

The Effect of Vit B12 Deficiency, Homocystein, and Lipid Metabolism in Association with Increased Risk of Gestational Diabetes Mellitus

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Abstract

Introduction: Gestational diabetes defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy. This definition applies whether or not insulin is used for treatment and undoubtedly includes some women with previously unrecognized overt diabetes. **Objectives:** To assess the effect of Vit B12 deficiency, Homocystein and Lipid metabolism in association with increased risk of Gestational Diabetes Mellitus. **Materials and Methods:** A prospective case control study. Sample collection: pregnant women at the 2nd and 3rd trimester ($n = 100$) were divided into two groups: Women with GDM considered as case group ($n = 50$) and healthy pregnant women as control group ($n = 50$) were enrolled in this study. **Results:** The mean level of serum B12 in case group were (169.3 ± 13.6) and (227.5 ± 29.9) of control group with highly significant decrease in case group than that in healthy control group ($P < 0.001$). Significant correlation between Vit B12 and BMI, and significant association with moderate correlation with Gestational age (P - values =0.042). Significant association with moderate correlation between Vit B12 and both insulin level and HOMA-IR test in GDM group ($P < 0.05$) respectively. Highly significant association ($P < 0.001$) with good correlation (0.712) was found between Homocysteine and B12. Significant correlation between Vit B12 and lipid profile (cholesterol, LDL, HDL, and TG) and LDL, HDL, and TG were presented with moderate correlation. Homocysteine [$\mu\text{mol/L}$] level in GDM group was (8.31 ± 2.02) and (7.33 ± 3.54) for healthy group with significant difference ($P < 0.001$). **Conclusion:** Highly significant decrease of vit B12 in patients with GDM than that in healthy group, while highly significant increase of Homocysteine and triglyceride in GDM patients than in healthy group.

Keywords: Gestational diabetes mellitus, homocystein, lipid metabolism, vit B12 deficiency

INTRODUCTION

Diabetes is the most medical condition encountered during pregnancy with about 7% of pregnancies are complicated by diabetes that either develops during pregnancy (GDM) or pregestational diabetes mellitus.^[1] The increasing prevalence of type 2 diabetes in general and in younger people in particular had led to an increasing number of pregnancies with this complication.^[2] The greater majority of women with carbohydrate intolerance during pregnancy do not have signs or symptoms so it should be suspected in patients with known risk factor for GDM which include age >25 years old, past obstetrical history, history of infant weighing more than >4000g, repeated spontaneous Miscarriage or history of unexplained still birth and

strong family history of diabetes). However (50%) of patients identified as having GDM don't have such risk factors.^[3] GDM is defined as impaired carbohydrate tolerance resulting in hyperglycemia, which first develops or becomes diagnosed during pregnancy some of these women have previously undiagnosed diabetes, usually type 2.^[4] **HbA1c (glycosylated Hb A1c):** Is derived from the non-enzymatic addition of glucose to amino groups of

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hemoglobin. HbA1c is a specific glycated hemoglobin that results from the attachment of glucose to the N-terminal valine of the hemoglobin β -chain.^[5] Hemoglobin A1c (glycated hemoglobin) reflects the average blood glucose concentration over the course of the RBC lifespan, roughly 120 days in normal individuals. It provides different, and complementary, information to a single glucose concentration. Observational studies show the lowest rates of adverse fetal outcomes in association with A1C <6–6.5% (42–48mmol/mol) early in gestation.^[6] HbA1C levels fall during normal pregnancy. In the second and third trimesters, A1C <6% (42mmol/mol) has the lowest risk of large-for gestational-age infants, whereas other adverse outcomes increase with A1C $\geq$ 6.5% (48mmol/mol). Taking all of this into account, a target of 6–6.1% (42–48mmol/mol) is recommended but <6% (42mmol/mol) may be optimal as pregnancy progresses also aimed RBS below 200mg/dl and FBS 120mg/dl. These levels should be achieved without hypoglycemia, which, in addition to the usual adverse sequel, may increase the risk of low birth weight.^[7,8] Hyperhomocysteinemia in pregnant women has been associated with various placental pathologies like abruption placentae, preeclampsia, fetal growth restriction and stillbirth.^[9] Supplementation with 250 μ g/day B12 during pregnancy and lactation substantially improved maternal, infant status.^[10] Vitamin B12 status during pregnancy is critical since maternal vitamin B12 deficiency can affect the pregnancy outcome for both mother and the offspring. In pregnant women, a B12 deficiency lead to B12 DEFICIENCY ANEMIA and GDM and hypertension.^[10,11] Babies of deficient mothers are at risk for low birth weight and neural tube defect.^[10] The aim of study is to assess the effect of Vit B12 deficiency, Homocystein and Lipid metabolism in association with increased risk of Gestational Diabetes Mellitus.

MATERIALS AND METHODS

A prospective case control study, conducted at the Department of Obstetrics and Gynecology in Al-Imamin Al-Khadimain Teaching Hospital, from the first of January 2020 to the end of October 2020.

Inclusion Criteria: Singleton pregnancy. GA >20 weeks by Us and LMP. Exclusion Criteria: Pregnant women with history of smoking, taking any medication for at least 3 months before recruitment, history of cardiovascular disease or previous medical history as well as those reported vit deficiency or significant disease. Should not have any disease, disorder or condition (e.g., Vegan), pernicious anemia, bariatric surgery etc. that lead to B12 deficiency. Should not take medications that interact with the absorption of B12, (e.g., heart burn medicines: proton pump inhibitor).

Matching Criteria: Maternal age, gestational age, and self-reported pre-pregnancy body weight and BW at the booking visit. Pregnant women at the 2nd and 3rd

trimesters ($n = 100$) were divided into two groups: Women with GDM previously diagnosed as case group ($n = 50$) and. Healthy pregnant women as control group ($n = 50$) were enrolled in this study.

Five mL of venous blood were collected from all participants after period of fasting of about 12 hours for testing. Specimens processed within 4h to avoid cell lysis. Blood fractionation was carried out centrifuge at 2500 x g for 10min, and 2–3 mL of the blood serum's supernatant was removed and stored at lab refrigerators. Vitamin B12 was analyzed using electrochemiluminescent immunoassay (ECLIA) with a Cobas e601 analyzer (Roche company). Moreover, assay for: Fasting blood sugar, fasting insulin, Homocystein, HbA1c, and lipid profile were done using Enzyme-linked immunosorbent assay (ELISA). **HOMA-IR=** Fasting insulin (μ U/L)/X fasting glucose (mmol/L)/22.5. Statistical analysis done by Statistical Package for Social Sciences (SPSS) version 23 used in this study. Descriptive statistics presented as (mean $\pm$ standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test used when expected variable was less than 20% of total) and t-test used to compare between two means. One-way ANOVA analysis used to compare between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs. R-value ranged between zero (indicates complete no correlation) to One (perfect correlation), however, the R-value close to one indicates the stronger correlation, additionally; the negative signed R indicates inverse correlation while non-signed (positive) R indicate direct (positive) correlation. Moreover, the strength of correlation based on the following levels: **Exactly 1:** A perfect correlation, **> 0.7:** A strong correlation, **0.4 – 0.7:** A moderate correlation, **< 0.4:** A weak correlation, **0.** **Complete:** No linear relationship.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 124 dated 1/11/2019 to get this approval.

RESULTS

One hundred participants were enrolled in the current study and the main age group were between (20–29) years old (48%), with the mean age (30.54 ± 4.9) years, multigravida were presented in (77%) and primigravida were (23%), for the parity it was found that (74%) were with (1–3) parity, (26%) in >3. (92%) of the respondents

were presented with no history of miscarriage and only (8%) with previous history of miscarriage. (5%) of the respondents were presented with previous history of GDM [Table 1].

No significant difference was found between the demographic criteria in the studied groups ($P > 0.05$) [Table 2].

No significant differences found between birth outcomes of the studied groups [Table 3].

Mean age of the case group (GDM group) were (28.52 ± 3.9) years and (28.07 ± 4.8) years for control group, gestational age in case group were (32.16 ± 0.78) wks. and (32.4 ± 0.6) wks. in control group, BMI of case group were (31.31 ± 2.44) kg/m^2 and (30.42 ± 3.05) kg/m^2

Table 1: Demographic characteristics of the studied groups and outcome

Parameters		No.	%
Age Group	<20	11	11.0
	20-29	48	48.0
	30-39	36	36.0
	≥ 40	5	5.0
Total		100	100.0
Mean $\pm$ SD (years)		30.54 $\pm$ 4.9	
Gravida	primigravida	23	23
	Multi Gravida	77	77.0
Total		100	100.0
Parity	1-3	74	74.0
	>3	26	26.0
Total		100	100.0
Miscarriage	No	92	92.0
	Yes	8	8.0
Total		100	100.0
Previous Hx of GDM	Yes	5	5.0
	No	95	95.0
Total		100	100.0

for control. No statistical differences was found between the mean of demographic criteria and the studied groups [Table 4].

Mean of FBG in case group were (142.05 ± 17.72) (mg/dl) and (94.10 ± 21.81) (mg/dl) in control group, fasting serum insulin level were (18.92 ± 3.63) $\mu\text{U/mL}$ in case group and (11.91 ± 2.87) $\mu\text{U/mL}$ in control, highly significant differences were found in FBG, and Fasting serum insulin between the studied groups ($P < 0.001$), and mean of HOMA-IR for GDM group was (3.52 ± 0.3) and (2.67 ± 0.6) for healthy group with highly significant differences ($P < 0.001$). HbA1c for GDM group was (5.67 ± 1.02) and (4.8 ± 0.7) for healthy group with highly significant difference ($P < 0.001$). Homocysteine [$\mu\text{mol/L}$] level in GDM group was (8.31 ± 2.02) and (7.33 ± 3.54) for healthy group with significant difference ($P < 0.001$), all these were shown in Table 5.

The mean of **LDL (mg/dL)** for case group was (70.16 ± 13.46) and (72.16 ± 14.84) for control group with no significant differences ($P = 0.48$), **HDL (mg/dL)** of the GDM group was (45.18 ± 10.28) and (47.10 ± 12.04) for healthy group with no significant differences ($P = 0.4$), and mean of **TG (mg/dL)** for GDM group was (97.20 ± 6.29) and (90.80 ± 14.28) for healthy group with significant differences ($P = 0.004$). Mean **cholesterol level (mg/dL)** for GDM group was (150 ± 16.42) and (153.20 ± 17.24) for healthy group with no significant difference ($P = 0.3$), all these were found in Table 6.

The mean level of serum B12 in case group (GDM group) were (169.3 ± 13.6) and (227.5 ± 29.9) of control group with highly significant decrease in case group than that in healthy control group ($P < 0.001$) [Table 7].

Table 8 shows that there is significant association with moderate correlation between Vit B12 and both of insulin level and HOM-IR test in GDM group ($P < 0.05$) respectively. Highly significant association ($P < 0.001$) with

Table 2: Comparison between demographic criteria of the studied groups

Parameters		Case (GDM group) (n=50)	Control (healthy group) (n=50)	P Value
Age Group	<20	5	6	0.8 Ns
	20-29	23	25	
	30-39	20	16	
	≥ 40	2	3	
Mean $\pm$ SD (years)		30.5 $\pm$ 2.1	30.9 $\pm$ 2.2	0.3 Ns
Gravida	primigravida	10	13	0.4 Ns
	Multi Gravida	40	37	
Parity	1-3	35	39	0.3 Ns
	>3	15	11	
Miscarriage	No	45	47	0.4 Ns
	Yes	5	3	
Previous Hx of GDM	Yes	4	1	0.1 Ns
	No	46	49	

Table 3: Comparison between abnormal birth outcomes of the studied groups

Birth outcome	Case (GDM group) (N=19)		Control (healthy group) (N=13)		P Value
	No.	%	No.	%	
Macrosomia	5	55.6	4	44.4	0.5 Ns*
Low birth weight	6	75.0	2	25.0	
Small gestational age	4	57.1	3	42.9	
Large for date	5	62.5	3	37.5	
Mean birth weight (gm)	3279 ± 475.37		3432.5 ± 533.21		0.1 Ns

* Not significant

Table 4: Comparison between demographic criteria mean between the studied groups

Parameters	Case (GDM group) (n=50)	Control (healthy group) (n=50)	P Value
	Mean ± SD	Mean ± SD	
Age/years	28.52 ± 3.9	28.07 ± 4.8	0.6 Ns
Gestational age / Wks.	32.16 ± 0.78	32.4 ± 0.6	0.08 Ns
Body mass index (kg/m ²)	31.3 ± 2.44	30.42 ± 3.05	0.1 Ns

Table 5: Comparison of different biochemical parameters between the studied groups

Parameters	Case (GDM group) (n=50)	Control (healthy group) (n=50)	P Value
	Mean ± SD	Mean ± SD	
Fasting blood sugar (mg/dl)	142.05 ± 17.72	94.10 ± 21.81	<0.001 Hs
Fasting serum insulin µU/L	18.92 ± 3.63	11.91 ± 2.87	<0.001 Hs
HOMA-IR	3.52 ± 0.3	2.67 ± 0.6	<0.001 Hs
HbA1c (%)	5.67 ± 1.02	4.8 ± 0.7	<0.001 Hs
Homocysteine [µmol/L]	8.31 ± 2.02	7.33 ± 3.54	<0.001 Hs

Table 6: Comparison of lipid profile in the studied groups

Parameters	GDM (n=50)	Control (n=50)	p-value
LDL (mg/dL), mean ± SD	70.16 ± 13.46	72.16 ± 14.84	0.48 Ns
HDL (mg/dL), mean ± SD	45.18 ± 10.28	47.10 ± 12.04	0.4 Ns
TG (mg/dL), mean ± SD	97.20 ± 6.29	90.80 ± 14.28	0.004 S
Cholesterol (mg/dL), mean ± SD	150 ± 16.42	153.20 ± 17.24	0.3 Ns

HDL: high density lipoprotein, LDL: low density lipoprotein; TG: triglyceride

Table 7: Comparison of serum B12 level between the studied groups

Parameter	Case (n=50)	Control (n=50)	P Value
	Mean ± SD	Mean ± SD	
Serum B12 (pg/mL)	169.3 ± 13.6	227.5 ± 29.9	<0.001

good correlation (0.712) was found between Homocysteine and B12. No relation between FBS and vit B12.

Table 9 shows significant correlation between Vit B12 and lipid profile (cholesterol, LDL, HDL, and TG) and LDL, HDL, and TG were presented with moderate correlation.

DISCUSSION

Vitamin B12 plays a vital role in the methylation of DNA and metabolism of cells. Activated coenzyme B12 acts as a methyl donor for the methylation developments of DNA and RNA and is also vital for proteins and lipids synthesis.

Table 8: Correlation between Vit B12 and insulin sensitivity/resistance parameters in GDM group

Variables	Vit B12	
	(r)	p-value
Fasting blood sugar (mg/dL)	0.233	0.149
Insulin (IU/ml)	0.432	0.01 S
HOMA-IR	0.457	0.003 S
Homocysteine [mcmol/L]	0.712	<0.001 Hs

FBS: fasting blood sugar; HOMAIR: homeostasis model assessment of insulin resistance.

Table 9: Correlation between Vit B12 with lipid profile in-patient with GDM

Variables	Vit B12	
	(r)	p-value
LDL (mg/dL)	0.382	0.014 S
HDL (mg/dL)	0.342	0.01 S
TG (mg/dL)	0.532	<0.001 HS
Cholesterol (mg/dL)	0.256	0.02 S

HDL: high density lipoprotein, LDL: low density lipoprotein; TG: triglyceride;

Its deficiency may lead to disruption of DNA synthesis, cellular inflammation, and adiposity dysfunction with elevated lipo-genesis and homocysteine levels. It has been proposed that B-vitamins may play crucial role in the pathogenesis of glucose intolerance because of their ability to regulate homocysteine synthesis.^[12] Vitamin B12 deficiency in human adipocytes changes tissue-specific microRNAs (mirRs) and circulating miRs (which are epigenetic modulators) leading to adverse metabolic phenotype and excessive lipid accumulation.^[13] Therefore, pregnant women with vitamin B12 deficiency are more prone to obesity, insulin resistance and, concomitantly, GDM. Regarding current study secondary endpoint, both homocysteine and triglyceride concentrations were higher in women with GDM compared to those with non-GDM which is in agreement with that mentioned by a previous studies carried by (Meigs J *et al*, Kothekar MA, and Taneja S *et al*).^[14,15] In the current study the mean level of serum B12 in GDM patients was (169.3 ± 13.6) (pg/mL) which was significantly lower than that in normal control group (227.5 ± 29.9) (pg/mL) with (P Value <0.001). These finding are in agreement with Similar results of lower vitamin B12 concentrations among pregnant women with diabetes (160.4 ± 32.1) (pg/mL) in comparison with healthy controls (234.5 ± 295.9) (pg/mL) (P-value=0.05), were presented in Seghieri's G *et al*. study in 2003.^[16] However, there are several European studies carried by many authors (Guvén M *et al.*, Idzior-Waluś B *et al.*, and Tarim E *et al.*) which they did not found differences in vitamin B12 concentrations between women with GDM and those in the control groups.^[17,18] This may be attributed to the differences in food habit. The data

of current study are in disagreement with the finding of a study that conducted by Radzicka S, *et al*, as they found that B12 were increased in GDM group than that in normal pregnant group.^[19] The possible explanation is due to the differences in sample size collection in the last study when the difference in the size between both groups of the study (case group was 60 patients and the control was 16 only). Sukumar N *et al*, showing that women with vitamin B12 deficiency were 2.14 (95% CI: 1.11–4.13) at higher risk of GDM development compared with vitamin B12 sufficient pregnant women.^[20] The author also found a link between vitamin B12 deficiency, adiposity and its related disorders and proposed the term “diabetesity” to describe all these together. The possible interpretations of their findings were that B12 deficiency may promote adiposity and that, conversely, adiposity itself may lower B12 concentrations, especially during pregnancy. The proposed mechanisms are the greater hemodilution, increased glomerular filtration rate and urinary losses as well as increased transfer of nutrients to the fetus. In this sense, insulin resistance is promoted as well. The Sukumar N *et al*, study investigating the association between maternal vitamin B12 levels during pregnancy and the risk of GDM was published in 2016.^[20] Chanarin I, *et al*. and Allen LH, *et al*. have reported low B12 values in developing countries in the population in general and in mothers during pregnancy. When maternal B12 status is low during pregnancy.^[21,22] In the current study significant correlation was found between Vit B12 and BMI which is in agreement with that found by Krishnaveni G.V *et al*, who mentioned that B12 inversely associated with maternal BMI.^[10] In the present study we found that women with GDM had, as expected, a higher insulin resistance index HOMA-IR. This remains in agreement with that found by Bartha JL *et al*, when the authors mentioned that women with gestational diabetes had higher insulin resistance, especially those who needed insulin therapy.^[23] In the current study we found there is increase in mean level of homocysteine in case group than that in control but with no significant differences (P value =0.3), but by study the correlation between homocysteine and GDM we found a significant association and moderate correlation in case group than that in control group ($r=0.712$, P Value<0.001). Which is proved by meta-analysis of Gong *et al.*, study who revealed that serum homocysteine concentrations were higher among women with GDM than among the controls and found that the evidence was more consistent among women in the second trimester and for women older than 30 years of age.^[24] The authors Idzior-Walus *et al*. did not observe any difference in homocysteine levels between these two groups. This difference may be attributed to the differences in genetic factors, or different diet in addition to difference in sample size (as the last study with small sample size and no matching were done for both groups).^[25]

CONCLUSION

Highly significant decrease of vit B12 in patients with GDM than that in healthy group, while highly significant increase of Homocysteine and triglyceride in GDM patients than in healthy group.

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Not applicable.

Conflicts of interest

There are no conflicts of interest.

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