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Investigating the Relationship between hs-CRP Serum Level and Insulin Resistance (HOMA IR) Six Weeks after Childbirth in Patients with Gestational Diabetes Mellitus

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Abstract

Background: Some patients with GDM (Gestational Diabetes Mellitus) still experience impaired glucose tolerance after childbirth and will be affected by diabetes mellitus type 2.
Objectives: The aim of this study is to investigate the relationship between hs-CRP serum levels with insulin resistance six weeks after childbirth in patients with gestational diabetes mellitus type 2.
Methods: In this descriptive cross-sectional study, 110 patients with GDM were evaluated in terms of the insulin resistance index (HOMA), hs-CRP serum, and the oral glucose tolerance test (OGTT) six weeks after childbirth. Their anthropometric indices were measured in the early pregnancy. Spearman's rank correlation coefficient and linear regression analysis were used to analyze data in SPSS 16.
***Results*:** The mean of hs-CRP was 8.72 µg/ml among the patients in this study. It is higher than the normal range. Moreover, 24.5% of the patients were suffering from impaired glucose tolerance, and hs-CRP levels were higher than the normal range in 92.6% of these patients. Furthermore, 41.8% of patients showed insulin resistance, and hs-CRP levels were high among 73.9% of them. After age adjustment, the increase in hs-CRP serum level was significantly correlated with insulin resistance (HOMA) and the one-hour and two-hour OGTTs ($p=0.007$ and $p<0.001$, respectively).
Conclusion: It appears that age adjustment can help us figure out the relationship between the increase in hs-CRP serum and insulin resistance in pregnant mothers with diabetes six weeks after childbirth.

Key words: Hs-CRP serum level, Insulin resistance, Postpartum, GDM (Gestational Diabetes Mellitus)

Introduction

GDM (Gestational Diabetes Mellitus) is the most prevalent metabolic disorder in pregnancy. It emerges in nearly 8.3% of all pregnancies (1). It refers to the condition in which blood glucose levels soars for the first time during pregnancy (2). In many patients with GDM, postpartum hypoglycemia improves automatically; however, nearly 20% of patients still experience impaired glucose tolerance after childbirth (3). In GDM, there is a chance of diabetes mellitus type 2 because GDM is accompanied by insulin

resistance and defective insulin secretion (4,5). The physiological changes in pregnancy can result in GDM in the predisposed people. In the first three months of pregnancy, sensitivity to insulin changes. With the development of the fetus, insulin secretion increases due to insulin resistance (6). In a normal pregnancy, insulin sensitivity increases in the second three months of pregnancy and reaches a level near diabetes mellitus type 2 (6,7). The majority of women remain in a normoglycemic state due to the high insulin secretion with the compensatory phase of β cells (7). Therefore, GDM develops when this compensatory phase of β cells is not enough for insulin resistance and hepatic glucose production (8). In pregnancy, there is a chance of decreased insulin sensitivity and emergence of insulin resistance due to the increase in hormones such as HPL (Human Placental Lactogen) in the blood which has anti-insulin effects as well as other diabetes-causing hormones such as cortisol, estrogen, and progesterone (9,10). The side effects of GDM in the first three months of pregnancy include birth defects, the increased chance of abortion, congenital malformations, and fatality near the time of birth (11,12). In the second and third three months of pregnancy, the excessive fetal growth leads to high risks of childbirth such as shoulder area injuries or hypoxia due to delay in delivery or a sharp drop in the baby's blood sugar in the early hours of birth (13). In the pathogenesis of metabolic syndrome and diabetes mellitus type 2, the role of inflammation is discussed (14,15). C-reactive protein (CRP), which is an inflammatory factor synthesized from hepatocytes, can increase insulin resistance in different tissues (16). The mechanism of relationship between diabetes mellitus type 2 and inflammation is caused by the activities of cytokines such as IL6 (Interleukin 6) and TNFα (Tumor Necrosis Factor Alpha) which stimulate the production of CRP, induce insulin resistance, and also stimulate the response to the chronic inflammatory phase (17). The long-lasting secretion of inflammatory cytokines result in impaired insulin secretion coming from pancreatic β cells (18). Many researchers have studied the relationships of inflammatory factors such as CRP and diabetes mellitus type 2. The results of futuristic studies indicate that the systemic inflammations can be regarded as the causes of the independent risk of diabetes mellitus type 2 (19,20). Given the fact that diabetes mellitus type 2 is one of the complications caused by GDM in mothers, the diagnosis of effective factors can improve preventive interventions faster and better because mothers may be affected by diabetes mellitus in the future. In fact, the prevention of type 2 diabetes in such mothers will be prevent the number of diabetic mothers from increasing. Finally, further problems can be prevented. The majority of previous studies investigated the relationship between gestational CRP and postpartum insulin resistance. Therefore, the aim of this study is to use OGTT to investigate the relationship between postpartum hs-CRP (high sensitive C reactive protein) with insulin resistance in mothers with GDM. This study is also meant to investigate the preventive mechanism of GDM mothers being affected by diabetes mellitus type 2 by inhibiting insulin resistance because CRP level decreases after childbirth. However, it can indicate insulin resistance.

Methods

This is a descriptive cross-sectional study. The simple sampling method was used to select 110 mothers with GDM visiting the pregnancy clinic of Metabolic Research Center in Zanjan. The GDM was diagnosed by an endocrinologist between 24 and 28 pregnancy weeks with respect to the results of fasting glucose and oral glucose tolerance tests. They were included in the study before childbirth. The inclusion criterion was the diagnosis of diabetes for the first time during pregnancy. The patients with previous records of diabetes, cardiovascular diseases or any other disorders increasing hs-CRP levels were excluded from the study. Moreover, the patients who used medications except insulin and glucose-reducing tables to control GDM and the patients who were could not be reached after childbirth were excluded from the study. After informing the participants about the research subject and importance, they were given a questionnaire including items on demographics. They were also asked to sign a written consent. The demographics

included age, height, prenatal weight, BMI (Body Mass Index) in W(kg)/H^2 (m), systolic and diastolic blood pressure, prenatal size of waist, and the familial history of diabetes. Furthermore, they were asked about their treatment and control methods of GDM including pills, insulin injections and diets. Finally, they were asked to visit the research center from six to 12 weeks after childbirth to participate in the study and give blood samples for the relevant experiments. During this interval, the mothers visited the center for blood sampling. First, five ml blood was taken after eight hours of fasting for the fasting sugar and insulin test and hs-CRP. According to the American Heart Association (21), they were then given 75 grams of glucose powder solved in 300 ml of water for OGTT. They were asked to drink the syrup completely in five minutes and come back for blood sampling to test the blood sugar in an hour. In this period, they were not supposed to eat or drink anything. After sampling, they were asked visit for the final sampling again after one hour. After the final blood sampling, their serums were separated to prevent low blood sugar. The serums were kept in a freezer at -70 degrees of Celsius until the time of analysis.

The samples were analyzed by the laboratory experts of Valiasr Hospital in Zanjan. The ParsAzmun kit (made in Iran) was used to measure sugar blood with the glucose oxidase method in which the auto-analyzer device BT 3500 (made in Italy) was used. Insulin was measured with ELISA method and a monobind kit made in Germany. Then hs-CRP was measured with ELISA method and a high-sensitive hs-CRP monobind kit made in Germany. HOMA IR (Homeostasis Model Assessment Insulin Resistance) was also calculated through HOMA-IR = {[fasting insulin (μU/ml)] × [fasting glucose (mmol/l)]}/22.5 by replacing fasting sugar and insulin (22,23). The acuracy of test was determined by %CV (regarding hs-CRP, the internal group percentage and the inter-group percentage were 7.5 and 9.4; regarding FBS, the internal group percentage and the inter-group percentage were 4.5 and 5.3). For statistical analysis, the information was described as mean and standard deviation (Mean±SD) after collecting clinical and demographic information and conducting tests. The data were analyzed in SPSS 16 using the Npar test. Then the one-sample Kolmogrov-Smirnov test was employed to determine the normality of data. Spearman correlation coefficient was used to investigate the correlation between CRP and variables. Then the linear regression analysis was employed to evaluate the relationship between hs-CRP and other variables. Finally, centrality and dispersion indicators were used to analyze data.

Results

The results of this cross-sectional study are shown in four tables and one figure. Table 1 indicates the demographic and biochemical features of mothers with GDM.

Table 1: Demographic and Biochemical Information on Mothers with GDM

Parameter	Mean± SD	Range
Age(year)	28.9±6.68	17-42
BMI(Kg/m^2)	27.63±3.81	21.5-38.0
FBS(mg/dl)	92.48±13.6	59-127
GTT 1(mg/dl)	150.43±33.64	100-221
GTT 2(mg/dl)	121.2±29.52	55-203
hs-CRP(μg/ml)	8.72±11.05	0.1-50.0
Insulin(μu/ml)	9.11±6.97	1.0-60.0
HOMA-IR	2.12±1.84	0.18-17.04
Systolic Blood Pressure(mm/Hg)	113.18±8.23	80-130
Diastolic Blood Pressure(mm/Hg)	64.09±6.68	60-90
Waist circumference(cm)	96.2±11.2	60-126

Table 2 shows the normal frequency distribution of mothers with GDM after childbirth and disorders related to insulin resistance six weeks after childbirth. The frequency distribution table shows that the highest percentage of glucose intolerance and the lowest frequency of diabetes mellitus. Therefore, 57.2% of participants had normal tests showing improved postpartum GDM, and 46.9% of these patients showed high hs-CRP levels. Moreover, 1.8% of them had diabetes mellitus type 2 with higher hs-CRP levels than normal. Unfortunately, GDM emerged as diabetes mellitus in them. Furthermore, 19.1% of patients were diagnosed with fasting sugar disorders and

impaired FBS tests. In 24.5% of the patients, there were some problems in the results of OGTT. In other words, their fasting sugar levels were normal; however, OGTT was disrupted. In details, 92.6% of them showed higher hs-CRP levels than normal. However, 1.8% of this group showed disorders both in fasting blood and OGTT. On the other hand, their glucose levels did not show diabetes mellitus.

Table 2: The Frequency Distribution of Disruptions in Insulin Resistance Six Weeks after Childbirth in Mothers with GDM

Disorder type	Percent	Frequency
Normal	52.7	58
Diabetes Mellitus	1.8	2
Disorder of FBS	19.1	21
Disorder of Glucose Tolerance	24.5	27
Disorder of FBS & Glucose Tolerance	1.8	2

Table 3 shows the relationship between hs-CRP and biochemical factors in the study groups. Statistically, the results of Spearman's correlation coefficient indicate that hs-CRP has a significant relationship with age and glucose after one and two hours. It is also significantly correlated with fasting insulin and HOMA IR (p=0.01, p=<0.001, p=<0.001, p=0.012, and p=0.007). However, it was not significantly related to other factors. In this test, p<0.05 is regarded as statistically significant. This comparison was drawn by the non-parametric test.

Table 3: The Relationship of hs-CRP with Demographic and Biochemical Factors in Mothers with GDM

Parameter	r	P value
Age	0.246	*0.010
BMI	-0.048	0.615
FBS	0.094	0.331
GTT 1	0.393	*<0.001
GTT 2	0.353	*<0.001
Insulin	0.239	*0.012
HOMA-IR	0.254	*0.007
Systulic Blood Pressure	-0.104	0.280
Diastolic Blood Pressure	0.050	0.602
Waist circumference	0.115	0.231

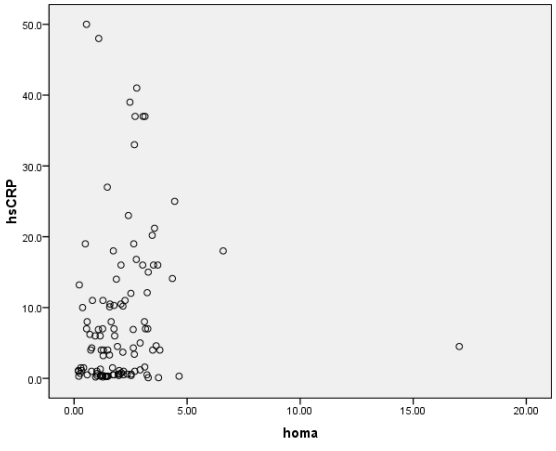

Figure 1: Scatter plots chart indicates the relationship between hs-CRP serum level and insulin resistance (r=0.254 and p=0.007)

Comparing the hs-CRP serum levels of the insulin resistance and normal groups indicated that 73.9% of patients experienced insulin resistance at higher hs-CRP levels than normal. However, this value was 46% in the group lacking insulin resistance.

In Table 4, linear regression analysis was used to evaluate the relationship between hs-CRP and other research factors. In this step, the linear regression analysis was employed to investigate the greatest relationship with hs-CRP levels.

According to Table 4, hs-CRP had the most significant statistical correlations with age (CI: 95%, -0.0-003.613, p=0.05) and one-hour glucose (CI: 95%, 0.005-0.242, p=0.041).

Table 4: Linear Regression Analysis for the Evaluation of Relationships between hs-CRP with Factors Influencing Diabetes

Parameter	Unstsndardized Coefficients		Stsndardized Coefficients Beta	p	% 95 Confidence Interval for B	
	B	Std.Error			Lower Bound	Upper Bound
Insulin	1.47	1.05	0.925	0.16	-0.610	3.543
Age	0.305	0.155	0.184	0.05	-0.003	0.613
GTT 1	0.123	0.060	0.375	0.04	0.005	0.242
GTT 2	-0.033	0.068	-0.089	0.63	-0.169	0.102
HOMA-IR	-5.671	4.053	-0.944	0.16	-13.714	0.373

In this study, the significance level was considered p≤0.05.

Discussion

This study determined the means and standard deviations of hs-CRP, FBS, insulin, one-hour GTT, two-hour GTT, and some other variables in the serums of 110 mothers with GDM. Then the relationships of variables were analyzed. In this study, 52.7% of the participants relapsed into the normoglycemic state after childbirth, and 1.8% of them were affected by postpartum diabetes mellitus type 2. A type of impaired glucose tests remained in the rest of participants. Age, one-hour glucose, two-hour glucose, fasting insulin, and HOMA IR were significantly correlated with hs-CRP. In this regard, the linear regression analysis showed that age and one-hour glucose were the most important factors influencing diabetes mellitus in OGTT.

Ozuguz (2011) conducted a study to investigate the relationships between inflammatory factors and glucose levels among patients with GDM. The results showed that FBS, hs-CRP, insulin, HOMA IR, and triglyceride in women with GDM were higher than the control group. Moreover, hs-CRP had positively statistical relationships with insulin, HOMA and glucose (24). In the abovementioned study, the variables were measured during the pregnancy. However, the measurement time of variables in the current study is different from the study conducted by Ozugus because they were measured postnatally here.

Liu (2012) conducted a study on 40 patients with GDM and 40 normal pregnancies. The results showed that the serum levels of CRP and leptin were significantly higher in the diabetic group than in the normal group. They had also significant relationships with HOMA IR (25). The results of this study are consistent with ours. However, in the current study leptin was not investigated, and the participants were only pregnant women with GDM. Unlike other studies reporting a relationship between BMI and CRP, no significant relationship was found between these two variables in the current study.

Qiu (2004) investigated the relationship of CRP with the risk of diabetes and BMI in women with GDM. Therefore, these results are inconsistent with the results of current study in which no relationships were found between BMI and hs-CRP (26). Retnakaran (2003) agreed with Qiu in this regard. They found out that the increased levels of CRP were observed in women with GDM, and that there was a significant relationship between CRP and prenatal BMI. Moreover, they showed that fasting insulin and fasting sugar were significantly related. After conducting the linear regression analysis, they introduced BMI as an important factor. Unlike the current study, they concluded that CRP was not related with GDM; however, it was significantly related to the prenatal obesity (27).

Fakhrzadeh (2013) found out the relationship between BMI and CRP in women with GDM (28). In the majority of studies conducted on the relationship between inflammation and diabetes mellitus type 2 among patients with diabetic

records, inflammatory factors such as CRP were measured during pregnancy. Then it was measured with postpartum insulin sensitivity. These studies are different form the current study in this regard. Moreover, the majority of studies considered prenatal BMI; however, the current study considered the BMI recorded in the first referral to examine pregnancy. The levels of hs-CRP were measured six weeks after childbirth, something which may be a reason for some differences such as the lack of relationships between BMI and the increased levels of hs-CRP in this study.

Caglar (2012) conducted a futuristic study to evaluate hs-CRP in 11-14 weeks of pregnancy. The results showed that hs-CRP could be a good predictor of GDM and its development with 3.9 OR (29). Maged (2014) investigated hs-CRP in 296 women in the 15th week of pregnancy and obtained the same results as Caglar (30). Moreover, Retnakaran R. (2010) conducted another study and concluded that the pregnant CRP levels were completely related to childbirth insulin resistance (31). In the current study, there is a significant relationship between age and the risk of diabetes after childbirth. In other words, the older a participant is, the higher the risk of diabetes becomes. Shahbazian (2013) confirmed these results in another study, and concluded that there were significant relationships among gestational age in diabetes, risk of diabetes, impaired glucose tolerance, and impaired fasting sugar. Moreover, the older an individual with GDM becomes, the higher the risk of postpartum diabetes increases (32).

Age was considered in the current study. Assuming p=0.01 in the evaluation of correlation coefficient with hs-CRP, it had a statistically significant relationship with age. The participants were aged between 17 and 42 in this study, something which is regarded as an advantage of this study due to the presence of people in old and young age ranges. Many studies determined the relationships between inflammatory factors, especially CRP, with the risk of diabetes mellitus type 2. These studies confirm the results of the current study. In some other studies, there was a significant relationship between CRP and fasting sugar. An instance can be the study conducted by Ghodrati (2009) on pregnant women with GDM (33). However, this relationship was significant between hs-CRP and one-hour glucose after OGTT in the current study which is also different from other studies in terms of variables investigated postnatally. Put another way, other studies investigated these variables during pregnancy.

In the current study, it appears that age adjustment can help figure out the relationship between the increased hs-CRP serum and insulin resistance in pregnant mothers six weeks after childbirth. In patients with higher hs-CRP serum levels, the risk of impaired glucose is higher than normal people after one hour. However, it is recommended that researchers investigate the effect of type of delivery and stressed caused during the childbirth on the increase in hs-CRP serum levels in the future complementary studies. It is also recommended that researchers study the effects of interleukins on the increased CRP level and induced insulin resistance after the childbirth.

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