instead of focusing on the prostate health only as a manifestation of hormonal imbalance, prostate hyperplasia can be considered as a result of bad venous health in general and internal seminal veins in particular (Donaldson 2015).

Vitamin D and prostate diseases

Unlike all other vitamins, vitamin D is not a classical vitamin, since it is formed *de novo* in the body from the biologically inactive precursors (25(OH)D_3, or calcidiol) and only due to a two-stage metabolism in the liver and kidneys, it is converted into its active form (1,25-[OH]2-D_3), or calcitriol) (Castro 2011). In addition, in contrast to true vitamins, which act as co-factors of various cellular enzyme systems, specific receptors to the active form of vitamin D 1,25-[OH]2-D_3, or calcitriol, called Vitamin D Receptors (VDR) have been found in cells of various organs and tissues (brain, prostate, breast, intestine, immunocompetent cells, muscle tissue, germ cells, etc.). That allows us to classify vitamin D not as a true vitamin, but as a D-hormone, which generates and modulates slow genomic and fast non-genomic molecular-cellular responses in more than 40 target tissues (Castro 2011). According to current data, D-hormone regulates from 3 to 10% of the entire human genome, including the genes of carbohydrate metabolism, steroidogenesis, innate immunity and reproduction, which makes it one of the key hormone, essential in sufficient quantities from birth to death (Kalinchenko et al. 2016).

The global vitamin D deficiency is now a new non-infectious pandemic of the XXI century among adults and children, which is primarily due to a sharp decrease in the duration of sun exposure of modern people, the geographical features of the areas of residence determining the intensity and nature of insolation, and insufficient consumption of animal products containing vitamin D (Yadav and Kumar 2020). People living in the countries located north of the 35th parallel forming the so-called "vitamin winter zone" are particularly amenable to vitamin D deficiency/insufficiency (Yadav and Kumar 2020). Since the entire Russian territory is a zone of increased risk of vitamin D deficiency/insufficiency due to complete location in the geographical "vitamin winter zone", this problem is relevant for the Russian medicine and should already become a key question in the concept of national health improvement (Tyuzikov et al. 2013; Vorslov et al. 2015; Zhilenko et al. 2017).

Current epidemiological data prove a high frequency of unrecognized vitamin (hormone) D deficiency/insufficiency in urological patients. For example, Pitman M. S. et al. (2011) analyzed the results of examination of 3,763 men from urological medical databases and concluded that currently 68% of urological patients have inadequate level of vitamin D, and 52% of them have unrecognized vitamin D deficiency or insufficiency (Pitman et al. 2011). Studies have revealed the ability of vitamin D to regulate the expression of steroidogenesis genes, which, in turn, regulates the expression of vitamin D metabolism genes (Mordan-McCombs et al. 2010; Wehr et al. 2010). In this regard, some authors believe that testosterone deficiency may hypothetically increase the adverse effects of vitamin D deficiency, i.e., there are not unilateral, but bilateral pathophysiological links between the exchange of testosterone and vitamin D (Blomberg 2012). Increased synthesis and secretion of testicular testosterone under the influence of vitamin D leads to the realization of a whole range of prostatoprotective effects of testosterone, which is one of the key androgen-precursors of the main prostatic androgen – 5-α-dihydrotestosterone (5-α-DHT), which provides most of the prostate gland functions, including immunomodulatory, anti-inflammatory and bactericidal, as well as the function of pain reception and perception. This view is supported by the results of a large-scale population study of 3,369 men, which showed that the proportion of men who had adequate vitamin D status was the highest in the group of normogonadal men (31%), and the lowest – among those with primary hypogonadism (18%) (Lee et al. 2012). According to the statistical analysis of the study results, it was concluded that vitamin D deficiency (25(OH)-vitamin D in blood <20 ng/ml) was

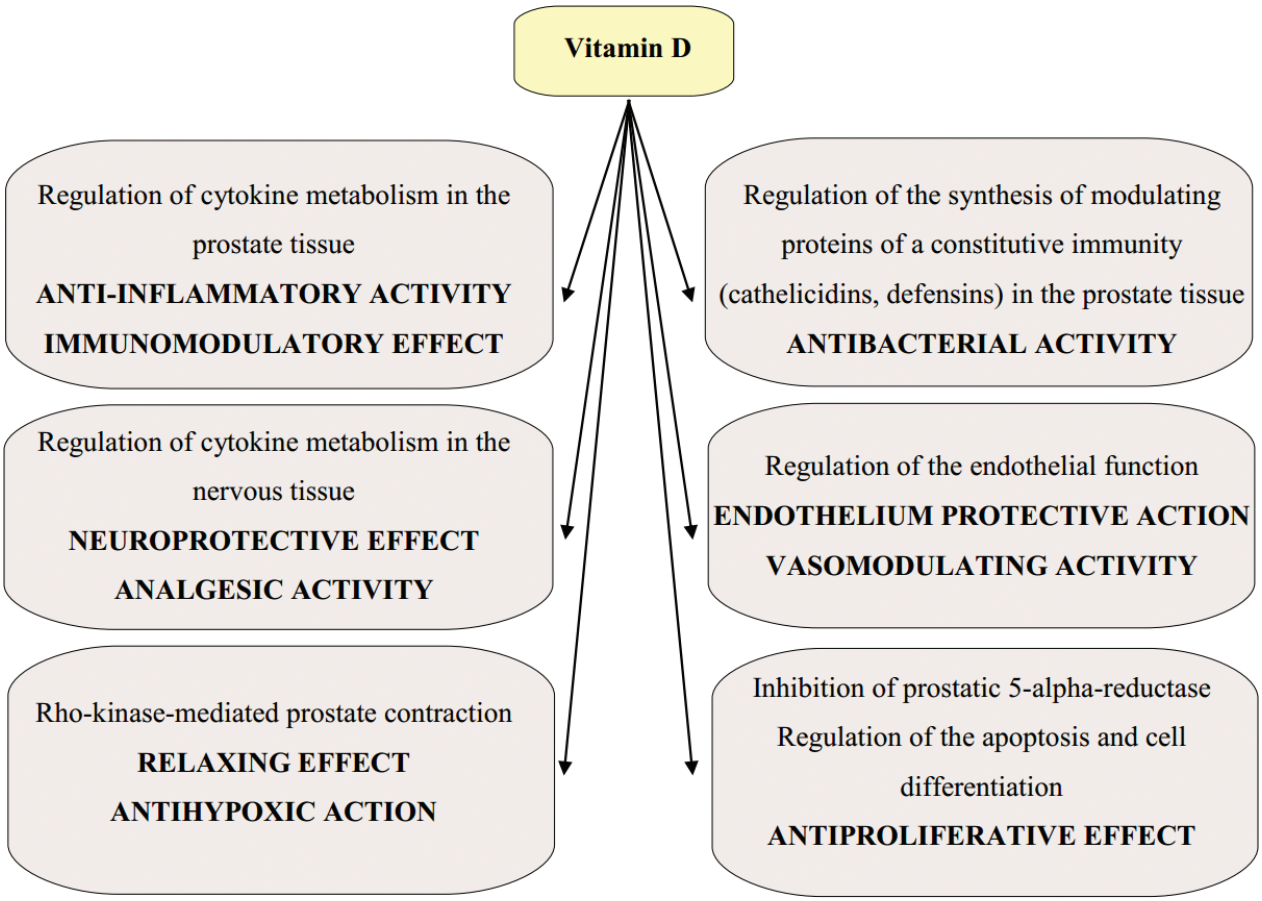

Figure 1. The most important physiological effects of vitamin D in the prostate gland (Haghsheno et al. 2013; Bratchikov et al. 2018; Bratchikov et al. 2019).

associated with secondary hypogonadism (relative risk 1.2; p=0.05) and with compensated hypogonadism (relative risk 1.5; p=0.03) in men, and the plasma levels of 25(OH)-vitamin D were directly proportional to the plasma levels of total and free testosterone and inversely proportional to the plasma levels of estradiol (Lee et al. 2012).

Modern studies have revealed numerous physiological effects of vitamin D that positively affect the metabolism of the prostate gland (Haghsheno et al. 2013; Bratchikov et al. 2018; Bratchikov et al. 2019) (Fig. 1.).

The important role of vitamin D was found in the regulation of cytokine-mediated cellular and systemic reactions in chronic subclinical (aseptic) inflammation, immunomodulatory effects on cell-mediated and humoral immunity, as well as on the fatty acid metabolism and adipocyte metabolism as one of the key producers of cytokines, which are the signaling molecules of the immune system (Watkins et al. 2011; Khadilkar and Khadilkar 2013). One of the potential mechanisms of anti-inflammatory effects of vitamin D in prostate tissue can be considered its proven ability to inhibit the ROK kinase system (a key enzyme system that can cause the development of local muscle spasm, not by changing the level of calcium in myocytes, but by increasing their sensitivity to calcium (calcium-independent muscle contractility)), as well as cyclooxygenase COX-2, prostaglandins E2 and pro-inflammatory interleukin-1 in the stromal cells of the prostate gland (Manchanda et al. 2012; Zhang et al. 2016).

In the animal experiments, it was shown that the blockade of prostatic receptors for vitamin D leads to the development of experimental autoimmune chronic prostatitis (Adorini and Penna 2008; Motrich et al. 2009). The results of studies that demonstrate the presence of pronounced antibacterial properties in vitamin D metabolites have appeared in the literature recently (Ghosn and Viard 2013). Thus, the active form of vitamin D (1,25-[OH]2-D3, or calcitriol) was found to activate cathelicidins and defensins – antimicrobial proteins that mediate constitutive immunity, which promotes wound healing and tissue repair (Hewison 2010).

Currently, the effect of vitamin D on the prostatic proliferation is being actively studied (Sampson et al. 2008). Thus, it is known that the plasma level of 25(OH)D3 inversely dependent on the volume of the prostate gland (Haghsheno et al. 2013). It has been shown that the polymorphism of the vitamin D receptor gene correlates with the frequency of prostate hyperplasia complicated by histological prostatitis and prostate cancer (Kivineva et al. 1998; Gsur et al. 2002; Ruan et al. 2015; Xiao et al. 2020). One of the multivariate analyses showed that the levels of 25(OH)D3, serum calcium adjusted for albumin, sex hormone binding globulin (SHBG), and high-density lipoprotein (HDL) significantly and inversely correlate with the prostate volume, which makes it possible to consider vitamin D as a natural prostatic antiproliferant (Haghsheno et al. 2013; Zhang et al. 2016).

The antiproliferative properties of vitamin D associated with its ability to reduce the activity of prostatic 5-α-reductase, a key enzyme system for triggering and progressing prostatic proliferation, have also been shown in a number of studies, which also makes it possible to consider vitamin D deficiency as a predictor of prostatic hyperplasia, which is quite often combined with the events of chronic inflammation in the prostate tissue (Elshazly et al. 2017; Murphy et al. 2017; Park et al. 2018). The antiproliferative effect of vitamin D on prostate tissue can be further mediated by its ability to inhibit excessive insulin cell signaling (insulin levels and insulin-like growth factor-1 (IGF–1)), which is responsible for activating the mechanisms of cell proliferation, including in the prostate. It is well known that insulin is a powerful mitogenic hormone, so long-term hyperinsulinemia (for example, in insulin resistance) is accompanied by an increased risk of hyperplastic cell-tissue processes and is considered as one of the key mechanisms of carcinogenesis (Inoue and Tsugane 2012).

Since vitamin D has a modulating effect on the immune system, hypovitaminosis D can cause a systemic subclinical inflammatory response, which, in turn, can induce insulin resistance, which leads to chronic hyperinsulinemia and activation of prostatic proliferation (Shoelson et al. 2007; Warren and Livingston 2021). In addition, the active metabolite 1,25-[OH]2-D3 activates the transcription of the human insulin gene (Maestro et al. 2003). Vitamin D regulates extracellular and intracellular calcium metabolism, which is necessary for insulin-mediated intracellular processes in insulin-dependent tissues (skeletal muscles, adipose tissue), and changes in the level of calcium in the cell can have adverse consequences for the secretion of insulin, the synthesis of which, in turn, is mediated by calcium (Saponaro et al. 2020).

In this regard, correction of vitamin D deficiency, according to some researchers, has a beneficial effect on the effects of endogenous insulin, stimulating the expression of insulin receptors and, thereby, improving the insulin-mediated intracellular glucose transport (Pittas et al. 2007). Preliminary determination of the level of vitamin (hormone) D in the blood before a puncture biopsy of the prostate gland in patients with suspected prostate cancer can be important in terms of predicting positive or negative results of the biopsy: the lower the vitamin D level, the more often the puncture biopsy revealed more malignant prostate cancer (Grant 2014; Murphy et al. 2017). Data from a systematic review suggest that vitamin D deficiency in men can be considered as a reliable predictor of an increased risk of prostate cancer (Mandair et al. 2014).

Omega-3 polyunsaturated fatty acids (Omega–3 PUFAs) and prostate diseases

Omega–3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in fish oil, seafood and egg yolk, as well as alpha-linolenic acid, derived from plants, are considered the most important for human health. The human body is not able to synthesize them, so omega-3 PUFAs are essential fatty acids and should be supplied daily with food in sufficient quantities (about 1.2–1.5 g/day). In human cells and tissues, Omega-3 PUFAs, like other fatty acids, are not found in free state, but are part of lipids of different classes, such as triacylglycerols (triglycerides), phosphoglycerides (phospholipids), cardiolipin, sphingolipids, esters of sterols, and fatty acids (esters of cholesterol, waxes). The key physiological role of Omega–3 PUFAs is they are part of the bilipid layer of the membranes of all cells of the human body, and therefore they have fundamental importance for cellular and organ-tissue metabolism (Vorslov et al. 2015; Jędrusek-Golińska et al. 2020).

It is important to note that certain optimal balance between the consumed with food Omega–6 PUFAs and Omega-3 PUFAs, which is on average 1–5:1, which has developed over the human evolution. However, in recent decades, the nature of nutrition and the quality of food has changed radically: the amount of Omega-6 PUFAs in the diet has increased significantly over the past 100 years, which has led to a changing of this ratio to 25–40:1 by increasing Omega–6 PUFAs. That indicates a significant global deficiency of Omega-3 PUFAs in the diet of modern humans, which, according to some authors, can have a significant negative impact on the clinical course of almost all diseases of modern humans (Muthuvattur Pallath et al. 2021; Van Dael et al. 2021).

Omega-3 PUFAs play an important role in the normal metabolism of a healthy prostate gland, in which they perform a number of critical physiological functions (membrane-protective, anti-inflammatory, immunomodulatory, antioxidant, receptor-regulatory, etc.) and are represented in the form of phospholipids and free fatty acids, as well as biologically active substances –prostaglandins (PGs), in particular PG-E and PG-F, related to substances (hormonoids) (Christensen et al. 2006; Espinosa 2013; Vignozzi et al. 2014; Wang et al. 2016; Ghadian and Rezaei 2017). They were first isolated in 1935 by Swedish physiologist Ulf von Euler from spermoplasm, so the term “prostaglandin” comes from the Latin name of the prostate gland (glandula prostatica) (Kerstjens and Gosens 2020). Since PGs don’t accumulate in the cell, their synthesis requires a constant supply of a biochemical substrate – essential PUFAs. PGs are a powerful autocrine and paracrine regulators and mandatory participants of any inflammatory processes (Kerstjens and Gosens 2020). Together with other PUFAs derivatives (thromboxanes and prostacyclin), PGs form a subclass of prostanoids, which, in turn, belong to the class of eicosanoids. Today, an important role of eicosanoids has been established not only in the regulation of blood circulation and metabolism in the prostate gland, but also in the regulation of male reproductive function, since PGs of the prostatic fluid reduce the contractile motility of the muscle layer of the uterus and fallopian tubes of women, providing conditions for

the motion of sperm to the egg and its normal fertilization (Davidyan et al. 2018). In addition, the prostatic fluid includes mandatory products of physiological secretory activity of the prostate gland, also of a lipid nature – lecithin grains (lipoid bodies), biogenic polyamines (spermidine and spermin), as well as cholesterol crystals, which are used as laboratory markers of its functional state. It is understood that the role of spermin, which is formed from spermidine, is participation in the metabolic reactions, the clearance of cells from the waste products, which contributes to their renewal and regeneration. At the same time, it was shown that the concentration of spermin in the prostate cells decreases as a man ages (Handa et al. 2018).

Zinc and prostate diseases

Zinc is one of the key vital trace elements that ensure the normal homeostasis of the human body. The total zinc content in the human body is on average 1.4–2.3 g. Zinc is present in the muscles (60%), bones (30%) and other organs (10%), such as the liver, kidneys, pancreas, brain, skin, prostate and mammary glands, etc. The daily requirement for zinc in an adult is about 15–20 mg (Hennigar and Kelleher 2012; Sayapina et al. 2015). In older people, zinc availability is disordered more often than in young people, so the deficiency of this important trace element may increase with age and contribute to the pathogenesis of age-associated diseases (Santos et al. 2019).

Zinc is part of or supports the activity of about 100 intracellular enzymes that catalyze the key steps of DNA and RNA synthesis, as well as more than 40 metalloenzymes. Zinc is involved in almost all stages of cell maturation, so it acts as a natural regulator of cell division, differentiation, proliferation, and apoptosis (Skalniy 2004; Tsimmermann 2006). In addition, one of the fundamental physiological functions of zinc in the body is that it is a powerful co-factor of the natural antioxidant defense system of cells, as it is part of the active center of the superoxide dismutase enzyme, a key specialized enzyme of the antioxidant defense system, and also zinc has the ability to stabilize cell membranes (to reduce the severity of cell membranopathies). Zinc has a pronounced immunomodulatory effect on the T- and B-cells of the immune system, and also participates in the biosynthesis of vitamins B and C (Skalniy 2004; Tsimmermann 2006).

Currently, it is known that zinc modulates the “hypothalamus-pituitary-testicular” regulatory system and is necessary for the synthesis of testosterone in men (Skalniy 2004; Tsimmermann 2006). Zinc plays a key role in male reproduction, as it stabilizes chromatin of the sperm DNA and provides a pronounced bactericidal activity of the prostatic fluid (participates in the synthesis of the zinc-protein antibacterial prostatic complex). In addition, angiotensin-converting enzyme (ACE) takes an active part in the maturation of spermatozoa, and a decrease in the activity of ACE in zinc deficiency can lead to testosterone synthesis disorders and inhibition of spermatogenesis (Alshahran et al. 2013). Zinc is part of the active center of receptors for sex steroid hormones (zinc-dependent domain, or ”zinc finger”), so its deficiency can lead to a decrease in cellular reception of sex steroid hormones, even at their normal concentration in a systemic circulation. Adequate synthesis of thyroid and adrenal hormones is impossible without zinc. Zinc has a known positive effect on carbohydrate metabolism (Skalniy 2004; Tsimmermann 2006; Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). It is believed that the beneficial effect on a diabetic patient (prolongation of the hypoglycemic effect) caused by the interaction of zinc with insulin, consists not only of the stabilizing effect of zinc on the insulin molecule, but also of the inhibition of insulin destruction by insulinase in tissues (Skalniy 2004; Tsimmermann 2006; Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014).

In a male body, the largest reserves of zinc are concentrated in the prostate gland, which determines the critical role of this vital trace element in the organ metabolism (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014; Sayapina et al. 2015). In addition, it was found that different parts of the prostate gland are characterized by different zinc concentrations, which obviously reflects their different functional loads (Kelleher et al. 2011). Dorsolateral parts of the prostate gland in rodents and peripheral parts of the human prostate gland are characterized by the highest zinc concentrations, and these parts of the gland are characterized by the greatest secretory activity (Kelleher et al. 2011; Sayapina et al. 2015). Unlike most other cells in which zinc is sequestered into vesicles and organelles, in the cytoplasm of prostate cells it is in free state, weakly bound to molecules with a small molecular weight (citrate), so it is considered biologically active (Costello and Franklin 1998). The current view suggests that this biologically active zinc is used to inhibit M-aconitase, an enzyme protecting citrate from oxidation in the Krebs cycle, which provides a large amount of citrate in prostate secretions (Costello et al. 2005). The ability of zinc to inhibit mitochondrial M-aconitase, in particular, accounts for its antiproliferative activity, different mechanisms of which have been recently identified. In particular, the fact established in many studies, that the level of prostatic zinc decreases in patients with prostate cancer, according to experts, may reflect the key pathophysiological role of this trace element in regulating the processes of prostatic proliferation and reducing the severity of oxidative stress in prostate cells, which can lead to DNA damage and impaired gene expression, increasing the risk of mutations and malignant transformation; therefore, the preventive role of zinc in relation to prostate cancer is now recognized by many researchers and clinicians (Daragó et al. 2021; Madej et al. 2021). This is also confirmed by the established fact of an age-associated decrease in the level of zinc in the prostate gland (including due to its alimentary deficiency), with a simultaneous increase in the manifestations of age-related oxidative stress (an increase in the frequency

of DNA damage) in prostate cells and an increase in the frequency of prostate diseases in a male population (Franklin and Costello 2007; Bianchi-Frias et al. 2010).

It was shown that, on the one hand, in chronic prostatitis, prostate cells lose their ability to accumulate zinc, and on the other hand, the presence of infection in the prostate gland is associated with a lower content of zinc and zinc-peptide complex in the prostate secret, which resulted in the view that there are reliable two-way links between zinc deficiency and the risk of developing chronic prostatitis, which has been confirmed in numerous clinical studies and experimental models of chronic prostatitis (Evliyaoğlu and Kumbur 1995; Cho et al. 2002; Cicero et al. 2019). The analysis of the available literature confirms the critical physiological role of zinc in ensuring the most important functions of the prostate gland, and almost all studies in recent years have demonstrated the presence of a reliable pathogenetic relationship between a low concentration of zinc in the prostate gland and its diseases, the fact of which is reflected in modern high-quality systematic reviews and meta-analyses (Gumulec et al. 2014; Cui et al. 2015; Mahmoud et al. 2016; Zhao et al. 2016). Thus, the results of modern studies allow us to consider the diagnostic of zinc deficiency and its nutritional supplementation as one of the effective pharmacotherapeutic options in the treatment of various prostate diseases, primarily of inflammatory origin (Goel and Sankhwar 2006; Zaichick and Zaichick 2014; Lo et al. 2020; Daragó et al. 2021).

Selenium and prostate diseases

Selenium, like zinc, belongs to vital trace elements that perform extremely important physiological functions in the body (Skalniy 2004; Tsimmermann 2006; Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). First of all, along with zinc, it is one of the most important trace elements of the cellular antioxidant defense system. Selenium and selenium-containing enzymes inhibit the activity of protein kinase C, 5-lipoxygenase, cyclooxygenase, and NADP oxidase, and also its synergistic effect with α-tocopherol and zinc has been found. Sodium selenite can be considered as modulators of the antioxidant enzymes. Its action is associated with the activation of the active center of glutathione peroxidase, which includes a selenium atom, the lack of which can lead to a decrease in the activity of this enzyme (Skalniy 2004; Tsimmermann 2006; Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). Selenium-dependent enzymes are thioredoxin reductase and 5-deiodinase (synthesis of thyroid hormones) (Rayman 2020; Winther et al. 2020). Selenium strengthens the immune system, so it is actively used in oncological practice, in the treatment of hepatitis, pancreatitis, and cardiomyopathy (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014). In addition, selenium protects the body from heavy metals. In the Russian Federation, there is a high frequency of selenium deficiency, reaching 70%. Selenium deficiency (or deficiency of its transport proteins – selenoproteins) is often induced by prolonged statin use and leads to iodine deficiency and, consequently, to a violation of homeostasis of calcium ("the main inorganic messenger"), with all the consequences following from this (Skalniy 2004; Tsimmermann 2006; Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014; Rayman 2020). Selenium monotherapy, and more often a combination of selenium and zinc, has long been used in urological practice in the treatment of various prostate diseases, primarily of chronic prostatitis and prostate adenoma, demonstrating its high effectiveness and safety (Sabichi et al. 2006; Morgia et al. 2010; Kim et al. 2012). At the same time, current evidence for the potential preventive role of selenium in relation to the risk of prostate cancer remains highly controversial and requires further research (Allen et al. 2016; Cicero et al. 2019).

Magnesium and prostate diseases

The huge role of magnesium in the widest range of physiological processes in the human body today is doubtless (Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014; Gröber et al. 2015; Ismail et al. 2018; Uwitonze et al. 2020). Magnesium is an essential macronutrient of the body and ranks fourth after sodium, potassium and calcium in its prevalence in the human body (Skalniy 2004; Tsimmermann 2006). The total amount of magnesium in humans is about 24 g, and about 40% of which is inside cells. The greatest amount of magnesium is contained in bone (about 60%) and muscle (about 20%) tissues. Currently, magnesium is considered one of the main regulators of metabolic processes, and its physiological effects in the human body are well studied (Skalniy 2004; Tsimmermann 2006; Gorbachev and Gorbacheva 2011; Veselovskiy 2013; Shikh and Makhova 2014; Gröber et al. 2015; Ismail et al. 2018; Rayman 2020; Uwitonze et al. 2020; Winther et al. 2020). Magnesium has an effect on energy metabolism, oxidative phosphorylation and glycolysis (through the synthesis of adenosine triphosphate (ATP) and changes in the activity of ATPase); the synthesis of protein, lipids, and nucleic acids determines the effect on plastic processes (among the most important pathogenetic mechanisms of connective tissue dysplasia is a magnesium chronic deficiency, which leads to a violation of the formation of connective tissue structures and causes chaotic arrangement of collagen fibers); it ensures the normal metabolism of about 300 enzymes: creatine kinase, adenylate cyclase, phosphofructokinase, K+-Na+-ATPase, Ca-ATPase, and ATP (Nedogoda 2009; Liu et al. 2020). It is also known that magnesium is a natural antagonist of calcium, which determines its myotropic, antispasmodic and disaggregational effects and its participation in ensuring normal electrophysiological processes of cells due to its influence on the transmembrane potential (Gromova and Gogoleva 2007). Recently, an important role of magnesium in the regulation of chronobiological processes and the development of endothelial dysfunction has been established,

with a direct linear correlation being revealed between the degree of endothelium-dependent vasodilation and a concentration of intracellular magnesium. One of the possible mechanisms explaining the beneficial effect of magnesium on endothelial function may be its anti-atherogenic activity (Dominguez et al. 2020). Today all these and a number of other important physiological effects of magnesium in the human body make it one of the most popular element of nutritional supplementation in various fields of medicine (Gromova and Torshin 2018).

In urological practice in the treatment of prostate diseases, magnesium supplements have not yet gained wide use, despite the fact that the available research results indicate that magnesium increases the activity of local immunity in the prostate tissue, increases the antiseptic properties of prostatic fluid (together with potassium and calcium), and also helps to relieve spasms and reduce pelvic pain by improving the condition of nerve fibers and regional blood circulation (Colleen et al. 1975; Stegmayr et al. 1982; Kavanagh 1985). Moreover, according to some authors, the content of magnesium in the man's sperm in a greater degree as the content of zinc shows stable correlations with the signs of chronic prostatitis, which makes it possible to consider it as a reliable biochemical marker of this disease (Bassey et al. 2019). In recent years, scientific data on the possible role of magnesium in the carcinogenesis of prostate cancer have begun to accumulate, but today they are quite heterogeneous and contradictory, which requires further research (Steck et al. 2018; Fowke et al. 2019; Zhong et al. 2020).

Conclusion

Modern science has accumulated a significant amount of information that reflects the physiological role of the most important vitamins and trace elements in maintaining prostate health, which can become a promising basis not only for improving the effectiveness of modern standard pharmacotherapy of prostate diseases, but also for developing a concept of their effective drug prevention. Various points of view are possible to nutraceuticals and their evidence base, but the most important thing is a clear understanding that, firstly, they do not replace medicines; secondly, only a skillful and personalized combination of medicines and various nutrients in the treatment of prostate diseases in a particular patient makes it possible to potentiate their effects and improve the results of standard pharmacotherapy, and, thirdly, most likely, nutritional supplementation can be an important component of the comprehensive prevention of prostate diseases, which necessarily also includes the optimization of lifestyle (including sexual life), a rational diet and water regime, sufficient physical activity and an optimistic view of life. All these contribute to the effective prevention of most age-associated diseases, including various prostate diseases.

Conflict of interests

The authors declare no conflict of interests.

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