Association of Insulin Resistance with Dyslipidemia in Gestational Diabetes Mellitus

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Abstract

Background: Gestational Diabetes Mellitus is the most common metabolic condition during pregnancy. Insulin resistance is a known risk factor for development of GDM. Women with Gestational Diabetes Mellitus are at increased risk for developing dyslipidemia. The aim of this study was to evaluate the occurrence of Dyslipidemia among women with GDM.

Materials and methods: This cross-sectional comparative study was conducted in Obstetrics and Gynecology Department, Chittagong Medical College Hospital. 100 patients were taken by non-probability convenience sampling where 70 women with GDM were taken as cases and 30 normal pregnant women as controls.

Results: GDM cases presented significantly higher mean HOMA-IR values and increased serum TC, TG, LDL-C and decreased HDL than those of controls. So from this point of view GDM cases had both insulin resistance and dyslipidemia. GDM patients with Insulin resistance had significantly higher Triglyceride level and decreased serum HDL-C level when compared to non-insulin resistance state of the same. This study revealed significant association of insulin resistance with dyslipidemia (Increased TG and decreased HDL-C, $p<0.01$) in GDM.

Conclusion: Insulin resistance was significantly associated with dyslipidemia in GDM. Soestimation of fasting lipid profile and fasting insulin in women with GDM may provide baseline information in course of planning and management of GDM patients.

Key words: Dyslipidemia; Gestational diabetes Mellitus; Insulin resistance.

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Introduction

Gestational Diabetes Mellitus (GDM) is defined as abnormal glucose tolerance firstly discovered during pregnancy, is the most common metabolic disease during pregnancy and the global prevalence of GDM have been steadily increasing, ranging from 1% to 28%.[1-2]

According to IADPSG criteria, GDM should be diagnosed at any time in pregnancy if one or more of the following criteria are met or exceeded:

1. Fasting plasma glucose ≥ 92 mg/dl (≥ 5.1 mmol/l)
2. 1-hourplasma glucose ≥ 180 mg/dl (≥ 10 mmol/l), following a 75g of oral glucose load
3. 2-hourplasma glucose 153mg/dl (≥ 8.5 mmol/l) following a 75g of oral glucose load.[3]

Maternal dyslipidemia is a common phenomenon during pregnancy.[4]Especially, hyperlipidemia is commonly discovered in the 2nd half of pregnancy.[5] The lipid level increases slightly in early pregnancy, but it significantly increases in later pregnancy.[6]

During the first two-thirds of gestation, hyperphagia, increased lipid synthesis and fat accumulation occurs.[7,8] Followed by a decrease in fat storage in the last third of gestation, due to enhanced lipolytic activity and decreased lipoprotein lipase activity in the adipose tissuethat causes hyperlipidaemia, mainly marked by elevated triglyceride levels.[9,10,11]

Diagnostic criteria of dyslipidemia using TC, LDL-C, TG and HDL according Fahraeus et al. [12]

Variable	Late pregnancy
Total cholesterol (mg/dl)	>250
LDL (mg/dl)	>150
HDL (mg/dl)	<65
Triglycerides (mg/dl)	>210

Physiological insulin resistance occurs in all pregnancies beginning around 24–28 weeks of gestation and progressing through the third trimester.[13] In women with GDM, the physiological changes in insulin and lipids are exaggerated and may cause underlying metabolic dysfunction.[14]

Among various indices for measurement of insulin resistance, the Homeostasis Model Assessment (HOMA) model is widely used in research because of its simplicity, an inexpensive and reliable measure of IR.[15]In this study, Insulin resistance was calculated by using the equations of original HOMA model described by Matthews et al.[16]

HOMA-IR = Fasting insulin (μIU/ml) × Fasting glucose (mmol/ml) / 22.5.

The cutoff point was used for defining IR corresponded with a HOMA-IR of 2.6.[17]

GDM can cause many consequences, such as fetal macrosomia, preeclampsia and high cesarean delivery, and so on.[18,19] In addition, both women with GDM and their offspring experience a greater risk of obesity, type 2 diabetes and many cardiovascular disorders in the future.[20]

GDM complicated with dyslipidemia causes an increased production of oxidisable particles and inoxidative damage.These effects may be related to long-term cardiovascular risk and metabolic syndrome in the future.[21]

Thus, considering the importance of maternal and fetal complications during/after pregnancy, the aim of thisstudy was to evaluate the presence of dyslipidemia in women with GDM and to find out whether abnormal lipid levels are consistently associated with insulin resistance in GDM.

Materials and methods

This cross sectional comparative study was conducted on100 pregnant women in 3rd trimester selected from outpatient Department of Obstetrics and Gynecology, Chittagong Medical College Hospital during July 2020 to June 2021.

Permission for this study was taken from concerned Departments and Ethical Review Committee of Chittagong Medical College, Chattogram. (Memo No. CMC/PG/2020/664; Date:22/11/2020) Sampling method was non-probability convenience sampling.

Inclusion criteria:

- Group-A: Women with GDM in 3rd trimester.
- Group- B:Normal pregnant women in 3rd trimester.

Exclusion criteria:

- Multiple pregnancies, type 1 or type 2 diabetes mellitus before pregnancy, pregnancy with hypothyroidism, H/O alcohol consumption, corticosteroid therapy.
- Important variables in this study were fasting lipid profile, fasting plasma glucose, fasting serum insulin and HOMA-IR index.

Serum insulin concentration was measured by ADVIA Centaur XP systems. Fasting plasma glucose and lipid profile were estimated by enzymatic method in an automated analyzer (Siemens Dimension clinical chemistry system). Insulin resistance index was determined by HOMA-IR. All the data were processed and analyzed using computer-based statistical software. Confidence level was fixed at 95% and P values <0.05 were considered to be statistically significant.Quantitative data (Fasting Lipid profile, Fasting plasma insulin, Fasting plasma glucose, HOMA-IR Index, Pre-pregnancy BMI, Blood pressure) were expressed as mean ± Standard Error of Means (SEM). Different tests of significance were done as appropriate.

Results

Table I Distribution of numerical variables among the study groups (n = 100)

	Study Groups	N	Mean ± SEM		Range	p Value
Age (Years)	Group A	70	25.60	0.54	18 – 37	p < 0.01
	Group B	30	22.90	0.67	18 – 33	Highly
	TOTAL	100	24.79	0.44	18 – 37	Significant
Pre-pregnancy BMI	Group A	70	23.92	0.32	16.66 – 31.24	p > 0.05
(Kg/m^2)	Group B	30	22.72	0.78	15.07 – 34.44	Not
	TOTAL	100	23.56	0.33	15.07 – 34.44	Significant

Table I shows that mean age was significantly higher in cases than those of controls (25.60 vs 22.90 years) Mean pre-pregnancy BMI was slightly higher in cases than those of controls (23.92 vs 22.72 kg/m2) but it was notstatistically significant difference (p > 0.05).

Table II Distribution of party, proteinuria and BP status among the study groups (n = 100)

		Study Groups			
		Group A (n = 70)	Group B (n = 30)	Total (n = 100)	p Value
Parity	Primigravida	30 (42.9%)	23 (76.7%)	53 (53.0%)	p < 0.001
	Multigravida	40 (57.1%)	7 (23.3%)	47 (47.0%)	Highly Significant
Proteinuria	Positive	45 (64.3%)	6 (20.0%)	51 (51.0%)	p < 0.01
	Negative	25 (35.7%)	24 (80.0%)	49 (49.0%)	Highly Significant
BP Status	Hypertensive	23 (32.86%)	4 (13.3%)	27 (27%)	p < 0.05
	Normotensive	47 (67.14%)	26 (86.7%)	73 (73%)	Significant

Table II shows that multigravida, Proteinuria and Hypertension were significantly associated with cases (57.1%, 64.3%, 32.86%) than those of controls (23.3%, 20.0%, 13.3%).

Table III Association between history of abortion and multiparity among the study groups (n = 47)

Past History of Abortion	Study Groups Group A (n = 40)	Group B (n = 7)	Total (n = 47)	p Value
Present	26 (65.0%)	1 (14.3%)	27 (57.4%)	p < 0.05 Significant
Absent	14 (35.0%)	6 (85.7%)	20 (42.6%)	

Table III shows that history of abortion was significantly associated with multiparus women in GDM (65%, n=26) than that of non-GDM female (14.3%, n =1).

Table IV Distribution of serum fasting lipid profiles and diabetic profiles among the study groups(n = 100)

	Study Groups	n	Mean	± SEM	Range	p Value
Serum Total Cholesterol (mg/dl)	Group A	70	195.16	4.92	121 – 306	p < 0.01
	Group B	30	167.73	5.42	123 – 230	Highly
	TOTAL	100	186.93	4.00	121 – 306	Significant
Serum Triglyceride (mg/dl)	Group A	70	229.51	7.61	110 – 412	p < 0.001
	Group B	30	163.03	6.84	118 – 265	Highly
	TOTAL	100	209.57	6.46	110 – 412	Significant
Serum LDL (mg/dl)	Group A	70	115.19	3.92	65 – 200	p < 0.01
	Group B	30	92.63	4.09	54 – 149	Highly
	TOTAL	100	108.42	3.17	54 – 200	Significant
Serum HDL (mg/dl)	Group A	70	42.64	1.10	31 – 72	p < 0.001
	Group B	30	53.23	2.55	37 – 72	Highly
	TOTAL	100	45.82	1.14	31 – 72	Significant
Fasting serum Insulin (mIU/L)	Group A	70	19.18	0.84	2.62 – 35.01	p < 0.001
	Group B	30	10.57	0.65	4.13 – 18.55	Highly
	TOTAL	100	16.60	0.73	2.62 – 35.01	Significant
HOMO-IR	Group A	70	5.52	0.41	0.61-19.11	p < 0.001
	Group B	30	2.21	0.14	0.87-4.04	Highly
	TOTAL	100	4.53	0.33	0.61 – 19.11	Significant

Table IV shows that mean serum Total Cholesterol level (TC) serum Triglyceride level (TG) serum LDL-C level, serum insulin and HOMO-IR were significantly higher and serum HDL-C level was significantly decreased in cases than those of controls.

Table V Association between insulin resistance status and serum lipid profile status among the GDM cases (n = 70)

Lipid Profiles	Insulin Resistance Status	Present (n = 60)	Absent (n = 10)	Total (n = 70)	p Value
Serum TC Status	Increased	6 (10.0)	0 (0.0)	6 (8.6)	p > 0.05
	Normal	54 (90.0)	10 (100.0)	64 (91.4)	Not Significant
Serum TG Status	Increased	42 (70.0)	2 (20.0)	44 (62.9)	p < 0.01
	Normal	18 (30.0)	8 (80.0)	26 (37.1)	Highly Significant
Serum LDL Status	Increased	13 (21.7)	2 (20.0)	15 (21.4)	p > 0.05
	Normal	47 (78.3)	8 (80.0)	55 (78.6)	Not Significant
Serum HDL Status	Decreased	57 (95.0)	7 (70.0)	64 (91.4)	p < 0.01
	Normal	3 (5.0)	3 (30.0)	6 (8.6)	Highly Significant

● Figures within parentheses indicate percentages.

Table V shows that in GDM Cases, Insulin resistance were significantly associated with increased serum TG and decreased serum HDL-C. (p<0.01) and there was no significant association of Insulin resistance with serum TC and serum LDL-C (p >0.05).

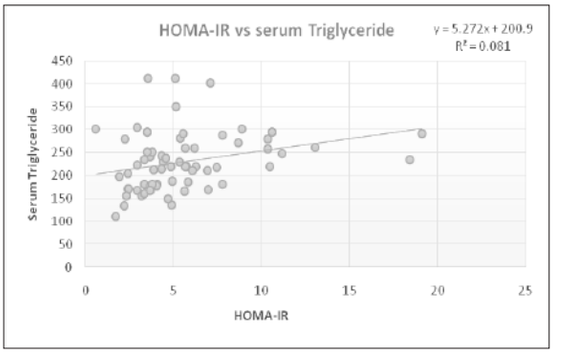

Figure 1 Scatter diagram showing statistically significant positive correlation between HOMA-IR and serum Triglyceride among the GDM cases (r= +0.290 p < 0.05, n = 70)

In summary, GDM cases had significant increased fasting insulin level and insulin resistance, TC, TG, LDL-C and decreased HDL than those of controls. [Table IV]. So from this point of view GDM cases had both insulin resistance and dyslipidemia. GDM patients with insulin resistance had significant dyslipidemia (Increased TG and decreased HDL) when compared with non-insulin resistance state of the same. [Table V]. The overall observation is that there is significant association of insulin resistance with dyslipidemia in Gestational Diabetes Mellitus.In this study design GDM occurs in elderly multigravida and was also associated with occurrence of abortion, hypertension and proteinuria. [Table I, II, III]. So TG/HDL ratio in third trimester may direct an index towards the risk of GDM and its complications.

Discussion

In the present study, GDM cases presented significantly higher mean fasting serum insulin level than those of controls (19.18 vs 10.57 mIU/L). They also showed significantly higher mean HOMA-IR values relative to those in controls (5.52 vs 2.21 14, p <0.001). These observations are in line that GDM is associated with hyperinsulinemia and insulin resistance and Chi square test supported the findings which are similar to previous results.[22,26]

Regarding the difference of observation of lipids between GDM and non-GDM women, Savvidou et al. found that women who developed GDM had higher TG, TC, LDL-C levels and lower levels of HDL-C compared to non-GDM group.[23,24] Similar findings were also observed here.

Ryckman KK, Wang Jet al found that GDM patients with insulin resistance had significant increased TG and decreased HDL –C when compared with non-insulin resistance state of the same.[13,6] Similar findings were also observed here. In this study, Insulin resistance were significantly associated with increased serum TG and decreased serum HDL-C, ($p<0.01$) and there was no significant association of Insulin resistance with serum TC and serum LDL-C, ($p >0.05$). Positive significant correlation was found between HOMA-IR and serum TG ($r=0.290$, $p <0.05$) in GDM. This study was consistent with those of other studies.[6, 25]

Ottanelli S, Napoli A, Festa C, et al demonstrated that Hyperinsulinemia and insulin resistance in GDM predispose to the development or worsening of high blood pressure and the development and progression of pre-eclampsia.It is recognized as a risk factor for cardiovascular disease and stroke, future diabetes and dyslipidemia.[27] Similarly, in this study GDM cases had significant Hypertension (32.86%, n = 23) than those of non-GDM women (13.3%, n = 4).In this study GDM cases showed significant proteinuria (64.3%, n = 45) than those of non-GDM women (20%, n = 6).Rawal S et al also demonstrated that proteinuria of late pregnancy is exaggerated in women with gestational diabetes.Itmay be associated with an increased risk of chronic kidney disease.[28]

A history of abortion was significantly associated with multiparus women in GDM in this study. This study was consistent with those of other studies.[29] Hod Met al demonstrated that the presence of hyperglycemia during organogenesis increases the risk of spontaneous abortion and it may increase the risk ofcongenital malformation.[30]

Wang J, Njete H, Lenge I et al reported that GDM was significantly associated with age ≥25 years, multigravida, and pre-pregnancy obesity (BMI of 27.5 or more).[6, 31] In this study, GDM was significantly associated with advance maternal age and multigravida but not associated with pre-pregnancy BMI.Mean pre-pregnancy BMI were slightly higher in cases than those of controls (23.92 vs 22.72 kg/m2), but it was not statistically significantly higher ($p > 0.05$). This may be due to either smaller sample size or geographic distribution of the sample.

This overall discussion informs about the pathophysiology of insulin resistance in GDM along with presence ofdyslipidemia. Low HDL-C levels and Hypertriglyceridemia are two important metabolic abnormalities associated with insulin resistance.[32,33] The TG/ HDL-C ratio was considered as an atherogenic index as cited by Khosrowbeygi A et al.[34]

So information regarding dyslipidemia may be appropriate for further research for the development of guidelines in GDM patients.

Limitations

The present study had certain limitations. The purposive method of sampling and relatively small size can be mentioned as examples. Besides, cross-sectional study is observational and causality cannot be inferred.

Conclusion

From this study, it can be concluded that hyperinsulinemia and insulin resistance were significantly associated with dyslipidemia in GDM. In the coming years, this alteration will lead to increases incidence of metabolic syndrome in GDM female. Hence, further cohort studies are needed to clarify these facts because early detection and treatment of insulin resistance in GDM female might slow down the progression of dyslipidemia and reduce the risk of further complications.

Recommendations

- Similar study with large sample size and of longer study duration are required.
- All pregnant women, irrespective of their clinical risk status, should be screened for GDM and all women with GDM, should be screened for dyslipidemia.
- Community based interventions should be aimed to convey awareness to follow a healthy lifestyle, promote healthy food alternatives and increase in physical activity.

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Contribution of authors
HH-Conception, design, acquisition of data, manuscript writing and final approval.
MHI- Design, critical revision and final approval.
MH- Interpretation of data, critical revision and final approval.
RK-Analysis, interpretation of data, manuscript writing and final approval.
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Disclosure
All the authors declared no conflict of interest.

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