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# ASSOCIATION BETWEEN VITAMIN D3 LEVELS AND INSULIN RESISTANCE IN GESTATIONAL DIABETIC PATIENTS OF KERBALA PROVINCE: IRAQ

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## ABSTRACT

**Background:** Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity that occurs during pregnancy. Women with GDM represent a heterogeneous group and are characterized by pancreatic β cell function that is insufficient to meet body insulin needs, probably due to autoimmune diseases, insulin resistance or genetic abnormalities. **Objectives:** This study aims to examine the levels of 25(OH)D3 in Iraqi women with normal pregnancies and pregnancies complicated with GDM and then to see its association with insulin, insulin resistance and HbA1c levels. **Materials and Methods:** This cross-sectional study includes three groups: Group I include 25 pregnant gestational diabetes mellitus (GDM) with age range between 24-43 years. Group II include 23 non-pregnant with type II diabetes mellitus (T2DM) with age ranged between 30 – 39 years. Group III include 29 normal pregnant without GDM and T2DM as control group whose age ranged between 20 – 37 years. All these samples were obtained from gynecology and obstetrics teaching hospital / Kerbala health directorates between Sep., 2019 and June, 2020. The body mass index (BMI), fasting blood glucose, insulin, HbA1c% and 25(OH)D3 were measured immediately, while HOMA-IR was calculated from the resultant data. **Results:** The mean ± SD value of age of GDM group (34.28 ± 6.44) years was significantly higher than that found in group III and less than that found in group II which contain only T2DM (41.65 ± 6.73) years and for BMI group I was non-significantly higher than that found in group II and significantly higher than that found in group III. Fasting blood glucose, glycated hemoglobin, insulin hormone and insulin resistance was obviously higher in GDM group as compared with normal pregnancy group. Serum insulin levels was higher in GDM group (16.78 ± 7.23) µIU/mL as compared with both normal pregnant group III (13.05 ± 4.1) µIU/mL and T2DM group II (14.29 ± 7.68) µIU/mL. Homeostatic model assessment insulin resistance (HOMA- IR) was found of significantly higher in gestational diabetes mellitus (6.06 ± 2.98) as compared with normal pregnancy group (3.11 ± 0.99) and lower that found in T2DM group (6.97 ± 4.55). In our study we have found a high prevalence of deficiency of 25(OH)D3 in overall study sample. The higher deficiency was found in 56% group I followed by T2DM group II which was present in 65% as compared with normal pregnant group III. The serum 25-(OH)D3 levels obtained were lower in patients who were overweight as compared with other individuals of normal pregnancy group. **Conclusion:** The diagnosis of GDM usually may occurs after the age of 30 years. The observed data indicated that 25(OH)D3 deficiency or insufficiency status was associated with an increased risk of diabetes mellitus and gestational diabetes and higher insulin and insulin resistance as compared with normal pregnancy..

**KEYWORDS:** GDM, T2DM, 25(OH)D3, Insulin Resistance, HbA1c%.

## INTRODUCTION

Diabetes Mellitus (DM) is a heterogeneous metabolic disorder characterized by the presence of hyperglycemia resulting from defect in insulin secretion, insulin resistance or both accompanied by greater or lesser impairment in the metabolism of carbohydrates, lipids and proteins.[1] The incidence of non-insulin dependent diabetes or what called diabetes mellitus type 2 (T2DM) is growing alarmingly worldwide. T2DM is a multifactorial metabolic syndrome, which influenced by both environmental and genetic factors and showed a wide range of dissimilarity among variant ethnic groups.[2,3] Type 2 diabetes mellitus is characterized by insulin resistance, with or without insulin deficiency (relative) that induces organ dysfunction.[4] Insulin resistance is recognized as a fundamental defect seen in obesity and T2DM. The incidence of disease increases with age, obesity, physical inactivity, unhealthy diet, and ethnicity.[2,4] The development of T2DM is strongly associated with overweight and obesity in both genders

and all ethnic groups. Type 2 diabetes mellitus is associated with a two to four fold excess risk of coronary heart disease and the usual risk factors for coronary artery disease account for only 25–50% of increased atherosclerotic risk in diabetes mellitus. Other obvious risk factor is dyslipidemia which contribute substantially to the increased risk of macro-vascular disease in diabetic patients.[5,6]

Gestational diabetes (GD) defined as first onset or diagnosis of diabetes in pregnancy.[7] in which hyperglycemia that develops during pregnancy (generally detected in the late second trimester (13–26 completed weeks of gestation) or early in the third trimester (27–40 weeks) and resolves following delivery.[8]

A possible cause of GDM is obesity, which is an important clinical risk factor for the development of diabetes and generally have higher body mass indices when compared with healthy pregnant women.[9] GDM is associated with adverse maternal health outcomes such as gestational hypertension and pre-eclampsia.neonatal outcomes including hyper-insulinaemia, macrosomia, shoulder dystocia, caesarean delivery, hypoglycaemia and later life risk of obesity and T2DM.[10] Hyperglycemia develops during pregnancy because of the secretion of placental hormones, which causes insulin resistance.[11]

GDM is usually the result of β-cell dysfunction on a background of chronic insulin resistance during pregnancy and thus both β-cell impairment and tissue insulin resistance represent critical components of the pathophysiology of GDM. During pregnancy, insulin resistance is increased due to production of placental hormones that antagonize insulin action. This increase is added to the insulin resistance due to genetic susceptibility and / or suboptimal lifestyle. However, when insulin release is inadequate, hyperglycemia occurs (gestational diabetes mellitus).[12] Risk factors for GDM include: glucoseurea, age over 30 years, obesity, family history of diabetes, past history of GDM and previous macrosomic child.[13]

Deficiency of a fat-soluble vitamin D3 may play a role in the pathogenesis of GDM.[14] In human, plasma vitamin D3 bound to the vitamin D3 binding protein and transported to the liver where both are hydroxylated to form 25-hydoxyvitamin D3 [25(OH)D3] which agreed that it is the metabolite form determine the overall vitamin D status as it is the major storage form of vitamin D3 in the human body.[15] This primary circulation form of vitamin D3 is biologically inactive with levels approximately 1000–fold greater than the circulating 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3]. The half-life of circulating 25(OH)D3 is 2-3 weeks and most of the vitamin D3 measurable in serum, is 25(OH)D3. Vitamin D3 is essential for bone health and a severe deficiency in children leads to bone–malformation, known as rickets. Vitamin D deficiency causes muscle weakness and in elderly the risk of falling has been attributed to the effect of vitamin D3 on muscle function.[9]

Relationship between the vitamin D3 receptor (VDR) gene and diabetes has been noted in several populations.[16] In addition, the VDR is present in pancreatic β-cells. Thus,1,25$(OH)_2$D3 may play an important role in insulin secretion and insulin sensitivity in diabetes by either increasing the intracellular calcium concentration in the β-cell to induce insulin secretion or by increasing the conversion of proinsulin to insulin.[17]

The aims of the presented cross-sectional study is to determine the levels of 25(OH)D3 in Iraqi women with T2DM, normal pregnancies and pregnancies complicated by GDM and to investigate the association between 25(OH)D3 levels, and fasting blood glucose (FBG), glycated hemoglobin (HbA1c) insulin levels and insulin resistance (HOMA-IR).

## MATERIALS AND METHODS

This cross-sectional study includes three groups: Group I include 25 pregnant women with gestational diabetes mellitus (GDM) with age range between 24-43 years. Group II include 23 non-pregnant with type II diabetes mellitus (T2DM) with age ranged between 30 – 50 years. Group III include 29 normal pregnant women without GDM and T2DM whose age ranged between 20 – 37 years. All these samples were obtained from diabetic center of Al-Hussein teaching hospital, Al-Hussein medical city and gynecology and obstetrics teaching hospital / Kerbala health directorates between Sep., 2019 and June, 2020, and the body mass index was determined for each case. The fasting blood was taken from venipuncture (3.0 mL from each) and each of glucose, insulin, HbA1c and 25(OH)D3 were measured immediately, while HOMA-IR was calculated from the resultant data of each sample. The information that taken from each of them include: age, smoking, duration of T2DM, type of treatment, physical exercise and the body mass index (BMI) were also measured. The inclusion criteria of group I include (BMI above 25 kg/$m^2$, GDM with insulin treatment), while the exclusion criteria include (pre-eclampsia, thyroid and parathyroid disease, any ovarian syndrome, T1DM or T2DM). The inclusion criteria of group II include (women with T2DM, BMI above 20 kg/$m^2$, and hypertension), while the exclusion criteria include (renal disease, T1DM, coronary artery disease and myocardial infarction, thyroid and parathyroid disease and women taken various medication like glucocorticoid). The inclusion criteria of the third apparently control group include (BMI above 20 kg/$m^2$) while the exclusion criteria include (GDM, T1DM and T2DM, liver diseases, thyroid and para-thyroid disease).

Blood samples was collected from healthy patient who has been fasting for at least 12 hours, the blood glucose was measured immediately by measurement device, then

3 ml of blood was taken from puncture vein and separated into two aliquots, first aliquot is EDTA tube with 1ml of blood for HbA1c determination and second aliquot is gel tube with 2 ml of blood used for serum separation to determine each of 25(OH)D3 and insulin levels. Verbal approval was taken from each patient before blood collection occurs. BMI was calculated by dividing a person's weight (kg) by length squared ($m^2$) as indicated in the following equation.[18]

**BMI ($kg/m^2$) = Weight (kg) / Length$^2$ ($m^2$)**

For each sample included insulin levels was determined by ELIZA kit, while 25(OH)D3 concentration was determined by using cobas analyzer, HbA1c% was also determined and then insulin resistance (HOMA-IR) was calculated according to the following equation.[19]

**HOMA-IR = [Glucose (mg/dL) x Insulin (µU/mL)] / 405**

Numerical variables were expressed as mean ±SD. Student's t-test and ANOVA was used to determine differences in means between two groups for numerical variables across genotypes using SPSS version 23.0 software (SPSS Inc., Chicago, IL). In all statistical analysis, the level of significance was <0.05.

## RESULTS

The presented work aimed to study the changes in some biomarkers in gestational diabetes mellitus (GDM) patients then compared with another groups of normal pregnancy and T2DM group. The age obtained for gestational diabetes mellitus (GDM) group collected was ranged between (24-43) year and that for group II which include T2DM group II was ranged between (30-50) year, whereas, the age ranged for group III as a normal pregnant women was (20-37) years.

The most predominant age obtained for group I GDM patients was ranged between (31- 40) year in which (14/25) or (56%) of them was ages in this range as shown in **Fig. 1,** as compared with each group II T2DM (9/23) and group III as a normal pregnancy with the same age range which was (16/29) or (41.02%). The most predominant age obtained in group II or T2DM was ranged between (41-50) year (13/23) or 56.52% as shown in the same figure.

The mean ± SD values of BMI obtained for gestational diabetes mellitus or group I was (32.31 ± 3.85) $kg/m^2$ which was significantly higher than that for T2DM group II (29.86 ± 5.02) $kg/m^2$ and group III (29.11 ± 4.77) $kg/m^2$ as a normal pregnancy without GDM and T2DM as shown in **Tables 1-3.**

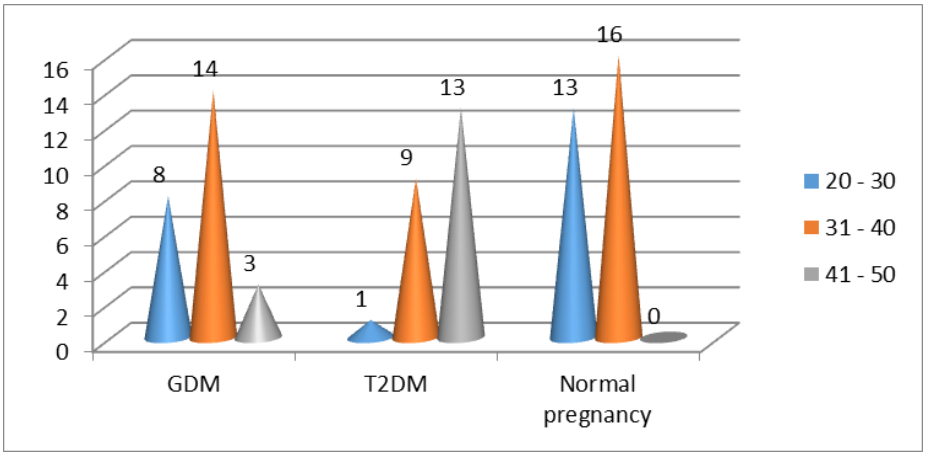


**Fig. 1: The mean ± SD of age profile in GDM women as compared with T2DM and control pregnancy groups.**

The mean ± SD values of blood glucose of group II T2DM was (189.54 ± 47.05) mg/dL which was significantly higher than that of GDM group I (144.36 ± 35.75) mg/dL. These data for both groups were significantly higher than that found in group III (97.47 ± 12.6) mg/dL as a normal pregnancy group without GDM and T2DM as indicated in the same tables.

The mean ± SD values of HbA1c% observed was elevated in group I of GDM reached to (6.064 ± 0.68%) as compared with group III (5.46 ± 0.65%) as a normal pregnancy without GDM and T2DM and less than that found in T2DM group II (9.42 ± 2.73%).

The insulin hormone profile found in this work indicate a mean ± SD values for gestational diabetes mellitus (GDM) group found to be (16.78 ± 7.23) µU/mL which was non-significantly higher than its levels observed in T2DM group II (14.29 ± 7.86) µU/mL and significantly higher than group III (13.05 ± 4.1) µU/mL as a normal pregnancy without GDM and T2DM. The insulin resistance (HOMA-IR) data observed indicated the mean ± SD values for gestational diabetes mellitus (GDM) group was (6.06 ± 2.98) which was less than that for T2DM group II (6.97 ± 4.55) and significantly higher than obtained in group III (3.11 ± 0.99) as a normal pregnancy without GDM and T2DM as indicated in **Tables 1-3.**

The mean ± SD values of 25(OH)D3 levels studied in the three groups as shown in tables (1 and 2) for group I was significantly decreased to (8.16 ± 2.65) ng/mL when compared with its levels found in both groups, T2DM group II (12.93 ± 5.17) ng/mL and group III (14.25 ± 4.37) ng/mL as a normal pregnancy without GDM and T2DM.

**Table 1: The mean ± SD values of various biomarkers determined and compared in group I GDM and group II T2DM patients.**

| Parameters | Group I GDM N = 25 Mean ± SD | Group II T2DM N = 23 Mean ± SD | P value |
|---|---|---|---|
| BMI, kg/m$^2$ | 32.31 ± 3.85 | 29.86 ± 5.02 | 0.06 |
| B. Glucose, mg/dL | 144.36 ± 35.75 | 189.54 ± 47.05 | ≤ 0.01 |
| 25(OH)D3, ng/mL | 8.16 ± 2.65 | 12.93 ± 5.17 | ≤ 0.01 |
| HbA1c% | 6.064 ± 0.68 | 9.42 ± 2.73 | ≤ 0.01 |
| Insulin, µU/mL | 16.78 ± 7.23 | 14.29 ± 7.68 | 0.25 |
| HOMA-IR | 6.06 ± 2.98 | 6.97 ± 4.55 | 0.4 |

**Table - 2: The mean ± SD values of various biomarkers determined and compared in group I GDM and group III normal pregnancy.**

| Parameters | Group I GDM N = 25 Mean ± SD | Group III Normal Pregnancy N = 29 Mean ± SD | P value |
|---|---|---|---|
| BMI, kg/m$^2$ | 32.31 ± 3.85 | 29.11 ± 4.77 | ≤ 0.01 |
| B. Glucose, mg/dL | 144.36 ± 35.75 | 97.47 ± 12.6 | ≤ 0.01 |
| 25(OH)D3, ng/mL | 8.16 ± 2.65 | 14.25 ± 4.37 | ≤ 0.01 |
| HbA1c% | 6.064 ± 0.68 | 5.46 ± 0.65 | ≤ 0.01 |
| Insulin, µU/mL | 16.78 ± 7.23 | 13.05 ± 4.1 | ≤ 0.05 |
| HOMA-IR | 6.06 ± 2.98 | 3.11 ± 0.99 | ≤ 0.01 |

**Table - 3: The mean ± SD values of various biomarkers determined and compared in group II T2DM and group III normal pregnancy.**

| Parameters | Group II T2DM N = 23 Mean ± SD | Group III Normal Pregnancy N = 29 Mean ± SD | P value |
|---|---|---|---|
| BMI, kg/m$^2$ | 29.86 ± 5.02 | 29.11 ± 4.77 | 0.57 |
| B. Glucose, mg/dL | 189.54 ± 47.05 | 97.47 ± 12.6 | ≤ 0.01 |
| 25(OH)D3, ng/mL | 12.93 ± 5.17 | 14.25 ± 4.37 | 0.3 |
| HbA1c% | 9.42 ± 2.73 | 5.46 ± 0.65 | ≤ 0.01 |
| Insulin, µU/mL | 14.29 ± 7.68 | 13.05 ± 4.1 | 0.45 |
| HOMA-IR | 6.97 ± 4.55 | 3.11 ± 0.99 | ≤ 0.01 |

## DISCUSSION

The mean (± SD) value of age of group I which include GDM was (34.28 ± 6.44) years was significantly higher than that found in group III which include normal pregnant without GDM and T2DM (31.02 ± 5.01) years and less than that found in group II which contain only T2DM (41.65 ± 6.73) years. The diagnosis of GDM usually occurs after the age of 30 years as mentioned previously.[20]

The mean ± SD values of BMI obtained for GDM group I was (32.31 ± 3.85) kg/m$^2$ which was non-significantly higher than that obtained in T2DM group II (29.86 ± 5.02) kg/m$^2$ and significantly higher than that found in group III (29.11 ± 4.77) kg/m$^2$ as a normal pregnancy without GDM as shown in **Tables 1-3**.

BMI provides a reliable indicator of body fatness for most individuals and BMI is used as a screen for weight categories that may lead to health problems.[21] In the present study, BMI was significantly associated with GDM compared to normal pregnant and diabetic patients. Increasing maternal BMI is a significant risk factor for the development of GDM.[22] Even though the association between BMI and GDM can still be used to counsel women about their risk of developing GDM, BMI as a screening tool does not have high enough

sensitivity and specificity to identify a group of women that should not receive GDM diagnostic This continues to support the notion for continuing universal screening programs for pregnant women rather than stratifying by BMI.[23]

The mean ± SD of fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and insulin hormone and insulin resistance (HOMA IR) was obviously higher in GDM group as compared with normal pregnancy group as controls. The mean ± SD value of FBG was significantly different between the studying groups. It was significantly higher in GDM (144.36 ± 35.75) mg/dL compared to group III or pregnant without GDM (97.47 ± 12.6) mg/dL and less than found in group II T2DM (189.54 ± 47.05) mg/dL.

The results correspond with the findings of previous studies. FBG values tend to stay constant throughout the entire period of pregnancy. FBG values have less individual variation compared to other glucose values, therefore, abnormal FBG level is a significant indicator in diagnosing GDM. FBG is a good screening test for GDM with advantages such as simple procedure, reasonable cost, reproducibility, easy access, and acceptance.[24] Other studies have reported that abnormal FBG alone is capable of detecting 50% of pregnant women who had already been diagnosed with DM with another screening method.[25]

The mean value of HbA1c% was obviously higher in GDM (6.064 ± 0.68%) respectively as compared with normal pregnant (5.46 ± 0.65%) and less than that found in group III T2DM (9.42 ± 2.73). This result is in agreement with the previous studies which proved that HbA1c% was higher in GDM.[20,26] HbA1c% test is currently considered to be the best measure and the gold standard for assessing glycemic control, it measures the amount of glucose that is bound to hemoglobin molecule, reflects average plasma glucose over the previous 2-3 months in a single measure which can be performed at any time of the day and does not require any special preparation such as fasting.[27]

Serum insulin levels was higher in GDM group (16.78 ± 7.23) µIU/mL as compared with both normal pregnant group III (13.05 ± 4.1) µIU/mL and T2DM group II (14.29 ± 7.68) µIU/mL. This result is agreement with the previous studies which proved that concentration of Insulin hormone was higher in GTM than in a normal pregnancy, women with GDM have an increase in Insulin production in the ß-cell of the pancreas.[28,29] β-cell adaption refers to the change that pancreatic islet cells undergo during pregnancy in response to maternal hormones in order to compensate for the increased physiological needs for mother and baby. These changes in the ß-cells cause increased Insulin secretion as a result of increased ß-cell proliferation.[30] Pregnancy causes increased Insulin resistance and so higher Insulin demand. The ß-cell must compensate this by either increasing insulin production or proliferating.[31]

Homeostatic model assessment insulin resistance (HOMA- IR) was found of significantly higher in gestational diabetes mellitus (6.06 ± 2.98) as compared with normal pregnancy group (3.11 ± 0.99) and lower that found in T2DM group (6.97 ± 4.55).

GDM can be regarded as the early pathogenesis of T2DM and it shares some physiological characterize.[32] Insulin resistance in pregnancy is consequent to the physiological adaption necessary to provide glucose to the growing fetus.[33] HOMA-IR in women with GDM increased significantly during pregnancy, mainly in 2$^{nd}$ and 3$^{rd}$ trimesters of pregnancy.[34] These findings are in agreement with a study performed in south Asians and Middle Eastern that showed gestational women were more insulin resistant as compared with western Europeans.[35]

In our study we have found a high prevalence of deficiency of 25(OH)D3 in overall study sample. The higher deficiency was found in 56% of GDM group I and the mean ± SD was (8.16 ± 2.65) ng/mL followed by T2DM group II which was present in 65% and the mean ± SD was (12.93 ± 5.17) ng/mL as compared with normal pregnant group III (14.25 ± 4.37) ng/dL. The serum 25-(OH)D3 levels obtained were lower in patients who were overweight as compared with other individuals of normal pregnancy group.

These data indicated that 25(OH)D3 deficiency or insufficiency status was associated with an increased risk of diabetes mellitus and gestational diabetes. Others showed an inverse association between 25(OH)D3 level and a risk of diabetes mellitus especially in T2DM patients,[36] whereas, other studies indicated that a higher serum 25-(OH)D3 concentration which provides the substrate for biosynthesis of 1,25-$(OH)_2$D3 inhibits the occurrence of insulin-requiring diabetes in animal models.[37]

Vitamin D3 deficiency is associated with major effects on the innate immune system. This could potentially influence the risk of diabetes that clarifies the role of 25(OH)D3 in both insulin secretion, insulin resistance and reducing the risk of infection of islet cells, whereas 25(OH)D3 may directly induce insulin secretion by binding the active form 1,25-$(OH)_2$D3 with receptors present on pancreatic β-cells and skeletal muscle, and the activating enzyme, 25(OH)D3-1α-hydroxylase, is expressed in pancreatic β-cells.[38]

GDM is a multifactorial disease involving various risk factors for example lifestyle factors, obesity, rapid weight gain and predisposing genetic factors. Furthermore, some of these factors are related with decreased 25(OH)D3 GDM and normal pregnant control status,[39] which further increases the challenge when

dissecting independent effect. It is possible that in previous studies no adjustment for confounding factors was performed, the association between 25(OH)D3 and GDM reflects shared factors such as unhealthy lifestyle or adiposity.[40] Yet, contrary to many studies, association between high 25(OH)D3 and GDM have been reported.[41] Although a biological mechanism between low vitamin D status and diabetes is plausible,[42] only a few interventions have been conducted, and these have not proved an effect of vitamin D supplementation on risk of GDM. On the other hand the data obtained concerning 25(OH)D3 in group II for T2DM was in agreement with other studies in which the level of this pro-vitamin was decreased in type II diabetic patients.-

## CONCLUSION

The diagnosis of GDM usually may occurs after the age of 30 years. The observed data indicated that 25(OH)D3 deficiency or insufficiency status was associated with an increased risk of diabetes mellitus and gestational diabetes and higher insulin and insulin resistance as compared with normal pregnancy. While HbA1c% was significantly higher in GDM group than that found in normal pregnancy group and less than that found in T2DM group.

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