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Evaluation of Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Atherogenic Indices in Gestational Diabetes Mellitus

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Authors' contributions

The whole process was under supervision and guidance of authors AA and MJ. They also revised the final version of the manuscript. Author SR gathered patients information and data record. Author PK completed the manuscript drafting and finalized the manuscript. Author SM performed the statistical analysis. All the authors read and approved the final version before submission.

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ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) is a common complication in pregnancy. Triglyceride (TG) to high-density-lipoprotein-cholesterol (HDL-c) ratio is an indicator of insulin resistance.
Methods: Controversial findings of recent studies suggest that ethnicity and other possible factors may affect risk of developing GDM. In this study, 130 pregnant women of 18 to 35 years old were recruited. Demographic data as well as gestational age at the time of the test and blood glucose levels before and after oral glucose tolerance test were obtained from all subjects. TG/HDL-C ratios were significantly higher in women with GDM compared to controls.
Results: The difference of mean levels of non-HDL-c and total-cholesterol was not statistically

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significant between cases and controls. The optimal cut off point for TG/HDL-C and GDM was 2.66 with sensitivity and specificity of 86.2% and 52.3%, respectively with positive and negative predictive values of 64.4% and 79.1%, respectively.

Conclusion: Our findings indicated that GDM can affect lipid profiles and lipoprotein metabolisms, of which, a contentious finding was lower LDL-c in women with GDM. The optimal cutoff point for predicting GDM was remarkably different from the values presented in earlier studies. It is suggested that a high TG/HDL ratio is independent of the role of family history.

Keywords: Gestational diabetes mellitus; triglyceride; high-density lipoprotein cholesterol; pregnancy; lipid profile.

1. INTRODUCTION

One of the most common complications of pregnancy is Gestational diabetes mellitus (GDM) which is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. Recent studies have shown that GDM's prevalence is increasing worldwide [2,3].

Physiologic insulin resistance starts from 24 to 28 weeks of pregnancy and progresses through the third trimester. Moreover, maternal lipid metabolism alters modestly in early pregnancy, and significant elevations of lipids, especially triglycerides, will happen later during pregnancy [4]. Women with GDM have endothelial disturbances and plasma lipid changes and they have risk for preeclampsia [5].

Triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio is an indicator of insulin resistance, as hypertriglyceridemia and low HDL-C levels are associated with insulin resistance states [6]. From the 12th week of pregnancy, lipid parameters, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and phospholipid gradually increase, especially in the second and third trimesters. Previous researches have indicated that pregnancy-induced Triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio contributes to an increased prevalence of GDM and preeclampsia. At all gestational stages, high TG/HDL ratios were associated with a raised risk for gestational impaired glucose tolerance (GIGT) and GDM [4-6]. A recent study have shown that ratios more than 2.5 in non-pregnant women and 3.5 in men (among the European population) provide useful cut off points to identify individuals who are insulin resistant and thus, at increased cardio-metabolic risk [7]. Another study suggests that optimal cut off point of TG/HDL-C ratio to predict GDM is 1.12 in Chinese pregnant women [8]. However, a recent study showed that a ratio of 3.68 among Iranian non-pregnant women is an appropriate cut off point for individuals who are insulin resistant and thus at increased cardio-metabolic risk [9].

To our knowledge, TG/HDL-C ratios and lipid profiles have not been studied in Iranian pregnant women yet and this is the first study in Iran, a part of the Middle East. Controversial findings of mentioned studies suggest that ethnicity and other possible factors may affect risk of developing GDM.

2. MATERIALS AND METHODS

2.1 Study Design and Subjects

In this case-control study, pregnant women were recruited at the time of antepartum screening for GDM. Ethnically Iranian women with a singleton pregnancy and a live delivery between October 1st 2015 and April 4th 2016 were included in the study. Sample size of 65 subjects in each group was determined in order to achieve 80% power, therefore, 130 non-relative pregnant women were included, of whom 65 had GDM diagnosed between 24th and 28th weeks of gestation (Case group) and 65 didn't have GDM (Control group).

Pregnant women of 18 to 35 years old were included in the study. Study exclusion criteria were as follows: Diagnosed type 1 or type 2 diabetes mellitus; hyperlipidemia, hypertension, cardiovascular diseases or metabolic syndrome before pregnancy, history of severe systemic disease such as liver cirrhosis, chronic renal failure, severe anemia or immune disorders, and untreated endocrinopathies (e.g. hyperadrenalism, hypoadrenalism, hyperthyroidism or hypothyroidism).

2.2 Measurements

The following data were obtained from all subjects in both case and control groups: Age,

family history, ante-partum weight (self-reported or any measured weights up to one year prior to the pregnancy), height and weight at the time of data collection, gestational age at the time of OGTT and blood glucose levels before and after OGTT.

BMI was calculated as weight in kilograms divided by height in meter squared.

According to the criteria established by American Diabetes Association [1] GDM was diagnosed when any of the following plasma glucose values were met or exceeded during a 75 grams, 2-hours oral glucose tolerance test (OGTT) at 24^{th} to 28^{th} weeks of gestation: fasting glucose level of 92 mg/dL, glucose level 1 hour after glucose ingestion of 180 mg/dL and glucose level 2 hours after glucose ingestion of 153 mg/dL.

For the biochemical analysis, blood samples were drawn from subjects after 12 hours overnight fasting for measuring lipid profiles and fasting blood sugar; these blood samples were obtained from an antecubital vein between 08:00 AM and 09:00 AM. Venous blood samples were again collected one hour and two hours after ingesting 75 grams of glucose. Blood glucose levels and other biochemical data including lipid profile parameters measured with standard enzymatic procedures on an automatic chemistry analyzer (Abbott Aeroset, Chicago, IL, USA).

Since atherogenic index of plasma (log10 TG/HDL-C) and Cholesterol/HDL ratios are good factors to predict risk of developing GDM [10], they were calculated in this study.

2.3 Data analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Values were expressed as mean ± standard deviation. Comparisons were performed via independent t-test for normally distributed variables and Mann–Whitney test for non-normally distributed variables. The correlation coefficient models were used to evaluate the association between triglyceride to high-density lipoprotein cholesterol ratios with BMI and age. A Receiver Operating Characteristic (ROC) curve was constructed and the area under the curve was calculated. Sensitivity and specificity were obtained based on optimal cut-off point. A level of $P< 0.05$ was considered as statistically significant. Analysis of the data was carried out using SPSS 23.0 (SPSS Inc., Chicago, IL, USA).

2.4 Ethics Statement

The study was approved by the research ethical committee of Zanjan University of Medical Sciences. The study was conducted in line with Helsinki declaration and was performed in accordance with considerations recommended by local ethics review committee of Zanjan University of Medical Sciences. Prior to inclusion, all subjects were informed about the details of study and after taking careful considerations, they gave written informed consent.

2.5 Findings

TG/HDL-C ratios were significantly higher in women with GDM compared to controls ($P < 0.0001$, Table 1). Moreover, among the women of GDM group, TG/HDL-C ratios were not significantly higher in subjects with positive family history compared to those without such history ($P =0.43$). There was no statistically significant correlation coefficient of TG/HDL ratios with age ($P =0.395$, $r =-0.11$) or BMI ($P=0.545$, $r =0.076$). The mean level of LDL was significantly lower in the GDM group, compared to subjects in the control group ($P <0.001$). The difference of mean levels of non-HDL cholesterol and total-cholesterol was not statistically significant between cases and controls. ($P =0.759$ and $P = 0.239$, respectively).

Atherogenic indices of Log10 TG/HDL ratios and Chol/HDL ratios, were detected significantly higher in the GDM group compared to the control group ($P < 0.0001$ and P= 0•008, respectively); however, LDL/HDL ratio was not significantly different between the two groups (P=0•881). HDL/VLDL ratios were found to be lower in cases compared to controls ($P <0.0001$). The relationship between the TG/HDL ratio and positive family history of diabetes mellitus were not significantly different between the two groups (Table 2).

ROC curve was generated to determine sensitivity and specificity of each of the earlier mentioned factors, in detecting the risk of GDM. The area under ROC curve was 0.771 (95% CI, 0.690–0.852). The optimal cut off value proposed by the ROC analysis for TG/HDL-C and GDM was 2.66 with sensitivity and specificity of 86.2% and 52.3%, respectively. The positive and negative predictive values of TG/HDL-C at cut-off point of 2.66 were 64.4% and 79.1%, respectively (Fig. 1). Multiple logistic regression analyses for the risk of GDM and TG/HDL ratios and BMI were performed (Table 3).

Table 1. Comparison of lipid profiles between GDM group and control subjects

Variables	Control Subjects n=65 (Mean ±SD)	GDM Group n=65 (Mean ±SD)	P-Value
TG(mg/dl)	177±27.8	220±81.4	<0.0001
Cho(mg/dl)	207±42.6	197±52.4	0.239
HDL (mg/dl)	68.2±19.5	55.9±11.5	<0.0001
LDL(mg/dl)	124±35.0	103. ±34.3	0.001
TG/HDL	2.7±0.7	4.1±2	<0.0001
Non HDL	139.1±38.8	141.5±49.5	0.759
VLDL (mg/dl)	35.4±5.5	44.1±16.2	0.0001
LDL/HDL	1.9±0.5	108±0.6	0.881
HDL/VLDL	1.9±0.5	1.4±0.4	0.0001
Cho/HDL	3.1±0.7	3.6±1	0.008
LogTG/HDL	0.42±0.1	0.58±0.1	0.0001
FBS(mg/dl)	75.6±8.5	93.4±12.4	0.0001
BS(1hour)	126.6±22	186±24.6	0.0001
BS (2hour)	116.5±25.2	174±33.6	0.000
Hb A1c %	5.5±0.7	4.8±0.3	<0.0001

Table 2. Comparing the mean TG / HDL ratios based on family history of diabetes

GDM group without a family history		GDM group with a family history of diabetes	
Variables	**(Mean±SD)**	**(Mean ±SD)**	**P-Value**
TG/HDL ratios	4.2±2.2	3.7±.2	0.43

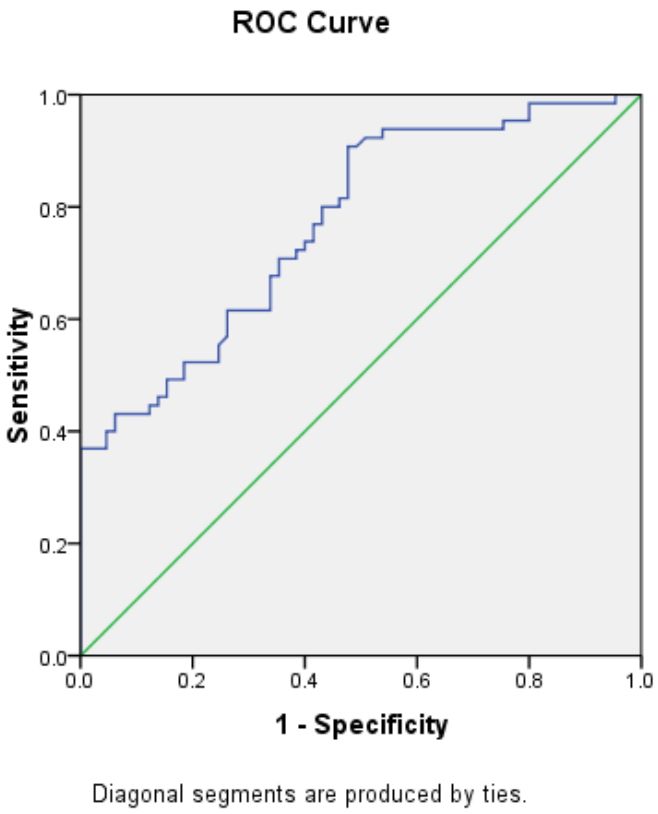

Fig. 1. ROC curve showing the ability of TG/HDL-C ratio for detecting GDM

Table 3. Multiple logistic regression analysis for the risk of GDM

Variables	Standard error	P Value	Odds Ratio	CI 95%	
				Lower	Upper
TG/HDL Ratio	0.307	<0.0001	4.022	2.202	7.346
BMI(Kg/m2)	0.057	0.012	1.156	1.033	1.294

3. DISCUSSION

In the current study, total-cholesterol levels in women with GDM were slightly lower than controls but this difference was not significant (p=0.239), but the LDL serum levels were significantly different between the two groups, as it was found to be lower in the subjects with GDM. TG and HDL levels between the two groups were statistically different, as significantly higher TG and lower HDL serum levels were found in the case group (P value < 0.0001 for both variables).

Other researchers such as Ryckman et al. [11] have shown that most of women with GDM have total-cholesterol and LDL-C levels similar to women who do not have GDM; although in our study LDL-C levels were found to be significantly different between cases and controls (p < 0•0001). In our study, mean total-cholesterol level was lower in the GDM group compared to those in the control group, however this difference was not statistically significant (p=0.239).

Although many studies suggest that women with GDM have increased levels of LDL-C and total-cholesterol [11], these findings are generally controversial and we have found contradicting results. These differences may be due to ethnical and epidemiological differences of examined subjects. Moreover, obesity could have an important rule, as levels of cortisol, insulin and prolactin hormones can alter the levels of Cholesterol and LDL [12]. Studies suggest that many Iranian women are obese and obesity leads to low HDL and high TG levels [13]. Furthermore, it has been suggested that smoking can increase Cholesterol and LDL levels [14], and all of our subjects (cases and controls) were non-smokers, whereas subjects in earlier mentioned studies may have been smokers; the reason we believe so is that Iranian women usually don't drink alcohol and are not smokers, and these habits are more common in European countries and the United States of America [15,16].

A recent meta-analysis showed non-significant differences of total-cholesterol (in the second trimester) and LDL-C (in the first trimester) between women with GDM compared to normal subjects. Moreover, in the mentioned study, women with GDM had higher levels of triglycerides and non-HDL cholesterol and lower levels of HDL-C [11].

In our study, levels of non-HDL-c were higher in women with GDM (141.56±49.5 mg/dl) compared to those without GDM (139±38.8 mg/dl), however this difference was not statistically significant (p=0.759). Furthermore, like findings of the earlier mentioned meta-analysis [11], HDL levels were significantly lower in women with GDM compared to women without GDM.

A study by Salazar et al showed that TG/HDL values of more than 2.5 in non-pregnant women and more than 3.5 in men (among the European population) provide appropriate cutoff points to identify individuals who are insulin resistant and thus are at increased cardio-metabolic risk [7]. Moreover, Wang D, et al reported that the optimal cut off point of TG/HDL-C ratio to predict GDM was 1.12 in Chinese pregnant women [8]. Although, a recent study showed that values of more than 3.68 among non-pregnant Iranian women provide better cutoff points as individuals who are insulin resistant and thus are at increased cardio-metabolic risk [9].

Mulukutla et al reported that the predictability of TG/HDL-C ratio depends on race and nationality [17]. Comparison of this value between Asian and other ethnic groups demonstrated that TG/HDL ratio values of greater than 3, significantly increases insulin resistance among Asian & Indian non pregnant women compared to American Caucasians [17,18]. To the best of our knowledge, the mentioned predictability of TG/HDL ratios has not been studied in Iranian pregnant women before, and this is the first study to examine it. In our study, mean TG/HDL values were 4.12±2.02 and 2.7±0.7 in case and control groups, respectively. In our study, the area under ROC curve of TG/HDL-C to detect GDM was 0.771 (95% CI, 0.690–0.852). The optimal cutoff point proposed by the ROC analysis for TG/HDL-C and GDM was 2.66, with sensitivity and specificity of 86.2% and 52.3% respectively. The

positive and negative predictive values of TG/HDL-C at cut off point of 2.66, were 64.4% and 79.1% respectively.

The cut off point based on the analysis on our findings is bigger than the points in studies mentioned earlier. We believe that since studies show that many Iranian women are obese [13] it can be assumed that the grade of insulin resistance is more than European and American women in the mentioned studies.

Studies suggest that insulin resistance and type 2 diabetes mellitus are associated with changes in plasma lipids as lipoprotein abnormalities lead to elevated triglyceride and decreased HDL-cholesterol concentrations; moreover, a consequence of malfunctioning carbohydrate metabolism is lipid changes [19]. Multiple defects in insulin's action along with impaired compensation for insulin resistance are reasons to develop GDM; furthermore, impairments of glucose regulation and clearance, and abnormal free fatty acid concentrations along with pancreatic β-cell dysfunctions increase risk of type 2 diabetes mellitus in women with GDM [19]. Visiedo and colleagues reported that high levels of glucose alter fatty acids metabolism by shifting flux of fatty acids away from oxidation and towards the esterification pathway, causing accumulation of placental triglycerides in human placenta [20]. The mechanistic link between high glucose levels and lower fatty acid oxidation capacities is via reduced activity of the carnitine palmitoyltransferase I (CPT I) enzyme, which normally regulates the first step of the entry of long-chain acyl-CoA into the mitochondrial matrix for β-oxidation. These findings shed light on the biochemical mechanisms by which maternal hyperglycemia may alter placental lipid pathways in diabetic mothers.

Dos Santos-Weiss and colleagues have shown that the plasma logarithm of the TG/HDL-C ratio is a valuable index to identify Euro-Brazilian pregnant women with low risk of GDM before 24 weeks of gestation. Their study has shown that plasma logarithm of TG/HDL-C ratio less than 0.099 indicates a low risk of GDM before 24 weeks of gestation [10].

In the current study, TG/HDL-C ratios were not significantly higher in subjects of the case group with positive family history of diabetes compared to those without such family history (p=0.43), and this finding shows that this high ratio is independent of the role of family history.

Hyperinsulinemia due to insulin resistance is associated with hypertriglyceridemia and low serum HDL-C concentrations; incidence of these lipoprotein abnormalities is related to the severity of the insulin resistance [21]. Insulin resistance has been shown to associate with larger very low density lipoprotein (VLDL) particles, and smaller LDL and HDL particles. Moreover, increased glucose and free fatty acid levels along with decreased lipolysis of VLDL triglyceride may lead to hypertriglyceridemia. Combination of insulin resistance and hormonal changes can affect lipoprotein abnormalities. Therefore, high serum estrogen concentrations and increased insulin resistance in pregnancy are considered to be responsible for the hypertriglyceridaemia observed during a "normal" pregnancy [22]. In women with GDM, higher insulin resistance may account for a further rise in triglyceride concentrations. Insulin resistance is associated with decreased LDL catabolism and a rise in plasma LDL cholesterol concentration, but the increased direct removal of triglyceride enriched VLDL may lead to decreased production of LDL [22,23]. The total pool of LDL may be further decreased by the effect of hyperoestrogenaemia on its catabolism. However, it has recently been pointed out that the Friedewald equation [24] should not be used in noninsulin dependent diabetes mellitus, as there are compositional changes in VLDL that result in overestimation of LDL cholesterol [23]. With this in mind, we would expect that women with GDM would have an even lower LDL cholesterol concentration as it happened in our study.

Koukkou et al. showed that Plasma Apo B concentrations were not significantly different between women with GDM and women who didn't have GDM, but the LDL cholesterol/Apo B ratio was lower in those with GDM, suggesting a difference in particle composition [25]. LDL in women with GDM is cholesterol depleted and triglyceride enriched [18]. Smaller and denser LDL particles with decreased numbers of cholesterol ester molecules per particle have been reported in patients with non-insulin dependent diabetes mellitus and impaired glucose tolerance, as well as in women during the third trimester of pregnancy [26]. Persson et al. showed that total-cholesterol levels were reduced by 14% in response to elevated endogenous estrogen levels which was due to reductions in LDL and VLDL, whereas HDL cholesterol concentrations were not changed; triglycerides and ApoA-I were increased and circulating PCSK9 levels decreased significantly,

supporting the hypothesis that estrogens increase the number of hepatic LDLRs partly by reducing PCSK9 and reducing PCSK9 can lead to LDL reduction [27]. It seems that the combination of hormonal changes such as estrogen, along with insulin resistance, can affect lipoprotein abnormalities. However, some studies showed that LDL cholesterol level was not significantly different between women with GDM and women without GDM [28]. On the other hand, some studies showed controversial results about LDL levels and high LDL levels in women with GDM, such as the study by Wang and colleagues [8]. The recent meta-analysis conducted by Ryckman et al showed that total-cholesterol or LDL-C levels were not different between women with GDM and the control subjects [11].

HOMA index can predict GDM, but TG/HDL ratio is more cost effective than HOMA index. Sokup et al. reported that HOMA index can assess insulin resistance in GDM and it is associated with the severity of GDM, moreover, HOMA-IR >2.89 can predict insufficient compensation for insulin resistance, and may indicate the need for insulin therapy [29].

4. CONCLUSION

Our findings indicated that GDM can affect lipid profiles and lipoprotein metabolisms, of which, a contentious finding was lower LDL-c in women with GDM. Moreover, the optimal cut off point for predicting GDM was calculated as 2.66 which is remarkably different compared to the values presented in earlier studies, and we believe ethnicity and other related factors to cause this difference. Last but not least, it is suggested that a high TG/HDL ratio is independent of the role of family history.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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