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ORIGINAL ARTICLE

Vitamin B_{12} deficiency is linked with dyslipidemia in gestational diabetes mellitus.

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ABSTRACT… Objective: To determine the vitamin B12 deficiency and dyslipidemia in Gestational Diabetes mellitus (GDM) diagnosed pregnant women. **Study Design:** Observational study. **Setting:** Department of Biochemistry and Gynecology/ Obstetrics LUMHS Hospital Jamshoro. **Period:** January 2018 to December 2018. **Material & Methods:** A sample of 216 diagnosed GDM pregnant women was selected according to study criteria. Venous blood samples were centrifuged to separate sera; that were used for the estimation of (hexokinase method), blood lipids and Vitamin B12 (ECLIA assay method) by Cobas chemistry analyzer. Statistical SPSS software 21.0 (IBM, Inc USA) was used for study research variables at 95% CI ($P \leq 0.05$). **Results:** Age of GDM cases was 36.12±9.5 years. Mean+/-SD vitamin B12 level was noted 154.7±81.7 ng/mL (P=0.0001). Serum cholesterol, triglycerides and LDLc were elevated and HDLc was low in GDM cases (P=0.0001). Of 216 GDM cases, vitamin B12 deficiency was present in 152 (70.3%) (P=0.0001) and dyslipidemia in 50 (23.1%) (X^2=452.0) (P=0.0001). Vitamin B12 shows inverse correlation with RBG (r= -0.41, P=0.005), CHOL (r= -0.25, P=0.024), TAG (r= -0.81, P=0.0001), LDLc (r= -0.797, P=0.0001) and positive correlation with HDLc (r= 0.76, P=0.0001). **Conclusion:** The present study finds vitamin B12 deficiency in 152 (70.3%) and dyslipidemia in 50 (23.1%). Vitamin B12 deficient GDM women show high cholesterol, triglycerides, LDLc and low HDLc. Hence, it is concluded, the vitamin B12 deficiency is linked with dyslipidemia in Gestational Diabetes mellitus.

Key words: Blood Glucose, Gestational Diabetes Mellitus, Vitamin B_{12}.

INTRODUCTION

Gestational diabetes mellitus (GDM) is a state of glucose intolerance observed in pregnant women for the first time. GDM is a full blown metabolic disorder of glycosuria, hyperglycemia and hyperlipidemia during pregnancy.[1] Exact prevalence of GDM for developing countries such as Pakistan is seriously lacking because of health registries. It`s suggested prevalence is 1-14% around the Globe. However, the prevalence varies around the Globe due to the different geography, ethnical & racial factors, dietary habits, etc. It is proposed that 7% of all women who conceive may develop glucose intolerance sufficient to make diagnosis of GDM. Annual burden of GDM is proposed as >200,000 cases across the Globe.[2] GDM may put the mother at risk of morbidities beside fetal malformation and macrosomia.[2,3] Urbanized world population is at increased risk of developing GDM due to obesity, dietary habits, and sedentary life style. Normal pregnancy is associated with a change in body hormones; many of them are anti – insulin. Insulin resistance (IR) is common in second and third trimesters of pregnancy. IR beings at 24–28 weeks of gestation and increases progressively. Alteration in glucose and lipid metabolism is noted in GDM women; this accounts for as primary metabolic defect that manifests as insulin resistance, glucose intolerance, hyperglycemia and gestational diabetes mellitus as it worsens.[4,5] Vitamins are vital amines essentially needed for the biochemical reactions of lipid and glucose and there deficiency is associated with faulty levels of both. Vitamin B12 deficiency[5] in pregnancy is linked with glucose intolerance, hyperglycemia, hyperlipidemia and insulin resistance. Vitamin B12 is a key micronutrient of metabolism and its

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deficiency shows altered lipid metabolism and endothelial dysfunction.

Previous studies linked vitamin B12 deficiency with as well as coronary artery disease (CAD), myocardial infarction and cerebral ischemia.[5-7] Microvascular complications such as neuropathy are common in diabetics with B12 deficiency. Low vitamin B12 levels worsen the diabetic neuropathy.[8] This highlights the clinical importance of micronutrients such as vitamin B12 in gestational DM. There is need of regular screening of vitamin B12 and blood lipid patterns in gestational DM that is too much overlooked particularly in the developing countries. Search of national literatures shows none of studies on the topic of vitamin B12 and dyslipidemia in gestational diabetes mellitus.

The present study was conducted to evaluate the vitamin B12 level, blood lipids and dyslipidemia in those suffering from vitamin B12 deficiency in GDM women presenting at our tertiary care hospital.

MATERIAL & METHODS

The present observational study was undertaken after the approval of ethics committee of institute (LUMHS/REC/634). The study took place over duration from Jan 2018 to December 2018 at Department of Gynecology/Obstetrics and Biochemistry Liaquat University of Medical and Health Sciences Hospital Jamshoro/Hyderabad. A sample of 216 (n=216) diagnosed GDM pregnant women were selected through the non-probability purposive technique. The records of pregnant women diagnosed as GDM were reviewed. Women were interviewed to gain confidence for participation and details were taken to fulfill the criteria of study protocol. Diagnosed GDM pregnant women of 2nd and 3rd trimester of 20 – 40 years age, ultrasound shows single fetus, and looking healthy were inclusion criteria. Pregnant women already diagnosed as DM, Post partum female, those suffering from polycystic ovarian syndrome (PCOS), and having family history of DM in first degree relatives were excluded from the study protocol. Physical examination was performed to exclude any major concomitant systemic disease. GDM pregnant women were informed of the purpose of study that the information collected will help them and other pregnant women in future. Study protocol, advantages and disadvantages, harms and benefits were discussed in detail. They were informed as the blood drawing will cause no harm to them and their fetus. They were further informed there will be no monetary expenses. Volunteer women were asked to sign the consent form. Patient handling was in accordance to the "Helsinki`s Declaration" for conducting human research. Confidentiality of patient data was secured by principal researcher.

Volunteers were asked for blood sampling fasting and after meal intake. Venous sampling was performed by venesection of a peripheral vein from the ante – cubital fossa. 5 ml venous blood sample was collected in sodium fluoride tubes. Blood was centrifuged for 14 minutes (at x3000 rpm). Sera were collected, stored and preserved in refrigerators at – 20^{0}C. Sera were used for the detection of blood glucose by hexokinase method; both fasting and random blood glucose levels were measured. Vitamin B12 (cobalamin) was measured by ELISA (Abcam, USA quality) (competitive immuno- assay – Neoplate) commercial kit. Vitamin B12 was estimated according to given protocol in brochure. Vitamin B12 reading was read at 450nm "absorbance". Samples were run on Cobas chemistry analyzer at Postgraduate laboratory. Normal and deficiency values of Vitamin B12 were taken as.[9] While Dyslipidemia was defined as the; cholesterol level (≥200 mg/dL), level of triglycerides (≥150 mg/dL), levels of LDLc (≥ 100 mg/dL) and HDLc (≤ 50 mg/dl) for the female gender.[10] Statistical software SPSS 21.0 version (IBM, Incorp, United States America) was used for statistical analysis of variables such as RBG, FBG, Cholesterol, TAGs, LDLc, HDLc and vitamin B12 by Student`s t-test (output presented as mean+/- SD) and categories of vitamin B12 deficiency and dyslipidemia by Chi- square ($X^2$) test. Correlation of vitamin B12 deficiency and dyslipidemia was analyzed by Pearson`s method. Analysis significance was taken at 95% CI ($P \leq 0.05$).

RESULTS

Age and laboratory findings of GDM women are shown in Table-I. Age of cases was 36.12±9.5 years (P=0.051). Fasting and random blood glucose levels were elevated significantly (P<0.05). Cases show vitamin B12 levels of 154.7±81.7 ng/mL (P=0.0001) (Table-I). Serum cholesterol, triglycerides and LDLc were elevated and HDLc was low in GDM cases (P=0.0001). Of 216 GDM cases, vitamin B12 deficiency was present in 152 (70.3%) (P=0.0001) (Table-II). While dyslipidemia was present in 50 (23.1%) (X^2=452.0 P=0.0001) (Table-III). Table-IV shows the lipid profile in dyslipidemia GDM cases, revealing elevated levels except that of HDLc that was low. Pearson`s correlation output is shown in Table-V. Vitamin B12 shows inverse correlation with RBG (r= -0.41, P=0.005), CHOL (r= -0.25, P=0.024), TAG (r= -0.81, P=0.0001), LDLc (r= -0.797, P=0.0001) and positive correlation with HDLc (r= 0.76, P=0.0001). Scatter plots 1 – 4 show the correlation of lipid fractions and vitamin B12.

	Cases (n=216)			P-Value
	Mean	SD	SEM	
Age	36.12	9.5	0.64	0.051
FBG (mg/dl)	147.93	55.5	3.77	0.001
RBG (mg/dl)	242.31	71.3	4.85	0.003
Cholesterol (mg/dl)	244.15	49.4	3.36	0.0001
Triglycerides (mg/dl)	702.56	249.9	17.06	0.0001
LDLc (mg/dl)	137.68	41.2	2.80	0.0001
HDLc (mg/dl)	32.96	5.45	0.37	0.0001
Vitamin B_{12} (ng/mL)	154.74	81.7	5.54	0.0001

Table-I. Age and Laboratory findings in GDM cases. (n=216)

GDM – gestational diabetes mellitus

	Cases (n=216)		X^2-Value	P-Value
	No.	%		
Yes	152	70.3	87.00	0.0001
No	64	29.6		
Total	216	100		

Table-II. Vitamin B12 deficiency in GDM cases. (n=216)

GDM – gestational diabetes mellitus

	Cases (n=216)		X^2-Value	P-Value
	No.	%		
Yes	50	23.1	452.00	0.0001
No	166	76.8		
Total	216	100		

Table-III. Dyslipidemia in GDM cases. (n=216)

GDM – gestational diabetes mellitus

	Mean	SD	95% CI for Mean		Min.	Max.
			L. Bound	U. Bound		
Cholesterol	209.5	51.3	131.39	219.5	167.00	278.0
Triglycerides	245.7	67.5	157.54	255.7	187.00	261.0
LDLc	165.4	37.8	136.69	174.4	97.00	261.0
HDLc	21.71	8.01	17.9.9	33.73	21.00	33.7

Table-IV. Lipids Profile in dyslipidemic GDM cases. (n=216)

GDM – gestational diabetes mellitus

Fasting blood glucose	r-value*	0.127
	P-value**	0.06
Random blood glucose	r-value*	-0.41
	P-value**	0.005
Cholesterol	r-value*	-0.25
	P-value**	0.024
Triglycerides	r-value*	-0.81
	P-value**	0.0001
LDL cholesterol	r-value*	-0.797
	P-value**	0.0001
HDL cholesterol	r-value*	0.76
	P-value**	0.0001

Table-V. Pearson's correlation of Vitamin B_{12} and study variables.

†. Correlation calculated at 0.05 level,
*. r-value - Correlation co-efficient
**. P-value - Statistical significance

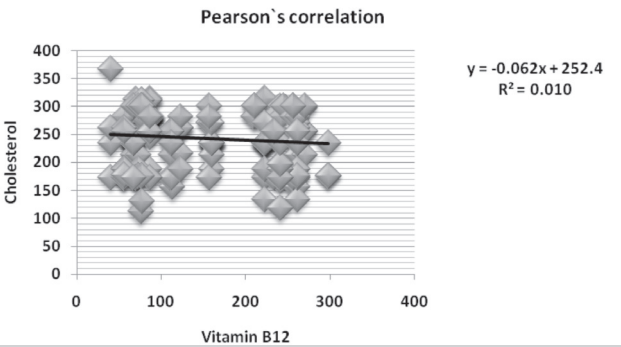

Figure-1. Scatter plot distribution shows inverse correlation (r= - 0.25, P=0.024) of cholesterol and vitamin B_{12}

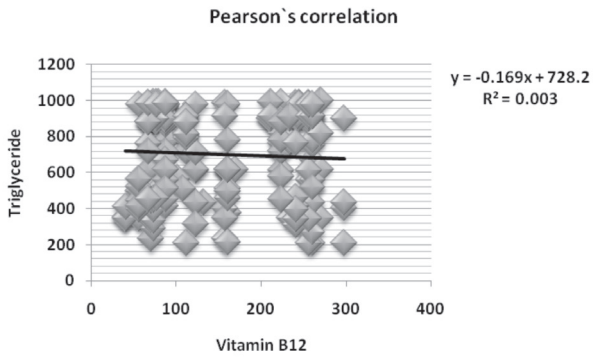

Figure-2. Scatter plot distribution shows inverse correlation (r= - 0.25, P=0.024) of triglycerides and vitamin B_{12}

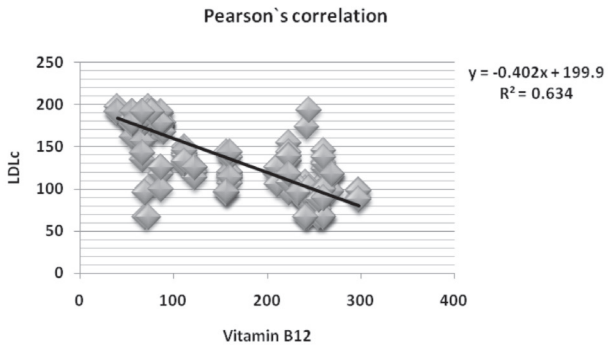

Figure-3. Scatter plot distribution shows inverse correlation (r= - 0.797 P=0.0001) of LDLc and vitamin B_{12}

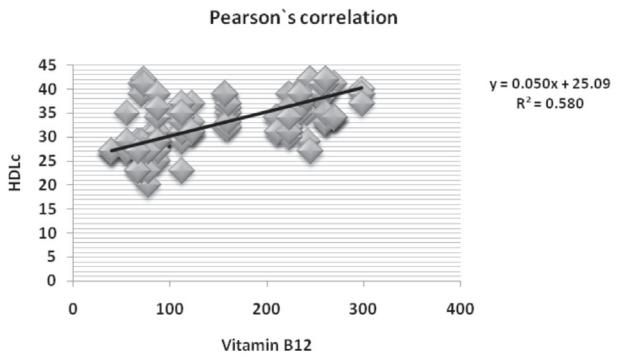

Figure-4. Scatter plot distribution shows inverse correlation (r= 0.76, P=0.0001) of HDLc and vitamin B_{12}

DISCUSSION

The present study is first cross sectional study probing into the problem of dyslipidemia in those GDM women suffering from vitamin B12 deficiency. Of 216 GDM cases, vitamin B12 deficiency was present in 152 (70.3%) (P=0.0001). While dyslipidemia was present in 50 (23.1%) (X^2=452.0 P=0.0001). Vitamin B12 deficiency is common in the general population of developing countries of Asia.[11,12] Vitamin B12 deficiency remains asymptomatic until complications manifest clinically.[13] Dyslipidemia caused by Vitamin B12 deficiency in GDM is a notorious findings as it is pro – atherogenic state. The findings are in keeping with previous studies.[14,15] Vitamin B12 deficiency in pregnant women with GDM is in line with a previous study.[16] Insulin resistance, adiposity and dyslipidemia has been reported in vitamin B12 deficient in pregnant women.[16] The findings are in keeping with the observations of present study. Hyperlipidemia and dyslipidemia associated with insulin resistance, glucose intolerance and hyperglycemia have been linked with vitamin B12 deficiency.[17]

Previous studies[17,18] reported linkage of vitamin B12 deficiency with coronary artery atherosclerosis, myocardial ischemia and infarction and the cerebral ischemia. The finding of vitamin B12 linked with dyslipidemia is consistent with Kaya et al.[19] The Kaya et al reported linkage of insulin resistance, glucose intolerance, obesity and dyslipidemia with vitamin B12 deficiency in polycystic ovary syndrome. Both animal[20] and human[21,22] studies have reported vitamin B12 deficiency is directly linked with altered blood lipid profile, dyslipidemia and metabolic disorder including glucose intolerance. A recent study conducted with type 2 diabetics including Indians and Europeans reported vitamin B12 deficiency was associated with severe dyslipidemia.[5] A previous animal study was the first that traced the evidence of vitamin B12 deficiency produced dyslipidemia in a Wistar rats model (in- vivo).[20] It was demonstrated vitamin B12 deficient Wistar rat mothers gave birth to offspring with adiposity, dyslipidemia, hyper cholesterolemia and triglycerides, IL-6 and TNF-α. They reported that the dyslipidemia was observed in both mothers and offspring.[20]

In present study, the vitamin B12 deficiency shows inverse correlation with RBG (r= -0.41, P=0.005), CHOL (r= -0.25, P=0.024), TAG (r= -0.81, P=0.0001), LDLc (r= -0.797, P=0.0001) & positive correlation with HDLc (r= 0.76,

P=0.0001). These findings are in agreement with previous studies.[5,13,23] Antonysunil et al[5] reported vitamin B12 deficiency was inversely correlated with cholesterol, triglycerides and cholesterol/ HDL ratio in type 2 diabetic subjects. The findings of above study are consistent with the present study. Previous studies from India[24] and Polish patients[25] had reported similar observations of inverse correlation of vitamin B12 deficiency and lipid fractions. Vitamin B12 functions as co – enzyme for the conversion of MM – CoA (methylmalonyl- CoA) to S – CoA (succinyl-CoA).[26] Accumulation of MM-CoA inhibits the CPT1 (carnitine palmitoyl transferase-1)[27] that lead to the lipogenesis resulting in elevated blood lipids; is consistent to the present study.

Vitamin B12 deficiency is linked to hyper – homocysteinemia[28] and dysregulation of cholesterol synthesis. This provides the pathogenic mechanism of how vitamin B12 deficiency is linked to the insulin resistance, glucose intolerance, obesity, type 2 DM and GDM.[29,23] These findings are in agreement with the present study. Antonysunil et al[23] reported vitamin B12 deficiency was associated with elevated total cholesterol, triglycerides, adiposity and increased de novo cholesterol biosynthesis. Finding of low HDLc of present study is supported by previous study of Chung et al[29] that reported similar finding was due to the deletion of cholesterol transporter ABCA1 in adipose tissue. A previous clinical study[30] study reported vitamin B12 deficiency in early pregnancy was independent risk factor of GDM and for T2DM at 5-years of delivery. The findings of present study are worth to report as currently there are no studies on the topic of vitamin B12 and dyslipidemia and no guidelines advocate for vitamin B12 screening. The present study warrants updating the World literature of GDM management in particular the vitamin deficiencies are concerned.

CONCLUSION

The present study reports vitamin B12 deficiency in 152 (70.3%) and dyslipidemia in 50 (23.1%). Vitamin B12 deficient Gestational Diabetes mellitus patients show high cholesterol, triglycerides, LDLc and low HDLc. Hence, it is concluded, the vitamin B12 deficiency is linked with dyslipidemia in Gestational Diabetes mellitus. Further studies are recommended and vitamin B12 screening should be advocated in the GDM pregnant women for fetal and maternal wellbeing.

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2	Sabreena Abbas Khokhar	Pt selection, data collection, manuscript writing.	
3	Fouzia Shaikh	Manuscript write, Proof reading.	