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Cellular Inflammatory Markers and Castelli Risk Indices in Women with Gestational Diabetes Mellitus

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Abstract

Background: The clinical importance of early identification of potential predictors of cardiovascular events in women with gestational diabetes mellitus (GDM) cannot be overemphasized. This study aimed to determine the plasma levels of Castelli risk indices (CRI) and selected cellular inflammatory markers in women with GDM.

Methods: A total of 40 pregnant women, consisting of 11 women with GDM and 29 women without GDM, were randomly enrolled into this case-control study using the convenient sampling method. Venous blood samples were taken. The plasma lipid profiles were determined using the spectrophotometric methods. White blood cell differential was counted using a microscope. Plasma levels of CRI-I, CRI-II, low-density lipoprotein cholesterol (LDL-C), neutrophil-lymphocyte ratio (NLR), and monocyte lymphocyte ratio (MLR) were calculated using the appropriate formula. Student's t-test, Mann Whitney U, Chi-square, and Spearman's rho correlations were used for statistical analysis. $P<0.05$ was considered statistically significant.

Results: The CRI-I [6.58(6.06–7.60) vs 3.42(2.83–3.89)], CRI-II [4.59(4.17–5.28 vs 1.82(1.36–2.16)) and NLR (3.72±0.52 vs 2.63±0.61) were significantly higher in women with GDM. Likewise, the mean age (34.18±3.49), gestational weight (92.82±11.23), fasting plasma glucose (FPG) (98.45±6.24), total cholesterol (TC) (310.92(290.81–360.78)), triglyceride (TG) (232.86(221.28–256.00), LDL-C (214.85(206.24–239.80), and neutrophil count (76.36±2.58) were significantly higher in women with GDM ($p<0.05$). In contrast, HDL-C (45.56(44.90–51.34), lymphocytes (20.82±2.14), and monocytes counts (2.73±1.10) were significantly lower in women with GDM. However, there was no difference in the MLR between the two groups.

Conclusion: The CRI-I, CRI-II, and NLR are significantly elevated in women with GDM. Dyslipidemia and systemic inflammation are associated with GDM, which are forerunners of cardiovascular diseases.

Keywords: Castelli risk indices, dyslipidaemia, gestational diabetes mellitus, inflammation, neutrophil-lymphocyte ratio

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Introduction

Gestational diabetes mellitus (GDM), the most common form of maternal dysglycaemia, is a serious pregnancy complication that correlates with multitude of adverse maternal and perinatal outcomes.[1] This disease is characterized by intolerance of carbohydrate which results in hyperglycaemia of variable severity with onset or first recognition during pregnancy.[2] GDM accounted for 86.4% of all hyperglycaemia in pregnancy.[3] In 2017, the International Diabetes Federation (IDF) reported a global prevalence of 16.2%.[3] In

2020, a prevalence of 7.7% was reported in Nigeria using the 2013 World Health Organization (WHO) criteria.[4] The global increase in prevalence of GDM is fuelled by risk factors such as energy-dense foods, sedentary lifestyle, overweight, obesity, micronutrient deficiencies, stress, advanced maternal age, family history of insulin resistance, and/or diabetes mellitus.[5]

Increased risk of cardiovascular diseases (CVDs) as well as other metabolic diseases such as metabolic syndrome and type 2 diabetes mellitus (T2DM) have been found in women with GDM.[6] Dyslipidaemia has been shown to be a major risk factor for the development of cardiovascular events and has been an important tool conventionally used in the diagnosis of CVDs.[7] However, reports are emerging that indices such as the Castelli risk index (CRI)-I, also known as the Cardiac risk ratio (CRR), and the CRI-II, which is derivative of the lipid profile components, are reliable diagnostic alternatives for predicting cardiovascular events especially when conventional lipid parameters appear normal or moderately high.[8,9] CRI-I has been shown to have comparable diagnostic utility to total cholesterol and could reflect coronary plaque formation.[10] Similarly, CRI-II has been reported to have excellent predictive value for cardiovascular risk and had a significant correlation with insulin resistance.[11] Furthermore, low-grade chronic inflammation has been shown to play a critical role in the pathogenesis of CVDs and in the development of GDM and T2DM.[12] Although several biological markers have been validated to predict CVD risk and prognosis, low-cost inflammatory markers such as neutrophil-lymphocyte ratio (NLR), which is derived from a simple ratio of immune cells, have been reported to be clinically useful in predicting CVD risk.[13]

The clinical importance of early identification of women with GDM who are at risk for cardiovascular events cannot be overemphasized. Therefore, this study was designed to discover plasma levels of Castelli risk indices I and II as well as selected cellular inflammatory biomarkers in women with GDM.

Methods

This case-control study examined 40 pregnant women at risk of GDM . They were randomly selected from pregnant women visiting the Metabolic Research Unit, Department of Chemical Pathology, University College Hospital, Ibadan, Nigeria for an oral glucose tolerance test (OGTT). All study participants underwent a 2-hour OGTT and thereafter, a diagnosis of GDM was made using the WHO criteria.[14] Participants with fasting plasma glucose (FPG) levels of 5.1–6.9 mmol/L (92–125 mg/dl) and/or ≥10.0 mmol/L (180 mg/dl) 1-hour post 75 g oral glucose load and/or 8.5–11.0 mmol/L (153–199 mg/dl) 2-hour post 75 g oral glucose load diagnosed with GDM.

Participants with T2DM, preeclampsia, pregnancy-induced hypertension, and a history of fetal anomalies, cardiovascular or renal diseases were excluded from the study. Also, active smokers and those whose ages were not in the 20 to 40 years range were excluded.

Ethical approval was obtained from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Review Committee (UI/EC/21/0633). Written informed consent was obtained from each study participant.

After an overnight fast of about 8 to 12 hours, a venous blood sample was obtained from each participant and dispensed into a sample bottle containing fluoride oxalate- and a sample bottle containing K3-EDTA anticoagulant as appropriate (0 minute). After 60- and 120-minutes post standard 75 g OGTT, venous samples were also obtained from each participant and dispensed into sample bottles containing fluoride oxalate- for plasma glucose analysis. Peripheral blood films for the white blood cell (WBC) differentials were made immediately from samples dispensed into sample bottles containing K3-EDTA anticoagulant- and WBC differential counts were carried out microscopically. Thereafter, neutrophil-lymphocyte ratio (NLR) was calculated as the ratio of the neutrophils' percentage to the lymphocytes' percentage. The remaining blood samples were centrifuged, and the plasma obtained was stored at -20 ^{0}C until analyzed.

Plasma levels of glucose, total cholesterol (TC), triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) were determined using the enzymatic method, whereas plasma level of low-density lipoprotein cholesterol (LDL-C) was calculated using the formula LDL-C= TC–HDL-C–TG/5.[15]

The CRI-I was calculated as the ratio of plasma TC to plasma HDL-C level (TC/HDL-C). Similarly, the CRI-II was calculated as the ratio of the plasma level of LDL-C to the plasma level

Table 1 Characteristics of the Study Participants with GDM and Controls

Characteristics	GDM		n	X2	P-value
	Yes	No			
Age					
20–29 years	1(9.1%)	16(55.2%)	17	6.937	0.031*
30–35 years	6(54.5%)	8(27.6%)	14		
35–40 years	4(36.4%)	5(17.2%)	9		
Educational status					
No formal or primary education	0(0.0%)	0(0.0%)	0	0.416	0.464
Secondary education	1(9.1%)	5(17.2%)	6		
Tertiary education	10(90.9%)	24(82.8%)	34		
Family history of GDM					
Yes	5(45.5%)	2(6.9%)	7	8.212	0.011*
No	6(54.5%)	27(93.1%)	33		

Note: *Significant at p<0.05, GDM= Gestational diabetes mellitus

of HDL-C (LDL-C/HDL-C).

Statistical analysis was conducted using SPSS statistical software version 23.0 for Windows. Data distribution was measured using a histogram with a normal distribution curve. Thereafter, differences in the means of data with a Gaussian distribution were determined using the Student's t-test. Meanwhile, the medians of data without a Gaussian distribution were compared using the Mann Whitney U. Chi-square or Fischer's exact test was used to determine association between categorical data, whereas Spearman's rho correlation was used to determine the correlation between the variables. Results were presented as mean ± standard deviation (SD) or median (interquartile range) as appropriate. A p-values less than 0.05 was considered statistically significant.

Results

Of the 40 pregnant women, 11 mothers had GDM and 29 mothers without GDM as controls. Slightly more than half pregnant women with GDM were aged 30–35 years (6

Table 2 Mean and Median in Age, Blood Pressure, Lipid Profile, Fasting Plasma Glucose (FPG) Level, and Immune Cells Counts in Woman with Gestational Diabetes Mellitus (GDM) and Controls

	GDM (n=11)	Controls (n=29)	P-value
Age	34.18 ± 3.49	30.34 ± 5.19	0.030*
Gestational body weight (kg)	92.82 ± 11.23	81.52 ± 5.19	0.035*
Blood pressure			
SBP (mmHg)	112.45 ± 8.04	112.31 ± 12.90	0.973
DBP (mmHg)	75.82 ± 6.98	69.14 ± 12.21	0.097
FPG (mg/dl)	98.45 ± 6.24	78.86 ± 7.98	0.000*
Lipid profile			
TC (mg/dl)	310.92 (290.81–360.78)	253.33 (226.41–282.52)	0.001*
TG (mg/dl)	232.86 (221.28–256.00)	206.45 (178.80– 232.97)	0.041*
HDL-C (mg/dl)	45.56 (44.90–51.34)	70.86 (65.74–85.16)	0.000*
LDL-C (mg/dl)	214.85 (206.24–239.80)	137.76 (102.22–155.67)	0.000*
Immune cells counts			
Neutrophil (%)	76.36 ± 2.58	68.48 ± 5.09	0.000*
Lymphocyte (%)	20.82 ± 2.14	26.90 ± 4.16	0.000*
Monocyte (%)	2.73 ± 1.10	4.17 ± 2.11	0.008*

Note: *Significant at p<0.05, SBP= Systolic blood pressure, DBP= Diastolic blood pressure, FPG= Fasting plasma glucose, TC= Total cholesterol, TG= Triglycerides, HDL-C= High density lipoprotein cholesterol, LDL-C= Low density lipoprotein cholesterol

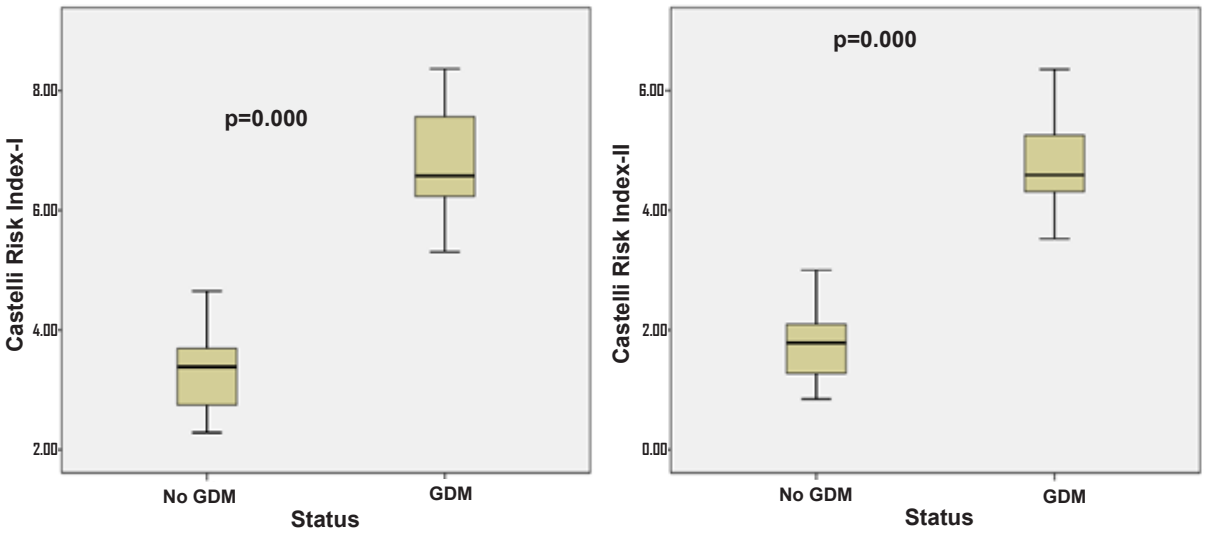

Figure 1 Castelli Risk Indices (CRI) in Women with GDM and Controls

of 11), meanwhile 16 of 29 (55%) pregnant woman without GDM were aged 20–29 years. It was found that older age was significantly associated with GDM (p=0.031). Similarly, the proportion of women with a family history of GDM was higher in women with GDM compared with the controls (Table 1).

The mean and median differences in age, gestational body weight, blood pressure and lipid profile were shown in Table 2. The mean age (34.18±3.49) and gestational body weight (92.82±11.23) were significantly higher in women with GDM than controls. Similarly, the levels of FPG (98.45±6.24), TC (310.92(290.81–360.78)), TG (232.86(221.28–256.00), LDL-C (214.85(206.24–239.80) and neutrophil count (76.36±2.58) were significantly higher in women with GDM than controls. In contrast, however, the level of HDL-C (45.56 (44.90–51.34), and counts of lymphocyte

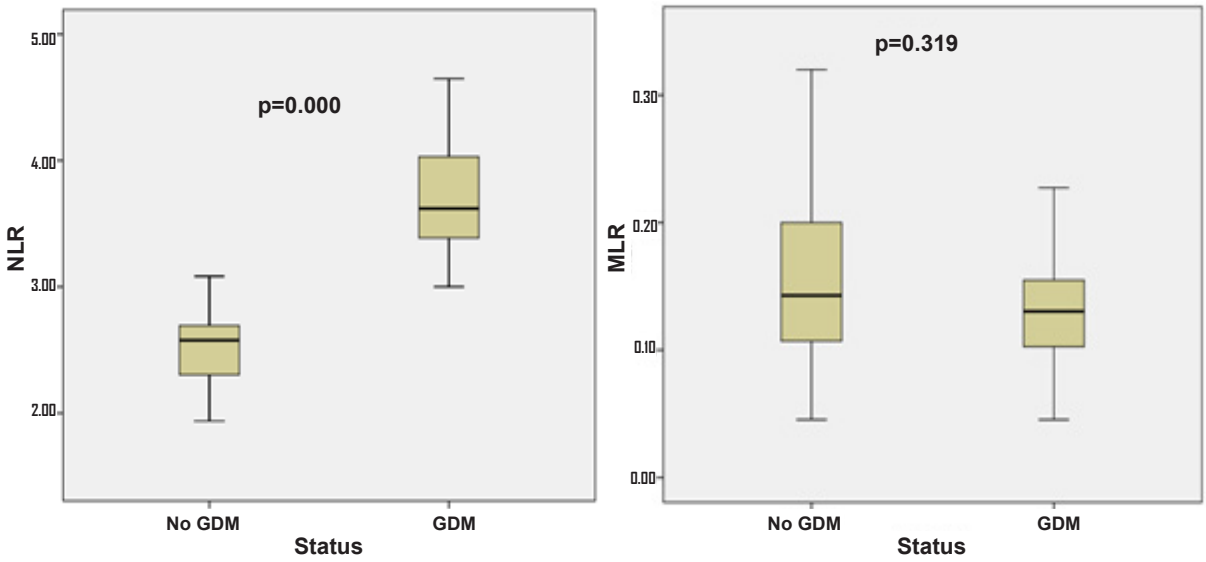

Figure 2 Levels of Neutrophil-lymphocyte Ratio (NLR) and Monocyte-lymphocyte Ratio (MLR) in Women with GDM and Controls

Table 3 Correlation between Fasting Plasma Glucose, Lipid Profile, Castelli Risk Indices, and Markers of Cellular Inflammation in Women with GDM and Controls

	Fasting Plasma Glucose (FTG)			
	GDM		Controls	
	r-value	p-value	r-value	p-value
Gestational body weight (kg)	0.192	0.572	-0.067	0.729
Lipid Profile				
TC (mg/dl)	-0.438	0.177	0.279	0.143
TG (mg/dl)	0.005	0.989	0.405	0.029*
HDL-C (mg/dl)	-0.357	0.281	-0.083	0.667
LDL-C (mg/dl)	-0.379	0.250	0.251	0.189
Castelli Risk Indices				
CRI-I	0.123	0.718	0.400	0.032*
CRI-II	0.183	0.591	0.345	0.067
Markers of Cellular Inflammation				
NLR	0.126	0.712	0.192	0.319
MLR	0.391	0.234	-0.055	0.776

Note: *Significant at p<0.05, GDM= Gestational diabetes Mellitus, TC= Total cholesterol, TG= Triglycerides, HDL-C= High density lipoprotein cholesterol, LDL-C= Low density lipoprotein cholesterol, CRI= Castelli risk index, NLR= Neutrophil-lymphocyte ratio, MLR= Monocyte lymphocyte ratio

(20.82±2.14) and monocyte (2.73±1.10) were significantly lower in women with GDM than controls (Table 2). Eosinophils were found in the films of only one patient with GDM and nine controls. Therefore, no statistical comparisons were done. In addition, basophils were not found on films of women with GDM and controls.

As shown in Figures 1 and 2, the values of Castelli risk indices I [6.58 (6.06–7.60) vs 3.42 (2.83–3.89)] and II [4.59 (4.17–5.28) vs 1.82 (1.36–2.16)] as well as the n-lymphocyte ratio (NLR) (3.72±0.52 vs 2.63±0.61) were significantly higher in women with GDM than the controls. However, no difference was observed in monocyte-lymphocyte ratio (MLR) between the two groups (Figure 2).

As shown in Table 3, FPG had positive correlation with TG (p=0.029) and CRI-I (p=0.032) in the control group. However, such significant correlations were not observed in the GDM group.

Discussion

GDM is characterized by increased insulin resistance, hyperglycaemia and dyslipidaemia with attendant adverse perinatal outcomes.[16] In this study, it was observed that women with GDM were older than the controls. This observation corroborates previous report that identified increasing maternal age as a risk factor for GDM and that the risk of GDM increased linearly with successive age groups.[17] Although the correlation between increasing maternal age and complications in pregnancy is still poorly understood, our observation could be due to physiological changes such as insulin resistance that occurs with advanced age.

Obesity has been evidently associated with dysglycaemia, and this tends to put many obese people at risk for diabetes mellitus. Another study has shown that gestational weight gain may symbolize a modifiable risk factor for GDM.[18] The observed results of significantly higher gestational body weight in women with GDM compared with the control are in accordance with another report suggesting that gestational weight gain, especially in early pregnancy, increases a woman's risk of developing GDM and could be considered a modifiable risk factor for GDM.[18] The gestational weight gain observed in women with GDM in this study could have been initiated in the first trimester, during which insulin sensitivity normally increases, and thereby promotes glucose uptake into adipose stores.

It is well established that chronic insulin resistance associated with GDM promotes high FPG at steady state. The observed increase in plasma level of FPG in women with GDM is not surprising as this is a well-established finding that can be attributed to the pathophysiology of GDM. This observation could be due to

impaired insulin-mediated glucose uptake as a result of insulin resistance; gestational weight gain results in increased adiposity and the desensitizing effects on placental hormones that promote insulin resistance.[19]

Physiological changes in lipid metabolism occur even during healthy pregnancy. Serum levels of TG, HDL-C, LDL-C, and TC have been reported to be elevated throughout the pregnancy.[20] In this study, plasma levels of TC, TG and LDL-C were significantly higher, meanwhile HDL-C was significantly lower in women with GDM than the controls. These observations support previous findings showing that women with GDM had elevated plasma levels of TG, TC, LDL-C, and reduced levels of HDL-C.[21] The observed alteration in the lipid profile could be due to insulin resistance in women with GDM.

Similar to the observation from this study, reports have shown that there is a significant elevation in serum TG in women with GDM.[22] Similarly, previous study has shown that there is an association between hypertriglyceridemia during pregnancy and increased gestational weight gain as well as GDM.[23] The observed elevation in plasma TG levels could be attributed to enhanced activity of hepatic lipase and reduced lipoprotein lipase activity, both of which promote increased circulating TG. Hyperinsulinemia is also associated with increased triglycerides levels.[24] In addition, the observed lower plasma level of HDL-C in women with GDM compared with the controls supports another study.[22] Lower level of HDL-C could be secondary to an elevated plasma level of triglyceride as it has been reported that the particle size of HDL-C correlates inversely with the concentration of plasma triglycerides.[25]

The association of GDM with dyslipidaemia evidently puts women with GDM at risk of developing cardiovascular disease. This, although it can be a financial burden and lead to an increase in mortality rates associated with cardiovascular diseases (CVD), is nevertheless considered quite important to predict the development of CVD in high-risk individuals such as pregnant women with GDM and to ensure appropriate and early preventive interventions. The observed elevation in both CRI-I and CRI-II in women with GDM compared with controls is in concordance with previous report showing that the CRI-I and CRI-II were higher in women with GDM compared with women with normal pregnancy.[26] The CRI, especially the CRI-II, sensitively indicate an offset in the balance between the pro-atherogenic and anti-atherogenic fractions of the lipid profile which are LDL-C and HDL-C, respectively.

Sub-clinical inflammatory processes are necessary in the pathogenesis of GDM.[12] In this study, an increased neutrophil count was found in women with GDM compared with controls, this finding supports previous reports.[27] Neutrophils have been shown to be involved in GDM and type 2 diabetes mellitus associated chronic inflammation.[28] Inflammation mediated by activated neutrophils and macrophages has been shown to impair placental function through tissue damage, and elevate the formation of neutrophil extracellular traps (NETs) causing vascular endothelial cell damage, and macrophages infiltration with subsequent changes to the placenta. These changes in placental function have a significant adverse effects on pregnancy outcomes.[28]

Elevated NLR, a marker of systemic inflammation, has been shown to have a significant association with GDM and poor pregnancy outcomes.[27] Elevated NLR might be a valuable biomarker for early prediction of preeclampsia and correlates with the severity of the disease.[29] The significant increase in NLR in women with GDM corroborates previous reports.[30] The increase in NLR found in women with GDM might be attributed to an elevation in the neutrophil count which is an indicator of the inflammatory process in GDM. It could also be due to a decrease in the lymphocyte count which is often seen in physiological stress.

The small sample size is a limitation in this study. Therefore, further studies with large populations are suggested to determine the cut-off values of Castelli risk indices and NLR that can predict cardiovascular risk in women with GDM.

In conclusion, the CRI-I, CRI-II, and NLR are significantly higher in women with GDM. Atherogenic dyslipidaemia and systemic inflammation are associated with GDM, which are known risk factors for cardiovascular diseases.

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