

25-HYDROXYVITAMIN D AND MATRIX METALLOPROTEINASES-2, -9 LEVEL IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA AND PSEUDOEXFOLIATIVE GLAUCOMA/SYNDROME

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For citation: Ophthalmology Journal, 2017;10(1):10-16

Received: 28.12.2016

Accepted: 22.02.2017

✧ **Aim.** To determine serum 25(OH)D and plasma MMP-2 and MMP-9 levels in patients with primary open-angle glaucoma (POAG), pseudoexfoliation glaucoma (PEG), and pseudoexfoliation syndrome (PES) – to assess potential associations between vitamin D status and the above mentioned diseases. **Methods.** We included 238 patients (105 males and 133 females) aged from 55 to 75 years. One hundred twenty two patients had PEG, 46 patients had POAG, 32 had PES. 38 subjects were healthy, and were considered as the control group. Cases with clinically significant systemic diseases and concomitant eye diseases were excluded, if there was a confirmed pathogenic impact of vitamin D and MMP. The serum 25(OH)D level was investigated by immunochemiluminescence method, plasma MMP-2 and MMP-9 levels – by ELISA. **Results.** Serum 25(OH)D level was between 4.6 and 82.25 nM/l (mean 41.7 nM/l), so most participants showed vitamin D deficiency. It was shown that mean serum 25(OH)D level in patients with PEG, POAG and PES was similar (39.3 ± 1.2 , 38.8 ± 2.1 and 40.51 ± 2.4 nM/l, $p > 0.05$), but it was lower than those in the control group (52.7 ± 2.1 nM/l, $p < 0.01$). Plasma MMP-2 concentration was the same in all study groups. Plasma MMP-9 level was higher in POAG and PES patients (48.23 ± 3.26 and 54.01 ± 3.57 ng/ml) than in the control group (32.60 ± 2.34 ng/ml, $p < 0.001$) and in patients with PEG (40.86 ± 3.60 ng/ml, $p < 0.05$). We found positive correlations between MMP-2 and MMP-9 levels in patients with PEG ($r = 0.48$, $p = 0.001$) and patients with POAG ($r = 0.43$, $p = 0.003$). The correlation analysis showed also a negative relation between 25(OH)D and MMP-9 ($r = -0.32$, $p = 0.02$), as well as MMP-2 ($r = -0.33$, $p = 0.02$) in patients with POAG. **Summary.** Study results confirmed a potential role of vitamin D in apoptosis regulation and tissue remodeling in patients with POAG and PES. Hence, vitamin D deficiency can be considered as a risk factor for glaucoma development.

✧ **Keywords:** open angle glaucoma; pseudoexfoliative glaucoma; pseudoexfoliation syndrome; matrix metalloproteinases; vitamin D.

УРОВЕНЬ 25-ГИДРОКСИВИТАМИНА D И МАТРИКСНЫХ МЕТАЛЛОПРОТЕИНАЗ-2 И -9 У БОЛЬНЫХ ПЕРВИЧНОЙ ОТКРЫТОУГОЛЬНОЙ ГЛАУКОМОЙ И ПСЕВДОЭКСФОЛИАТИВНОЙ ГЛАУКОМОЙ/СИНДРОМОМ

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Для цитирования: Офтальмологические ведомости. – 2017. – Т. 10. – № 1. – С. 10–16

Дата поступления: 28.12.2016

Статья принята к печати: 22.02.2017

✧ **Цель работы:** определить уровень 25-гидроксивитамина D в сыворотке крови и матриксных металлопротеиназ-2 и -9 (ММП) в плазме крови у больных первичной открытоугольной глаукомой (ПОУГ),

псевдоэксфолиативной глаукомой (ПЭГ) и псевдоэксфолиативным синдромом (ПЭС), для уточнения влияния уровня обеспеченности витамином D на развитие указанных состояний. **Методы.** Обследовано 238 человек (105 мужчин и 133 женщины) в возрасте от 55 до 75 лет: 122 человека с диагнозом ПЭГ, 46 — с ПОУГ, 32 — с наличием ПЭС без глаукомы, 38 участников составили группу контроля. Критериями не включения были наличие системных и офтальмологических заболеваний, в патогенезе которых подтверждено участие витамина D и ММП. Уровень 25(ОН)D в сыворотке крови определяли методом иммунохемилюминесцентного анализа, концентрацию ММП-2 и -9 в плазме крови — методом твердофазного иммуноферментного анализа. **Результаты.** Уровень витамина D в сыворотке крови варьировал от 4,6 до 82,25 нмоль/л (в среднем — 41,7 нмоль/л) и в основном соответствовал недостатку и дефициту витамина D. Выявлено, что у пациентов ПЭГ, ПОУГ и ПЭС уровень 25(ОН)D в сыворотке крови не отличался ($39,3 \pm 1,2$, $38,8 \pm 2,1$ и $40,51 \pm 2,4$ нмоль/л соответственно, $p > 0,05$), но был ниже, чем в группе контроля ($52,7 \pm 2,1$ нмоль/л, $p < 0,01$). Концентрация ММП-2 в плазме крови не отличалась во всех группах обследованных и по сравнению с группой контроля. Уровень ММП-9 в плазме крови у пациентов с ПОУГ и ПЭС был достоверно выше ($48,23 \pm 3,26$ и $54,01 \pm 3,57$ нг/мл соответственно), чем в контрольной группе ($32,60 \pm 2,34$ нг/мл, $p < 0,001$) и в группе ПЭГ ($40,86 \pm 3,60$ нг/мл, $p < 0,05$ и $p < 0,01$ соответственно). Выявлены положительные корреляционные связи между ММП-2 и ММП-9 в группе больных ПЭГ ($r = 0,48$, $p = 0,001$) и больных ПОУГ ($r = 0,43$, $p = 0,003$). Также у больных ПОУГ была установлена отрицательная корреляционная связь между ММП-9 и уровнем 25(ОН)D ($r = -0,32$, $p = 0,02$), а также ММП-2 и 25(ОН)D ($r = -0,33$, $p = 0,02$). **Выводы.** Результаты настоящего исследования подтверждают возможность участия витамина D в регуляции апоптоза и тканевого ремоделирования у больных ПОУГ и ПЭС и позволяют отнести дефицит витамина D к факторам риска развития глаукомы.

✧ **Ключевые слова:** открытоугольная глаукома; псевдоэксфолиативная глаукома; псевдоэксфолиативный синдром; матриксные металлопротеиназы; витамин D.

BACKGROUND

High prevalence of glaucoma and its social importance encourage researchers to work on the identification of new causes of the disease [22]. Several recent publications confirmed the role of vitamin D deficiency in the development of primary open-angle glaucoma (POAG) and pseudoexfoliation syndrome (PES) [16, 24, 25]. It could be attributed perhaps to the immunosuppressive activity of vitamin D or its involvement in the regulation of cell proliferation, differentiation, and apoptosis (including those in the ocular neuroglia) [8, 14, 19]. Alsalem et al. (2014) demonstrated that epithelial cells of the eye border (non-pigmented ciliary epithelium, retinal pigment epithelium, and corneal endothelium) can demonstrate both first and second stages of vitamin D enzymatic hydroxylation with the synthesis of biologically active form of vitamin D (calcitriol). This finding was confirmed by discovering vitamin D receptors in the non-pigmented ciliary epithelium and corneal endothelium [10]. In addition to that, there are some data suggesting the ability of vitamin D to regulate intraocular pressure (IP) through gene-gene interactions. The 1,25-dihydroxyvitamin D (calcitriol) was shown to downregulate the expression of genes responsible for the synthesis

of carbonic anhydrase 1, angiotensin-converting enzyme, and aquaporin 1. Besides, calcitriol is likely to regulate the expression of genes involved in the synthesis of some cytoskeleton and extracellular matrix components, such as fibronectin 1 and alpha actin [17]. Calcitriol can upregulate the expression of genes encoding matrix metalloproteinases (MMP) and simultaneously decrease the activity of their tissue inhibitors involved in the regulation of the trabecular meshwork metabolism [17].

So far, very few studies have attempted to investigate the association between glaucoma and its severity, and the level of vitamin D [12, 25]. Despite the high prevalence of both vitamin D deficiency and glaucoma, there are no Russian studies devoted to this problem.

The objective of this study is to assess serum levels of 25-hydroxyvitamin D and classic markers of apoptosis and tissue remodeling, like MMPs, and to clarify their impact on the development of various forms of glaucoma.

MATERIALS AND METHODS

We enrolled 238 individuals (105 males and 133 females; aged 55–75 y) in this study, after they signed an informed consent. We excluded patients

who had at least one of the following conditions: diabetes mellitus; cancer; autoimmune disorders; severe comorbidity; therapy with corticosteroids, immunosuppressants, or vitamin D; acute circulatory disorders of the central retinal artery/vein; ocular trauma; corneal disorders; wet form of age-related macular degeneration.

In all patients, diagnosis was confirmed by an ophthalmologic examination that included autorefractometry, visual acuity assessment, Maklakov's applanation tonometry, biomicrophthalmoscopy, automated perimetry, and Heidelberg Retinal Tomography II. Patients were examined at the out-patient department, and at the Department of Ophthalmology of the Pavlov First Saint Petersburg State Medical University.

We measured the serum 25(OH)D levels by immunochemiluminescence method using the Architect i2000SR System (Abbott Laboratories, USA). We followed the recommendations of the Russian Association of Endocrinologists (2015) in assessing Vitamin D deficiency: serum 25(OH)D levels of 75 nmol/L (normal); 50–75 nmol/L (insufficient); 50 nmol/L (deficient) [6]. We used ELISA to measure the concentrations of serum MMP-2 and MMP-9 using the Quantikine Total MMP-2 Immunoassay (R&D Systems, Inc., USA & Canada) and Human MMP-9 Platinum ELISA Kit (eBioscience, USA), respectively.

Statistical analysis was performed using the SPSS17.0RU for Windows. We calculated the rates and mean values with standard deviations. Pearson χ^2 test was used to compare categorical variables. Continuous variables were compared using ANOVA. We calculated the Pearson's correlation coefficient to assess the correlation between the variables.

RESULTS

Mean age of the participants was 66.7 ± 0.3 y. Out of 238 individuals tested, 196 were diagnosed with pseudoexfoliation glaucoma (PEG)/POAG/PES, and the remaining 38 individuals comprised the control group (mean age 65.2 ± 0.8 y). All patients were divided into three groups: group 1—patients with PEG ($n = 122$; mean age 67.4 ± 0.4 y), group 2—patients with POAG ($n = 46$; mean age 65.5 ± 0.9 y), and group 3—patients with PES without glaucoma ($n = 32$; mean age 67.4 ± 1.0 y). Patients in all the groups were matched for gender and age.

The serum 25(OH)D level in patients and controls varied between 4.6 and 82.3 nmol/L (mean level was 41.7 nmol/L); most of the study participants were vitamin D deficient. Our results were similar to the

results of the study that evaluated the prevalence of vitamin D deficiency in the Northwest region of the Russian Federation [5]. The level of 25(OH)D did not significantly differ among patients with PEG, POAG, and PES (39.3 ± 1.2 nmol/L, 38.8 ± 2.1 nmol/L, and 40.51 ± 2.4 nmol/L, respectively; $p > 0.05$), but it was lower than in controls (52.7 ± 2.1 nmol/L; $p < 0.01$). None of the patients with PEG, POAG, or PES had normal serum levels of 25(OH)D. The number of patients with vitamin D deficiency did not vary across the experimental groups and comprised 87.4%, 80.0%, and 78.1% in the first, second, and third group respectively. Only three (8.1%) participants from the control group had normal serum 25(OH)D levels (over 75 nmol/L); the number of individuals with vitamin D deficiency was lower among the controls (62.2 %, $p < 0.05$) compared to the patients with PEG/POAG/PES.

We found no significant difference in the levels of MMP-2 across the groups: it was 248.3 ± 18.5 , 249.9 ± 15.8 , 224.7 ± 11.3 , and 224.7 ± 11.3 ng/mL, in patients with PEG, POAG, PES, and in controls, respectively ($p > 0.05$).

The serum MMP-9 level was significantly higher in patients with POAG and PES (48.2 ± 3.3 and 54.0 ± 3.6 ng/mL, respectively) when compared to either the controls (32.6 ± 2.3 ng/mL, $p < 0.001$) or patients with PEG (40.9 ± 3.6 ng/mL, $p < 0.05$ and $p < 0.01$, respectively).

We also analyzed the concentrations of MMP-2 and MMP-9 depending on the stage of glaucoma. We divided glaucoma patients into three groups depending on the disease stage: early (stage 1), advanced (stage 2), and severe (stage 3) (in accordance with the National Guideline on Glaucoma) [4]. The results of the analysis are shown in the Table 1.

Serum levels of 25(OH)D, MMP-2, and MMP-9 did not significantly differ in patients with different stages of POAG and PEG ($p > 0.05$). Then, we merged the stage-2 and stage-3 to form a single group (AS), and compared against the early stage glaucoma (ESG). Individuals with both ES- and AS-POAG were found to have higher levels of MMP-9 (47.8 ± 3.6 ng/mL and 48.6 ± 5.5 ng/mL, respectively) compared to patients with advanced/severe PEG (38.7 ± 4.6 ng/mL; $p < 0.01$ and $p < 0.05$ for ESG vs. PEG and AS vs. PEG, respectively).

We found a positive correlation between the levels of MMP-2 and MMP-9 in patients with PEG ($r = 0.48$, $p = 0.001$) and POAG ($r = 0.43$, $p = 0.003$) and a negative correlation between

Table 1

The serum 25(OH)D level, plasma MMP-2 and MMP-9 levels in patients with different pseudoexfoliation and primary open-angle glaucoma severity

Таблица 1

Уровень 25(OH)D в сыворотке крови и концентрация матричных металлопротеиназ (ММП-2, ММП-9) в плазме крови у больных с различной степенью тяжести псевдоэкзофоллиативной и первичной открытоугольной глаукомы

Parameter	Stage 1	Stage 2	Stage 3	<i>p</i>
PEG (<i>n</i> = 122)	<i>n</i> = 55	<i>n</i> = 27	<i>n</i> = 40	
Age, years	67.2 ± 0.6	67.3 ± 0.9	67.6 ± 0.8	> 0.05
25(OH)D, nmol/L	38.8 ± 2.1	42.6 ± 2.0	37.8 ± 2.2	> 0.05
MMP-2, ng/mL	233.1 ± 41.9	276.0 ± 38.4	246.0 ± 21.6	> 0.05
MMP-9, ng/mL	44.9 ± 5.7	33.2 ± 5.2	40.6 ± 5.9	> 0.05
POAG (<i>n</i> = 46)	<i>n</i> = 24	<i>n</i> = 10	<i>n</i> = 12	
Age, y	65.5 ± 1.2	63.5 ± 2.3	67.2 ± 1.9	> 0.05
25(OH)D, nmol/L	38.1 ± 2.9	40.5 ± 3.1	38.8 ± 5.1	> 0.05
ММП-2, ng/mL	250.9 ± 21.7	236.2 ± 17.2	259.7 ± 40.9	> 0.05
ММП-9, ng/mL	47.8 ± 3.6	43.7 ± 7.0	52.3 ± 8.2	> 0.05
POAG—primary open-angle glaucoma, PEG—pseudoexfoliation glaucoma, 25(OH)D—25-hydroxyvitamin D, MMP-2—matrix metalloproteinase-2, MMP-9—matrix metalloproteinase-9				

Table 2

The serum 25(OH)D level, plasma MMP-2 and MMP-9 levels in patients with pseudoexfoliation glaucoma, pseudoexfoliation syndrome and in the control group

Таблица 2

Уровень 25(OH)D в сыворотке крови и концентрация матричных металлопротеиназ (ММП-2, ММП-9) в плазме крови у пациентов с псевдоэкзофоллиативным синдромом, псевдоэкзофоллиативной глаукомой и группы контроля

Parameter	PEG <i>n</i> = 122	PES <i>n</i> = 32	Control group <i>n</i> = 38	<i>p</i>
25(OH)D, nmol/L	39.3 ± 1.2	40.5 ± 2.4	52.7 ± 2.1	$p_{3-к} < 0.01$ $p_{1-к} < 0.01$
ММП-2, ng/mL	248.3 ± 18.5	234.4 ± 23.9	224.7 ± 11.3	$p > 0.05$
ММП-9, ng/mL	40.9 ± 3.6	54.0 ± 3.6	32.6 ± 2.3	$p_{3-к} < 0.01$ $p_{1-3} < 0.01$
PEG—pseudoexfoliation glaucoma, PES—pseudoexfoliation syndrome, 25(OH)D—25-hydroxyvitamin D, MMP-2—matrix metalloproteinase-2, MMP-9—matrix metalloproteinase-9				

the levels of 25(OH)D and MMP-9 ($r = -0.32$, $p = 0.02$), 25(OH)D and MMP-2 ($r = -0.33$, $p = 0.02$) in patients with POAG.

Levels of 25(OH)D, MMP-2, and MMP-9 were comparable in patients with PES, PEG, and controls (Table 2).

Participants in the control group had the highest level of serum 25(OH)D ($p < 0.01$) compared to those with PEG and PES. The highest level of MMP-9 was observed in patients with PES (which differed significantly from the control and PEG groups), whereas the level of MMP-2 was approximately equal in all groups (Table 2).

DISCUSSION

The results of our study confirmed high prevalence of vitamin D deficiency in patients with different types of glaucoma. The serum 25(OH)D level does not depend on the stage of glaucoma, a finding that correlates with the results obtained by Goncalves et al. (2015) [12]. Glaucoma is a chronic progressive optic neuropathy with multiple factors (immunological disorders, ischemia, oxidative stress, and apoptosis) potentially contributing to its development. Vitamin D is known to have pleiotropic effects, including its ability to regulate cell differentiation, inflammatory and immune

processes, and apoptosis. Moreover, some eye disorders, including glaucoma, were found to be associated with certain geographic regions and the level of insolation [1, 3, 9]. Some authors believe that vitamin D deficiency can activate several pathogenic mechanisms of glaucoma [17, 25]. MMPs are known to play an important role in the development of glaucomatous optic neuropathy [7, 11, 13, 15, 20, 21]. Our findings indicate higher levels of MMP-9 in patients with POAG and PES compared to controls. Furthermore, patients with both early and advanced POAG, as well as patients with PES, had higher concentrations of MMP-9 compared to patients with severe PEG ($p < 0.01$, $p < 0.05$, and $p < 0.01$, respectively). Patients with PEG tended to have higher levels of MMP-9 than controls, but the difference was not statistically significant. Our data confirm the earlier published results suggesting high serum concentrations of MMP-9 in patients with POAG [7, 11]. At the same time, serum level of MMP-2 appeared to be approximately equal in individuals with POAG, PEG, and PES, and did not depend on the disease severity. A negative correlation between the serum 25(OH)D level and concentrations of MMP-2 and MMP-9 possibly indicates elevated levels of apoptosis markers associated with vitamin D deficiency, but these changes were found only in patients with POAG. Our findings provide support to the idea of vitamin D playing a regulatory role in patients with systemic disorders [18, 23].

PES is a well-known risk factor for PEG, which is characterized by a more aggressive course, and is poorly amenable to medical and surgical correction [2, 3]. Within this study, patients with PES had lower serum 25(OH)D levels compared to controls ($p < 0.01$), but was not significantly different from those with PEG and POAG, whereas the concentration of MMP-9 occurred to be the highest in participants with PES. Moreover, we found no difference in the level of MMP-9 between patients with PES and early stage PEG. Our results suggest that patients with PES/early stage PEG, along with vitamin D deficiency, are likely to have an active apoptotic process, and intensive compensatory remodeling of connective tissues and neuroglia, in the posterior pole and optic disc.

CONCLUSION

Our study revealed high prevalence of vitamin D deficiency in patients with POAG, PEG, and PES. A correlation between the level of vitamin D and MMPs (MMP-2 and MMP-9) was found only in patients

with POAG. This may indicate the involvement of vitamin D in the regulation of apoptosis and tissue remodeling in patients with POAG. Besides, it allows considering vitamin D deficiency as a risk factor for glaucoma.

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