REVIEW ARTICLE

AGE-RELATED MACULAR DEGENERATION – CURRENT STATE OF THE PROBLEM AND PROPHYLAXIS METHODS

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ABSTRACT

The aim: Analyze the ophthalmic studies on diagnostics and treatment of patients with age-related macular degeneration to optimize diagnostics and management tactics.

Materials and methods: The analysis of scientific papers due to age-related macular degeneration, vitamin D and its functions from scientometric databases: PubMed, Scopus, Web of Science. The methods were next: systematic approach, analysis, summarization and comparison.

Conclusions: Age-related macular degeneration is a chronic, progressive disease among people older than 50 years. Late diagnostics and inappropriate treatment may lead to irreversible central vision loss and social disadaptation. Modern studies on the pathogenesis and treatment of this pathology (that are due to the role of the immune system, antioxidants and microelements) demonstrate the effectiveness and prospects for further development around the world to find new ways to solve this problem.

KEY WORDS: age-related macular degeneration, vitamin D, vitamin D receptor, oxidative stress, immune response

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INTRODUCTION

Nowadays irreversible vision loss is one of the global problems. This is not only a medical problem, but also a socio-economic one. Age-related macular degeneration (AMD) is third in the world (causes about 6,6% of cases of blindness) after cataract and glaucoma, and each year this amount continues to grow, adding 600,000 new cases [1 - 4]. This can be characterized by the fact that in the developed world the average life expectancy is increasing, the nation is aging, the incidence of chronic diseases is growing, and the population has more opportunities for adequate diagnosis of eye diseases.

Wong and colleagues, analyzing the main trends in the incidence of AMD, has estimated that by 2020 around 196 million people will suffer from this disease in the world, and by 2040 this figure will almost double to 288 million people [5, 6]. European research shows that by 2050, 77 million people in Europe will suffer from AMD. The incidence of new cases will increase by 75% [7].

A prospective multicenter randomized clinical trial of age-related macular degeneration (AREDS – Age-Related Eye Disease Study) [8] has found that more than 10% of the population aged 65-74 had symptoms and signs of AMD, whereas in population older than 75 years this figure has increased significantly and was 25%, while among people older than 85 years – was more than 30%. It has been reported that in the presence of symptoms and signs of AMD in one eye, the other eye is affected in 5 years [9]. AMD does not cause complete blindness among people older than 50 years, this disease significantly affects their perception of the outside world: every day it becomes harder to go shopping, to recognize the faces of beloved ones, people are gradually losing the ability to self-care. Rapid loss of vision occurs when AMD becomes exudative. Measures that slow down the AMD transition from dry to exudative form by the correction of pathogenetic changes, thus, are relevant. This, in turn, is the social significance of this issue around the world.

THE AIM

Analyze the ophthalmic studies on diagnostics and treatment of patients with age-related macular degeneration to optimize diagnostics and management tactics.

MATERIALS AND METHODS

The analysis of scientific papers due to age-related macular degeneration, vitamin D and its functions from scientometric databases: PubMed, Scopus, Web of Science. The methods were next: systematic approach, analysis, summarization and comparison.

REVIEW AND DISCUSSION

Age-related macular degeneration (AMD) is a multifactorial disease: metabolic and genetic factors play a role in its pathogenesis. One of the main causes of AMD today is considered to be oxidative stress and inflammation, which cause irreversible progressive loss of retinal photoreceptors [10, 11]. As one of the most highly differentiated nerve tissues in the human body, the retina is extremely sensitive

to hypoxia and ischemia [10]. As a result of numerous biochemical reactions, a significant amount of free radicals is formed, which have a detrimental effect on retinal cells.

There are the following processes in the pathogenesis of AMD [12 -16]:

1) primary aging of the retinal pigment epithelium (RPE) and Bruch's membrane – macular pigment – is the only antioxidant in the retina that actively neutralizes the action of free radicals and passively retains or absorbs blue light, which causes photooxidative damage;

2) damage of the retina by the products of lipid peroxidation – activation of free radical oxidation causes the damage of proteins, nucleic acids, especially lipids of cell membranes, which are very easily involved in the free radical reaction chain. Disturbance of the balance between oxidative and antioxidant systems affects the integrity of the complex of photoreceptors and RPE, leads to the accumulation of cell breakdown products, lipofuscin granules and the formation of drusen;

3) primary genetic defects – inherited nature of AMD with autonomous-dominant type of inheritance. It was found that people who are relatives in the first generation are 3 times more likely to get AMD, provided that one person has already shown signs of AMD;

4) pathological changes in the blood supply of the eyeball – impaired microcirculation in the choriocapillaris – the only source of blood supply of the macular area – due to the background of age-related changes in the RPE and Bruch's membrane may be the beginning of the dystrophic process. In the presence of atherosclerosis, the risk of developing AMD increases 3 times (localization of plaque in the common carotid artery – 2,5 times, in the bifurcation of the carotid arteries – 4,7 times).

According to the classification, AMD is divided into dry (non-exudative) and wet (exudative) form, with a predominance of dry (about 90%) in the incidence of the population [8, 17]. The AREDS classification, proposed by the American Academy of Ophthalmology, is the most often used one in the world. According to this classification, dry AMD includes the following stages:

category 1 – absence of AMD – absence or insignificant number of small drusen (up to 63 microns in diameter according to optical coherence tomography);

category 2 – early stage of AMD – a significant number of small drusen, a small number of medium size drusen (diameter 64–124 microns) or changes in the RPE;

category 3 – intermediate stage of AMD – a significant number of medium size drusen, at least one large drusen (diameter more than 125 microns) or geographical atrophy of the retina, which does not affect the central fovea;

category 4 – late stage of AMD – geographical atrophy of the retina, which affects the central fovea.

The wet form of AMD involves exudative detachment of the retinal RPE and retinal neuroepithelium, choroidal neovascularization and the formation of fibrovascular scar in the central fovea of the retina.

Nowadays, scientists around the world recommend the use of antioxidant drugs in treatment of dry AMD. One of the good combinations is a special formula AREDS2, which includes: 500 mg of vitamin C, 400 ME of vitamin E, 10 mg of lutein, 2 mg of zeaxanthin, 80 mg of zinc in the form zinc oxide, 2 mg of copper in the form of copper oxide [18 - 20]. Intravitreal injections of anti-VEGF factor inhibitors (aflibercept, bevacizumab, ranibizumab) are used to treat the wet form of AMD [9, 17]. However, these injections have a limited duration of action on patients and require frequent use (every few months), which to some extent limits patients and their relatives.

In recent years, many studies have been conducted on the role of vitamin D in chronic eye diseases, including AMD [21 - 25]. Performing the functions of both vitamin and hormone in the human body, its active metabolites are involved in the regulation of calcium-phosphorus metabolism, cell proliferation and have an immunomodulatory effect. Its receptors (vitamin D receptor – VDR) are found in many organs, including the retina and immune system cells [26 - 28, 31, 32].

Vitamin D is not a biologically active vitamin; its clinical effects are manifested after interaction with specific receptors located in cell nuclei, after activation in liver and kidneys [29, 30]. These conditions give the second name to vitamin D – D-hormone. Vitamin D is a combination of several different compounds (seco-steroids), but only D_2 and D_3 types are biologically important:

D_1 – ergocalciferol in combination with lumisterol;

D_2 – ergocalciferol, enters the body with plant products (bread, etc.). It is synthesized from ergosterol – sterol secreted by yeast fungi. It is produced under the influence of ultraviolet light;

D_3 – cholecalciferol, 80% of vitamin D_3 is formed in the skin from dehydrocholesterol under the action of ultraviolet light. 20% of it enters the body with food of animal origin (fish oil, liver, egg yolk);

D_4 – dehydrocholesterol, is found in the body and skin of animals and humans. Due to the action of ultraviolet light on human skin it synthesizes vitamin D_3;

D_5 – sitocalciferol, is extracted from wheat grains by chemical synthesis; is a nutrient component of wheat germ.

D_6 – sigma-calciferol, is found in plant foods, has little value, but may be an alternative for people who are vegetarians.

Absorption of ergocalciferol (D_2) from food occurs in the duodenum with the participation of bile acids [33, 34].

Cholecalciferol (D_3) is formed from the precursor of 7-dehydrocholesterol (located in the malpighian layer of the skin) under the action of ultraviolet light [29, 30].

Once in the human body, vitamin D is incorporated into the structure of chylomicrons, circulates in the blood and binds to vitamin D-binding protein, from which it is separated in the liver [33, 34].

Then in the liver (especially in hepatocytes) 25-OH-hydroxycholecalciferol (calcidol) is formed from both forms of vitamin D as a result of hydroxylation (addition of the OH group) [29, 30]. This form is both a depot and a transport, and it is determined in the blood to estimate the level of vitamin D. The hydroxylation reaction is a substrate-de-

pendent process, proceeds rapidly and causes an increase in serum 25-OH-D_3. [29, 30] The half-life time of 25-OH-D_3 in blood is up to 30 days, which can be explained by the relatively high affinity of 25(OH)D_3 to vitamin D-binding protein [29, 30]. Some amount of vitamin D is deposited in adipose and muscle tissue.

After this the second stage of hydroxylation is done in the kidneys with the help of parathyroid hormone (hormone of the parathyroid glands). It includes the interaction with ⟨1-hydroxylase enzyme (localized in the mitochondria of the proximal convoluted tubules of the kidneys). And there is the formation of the active form – 1,25(OH)-dihydroxycholecalciferol. From 0,3 μg to 1,0 μg of calcitriol is formed per day [29, 30]. It is calcitriol that provides the main biological effects of vitamin D in the body: increasing the serum calcium concentration by increasing its absorption from the intestine and reabsorption in the kidneys [29, 30, 33]. The half-life time of 1,25$(OH)_2D_3$ in the blood is 4 hours. When the concentration of calcium and phosphorus in the blood reaches normal values, the activity of 24-hydroxylase enzyme increases and 24,25-dihydroxycholecalciferol is formed. It fixes calcium and phosphorus in the bone tissue [29, 30]. Parathyroid hormone is regulated by a feedback mechanism – an increase in the concentration of calcitriol in the blood causes a decrease in its secretion [29, 30, 35]. Also, the processes of ⟨1-hydroxylation are influenced by sex hormones (androgens, estrogen), prolactin, calcitonin and others [29, 30].

Most of the metabolites of vitamin D in the blood are associated with albumin (10-20%) or vitamin D-binding protein (80-90%). The complex of vitamin D and transport protein is able to bind with specific receptors and enter the cell, where vitamin D exhibits active properties. Only a small fraction (0,02-0,05% of 25-hydroxyvitamin D and 0,2-0,6% of 1,25-dihydroxyvitamin D) of vitamin D metabolites is present in the blood in the free state [29, 30]. The concentration of non-protein metabolites of vitamin D is maintained at a fairly stable level even in liver disease and reduced production of vitamin D-binding protein and therefore is not a good indicator of the dynamics of vitamin D status of the body [29, 36].

Because vitamin D is a fat-soluble vitamin, it is able to accumulate in the human body in various organs. The largest amount is contained in the subcutaneous fat and liver [29]. Thus, there is always some depot of vitamin D, from which this compound is consumed in case of insufficient food intake.

Vitamin D production is inhibited by indoor glass, clouds, air pollution, clothing and sunscreen. The use of sunscreen with a factor of 15 (SPF 15) reduces the synthesis of vitamin D in the skin by 99% [37].

Sufficient amount of fat and bile are needed to absorb the vitamin into the blood from the intestines [29, 33, 34]. Therefore, for better absorption of vitamin D, it should be taken with vegetable fats. With sufficient amount of fat and bile, vitamin D is absorbed up to 90%, but in their absence – only up to 60%. The absorption of synthetic vitamins D does not depend on the amount of fat and bile, so pharmacological drugs may be more effective than natural compounds [29, 30, 33, 34].

One of the functions of vitamin D is an anti-inflammatory effect [21, 26, 27].

VDRs to 1,25$(OH)_2D_3$ have been identified in more than 38 tissues, where vitamin D clearly controls vital genes associated with bone metabolism, oxidative damage, chronic disease and inflammation [21, 26, 27].

VDR is expressed by macrophages and dendritic cells, suggesting that vitamin D plays an important role in modulating the inflammatory response [26, 27, 39]. 1,25$(OH)_2D_3$ can be synthesized by both cell types because they express the enzymes 25-hydroxylase and α1-hydroxylase, which allow to produce 25(OH)D_3 and 1,25$(OH)_2D_3$, respectively [39, 41, 42]. In macrophages and dendritic cells, the enzyme α1-hydroxylase is predominantly regulated by inflammatory mediators such as interferon-γ (IFN-γ) and lipopolysaccharides [39, 43].

Macrophages are cells with a high capacity to produce cytokines, in particular TNF-α, which is one of the most important products secreted by these cells [39, 44]. Transcriptional activation of the TNF-α gene in macrophages largely depends on the activation of NF-κB transcription, which is the main regulator of immune, inflammatory and stress responses [39, 45]. In lipopolysaccharide- stimulated mouse macrophages, 1,25$(OH)_2D_3$ regulates the NF-κB (IκB-α) inhibitor by increasing mRNA stability and reducing IkB-α phosphorylation. An increase in the level of IκB-α leads to a decrease in the nuclear translocation of NF-κB, thereby causing a decrease in activity. Given the key role of NF-κB as a transcription factor for inflammatory mediators, it should be assumed that 1,25$(OH)_2D_3$ has anti-inflammatory effects in macrophages [39, 46]. In addition, 1,25$(OH)_2D_3$ inhibits the expression of TLR2 and TLR4 protein and mRNA in human monocytes. [39, 47]. Incubation of isolated monocytes with 1,25$(OH)_2D_3$ attenuates the expression of proinflammatory cytokines such as IL-1, IL-6 and TNF-α [39, 48, 49, 50].

Some studies show that hypovitaminosis of vitamin D is associated with higher levels of serum inflammatory biomarkers, such as IL-6, TNF-α and C-reactive protein (CRP), in healthy [39, 51 - 54] and obese people.

Studies have shown the presence of VDR in immune system cells and α1-hydroxylase in macrophages and dendritic cells. The data obtained indicate the local production of 1,25(OH)-dihydroxycholecalciferol, which has auto- and paracrine properties at the site of inflammation [26, 27, 55]. Next, 1,25$(OH)_2D_3$ binds to VDR and modulates tissue gene expression in a specific way. Some cells, including cells of the immune system, have α1-hydroxylase and VDR and can synthesize the hormonal form of vitamin D from circulating in the blood 25(OH)D_3, and therefore extrarenal α1-hydroxylase acts differently in response to parathyroid hormone, calcium and phosphorus compared with renal α1-hydroxylase. Thus, extrarenal α1-hydroxylase is not regulated by parathyroid hormone, the secretion of 1,25$(OH)_2D_3$ depends on the substrate concentration of 25(OH)D_3. The process is substrate-dependent and

requires a sufficient level of saturation of the body with vitamin D [26, 27, 55].

In a number of studies, scientists have observed that cells from foci of inflammation (compared to healthy cells of the same organism) have an increase in the concentration of active metabolites of vitamin D, which may indicate its anti-inflammatory effect [26, 27, 56]. Active metabolites of vitamin D with the help of cytokines inhibit the occurrence of severe inflammation in various organs and tissues of the body, where there are receptors for vitamin D, including eye tissues. Nuclear receptors for calcitriol are found in cells of the central and peripheral nervous system (neurons of the brain, glial cells, spinal cord) [26, 56, 57].

The daily requirement of vitamin D is 400 IU for children and 200 IU for adults, sufficient supply of vitamin D is in the range of 40-100 ng/ml. Decreased levels of vitamin D in the blood cause a state of its deficiency and insufficiency, thus disrupting metabolic processes in the body [29, 30].

The action of vitamin D is of interest to scientists around the world. There are many studies that observe the effects of vitamin D metabolites on AMD. However, data from various studies have led to controversial conclusions, not giving the opportunity to unambiguously answer questions about the benefits of adding vitamin D drugs to stabilize the process.

CONCLUSIONS

Age-related macular degeneration is a chronic, progressive disease among people older than 50 years. Late diagnostics and inappropriate treatment may lead to irreversible central vision loss and social disadaptation. Modern studies on the pathogenesis and treatment of this pathology (that are due to the role of the immune system, antioxidants and microelements) demonstrate the effectiveness and prospects for further development around the world to find new ways to solve this problem.

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