The relationship between serum vitamin D concentrations and development of diabetic retinopathy in type 2 diabetes mellitus

Abstract. Background. The literature does not provide enough information about the role of vitamin D in the genesis of diabetic retinopathy. The active metabolite of vitamin D, calcitriol, is a potent retinal neovascularization inhibitor in an experimental model of ischemic retinopathy. There is very few evidence on the possible relationship between the content of vitamin D and the incidence of diabetic retinopathy in type 2 diabetes mellitus (DM) patients in the European population, including Ukraine. The purpose of the study is to establish the association between vitamin D status and the incidence of diabetic retinopathy in patients with type 2 DM. Material and methods. In the case-control observational study, two groups of patients with type 2 DM were examined: 55 with diabetic retinopathy (cases) and 35 without retinopathy (controls). All of them had normal kidney function (glomerular filtration rate > 60 ml/min, without microalbuminuria) in the absence of cardiovascular complications. Patients did not receive calcium and/or vitamin D preparations. Results. The study confirms the relationship between 25(OH)D content and the presence of diabetic retinopathy in patients with type 2 DM. Patients with retinopathy had a significantly lower concentration of 25(OH)D — 14.6 ± 2.9 ng/ml versus 23.9 ± 3.1 ng/ml in patients without retinopathy, p < 0.05. The multivariate analyses demonstrated a significant association of diabetic retinopathy and 25(OH)D. Conclusions. The results indicate the potential role of vitamin D in the pathogenesis of diabetic retinopathy. Further experimental and prospective studies are needed to determine the role of vitamin D status in the development of diabetic retinopathy and other diabetic microvascular complications.

Keywords: type 2 diabetes mellitus; diabetic retinopathy; vitamin D

Introduction

Vitamin D insufficiency and deficiency are highly prevalent even in sunny regions, proposing it is a global problem [1]. The primary biological activity of vitamin D contains the sustenance of mineral homeostasis and the arrangement of bone remodeling [2]. Nevertheless, there is an immense pattern of pleiotropic activity of cholecalciferol that was already observed some decades ago [3]. This sector of research conducted to amend enlightenment on the capable part of this vitamin on glucose metabolism and homeostasis and in the pathogenesis of type 2 diabetes mellitus (DM). Aggregated considerations have formerly conferred that vitamin D insufficiency and deficiency are exceptionally prevalent in patients with type 2 DM [4]. Furthermore, there is a raising attention on the inherent role of cholecalciferol in the developing of diabetic microangiopathy [5]. In particular, the potential influence of vitamin D in the pathogenesis of diabetic retinopathy (DR) has been a topic of certain attention over the past years. There are some experimental data on the prophylactic influence of cholecalciferol in the development of DR in a rodent model [6]. However, the evidence of vitamin D involvement in DR development is clearly not enough.

Among studies addressed the potential relationship between vitamin D and the presence of DR in patients with type 2 DM, there are only a few publications [6, 7]. The design of these studies only suggested a connection between lower serum concentrations of 25(OH)D and vitamin D deficiency or insufficiency and the presence of DR in type 2 DM patients.
Vitamin D may execute a part in the pathogenesis of DR because of its effects on the immune system and on angiogenesis [8]. Vitamin D has an anti-inflammatory effect by reducing the proliferation of lymphocytes, natural killer cells and several pro-inflammatory cytokines [9].

In addition, it has been found that the active metabolite of vitamin D, calcitriol, is a potent retinal neovascularization inhibitor in an experimental model of ischemic retinopathy [10]. Taking into account these associations, we tried to establish the relationship between vitamin D deficiency and diabetic retinopathy in patients with type 2 DM.

The purpose of the study is to establish the association between vitamin D status and the incidence of diabetic retinopathy in patients with type 2 diabetes mellitus.

Materials and methods

In this observational case-control study patients were selected from a group of type 2 DM with (cases) and without DR (controls). We included a total number of 90 type 2 diabetic patients with complete data for the current study outcomes (55 patients with DR and 35 without this complication). All study subjects had normal kidney function (calculated glomerular filtration rate > 60 ml/min). All study participants had no known cardiovascular complications (myocardial infarction, stroke or diabetic foot disease).

Blood samples were obtained from all participants in the fasting state. HbA1c was measured with Bio-RAD, USA. Intact PTH was determined by electrochemiluminescence immunoassay in an Elecsys E170 analyzer (Roche Diagnostics, USA). Serum concentrations of 25(OH)D were measured by a chemiluminescent microparticle immunoassay. All patients were enrolled between November 10, 2020 and March 15, 2021 to minimize seasonal bias.


The study protocol was approved by the ethics committee of Ukrainian Research and Practical Centre of Endocrine Surgery, Transplantations of Endocrine Organs and Tissues of the Ministry of Health of Ukraine in accordance with the Declaration of Helsinki (Protocol No. 2/04 dated April 3, 2020). All participants signed the written informed consent form.

Mean (and standard deviations) or absolute and relative frequencies (in percentages) were computed for quantitative or qualitative variables, respectively. Differences between groups were assessed by means of Mann-Whitney tests or Chi-squared tests as adequate. To analyze the interconnection of DR with vitamin D status, linear regression models were operated to evaluate serum levels of vitamin D and logistic regression models to determine 25(OH)D insufficiency and deficiency, providing a suitable threshold in the serum concentrations for this objective.

Multivariate regression analyses were also carried out including age, sex, duration of type 2 DM, BMI as potential predictors. A significance level of 0.05 was used. Statistical analyses were conducted with program Statistica 10 (StatSoft, Inc., USA).

Results

Demographic and clinical data of the present study were recorded and are shown in Table 1. Arterial hypertension or dyslipidemia were considered present when the patient was being treated with antihypertensive or lipid-lowering drugs, respectively. Weight and height were measured by standardized methods, and the body mass index (BMI) was then calculated (expressed as kg/m²). We did not observe a significant difference in lipid metabolism indicators depending on the presence or absence of DR.

Table 1 shows the results of the different study variables and the differences between patients with and without DR. Patients with DR had longer DM duration, had higher HbA1c concentrations, and were more frequently on insulin treatment. No differences were observed in other clinical and laboratory parameters in the unadjusted analysis of the data. Patients with DR had a significantly lower concentration of 25(OH)D — 14.6 ± 2.9 ng/ml versus 23.9 ± 3.1 ng/ml in patients without DR, p < 0.05.

Table 1. Clinical and biochemical characteristics of patients with type 2 diabetes mellitus with (cases) and without diabetic retinopathy (controls)

<table>
<thead>
<tr>
<th></th>
<th>Type 2 DM without DR (n = 35)</th>
<th>Type 2 DM and DR (n = 55)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.2 ± 9.7</td>
<td>60.1 ± 8.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>26/34</td>
<td>28/27</td>
<td>1</td>
</tr>
<tr>
<td>DM duration, years</td>
<td>5.7 ± 1.2</td>
<td>9.6 ± 1.4</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Insulin treatment (with or without OHA), n (%)</td>
<td>8 (13.3)</td>
<td>29 (52.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.4 ± 3.7</td>
<td>31.7 ± 3.4</td>
<td>0.31</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.8 ± 0.9</td>
<td>8.3 ± 1.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.7 ± 0.7</td>
<td>5.6 ± 0.6</td>
<td>0.83</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1.8 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>0.68</td>
</tr>
<tr>
<td>Calcium ionized, mmol/l</td>
<td>1.22 ± 0.07</td>
<td>1.24 ± 0.08</td>
<td>0.72</td>
</tr>
<tr>
<td>PTH, ng/ml</td>
<td>49.5 ± 8.2</td>
<td>51.3 ± 8.7</td>
<td>0.14</td>
</tr>
<tr>
<td>25(OH)D, ng/ml</td>
<td>23.9 ± 3.1</td>
<td>14.6 ± 2.9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Vitamin D insufficiency and deficiency, n (%)</td>
<td>49 (81.7)</td>
<td>52 (94.5)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Notes: most data are given as mean ± SD; OHA — oral hypoglycemic agents; BMI — body mass index; HbA1c — glycated hemoglobin; PTH — parathormone; 25(OH)D — 25-hydroxyvitamin D.
The frequency of vitamin D insufficiency and deficiency, defined as serum 25(OH)D below 30 ng/ml, was higher in subjects with DR and this difference reached statistical significance (p < 0.05).

The prevalence of DR for 25(OH)D thresholds below 20 ng/ml was significantly higher (thresholds 15 to 19), and the associated relative risk (RR) of DR was higher for all these thresholds. For the purpose of the multivariate analysis, a concentration of 20 ng/ml was chosen as the threshold to define vitamin deficiency; this threshold yielded the highest relative risk of DR (RR 1.47).

The multivariate analyses demonstrated a significant association of DR and 25(OH)D. These results were dependable when evaluating both the 25(OH)D content and the presence of vitamin D deficiency defined by a 25(OH)D < 20 ng/ml. BMI was inversely associated with 25(OH)D concentrations and positively associated with vitamin D deficiency.

We did not observe a significant difference in parathyroid hormone and ionized calcium depending on the presence or absence of diabetic retinopathy.

Discussion

Conducted investigation which studied the relationship between the vitamin D status and DR in patients with type 2 DM is one of the first in Ukraine. Earlier articles evaluated the results according to differences in cholecalciferol content between groups or, willingly, as the frequency of DR corresponding to a given vitamin D threshold to determine deficiency or insufficiency.

Our research verified the relationship of 25(OH)D insufficiency and deficiency with retinopathy in patients with type 2 DM. As in former reports, type 2 diabetic subjects with DR had lower serum vitamin D concentrations. In addition, a higher proportion of vitamin D deficiency/insufficiency was established in patients with this microvascular complication.

An earliest study on 66 type 2 diabetic patients (46 with DR) detected no differences in serum vitamin D concentrations between type 2 diabetic subjects agreeably to the presence or absence of DR [12].

On the other hand, Suzuki A. et al. showed that type 2 diabetic patients with proliferative DR had lower serum 25(OH)D [13]. Population-based investigation [14] on this topic could not describe an association between DR and serum 25(OH)D content.

In patients with type 2 DM and DR, lower levels of 25(OH)D were also detected; furthermore, vitamin D was an independent predictor of DR [15]. Chinese study with the greatest number of persons with DR showed an unconstrained relation between 25(OH)D levels and DR, particularly for advanced sight-threatening DR [16]. This investigation exposed a duplicated increase in sight-threatening DR in persons with level 25(OH)D below 15.57 ng/ml.

Immense, population-based, cross-sectional investigation also verified a converse association of vitamin D levels with the presence of DR [17]. This study did not supply information on the type of DM of the included patients. Therefore, most of the reports were able to tell relationship between 25(OH)D and DR.

Summing up, our findings are in line with most previous reports that conducted relationship of vitamin D with DR in type 2 DM. In contrast, our results are discordant with previous study that did not demonstrate an association of vitamin D with DR in type 2 DM [18].

Conclusions

Patients with type 2 diabetes mellitus and diabetic retinopathy have significantly lower serum 25(OH)D level — 14.6 ± 2.9 ng/ml versus 23.9 ± 3.1 ng/ml in persons without retinopathy, p < 0.05.

The multivariate analyses established a significant relationship between DR and 25(OH)D concentration. These findings are faithful when considering both the vitamin D level and the presence of vitamin D deficiency defined by 25(OH)D < 20 ng/ml.

Body mass index was inversely correlated with 25(OH)D levels and positively associated with vitamin D deficiency.

The data we have received indicate the possible significance of vitamin D in the development of diabetic retinopathy. Conducting future experimental and clinical studies will determine the role of vitamin D status in the pathogenesis of diabetic retinopathy and other diabetic microvascular lesions.

Limitation of the study. Our study shares the most important limitation with previous studies because all of them were cross-sectional. This design allows only for the identification of relationship between study variables. There is no prospective follow-up investigation in type 2 DM and the question on the potential role of vitamin D in the development of DR has not been confirmed yet.

References

8. Tecliahuz F, Formenti AM, Giustina A. Role of vitamin D in diabetic retinopathy: Pathophysiological and clinical aspects. Rev En-
У спостережному дослідженні типу «випадок — контроль» обстежено дві групи хворих на ЦД 2-го типу: 55 хворих на діабетичну ретинопатію у хворих на ЦД 2-го типу та 36 без ретинопатії у хворих на ЦД 2-го типу. У пацієнтів із ретинопатією була вірогідно нижча концентрація 25(ОН)D — 14,6 ± 2,9 нг/мл проти 17,0 ± 3,4 нг/мл у хворих без ретинопатії, р < 0,05. Багатофакторний аналіз підтвердив вірогідний взаємозв’язок між вмістом 25(ОН)D і наявністю діабетичної ретинопатії у хворих на ЦД 2-го типу. У пацієнтів із ретинопатією була вірогідно нижча концентрація 25(ОН)D — 14,6 ± 2,9 нг/мл проти 17,0 ± 3,4 нг/мл у хворих без ретинопатії, р < 0,05. Багатофакторний аналіз підтвердив вірогідний взаємозв’язок між вмістом 25(ОН)D і наявністю діабетичної ретинопатії у хворих на ЦД 2-го типу.

Висновки.

Опрацювання патологічної структури звичайно здійснюють за допомогою статистичних пакетів з числом виділених груп, використовуючи при цьому методи випадкового вибору (випадковим порядком) з використанням програмних комплексів (например, SPSS, R, Python, інші). В результаті аналізу отримані значність тесту на рівень значущості, яка характеризує силу зв'язку інтересу встановленого взаємозв'язку.

Ключові слова: діабетична ретинопатія; статус вітаміну D.