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Serum vitamin D receptor levels in gestational diabetes mellitus

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Abstract

Background: Vitamin D affects glucose metabolism by increasing insulin secretion and insulin receptor expression. Also, it exerts these effects by binding to its primary receptor, the vitamin D receptor (VDR). In this preliminary study, we aimed to examine serum 25-(OH) vitamin D_3 and serum VDR levels in gestational diabetes mellitus (GDM) patients.

Methods: Blood samples were obtained during 24–28 weeks of pregnancy from patients with GDM (n = 30) and age, body mass index (BMI), and gestational age-matched control subjects (n = 33). Both groups were examined for changes in the levels of glucose, insulin, glycated hemoglobin (bA_{1c}), 25-(OH) vitamin D_3 and VDR.

Results: There were no significant differences in serum 25-(OH) vitamin D_3 and fasting insulin levels between the control and GDM groups (p = 0.115, p = 0.182). But serum VDR levels were significantly higher in the GDM group than in the control group (p = 0.001).

Conclusions: Although there was no significant difference between the two groups regarding 25-(OH) vitamin D_3 levels, it is notable that VDR levels were higher in GDM patients. To further define the role of vitamin D in the prophylaxis and treatment of GDM, it may be useful to conduct more extensive studies on VDR.

Keywords: gestational diabetes mellitus; insulin; vitamin D; vitamin D receptor.

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Introduction

Vitamin D deficiency (VDD) is very common throughout the world [1]. Besides the adverse effects of VDD on bone and calcium metabolism, it is recognized that it is associated with many chronic diseases including diabetes [2–5]. The immunoregulatory role of vitamin D and its effects on insulin secretion and insulin receptor expression suggest that it may be a protective factor in diabetes [6].

Gestational diabetes mellitus (GDM) is a clinical state of glucose intolerance which is first seen or detected in pregnancy. Fetal loss and neonatal disease rates in GDM pregnancies have been reported to be approximately 4 times higher than in normal pregnancies. The International Diabetes Federation stated that in 2015, gestational diabetes affected approximately 13.2% of all pregnancies which resulted in live births worldwide. Moreover, this rate is expected to increase in parallel with the frequency of diabetes in the future [7].

With the increase in placental hormones in pregnancy, especially from the end of the first trimester, peripheral insulin sensitivity is reduced and there is an increased tendency towards hyperglycemia. The addition of genetic and environmental risk factors for impaired glucose tolerance, to the decreased peripheral insulin sensitivity, may lead to GDM [8, 9].

Although it is not possible to say that VDD is a definite risk factor for GDM, patients with GDM are more likely to have VDD [10, 11].

Vitamin D receptor (VDR) is the target receptor for 1,25-$(OH)_2$ vitamin D_3, the active form of vitamin D, which exerts its antidiabetic influence on carbohydrate metabolism (e.g. insulin secretion, insulin receptor expression) through VDR [12]. Therefore, the role of VDR in GDM is worth investigating.

The aim of this study was to clarify the relationship between GDM and vitamin D by revealing vitamin D levels in patients with GDM. It was also aimed to learn more about VDR expression in GDM patients by reviewing serum VDR levels.

Materials and methods

Subjects

This study was carried out in Antalya, Turkey (latitude: 36°53′) between December 2012 and March 2013. Participants to be included in the study were identified and grouped at the time of GDM screening (75 g, 2-h oral glucose tolerance test [OGTT]) between 24 and 28 weeks of pregnancy. Two working groups were constituted according to the OGTT results. The GDM group was formed from 30 pregnant women with GDM who were diagnosed according to the International Association of Diabetes in Pregnancy Study Groups criteria [13]. The control group was formed from 33 pregnant women whose OGTT results were normal.

All the participants were informed about the study and a signed permission document was obtained in accordance with the Declaration of Helsinki. The Antalya Training and Research Hospital Ethics Committee approved the study. Patients who had pre-gestational diabetes mellitus (DM), a family history of DM (first-degree relatives), multiple pregnancies, the presence of any acute or chronic disease, fetal anomalies, pre-eclampsia, chronic hypertension and a history of smoking or chronic alcohol consumption were excluded from the study.

Control and GDM groups were matched in terms of maternal age, body mass index (BMI) and gestational age at the time of blood sampling. BMI is calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). Gestational age was calculated based on the last menstrual history and confirmed by ultrasound imaging in the first trimester of pregnancy. The blood pressures of those participating in the study were measured in the sitting position, after a rest period of 10 min.

Biochemical parameters

One week before blood sampling, patients who had received drugs that could affect glucose metabolism (e.g. statins, β-blockers) were not included in the study. Venous blood samples to be used for the analysis of biochemical parameters were collected in tubes with Serum Clot Activator and Gel (BD Vacutainer® SST™ II Advance, Beckton Dickinson and Company, Franklin Lakes, NJ, USA) on the day of OGTT screening. Fasting OGTT blood samples were used for the analysis of all biochemical parameters except first- and second-hour OGTT glucose parameters. After 30 min, blood samples were centrifuged at 1150 *g* for 15 min at 4 °C. Serum samples were stored at −80 °C until assayed for 25-(OH) vitamin D_3 and VDR. Other biochemical parameters were analyzed on the day of OGTT screening. Serum glucose levels were measured using the hexokinase method (Beckman AU5800; Beckman Coulter Diagnostics, CA, USA). Serum creatinine levels were determined photometrically in a Beckman Coulter AU2700 auto-analyzer (Beckman Coulter Inc., CA, USA). Insulin levels were determined by the chemiluminescence method (Access® DxI800; Beckman Coulter, Inc., CA, USA). Glycosylated hemoglobin (HbA_{1c}) was measured using an automatic glycohemoglobin analyzer (Tosoh HLC 723 G8; Tosoh Bioscience, Japan) with the principle of high-performance liquid chromatography. Insulin resistance was calculated from fasting serum glucose and insulin using the homeostatic model assessment of insulin resistance (HOMA-IR) [14].

25-(OH) Vitamin D_3 levels were measured by a direct competitive chemiluminescence immunoassay method using 25-(OH) vitamin D_3 kit (Diasorin Inc., Stillwater, MN, USA) in a Liaison (DiaSorin S.p.A. Via Crescentino 13040 Saluggia, VC, Italy) autoanalyzer.

Serum VDR levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Sunred® Biological Technology, Shanghai, China; Catalogue No: 201-12-1554). Calibration was done with a serial dilution of the standard solution of the kit which contains 240 ng/mL of recombinant human VDR. Detection of serum VDR was performed following the manufacturer's recommendations. Briefly, standards, serum samples, monoclonal VDR antibody labeled with biotin and horseradish peroxidase (HRP) tagged streptavidin solution was added to a micro-ELISA plate coated with a monoclonal antibody specific for VDR. After 60 min of incubation at 37 °C, the plate was washed 5 times and chromogen solutions were added. After another incubation period of 10 min, color development was stopped by adding a stop solution. Optical densities (OD) were read at a wavelength of 450 nm and calculations were performed. The minimum detectable concentration of VDR was 0.75 ng/mL, with intra-assay and inter-assay coefficients of variation being <10% and 12%, respectively (information is taken from the kit insert and was not verified by our experiments). In order to avoid variation within an assay, measurements were performed in duplicate and simultaneously using the same ELISA kit.

All statistical analyses were carried out using SPSS 18.0 statistical software (SPSS for Windows, Chicago, IL, USA). Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed data (presented as mean ± standard deviation) for the comparison of groups was carried out using Student's T-test,

and for the non-normal distributed data (presented as medians [minimum–maximum]) the Mann-Whitney U-test was used. A two-tailed probability value of $p < 0.05$ was regarded as statistically significant.

Results

The demographic data of the subjects are shown in Table 1. There were no significant differences between the GDM and control groups for age, gestational age and BMI ($p > 0.05$).

Table 2 shows the biochemical serum parameters of both control and GDM groups. Concentrations of 75 g OGTT glucose and HbA_{1c} were significantly higher in the GDM group as expected ($p = 0.012$, $p = 0.007$, $p = 0.001$ and $p = 0.001$, respectively). However, it is noteworthy that there was no significant difference in serum fasting insulin levels between the two groups ($p = 0.182$). Also there was no significant difference in serum 25-(OH) vitamin D_3 levels ($p = 0.115$). Besides all these, serum VDR levels were significantly higher in the GDM group compared to controls ($p = 0.001$). However, no significant correlation was found between serum VDR levels and other biochemical parameters.

Discussion

To the best of our knowledge, this preliminary study is the first in the literature to attempt to determine the relationship between serum VDR levels and GDM. The results showed no significant difference in the levels of 25-(OH) vitamin D_3 between the GDM group and the control group. However, the serum VDR levels of the GDM group were significantly higher than those of the control group.

In the literature, there have been many clinical studies conducted to investigate the relationship between GDM and vitamin D, but conflicting results have emerged. Based on the results of a prospective study, it is stated that a low level of 25-(OH) vitamin D_3 in the first trimester of pregnancy is an independent risk factor for GDM

Table 1: Demographic variables in control and GDM groups.

	Controls (n = 33)	GDM (n = 30)	p-Value
Age, years	28.3 (±5.4)	29.8 (±6.5)	0.332
Gestational age at sampling, weeks	25.5 (±1)	25.8 (±1.1)	0.262
Gravidity	2 (1–8)	2 (1–7)	0.867
BMI, kg/m^2	27.7 (±4.1)	29.1 (±6)	0.275
Weight gain, kg	8.4 (±3.2)	7.8 (±4.4)	0.681
Systolic blood pressure, mm Hg	110 (100–130)	110 (90–130)	0.93
Diastolic blood pressure, mm Hg	70 (50–90)	70 (60–90)	0.948
Gestational age at delivery, weeks	38 (37–40)	38.6 (37–40)	0.75
Birth weight, g	3505 (±375)	3634 (±374)	0.176

Data are presented as mean ± standard deviation or median (range). BMI, body mass index; GDM, gestational diabetes mellitus.

Table 2: Biochemical characteristics of the control and GDM groups.

	Control (n = 33)	GDM (n = 30)	p-Value
Fasting insulin, mIU/mL	8.34 (2.51–87.66)	10.6 (3.47–48.97)	0.182
75 g OGTT, mg/dL			
Fasting glucose	79.4 (±12.5)	90.8 (±21.3)	0.012[a]
First hour	125.1 (±23.2)	147 (±38.1)	0.007[a]
Second hour	97.1 (±20.9)	136.1 (±26)	0.001[a]
HOMA-IR, mIU/L	1.43 (0.42–27.27)	2.35 (0.69–11.73)	0.12
HbA_{1c}, %	4.69 (±0.37)	5.25 (±0.65)	0.001[a]
Creatinine, mg/dL	0.57 (±0.06)	0.59 (±0.05)	0.288
25-(OH) vitamin D_3, ng/mL	13.1 (±6.1)	15.8 (±7.7)	0.115
VDR, ng/mL	29.84 (16.9–116.3)	40.5 (19.9–171.2)	0.001[a]

Data are presented as mean ± standard deviation or median (range). OGTT, oral glucose tolerance test; HOMA-IR, homeostatic model assessment of insulin resistance; HbA_{1c}, hemoglobin A_{1c}. [a]Statistically significant difference.

[15], whereas another prospective study of 5109 pregnancies did not determine any association of low 25-(OH) vitamin D_3 levels with GDM [16]. A cross-sectional study by Maghbooli et al. of 741 pregnancies showed a positive correlation between insulin sensitivity and 25-(OH) vitamin D_3 levels in the second trimester [17]. In another similar study, it was determined that second trimester 25-(OH) vitamin D_3 levels were not associated with insulin sensitivity or GDM [18]. Moreover, meta-analysis studies have reported that VDD increases the GDM risk [19–21].

The most fundamental element in the pathophysiology of GDM is the inability of the pancreatic β cells to compensate physiologically for increased peripheral insulin resistance emerging in the second trimester [22]. As fasting insulin and HOMA-IR levels do not differ between the two groups in the current study, it can be said that the clinical course of the patients in the GDM group was mild and explains why there were no differences in the levels of 25-(OH) vitamin D_3 between the GDM group and the control group. In the majority of similar studies showing that GDM is associated with VDD, fasting insulin levels were lower than in the control group. Therefore, when examining the relationship between VDD and GDM, the clinical grading of GDM may reveal the possible relationship more clearly. Although there is no difference between the two groups in terms of 25-(OH) vitamin D_3 levels, we believe that lower vitamin D levels affect insulin sensitivity in a negative manner during pregnancy.

The proportions of vitamin D insufficiency (which is defined as serum 25-(OH) vitamin D_3 levels between 10 and 30 ng/mL [23]) in both control and GDM groups were high. Also studies conducted on pregnant Turkish women population demonstrated a high prevalence of VDD and vitamin D insufficiency [24, 25]. Thus, it can be concluded that the pregnant Turkish women population has a high prevalence of VDD and vitamin D insufficiency.

The effects of vitamin D on insulin have been shown in experimental studies. Significant studies have been conducted on vitamin D leading to the release of insulin from pancreatic β cells [26–30]. This effect of vitamin D is believed to be achieved by binding to the caveolar VDR on the cell membrane [31, 32]. Stimulation of the second messenger system by VDR-1,25-$(OH)_2$ vitamin D_3 complex leads to the opening of the voltage-dependent calcium channels. The rise in intracellular calcium concentration triggers exocytosis of insulin granules [32]. Furthermore, the presence of VDR expression in the promoter region of the insulin receptor gene and the increase in the transcription of the insulin receptor in cells that are stimulated with 1,25-$(OH)_2$ vitamin D_3 shows that vitamin D can also affect peripheral insulin sensitivity [33].

There are few studies in the literature that show VDR expression levels associated with DM. Two different studies by Filipović et al. in rat models of type 1 DM have demonstrated that VDR expression increases both in the dorsal root ganglia and in hepatocytes [34, 35]. In another study conducted on type 1 DM rat models, VDR expression in pancreatic β cells was found to be less than that of the control group, and both VDR expression and insulin levels were increased with vitamin D treatment [36]. In a study in type 2 diabetes mellitus patients, decreased VDR expression was observed in macrophages compared to the control group [37]. In the first of two studies showing VDR expression in GDM patients, VDR expression in the placenta was no different from that of the control group [38], and in the second study, it was demonstrated that VDR expressions in trophoblasts and fetoplacental endothelial cells were higher than in the control group [39].

It is noteworthy that serum VDR levels in GDM patients were higher than in the control group; while there was no significant difference in serum 25-(OH) vitamin D_3 levels between the two groups. It can be argued that this difference may be due to reinforcement of the effects of 25-(OH) vitamin D_3 on glucose metabolism. An increase in the number of VDR in patients with insulin resistance may be a response mechanism to increase insulin sensitivity and secretion.

VDR is expressed in at least 37 different tissues [40–42]. More than 100 genomic promoter regions have also been found to contain VDR expression [43–45]. Therefore, it is not surprising that intracellular VDR concentrations are regulated by other hormones and growth factors (heterologous regulation) besides 1,25-$(OH)_2$ vitamin D_3 and other VDR ligands (homologous regulation) [46].

The fact that VDR, a member of the nuclear receptor family, is also expressed on the cytoplasmic membrane suggests that the amount of VDR in serum may be directly proportional to VDR expression. It is not known which tissues and at what rates contribute to the amount of circulating VDR. However, considering that VDR expression occurs in pancreatic β cells far above the average in comparison to other cell types, it can be considered that serum VDR concentration may provide important clues about the relationship between DM and vitamin D.

A limitation of our study is that there was no measurement of the first-hour insulin of OGTT, which is a better indicator of pancreatic β cell function than fasting insulin. An important feature of this preliminary study was that serum VDR levels were shown in GDM patients for the first time. Another strength of our study is that there was no significant difference regarding age, ethnicity and BMI between the two groups participating in the study.

In this preliminary study, serum VDR levels were determined to be higher in the GDM group than those in the control group and serum 25-(OH) vitamin D_3 levels were found not to be significantly different between the two groups. As VDR has a major role in the interaction between vitamin D and insulin, it would be meaningful to investigate VDR levels in GDM patients in larger population studies.

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