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Serum Vitamin D level in Jordanian patients with exfoliation syndrome and exfoliative glaucoma

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虹膜色素剥脱综合征和剥脱性青光眼中血清维生素D水平分析

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摘要

目的:虹膜色素剥脱综合征(XFS)和剥脱性青光眼(XFG)患者与对照组血清维生素D水平比较。

方法:使用液相色谱法测量25羟基维生素D血清水平。记录性别、年龄、高血压、糖尿病和缺血性心脏病病史等可变因素。

结果:研究包括55例XFS/XFG患者和正常对照组60例。XFS/XFG患者较为年长(平均年龄:71.8y *vs* 67.5y, P=0.002)。两组性别分布相似且糖尿病、高血压和缺血性心脏病的患病率无显著性差异。XFS/XFG患者平均维生素D水平为14.7 ng/mL,正常对照组为14.9 ng/mL,两组间无显著性差异。虽然XFS/XFG组维生素D水平较低,但在对年龄、性别和医疗条件进行校正后,多变量分析显示两组之间维生素D缺乏无显著差异。

结论:XFS/XFG组和正常对照组维生素D水平均较低,而XFS/XFG组低于正常对照组,两组间无明显差异。XFS和维生素D缺乏症与某些系统性疾病有共同联系。

关键词:维生素D;虹膜色素剥脱综合征;剥脱性青光眼

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Abstract

• AIM: To compare the level of serum Vitamin D in patients with exfoliation syndrome (XFS) and exfoliative glaucoma (XFG) with that in control subjects.

• METHODS: Serum levels of 25-hydroxy Vitamin D (Vitamin D) were measured using liquid chromatography. Variables like age, sex and medical history of hypertension, diabetes mellitus and ischemic heart disease were reported.

• RESULTS: This study included a total of 55 patients with XFS/XFG and 60 control subjects. Patients with XFS/XFG were significantly older than control subjects (mean age: 71.8y *vs* 67.5y, P=0.002). Gender distribution was similar. The prevalence rates of diabetes, hypertension, and ischemic heart disease were not significantly different between the two groups. The mean of Vitamin D was 14.7 ng/mL for patients with XFS/XFG and 14.9 ng/mL for control subjects with no significant difference. Although Vitamin D level was lower in the XFS/XFG group but multivariate analysis did not show significant difference in Vitamin D deficiency between the two groups after adjusting for age, gender, and medical conditions.

• CONCLUSION: The outcomes of our study are different from those in the literature. Vitamin D levels were low in both the XFS/XFG group and the control group being lower in the first one but that difference was not statistically significant. XFS and Vitamin D deficiency share common associations with certain systemic diseases. Further studies with larger numbers are needed to elaborate more on these associations and to support further the controversial literature.

• KEYWORDS: Vitamin D; exfoliation syndrome; exfoliative glaucoma
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INTRODUCTION

Exfoliation syndrome (XFS) is an age-related generalized disorder characterized by production and progressive accumulation of fibrillary extracellular material in various ocular and extraocular tissues, namely the skin, extraocular muscles, heart, lung, liver, kidney, and meninges[1]. The

reported prevalence of XFS varied from as low as 0.2% up to 23% in different studies with different study populations and detection methods[2-3]. It is known that XFS is the most common identifiable cause of glaucoma, accounting for the majority of cases in some countries[4].

XFS and Vitamin D deficiency share common associations with certain diseases. XFS has been associated with hypertension, ischemic heart disease and cerebrovascular accidents, suggestive of vascular effects of the disease[5]. XFS has also been found to have a higher prevalence in patients with cognitive impairment, including Alzheimer's disease, compared to age-matched general population[6]. Interestingly, Vitamin D deficiency increases the risk of hypertension, cardiovascular diseases, schizophrenia and depression[7-8]. In addition, studies have shown that both, XFS and Vitamin D deficiency are associated with an increase in oxidative stress at the molecular level[9-10].

Several studies on XFS patients have measured serum levels of Vitamin B_6, Vitamin B_{12}, folic acid, homocysteine and trace elements, namely selenium, zinc and copper[11-12]. To our knowledge, only one study conducted in Turkey has evaluated the association of Vitamin D serum levels and XFS and its impact on associated systemic diseases[13]. In our study, we also measured serum levels of Vitamin D in patients with XFS/XFG and compared that to controls in a population with a different ethnic background to see how our results compare to the Turkish study.

SUBJECTS AND METHODS

In this cohort, patients visiting the ophthalmology clinic at King Abdullah University Hospital (a referral hospital in Northern Jordan) aged 50y and above were divided in two groups. The first group has XFS/XFG and the second group were considered as controls. Medical history of the enrolled subjects reported. The tenets of the Declaration of Helsinki were followed throughout the study. Informed consent was obtained from all patients and the study was carried out with approval from the Institutional Review Board of King Abdullah University Hospital.

A total of 115 subjects were recruited over a period of 6mo. All consecutive patients with XFS/XFG were recruited. Control subjects were randomly selected. Patients already on Vitamin D supplements, patients with malabsorption syndromes and patients with glaucomas other than XFG were excluded from the study.

Venous blood samples for the measurement of Vitamin D levels were withdrawn in the outpatient clinic. An amount of 2-3 mL of blood was collected from each subject and transferred to the lab instantly in an EDTA-coated tube.

Serum Vitamin D measurement was conducted using the MassChrom® (CHROMOSYSTEMS® DIAGNOSTICS by HPLC & LC-MS/MS, Germany). After centrifugation of the original blood sample, 100 μL of serum was taken and treated with 25 μL of precipitating reagent. A volume of 200 μL of the internal standard was added and vortexed for 20s, incubated for 10min at 2-8 ℃, centrifuged for 5min at 15000 g and then a volume 50 μL of the supernatant was injected into the LC-MS/MS system for analysis and measurement. Vitamin D level below 20 ng/mL was considered deficient.

The post hoc power was calculated for the given sample size of 55 patients with XFS/XFG and 60 control subjects, assuming that the prevalence of Vitamin D deficiency (25-OH Vitamin D < 15 ng/mL) is 60% in the control group and using alpha level of 0.05. Using the GPower 3.0.10, the power to detect odds ratio of 2 is approximately 60%. Data were described and analyzed using the Statistical Package for Social Sciences (IBM SPSS) version 20. Means and percentages were used to describe the data. Differences between means were tested using independent test and differences between proportions were tested using Chi-square test. Binary logistic regression was conducted to determine the association between exfoliation (independent variable) and Vitamin D deficiency (dependent variable) after adjusting for the effects of age and gender. A P value of less than 0.05 was considered statistically significant.

RESULTS

This study included a total of 55 patients with XFS/XFG and 60 control subjects. Patients with XFS/XFG were significantly older than control subjects (mean age: 71.8y *vs* 67.5y, P=0.002). Gender distribution was similar for the two groups with males being 43.6% (24 out of 55) and 48.3% (29 out of 60) in the XFS/XFG and control groups respectively (P=0.614). No significant difference was observed in the prevalence of Vitamin D deficiency between both groups. The mean value of Vitamin D serum level was 14.7±7.0 ng/mL for patients with XFS/XFG and 14.9±8.3 ng/mL for control subjects (P=0.937). Vitamin D deficiency (Vitamin D <20 ng/mL) was 76.4% (42 out of 55) in the XFS group and 78.3% (47 out of 60) in the control subjects (P=0.801). The prevalence of Vitamin D deficiency at different levels was not significantly different between the two groups (Table 1). The prevalence rates of diabetes, hypertension and ischemic heart disease were not significantly different between the two groups. The prevalence rates of diabetes were 40% (22 out of 55) in XFS/XFG and 53.3% (32 out of 60) in control subjects (P=0.152). Similar difference in hypertension was observed between the XFS/XFG and control groups, 50.9% and 63.3% respectively (P=0.178). The prevalence rate of ischemic heart disease was 14.5 % (8 out of 55) in XFS/XFG and 25 % (15 out of 60) in control subjects (P=0.161) (Table 2).

Multivariate analysis did not show a significant difference in Vitamin D deficiency between the two groups after adjusting for age and gender (Table1). The age- and sex- adjusted odds ratio (95% confidence interval) for Vitamin D deficiency in patients with XFS/XFG compared to controls was 0.52 (0.19, 1.43) (P=0.206).

DISCUSSION

Exfoliation syndrome is an age-related disease characterized by progressive deposition of fibrillary extracellular material in

Table 1 Vitamin D deficiency among patients with exfoliation syndrome and control subjects in univariate analysis and multivariate analysis

Mean (SD)

Parameters	Exfoliation syndrome				
	No	Yes	P^a	OR^b(95% CI)	P^c
Number (n, %)	60	55			
25-OH Vitamin D (ng/mL)	14.9 (8.3)	14.7 (7.0)	0.937		
25-OH Vitamin D					
<10 ng/mL	17(28.3)	16(29.1)	0.929	0.63 (0.25, 1.60)	0.334
<15 ng/mL	36(60.0)	28(50.9)	0.327	0.41 (0.16, 1.03)	0.051
<20 ng/mL	47(78.3)	42(76.4)	0.801	0.52 (0.19, 1.43)	0.206

[a]P for Chi-square test; [b]OR: Age and sex adjusted odds ratio; [c]P from logistic regression.

Table 2 The demographic and clinical characteristics of patients with exfoliation syndrome and control subjects

Variable	Exfoliation syndrome		P
	No	Yes	
Number	60(%)	55(%)	
Gender			0.614
F	31(51.7)	31(56.4)	
M	29(48.3)	24(43.6)	
Age (a)			0.012
<70	37(61.7)	21(38.2)	
≥70	23(38.3)	34(61.8)	
Diabetes mellitus	32(53.3)	22(40.0)	0.152
Hypertension	38(63.3)	28(50.9)	0.178
Ischemic heart disease	15(25.0)	8(14.5)	0.161

many ocular and non-ocular structures[1,14]. Both XFS and Vitamin D deficiency are associated with essentially the same systemic conditions, mainly cardiovascular diseases. In addition, several markers of oxidative stress have been found to be elevated in the serum and/or eyes of XFS patients[15]. Interestingly, there is also a protective effect of Vitamin D against oxidative stress at the cellular and molecular level especially of vascular endothelial cells[9-10,16]. All of this has attracted our attention to investigate the presence of a direct association between XFS and Vitamin D deficiency, both of which are common in our country[17].

The current evidence suggests an association between XFS and ischemic heart disease, aneurysms of abdominal aorta, and cerebrovascular diseases[5,18]. However, our results show a slightly higher prevalence of systemic co-morbidities in the group without XFS with no statistical significance. The prevalence of ischemic heart disease was 14.5% in patients with XFS and 25% in subjects free of XFS (P=0.161). Likewise, hypertension was less common in the XFS group than the non-XFS group with a prevalence of 50.9% and 63.3%, respectively, again, with no significant difference (P=0.178). This could be explained by the small sample size. On the other hand, the similar yet slightly lower occurrence of diabetes mellitus in the XFS group compared to the non-XFS group with no statistical significance (40% and 53.3% respectively, P=0.152), concurs with previous studies that showed no association between the two diseases[13,19-20].

The association of Vitamin D deficiency with cardiovascular disorders and diabetes mellitus has been reported in several studies. Low serum levels of Vitamin D are associated with an increased risk of hypertension and some studies have even showed a better control of blood pressure with Vitamin D administration[21]. Similarly, Vitamin D deficiency increases the risk of development and death from myocardial infarctions[22]. Additionally, both major types of diabetes, whether insulin or non-insulin dependent, relate to Vitamin D deficiency. The dependence of normal insulin secretion in pancreatic β-cells on Vitamin D and the increase in insulin resistance and reduced insulin secretion with Vitamin D deficiency explains the connection with non-insulin dependent type[23]. Moreover, geographic areas with low serum levels of Vitamin D show higher prevalence of insulin-dependent diabetes mellitus and sufficient intake of Vitamin D have been documented to decrease the incidence of insulin dependent diabetes mellitus in children[24-25]. The presence of Vitamin D in adequate levels at the cellular level modifies the function of macrophages and the production of inflammatory mediators[16]. Our study showed low serum levels of Vitamin D in both the XFS and non-XFS groups with a prevalence of 76.4% and 78.3%, respectively with no statistically significant difference (P=0.801). The mean level of Vitamin D was 14.7±7.0 ng/mL in patients with XFS/XFG and 14.9±8.3 in subjects without XFS also with no significant difference (P=0.801). The high prevalence of Vitamin D deficiency in Jordan has already been documented and perhaps this along with a relatively small sample size could explain the similarly low Vitamin D levels in both study groups[26].

To our knowledge, only one study, conducted in Turkey, has previously investigated the association between XFS and Vitamin D deficiency and their correlation to systemic diseases. The study was a prospective university-based study. Patients who had a diagnosis of exfoliative glaucoma and who were on topical IOP-lowering drugs were excluded from the study and this is unlike our study where XFS indistinctively included both of these subsets. Besides hypertension, ischemic heart disease, and diabetes, the investigators included autoimmune diseases and neurological disorders.

Their results showed no association between low serum Vitamin D and XFS. Nevertheless, an association of cardiovascular and cerebrovascular disease with XFS was evident. We agree with their suggestion of further investigations before concluding no causal relationship between the two entities[18].

In conclusion, the outcomes of our study were different from those in the literature. We did not find an association between XFS syndrome and Vitamin D deficiency. Given the fact that Vitamin D deficiency is common in the Jordanian population, a direct association between Vitamin D and XFS should not be simply given up to the results of our study or, by the same token, the study from Turkey. It is suggested to conduct a larger prospective longitudinal study, probably on a population with low prevalence of Vitamin D deficiency, if finite conclusions are to be made.

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