REVIEW ARTICLE

CONTENTS

D-hormone and its significance for function of prostate gland (literature review and personal observations)

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ABSTRACT

Aim: The aim of this article is to present literature data and personal research of the role of D-hormoneon the functioning of the male reproductive system, and more specifically of the prostate gland, as well as the use of this vitamin D during the complex and independent treatment of benign prostatic hyperplasia in preclinical studies and clinical practice.

Materials and Methods: The collection of relevant data were done using the scientific databases Pubmed, Google Scholar. A manual search on reproductive endocrinology and pharmacology sources were also conducted for related published studies . Selected keywords ("benign prostatic hyperplasia" OR "BPH") AND ("prostate") AND ("reproductive system and vitamin D") were used to collect data. The article also presents our personal data of preclinical studies and clinical data of the use of vitamin D as monotherapy and in the complex therapy of reproductive disorders.

Conclusions: The effect of vitamin D on prostate volume and BPH has shown perspective results, therefore, it is proposed to conduct further studies on the role of vitamin D in the formation of BPH and reproductive disorders, their prevention and treatment. The use of vitamin D as monotherapy or in the form of pharmaceutical compositions and its inclusion in basic treatment regimens can increase the effectiveness of the prevention and correction of reproductopathies in the presence of or due to BPH and suggests the possibility of restoring the generative potential of individuals with BPH, both with and without D-hypovitaminosis.

KEY WORDS: vitamin D , reproductive system, benign prostatic hyperplasia

Wiad Lek. 2024;77(1):135-143. doi: 10.36740/WLek202401117 DOI

INTRODUCTION

It is known that the number of patients with benign prostatic hyperplasia (BPH) is increasing. It is estimated that BPH occurs in an average of 80% of men after the age of 60. However, under the influence of the rapid aging of the population, dynamic pace of life, stress and the effects of harmful environmental factors, BPH has become an important health problem worldwide. The researchers' search is focused on finding substances for the treatment of BPH among natural medicines as an adequate alternative, devoid of the main disadvantages of systemic prostatoprotectors. prevention and treatment of diseases of the prostate gland has not only medical, but also social significance. A prostatogenic decrease in fertility can have various causes, which are more often associated with a violation of the structure and function of this gland. One of the current problems is the study of the effect of D-hormone on the body, and in men its effect is closely related to the pathogenesis of androgen deficiency and hypofertility.

AIM

The aim of this article is to present literature data and personal research of the role of D-hormoneon the functioning of the male reproductive system, and more specifically of the prostate gland, as well as the use of this vitamin D during the complex and independent treatment of benign prostatic hyperplasia in preclinical studies and clinical practice.

MATERIALS AND METHODS

The collection of relevant data were done using the scientific databases Pubmed, Google Scholar. A manual search on reproductive endocrinology and pharmacology sources were also conducted for related published studies . Selected keywords ("benign prostatic hyperplasia" OR "BPH") AND ("prostate") AND ("reproductive system and vitamin D") were used to collect data. The article also presents our personal data of preclinical studies and clinical data of the use of

vitamin D as monotherapy and in the complex therapy of reproductive disorders.

REVIEW AND DISCUSSION

It is well known that the prostate affects fertility and any pathological processes in it affect the male reproductive system. The prostate gland produces a secret that makes up 25% of the volume of seminal fluid, which is necessary for the maintenance and protection of spermatozoa [1].

The secret of the prostate gland mainly consists of prostaglandins, prostatic acid phosphatase, as well as other enzymes (for example hyaluronidase), fibrinolysin and fibrokinase, which contribute to the liquefaction of the seminal fluid and activating the movement of spermatozoa [1].

It also plays an important role in regulating the level of male hormones and can affect the functioning of the genitourinary system in general. There are barrier and secretory functions of the prostate gland. Therefore, maintaining prostate health is an important aspect of men's health. In case of chronic inflammation of the prostate gland, its functions are impaired. Features of the location of the prostate gland, direct connection with the urethra make it vulnerable to the development of infectious and different inflammatory diseases, in particular prostatitis [1].

Chronic diseases of the prostate gland (PG): chronic prostatitis (CP) and benign prostatic hyperplasia (BPH) - significantly affect the work efficiency, health and general psycho-emotional state of men [2].

Every year due to these diseases the population and states suffer significant economic damage, and prevalence rates are constantly increasing due to an increase in average life expectancy and the percentage of men in older age groups. Important factors in the development of inflammation of the prostate are blood circulation disorders in the organs of the small pelvis (congestion), sedentary work, irregular sex life or its absence, excessive cooling, stress, overload. According to current data, chronic inflammation of the gland as a result of microbial infection, the influence of polymorphic factors or hereditary predisposition often precedes or accompanies the development of BPH - a chronic progressive benign disease [2].

Against the background of age-related imbalance of sex hormones, prostatic glandular-stromal hyperplasia develops, accompanied by symptoms of the Lower Urinary Tract (LUTS) [2]. To date, there are no large-scale epidemiological studies of the internal population that would be similar to foreign ones. The etiology of BPH is multifactorial, and the development of the disease directly correlates with age, the level of prostate-specific antigen (PSA) and the volume of prostate [2].

Benign prostate hyperplasia is a benign disease characterized by an increase in the size of prostatic epithelial cells and stromal tissues, a decrease in the rate of urine flow, which causes disturbances, commonly known as LUTS [2].

Taking into account that the growth, differentiation and functioning of the PG are controlled by sex hormones, most theories of the pathogenesis of BPH contain questions of hormonal regulation. This is based both on the fact of the presence of androgen receptors and estrogen receptors in this gland, and on the facts of the formation of these hormones in the basal and luminal cells of the PG [2].

Sex hormones such as testosterone (T), dihydrotestosterone (DHT), progesterone and estrogens have been studied in the most detail, although the role of each in the progression and development of BPH and their pathogenetic role in the "hormone / receptor" interaction, mutual regulation remains insufficiently understood [2, 3].

The main hormone which regulates the growth of the prostate gland is 5α-DHT, which is formed from T in the epithelial and stromal cells of the gland with the participation of the enzyme 5α-reductase [2]. It has been established that DHT carries out direct and indirect modulation of cell differentiation, proliferation and apoptosis of cells, induces glandular hyperplasia of the PG, while stromal hyperplasia is regulated by estrogens [2, 4].

The T metabolite is also considered to play a central role in the pathogenesis of BPH, based on the results of large-scale studies that have found a positive correlation between the presence of BPH/ LUTS and changes in the levels of endogenous sex steroid hormones, in particular T and estrogens.

Several studies have described inversely proportional relationship between serum T levels (total or bioavailable) and the degree of BPH or LUTS expression [2, 5], which correlates well with the state of age-related androgen deficiency and the frequency of PG disease [2]. This was the basis for attempts to use T for replacement therapy in order to prevent age-related changes in PG. However, the Proscar study found low T levels (<300 ng/dl) in 21,7% of older men only who also had BPH [2, 6]. Therefore, the idea of androgen replacement therapy was rejected due to fears of a possible increase in BPH and LUTS [2].

The importance of the problem of treating CP can be based on the knowledge of the fact that it is the third leading disease after cancer and it can take the development of BPH and has social significance for

many reasons [2]. Conservative therapy of prostatitis requires an integrated approach, namely the use of drugs of different types of action [2, 7].

So, recently the traditional ideas about the importance of vitamin D in providing calcium-phosphorus metabolism and bone mineral density have been supplemented with data on its role in the regulation of reproductive and sexual functions in men [8-10]. At the same time, it has been shown that in the presence of D-hypovitaminosis, disturbances in spermatogenesis occur, and also disturbance in the erectile and ejaculatory components of the copulatory cycle [8, 11]. The authors proved that erectile dysfunction in men with D-hypovitaminosis is associated with a decrease in the level of testosterone in the blood [8, 12].

Also, in our own studies at the clinic of the SI «V. Danilevsky Institute for endocrine pathology problems of NAMS of Ukraine» (Kharkiv, Ukraine) the features of changes in erectile function has been established and its depending on the levels of vitamin D in the blood and androgen status in 47 young and middle-aged men (23-59 years old). The research was conducted in the autumn-winter period of 2019-2020. According to the results of own observations, it has been proven that the content of 25(OH)D in the blood of middle-aged men, regardless of the presence or absence of type 2 diabetes, was significantly lower compared to the group of young men. It has been proven that the formation of erectile dysfunction in both young and middle-aged men is due to a decrease in testosterone levels in the blood and a decrease in the T/E2 (testosterone/estradiol) ratio [8]. So, it has been established that a predecessor of the development of hypotestosterone and androgen-estrogen balance disorders in men regardless of age, in particular, patients with type 2 diabetes, can be a decrease in the blood content of 25(OH)D [8].

According to the World Health Organization, more than one billion people have vitamin D deficiency. Vitamin D deficiency is also present (in 81.8% of cases) in Ukraine. It has been established that vitamin D is necessary for adequate production of steroid hormones and full-fledged spermatogenesis, but its deficiency causes the development of androgen deficiency and pathospermia, which generally leads to a decrease in fertility. Also it has been reported that vitamin D receptor has an expression in cells of reproductive organs such as testes (Sertoli cells, seminiferous tubules, spermatogonial stem cells, etc.), epididymis, seminal vesicles (SV), prostate (PG), and even spermatozoa [13]. It indicates the necessity of vitamin D for adequate production of steroid hormones, and its deficiency can have a negative impact on the reproductive function of men [13].

In direction testosterone is a regulator of vitamin D receptor activity in the testicles. Vitamin D treatment led to an increase in the level of male sex hormones in the blood serum of patients with D-hypovitaminosis [13].

In addition, application of vitamin D in men with idiopathic oligoasthenozoospermia for three months, even without taking into account its concentration in the blood during treatment, improved sperm motility [13].

This indicates that the use of vitamin D for the treatment of reproductive disorders in men with pathology of the genital and prostate glands is possible both with and without D-hypovitaminosis.

Well known that only experimental arguments of vitamin D prescribing in pathology models simulating the most common variants of infertility can confirm these assumptions. These pathologies include chronic inflammatory processes in PG and SV, because subfertility in men with prostatitis remains one of the main causes of infertile marriages.

According to our observations at the laboratory of reproductive endocrinology of the SI «V. Danilevsky Institute for endocrine pathology problems of NAMS of Ukraine» (Kharkiv, Ukraine), experimental data about changes in the hormone synthetic function of the testicles during modeling of prostatitis, as well as cholecalciferol (D3) together with drugs which protect prostate gland have been presented. Thus 36 sexually active rats were administered vitamin D at a dose of 4000 IU (both monotherapy and in complex baseline regimens) to correct sex hormone levels and fructose concentrations in male rats with experimental abacterial prostatitis induced by cryotraumatization of the ventral part of the prostate gland. In this study, as in our previous ones, it was shown that modeling experimental prostate pathology by prostate cryotrauma leads to hypotestosteronemia and a decrease in serum testosterone/estradiol ratio in male rats. The concentration of fructose decreases almost 3 times in the seminal vesicles of animals with experimental prostatitis [13, 14]. The use of Prostatilenum* as monotherapy or in combination with vitamin D3 for the experimental treatment of prostatitis regardless of the methods of administration led to the normalization of testosterone levels (increased testosterone concentration in blood serum) and fructose content in the testicles but did not affect the concentration of estradiol. Independent use of vitamin D per os in conditions of experimental prostatitis did not lead to regeneration of testosterone secretion, but increased its effect on seminal vesicles. Prostatilenum* (Biopharma, Ukraine) is a biogenic preparation with prostate-protective action. This procedure is indicated by an increase in the mass of seminal vesicles and the concentration of fructose in them [13]. Therefore, the

introduction of complex treatment regimens of vitamin D with Prostatilenum* is advisable, because it positively affects the androgen saturation of the body, increases the concentration of fructose in the seminal vesicles, which can contribute to spermatogenesis and fertility [13].

This indicates an increase in the mass of seminal vesicles and the concentration of fructose in them [13].

Recently, the number of patients with benign prostatic hyperplasia (BPH) has been increasing. It was supposed earlier that BPH is observed in an average of 80% of men after the age of 60 [15]. Due to the rapid aging of the population, dynamic steps of life, stress and the effects of harmful environmental factors, BPH has become an important health problem worldwide. It is supposed that under such conditions, the number of men under the age of 50 who will have this disease increases [15], because such conditions cause a decrease in the secretion of androgens in men, metabolic disorders and dyshormonal conditions, which are now observed more often in the stressful existence of society than before. It is well known sexual function is very sensitive to harmful factors, under their influence both reproductive and copulatory components of male health change. Prolonged stress can cause hypofertility even infertility and sexual disorders. One of the main suppressing factors of spermatogenesis due to the stress is the occurrence of a number of hormonal changes – a decrease in the circulating level of testosterone, follicle-stimulating and luteinizing hormones with an increase in the concentration of corticosteroids, prolactin, and predominance the content of estrogens over androgens [16].

It is known that lifestyle factors, which are currently complicated by external influences, have a specific weight in the development of BPH [17]. Prevention and treatment of BPH is not only a medical, but also a serious social problem. Today, based on the results of research into the pathogenesis of the hyperplastic process in the gland and the mechanism of action of drugs, not only surgical, but also therapeutic treatment of BPH has taken an important place among other methods of its rehabilitation [18].

The pathogenesis of BPH is associated with regulatory disturbances in the hypothalamic-pituitary system and a change in the intensity of regulatory signals sent to the reproductive organs. The central pathogenetic links in the development of this pathology include a decrease in the efficiency of the regulation of hypothalamus functions, which is carried out according to the principle of feedback, the change in the sensitivity of pituitary cells to the releasing hormones of the hypothalamus and an imbalance between the production of estrogens and androgens. At the organ level the development of BPH is caused by an increasing in the activity of the enzyme 5-alpha-reductase which promotes the conversion of testosterone into dihydrotestosterone, an increasing in the synthesis of tissue growth factors and an increase in the expression of androgenic and alpha-1-adrenoceptors [2]. Among the adenohypophyseal hormones in addition to follicle-stimulating and luteinizing the development of BPH is greatly influenced by prolactin, the hypersecretion of which is considered to be a very significant cause of age-related hyperplastic processes in the prostate gland.

Prolactin stimulates proliferation and acts as an androgen-dependent suppressor of prostatic epithelial apoptosis, leading to prostatic hyperplasia. By the way, the increase in the level of prolactin under conditions of stress and its important etiopathogenetic role in reducing the reproductive capacity of the body are are universally accepted [19]. The experimental administration of dopamine receptor blockers, namely sulpiride, in BPH modeling, for a long time contributes to an increase in the level of prolactin and a decrease in the release of gonadotropic hormones [14, 20].

This model is widely used in experiments to study the prostatotropic activity of BPH drugs [21]. The sulpiride model which is characterized by the development of an imbalance of sex hormones and an inflammatory process in the body of rats [22] provoke the development of BPH is associated with a violation of testosterone synthesis in the testicles due to insufficient function of the PG, an increase in the content of prolactin and estradiol which then provokes proliferative changes in the organ which we have observed in 64 male rats during our the experiment at the laboratory of reproductive endocrinology of the SI «V. Danilevsky Institute for endocrine pathology problems of NAMS of Ukraine» (Kharkiv, Ukraine) [22].

With prolonged administration of sulpiride, whose neuroleptic properties are associated with antidopaminergic action, induces hypersecretion of prolactin, which leads to stimulation of the proliferation of the glandular epithelium of the PG. The pathogenesis of acinar hyperplasia is related to an increase in the activity of 5-alpha-reductase and an increase in the sensitivity of epithelial cells; in 50% of cases, the pathology develops against the background of chronic prostatitis and reduced sensitivity to androgens [22]. Considering the fact that the growth, differentiation, and functioning of PG is controlled by sex hormones, most theories of the pathogenesis of BPH pay attention to hormonal regulation also. This is based both on the presence of androgen receptors (AR) and estrogen receptors (ER) and on the formation of these hormones in the basal and luminal PG cells. The main hormone regulating gland growth is 5α-dihydrotestosterone

(5α-DHT), which is formed from testosterone (T) in epithelial and stromal cells [22].

BPH may occur due to their excessive growth in these cells of the epithelium and stroma of the gland. Espinosa G (2013) writes that the prevalence of vitamin D deficiency in the «male urological population» may indicate an association between BPH and vitamin D. Vitamin D has an inhibitory effect on the RhoA/ROCK pathway together with cyclooxygenase-2 expression and prostaglandin E2 production in stromal cells of BPH. It has been shown increasing of dietary vitamin D intake with food and nutritional supplements correlate with a decrease in the prevalence of BPH, and vitamin D analogues reduce prostate volume in patients with this pathology. Preclinical studies have shown that vitamin D not only reduces prostate cell proliferation in BPH when induced by well known growth-promoting molecules such as IL-8, Des(1-3) IGF-1, testosterone and dihydrotestosterone [15].

Among all these studies, there were no side effects or negative effects with increased vitamin D intake (Espinosa G., 2013). Against the background of BPH, reproductive disorders have been diagnosed, such as sexual disorders, spermatopathy, hypofertility, which may be caused by increased production of reactive oxygen radicals during inflammation due to prostatitis [23].

Usually BPH therapy includes a complex of measures such as the use of α1-blockers (in particular, doxosazin, tamsulosin, silodosin), 5α-reductase inhibitors, phosphodiesterase type 5 inhibitors, anticholinergic and pronorepine drugs (3β). However, when prescribing such therapy one should take into account a large number of side effects associated with the consequences of prolonged dilation of small vessels such as a decrease in sperm production, gynecomastia (breast enlargement) and other [22].

Based on the recommendations of international urological associations for the conservative therapy of BPH, the following pharmacotherapeutic groups are selected: α1-adrenergic agents, 5α-reductase inhibitors, anticholinergic drugs, antihormonal drugs, NSAIDs. Systemic drugs may have a significant number of side effects. So, for example: the effect of 5α-reductase inhibitors is negative in damage from the side of the reproductive system. This is unacceptable, because according to statistics, BPH occurs in men of reproductive age, reduces their sexual activity, impairs fertility, which significantly affects the quality of life. However, taking into account the positive results of the treatment of pathology, this group of pharmaceuticals continues to be chosen by many doctors as an alternative to surgical intervention [23].

More often the search of scientists is focusing on the search for substances for the treatment of BPH among herbal medicines as an adequate alternative, devoid of the main disadvantages of systemic prostate protectors [14]. According to Zaijchenko G.V. (2018) herbal drugs have a wider therapeutic range, are safer than other groups of drugs, often acting as the drugs of choice for men with BPH under 55 years of age. However, their lack of knowledge does not allow them to be considered more effective than α1-agonists and 5α-reductase inhibitors. It is perspective to use combined drugs which contains several active ingredients with different mechanisms of action and using drugs of different pharmacological groups. So, recently a pharmaceutical composition has been created which includes indole-3-carbinol and meloxicam, capable of inhibiting the biosynthesis of prostaglandins - inflammatory mediators and preventing carcinogenesis in the prostate gland. Currently, there are several drugs and dietary supplements containing indole-3-carbinol (Indigal, Prostadoz, Saluprost, Indole forte, etc.) in combination with vitamins, epigallocatechin-3-gallate and the most active green tea catechin [2, 24].

This motivates to look for new ways of prevention and treatment of BPH. The data accumulated in recent decades indicate that traditional methods of treating BPH disease are not very effective and the use of antibiotics and alpha-blockers in chronic nonspecific prostatitis does not change the so-called Chronic Prostatitis Symptom Index (National Institutes of Health, USA), although a positive effect has been found of muscle relaxant therapy [25]. They also note a significant placebo effect and suppose that it is combination therapy with the introduction of anti-inflammatory and immunomodulatory agents that increases the effectiveness of therapy [26]. IL-1 and C-reactive protein are objective criteria for the severity of chronic inflammation, the levels of which can be used to monitor the effectiveness of therapy [27].

There are drugs based on natural compounds in particular from plant materials among the drugs with anti-inflammatory and immunomodulatory effects [28].

Serenoa repens fruit extract (Prostamol® Uno) is widely used for the treatment of chronic prostatitis and the prevention of prostate adenoma [29], although the data obtained are contradictory. A drug composition containing an extract of broccoli and nettle has been created, and its effect on the inhibition of BPH has been shown [30].

As noted above, the prevention and treatment of PG diseases has not only medical, but also social significance. Prostatogenic decrease in fertility can have different causes, most often associated with a violation of the

structure and function of the prostate gland by itself. One of the urgent problems of today is the study of the effect of the D-hormone on the body [31], while in men its action is closely associated with the pathogenesis of androgen deficiency and hypofertility [32].

There is evidence that the level of vitamin D describes the qualitative and quantitative characteristics of the ejaculate in young people [33], including the motility and morphology of spermatozoa [34], is important in the maturation of spermatozoa.

A relationship has been found between low levels of vitamin D and a decrease in the number of motile and morphologically normal spermatozoa [35]. Vitamin D deficiency in animals leads to disruption of the maturation of the vas deferens, a decrease in testicular mass and sperm concentration [36]. Experimental studies have shown that vitamin D saturation leads to a significant improvement in spermatogenesis in experimental reproductive disorders [37-38].

Data reported in the literature about the use of vitamin D in males demonstrate wide variability in design, methodology, patient population, reference values, and routes of administration for both vitamin D itself and its metabolites, and require further research. Vitamin D belongs to the group of fat-soluble secosteroids. A secosteroid is a molecule that is very similar to steroids, but with a torn-apart of steroid ring. Vitamin D occurs in nature in several forms, but only two forms (D2 and D3) are important to the human body, which differ chemically in their side chains. These structural differences change their binding to the carrier protein, vitamin D-binding protein and their metabolism, but in general, the biological activity of these active derivatives is similar [39].

Data from the literature indicate that vitamin D has an inhibitory effect on the production of prostaglandin E2 in the stromal cells of BPH. An increase in dietary and supplemental vitamin D intake was correlated with a decrease in the prevalence of BPH. It has been shown by Espinosa G. (2013) vitamin D analogues can reduce prostate volume in patients with BPH. Preclinical trials have shown that vitamin D reduces BPH cell proliferation through induction by known growth-promoting molecules such as IL-8, Des(1-3) IGF-1, testosterone, and dihydrotestosterone. Among all studies, there were no side effects or adverse effects with increased vitamin D intake [15]. The effect of vitamin D on prostate volume and BPH has shown perspective results, therefore, it is proposed to conduct further studies on the role of vitamin D in the formation of BPH and reproductive disorders, their prevention and treatment. The use of vitamin D as monotherapy or in the form of pharmaceutical compositions and its inclusion in basic treatment regimens can increase the effectiveness of the prevention and correction of reproductopathies in the presence of or due to BPH and suggests the possibility of restoring the generative potential of individuals with BPH, both with and without D-hypovitaminosis [40].

Summing up this report, the following conclusion can be exposed leaving some questions open for research:

CONCLUSIONS

1. Considering the fact that one of the main reasons for the impairment of male fertility is the disease of the reproductive system, in particular, BPH, which is a common pathology of the male reproductive system, however, the reconstruction of male health in this pathology is not effective enough, this determines the urgency of developing new drugs for the correction of BPH and consequences for the reproductive system.
2. Particular attention needs to be given the answer to the question if the introduction of cholecalciferol (D3), which is the most active of the metabolites of this vitamin and is often used in the clinic, has a negative effect on the gonads and spermatogenesis of intact individuals during long-term use, since vitamin D therapy is used in reproductive diseases such as with vitamin D deficiency and without it

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The research was carried out as part of investigation works at the SI «V. Danilevsky Institute for Endocrine Pathology Problems of NAMS of Ukraine»: 1) «Mechanisms of development, diagnosis and therapy of infertility in individuals with gonadal dysfunction and comorbid pathology» (state registration number 0116U007259);
2) "Determination of the role of vitamin D deficiency and insufficiency in the development of gonadal dysfunction, substantiation of approaches to their therapy" (state registration number 0119U102387);
3) Determination of the role and deficiency of vitamin D in the development of the sexual glands dysfunctions, definition to ways to their therapies (state registration number 0119U 102387).
The authors assume responsibility for the published work.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 18.07.2023
ACCEPTED: 01.12.2023