Association between markers of systemic inflammation, oxidative stress, lipid profiles, and insulin resistance in pregnant women

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Original Article

Abstract

BACKGROUND: Increased levels of pro-inflammatory factors, markers of oxidative stress and lipid profiles are known to be associated with several complications. The aim of this study was to determine the association of markers of systemic inflammation, oxidative stress and lipid profiles with insulin resistance in pregnant women in Kashan, Iran.

METHODS: In a cross-sectional study, serum high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), fasting plasma glucose (FPG), serum insulin, 8-oxo-7, 8-dihydroguanine (8-oxo-G), total cholesterol, triglyceride, High density lipoprotein-cholesterol (HDL-cholesterol), and plasma total antioxidant capacity (TAC) were measured among 89 primigravida singleton pregnant women aged 18-30 years at 24-28 weeks of gestation. Pearson's correlation and multiple linear regressions were used to assess their relationships with homeostatic model assessment of insulin resistance (HOMA-IR).

RESULTS: We found that among biochemical indicators of pregnant women, serum hs-CRP and total cholesterol levels were positively correlated with HOMA-IR (β = 0.05, P = 0.006 for hs-CRP and β = 0.006, P = 0.006 for total cholesterol). These associations remained significant even after mutual effect of other biochemical indicators were controlled (β = 0.04, P = 0.01 for hs-CRP and β = 0.007, P = 0.02 for total cholesterol). Further adjustment for body mass index made the association of hs-CRP and HOMA-IR disappeared; however, the relationship for total cholesterol remained statistically significant.

CONCLUSION: Our findings showed that serum total cholesterol is independently correlated with HOMA-IR score. Further studies are needed to confirm our findings.

Keywords: Inflammation, Oxidative Stress, Insulin Resistance, Pregnancy

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Introduction

Insulin resistance is a physiological condition in which cells could not respond to the normal actions of the insulin hormone.[1] The normal compensatory response to insulin resistance is an increase in insulin secretion, which in turn leads to hyperinsulinemia.[2] Several factors including obesity, storing fat predominantly in the abdomen, sedentary lifestyle, lack of physical exercise,[3] hypertension,[4] hypertriglyceridemia and low levels of serum HDL-cholesterol[5] are associated with insulin resistance.

Furthermore, elevated levels of adipocytokines, including tumor necrosis factor-alpha (TNF-α), might accelerate insulin resistance through releasing free fatty acids (FFA) from adipocytes, which in turn block the synthesis of adiponectin.[6] Increased

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production of pro-inflammatory cytokines can potentially disturb mitochondrial function for mitochondrial DNA damage, the production of reactive oxygen and nitrogen species.[7] The generation of these reactive species lead to hyperglycemia and hyperlipidemia that will then result in decreased biological efficacy of insulin in target tissues (insulin resistance).[8] Oxidative stress has also been widely recognized as an important feature of several diseases such as diabetes mellitus, mutagenesis, cancer, rheumatoid arthritis, atherosclerosis and strokes.[9]

Insulin resistance is primarily related to carbohydrate, lipid and protein metabolism disorders in the different tissues especially skeletal muscles, adipose tissue and liver.[10] It can also cause type 2 diabetes (T2D) and gestational diabetes mellitus (GDM).[10] It is reported that T2D can play an active role in the pathogenesis of both microvascular and cardiovascular complications of diabetes,[11] oxidative damage of DNA, protein and lipid membranes.[12,13]

To our knowledge, no reports exist about the association of biomarkers of inflammation, oxidative stress and lipid profiles with insulin resistance during normal pregnancy. Therefore, the aim of current study was to investigate the association between inflammatory biomarkers including serum high sensitivity C-reactive protein (hs-CRP) and TNF-α levels, measures of oxidative stress including serum 8-oxo-7, 8-dihydroguanine (8-oxo-G) and plasma total antioxidant capacity (TAC), and lipid profiles (serum total cholesterol, triglycerides and HDL-cholesterol levels) and insulin resistance during normal pregnancy.

Materials and Methods

Participants: This cross-sectional study was carried out in Kashan, Iran, from October 2010 to March 2011. A total of 89 pregnant women, primigravida, aged 18-30 years old who were carrying singleton pregnancy were recruited in this study. To recruit participants, we applied multi-stage random sampling method in the study; such that we first randomly selected 30 health centers where the pregnant women attended for prenatal care. Then, by the use of proportional-to-size method, we randomly selected pregnant women among those that were visited in these centers, affiliated to Kashan University of Medical Sciences, Kashan, Iran. Individuals with the above-mentioned inclusion criteria were called for participation in the study. Women with multiparity, maternal hypertension, liver or renal disease and gestational diabetes mellitus (GDM), complete bed rest (CBR), genitalia and systemic infection, history or evidence of rheumatoid arthritis, thyroid and parathyroid or adrenal diseases were not included in the study.[14] Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment. The study was conducted according to the guidelines of Declaration of Helsinki. The ethical committee of Tehran University of Medical Sciences approved the study (No: 20402-89-7-18) and informed written consent was obtained from all participants.

Assessment of anthropometric measures: Anthropometric measurements were assessed at pre-pregnancy and at week 24-28 of gestation. Body weight was measured in an overnight fasting state, without shoes, with minimal clothing and by the use of a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. The pre-pregnancy weight and BMI were taken from the existing records of patients in the clinic.

Biochemical assessment: Fasting blood samples (10 mL) were taken at week 24-28 of gestation at Kashan reference laboratory in an early morning after an overnight fast. Serum samples were analyzed for concentrations of hs-CRP, TNF-α, plasma glucose levels, insulin, 8-oxo-G, and serum total cholesterol, triglycerides, and HDL-cholesterol levels. Serum hs-CRP and TNF-α concentrations were quantified by ELISA. Fasting plasma glucose was measured by glucose oxidase/peroxidase (GOD-POD) method using commercially available kits (Pars Azmun Co, Tehran, Iran). Serum insulin levels were determined by ELISA (Demeditec, Germany). Insulin resistance was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR).[10] Serum 8-oxo-G was assayed by ELISA (Cusabio Biotech Co, China). Serum total cholesterol and triglycerides concentrations were measured enzymatically using Pars Azmoon kits through cholesterol oxidase p-aminophenazon (CHOD-PAP) and glycerol phosphate oxidase-p-aminophenazon (GPO-PAP) methods. HDL-cholesterol levels were also measured enzymatically using commercial kits.[14] The plasma TAC levels was quantified with the FRAP method.[15] The test was performed at 37° C and the 0-4 minute reaction time window was used.

Statistical analysis: To ensure the normal distribution of variables, Histogram and Kolmogorov-Smirnov tests were applied. We used Pearson's correlation and multiple linear regression analysis to assess the relationships. The linear regression analyses were performed in crude and adjusted models which were controlled for mutual effects of other biochemical factors. To reach an independent-of-obesity association, we also added BMI to the regression models. $P < 0.05$ was considered statistically significant. The SPSS version 17 (SPSS, Inc., Chicago, IL) was used for data analysis.

Results

Totally, 89 pregnant women aged 18-30 years who were primigravid participated in the study. Mean maternal age and pre-pregnancy weight was 24.6 ± 3.6 years and 64.1 ± 11.7 kg, respectively. Mean weight at week 24-28 of gestation was 69.2 ± 12.2 kg.

Serum concentrations of hs-CRP, TNF-α, 8-oxo-G, triglycerides, total- and HDL-cholesterol, fasting blood glucose, insulin and plasma TAC at week 24-28 of gestation were 11.53 µg/ml, 88.38 pg/ml, 336.62 ng/ml, 247.54, 263.88, 81.01, 97.33 mg/dl, 7.70 µIU/ml, and 720.70 mmol/l, respectively (Table 1).

We found that pre-pregnancy weight ($r = 0.463$, $P < 0.001$) and weight at week 24-28 of gestation ($r = 0.451$, $P < 0.001$) was significantly associated with HOMA-IR score. This was also the case for pre-pregnancy BMI ($r = 0.450$, $P < 0.001$) and the BMI at week 24-28 of gestation ($r = 0.428$, $P < 0.001$) (Table 2). Serum hs-CRP and cholesterol levels were also positively correlated with HOMA-IR score ($r = 0.288$, $P = 0.006$ and $r = 0.291$, $P = 0.006$, respectively).

Table 1. Biochemical parameters of pregnant women at weeks 24-28 of gestation

Variables	Mean ± SD
hs-CRP (µg/mL)	11.50 ± 9.5
TNF-α (pg/mL)	88.40 ± 51.9
TAC (mmol/L)	720.70 ± 87.6
8-oxo-G (ng/mL)	336.60 ± 156.6
Total cholesterol (mg/dL)	263.90 ± 82.2
Triglycerides (mg/dL)	247.50 ± 117.1
HDL-cholesterol (mg/dL)	81.00 ± 22.7
FPG (mg/dL)	97.30 ± 26.6
Insulin (µIU/mL)	7.70 ± 6.4
HOMA-IR	1.87 ± 1.7

Hs-CRP: High sensitivity C-reactive protein; TNF-α: Tumor necrosis factor alpha; TAC: Total antioxidant capacity; 8-oxo-G: 8-oxo-7, 8-dihydroguanine; HDL-cholesterol: High density lipoprotein-cholesterol; FPG: Fasting plasma glucose; HOMA-IR: Homeostatic model assessment of insulin resistance

Table 2. Pearson's correlation coefficients of anthropometric and biochemical measures with HOMA-IR in pregnant women

Variables	HOMA-IR	P
Anthropometric factors		
Maternal age (year)	-0.006	0.9500
Pre-pregnancy weight (kg)	0.463	<0.0001
Weight at week 24-28 of gestation (kg)	0.451	<0.0001
Pre-pregnancy BMI (kg/m^2)	0.450	<0.0001
BMI at weeks 24-28 of gestation (kg/m^2)	0.428	<0.0001
Biochemical characteristics		
Hs-CRP (µg/mL)	0.288	0.0060
TNF-α (pg/mL)	0.022	0.8300
TAC (mmol/L)	-0.002	0.9800
8-oxo-G (ng/mL)	-0.108	0.3100
Total cholesterol (mg/dL)	0.291	0.0060
Triglycerides (mg/dL)	0.126	0.2300
HDL-cholesterol (mg/dL)	0.095	0.3700

HOMA-IR: Homeostatic model assessment of insulin resistance; BMI: Body mass index; Hs-CRP: High sensitivity C-reactive protein; TNF-α: Tumor necrosis factor alpha; TAC: Total antioxidant capacity; 8-oxo-G: 8-oxo-7, 8-dihydroguanine; HDL-cholesterol: High density lipoprotein-cholesterol

Table 3. Multiple regression analysis between biochemical indicators of pregnant women with HOMA-IR

	HOMA-IR		
	β	95% CI	P
hs-CRP			
Crude	0.050	0.050, 0.090	0.006
Adjusted	0.040	0.008, 0.080	0.010
Adjusted + BMI	0.010	-0.020, 0.040	0.580
TAC			
Crude	-0.002	-0.004, 0.004	0.980
Adjusted	0.001	-0.003, 0.005	0.730
Adjusted + BMI	0.001	-0.004, 0.001	0.310
8-oxo-G			
Crude	-0.001	-0.004, 0.001	0.310
Adjusted	0.000	-0.003, 0.002	0.490
Adjusted + BMI	-0.001	-0.003, 0.001	0.310
Total cholesterol			
Crude	0.006	0.002, 0.010	0.006
Adjusted	0.007	0.001, 0.010	0.020
Adjusted + BMI	0.009	0.030, 0.010	0.002
Triglycerides			
Crude	0.002	-0.001, 0.005	0.230
Adjusted	-0.001	-0.005, 0.002	0.460
Adjusted + BMI	-0.003	-0.007, 0.000	0.070
HDL-cholesterol			
Crude	0.007	-0.009, 0.02	0.370
Adjusted	-0.003	-0.020, 0.01	0.720
Adjusted + BMI	0.000	-0.010, 0.01	0.960

Adjusted: After controlled mutual effect of other biochemical indicators
HOMA-IR: Homeostatic model assessment of insulin resistance; hs-CRP: High sensitivity C-reactive protein; TAC: Total antioxidant capacity; 8-oxo-G: 8-oxo-7, 8-dihydroguanine; HDL-cholesterol: High density lipoprotein-cholesterol

Simple linear regression analysis showed that among biochemical characteristics of pregnant women, serum hs-CRP and total cholesterol levels were positively correlated with HOMA-IR score (β = 0.05, P = 0.006 for hs-CRP and β = 0.006, P = 0.006 for total cholesterol) (Table 3). These associations remained significant even after controlling for other biochemical indicators (β = 0.04, P = 0.01 for hs-CRP and β = 0.007, P = 0.02 for total cholesterol). Further adjustment for BMI made the association of hs-CRP and HOMA-IR disappeared; however, the relationship for total cholesterol levels remained statistically significant (β = 0.009, P = 0.002). Multiple linear regression analysis revealed that there was no association between TAC, 8-oxo-G, triglycerides, and HDL-cholesterol with HOMA-IR score.

Discussion

Insulin resistance, which is associated with abnormal glucose metabolism and insulin secretion, is a common complication during pregnancy.[10] We found that serum hs-CRP and total cholesterol levels are associated with insulin resistance among pregnant women. Our findings also indicated that pre-pregnancy weight and BMI as well as BMI at weeks 24-28 of gestation are positively correlated with HOMA-IR score.

In line with our study, Stuebe et al. has shown a positive association between maternal fasting insulin levels and gestational weight gain.[16] In addition, it is well documented that several pro-inflammatory

factors are related with obesity.[17] The enlarged adipocytes are probably able to activate macrophages and trigger inflammatory reactions in body.[18] However, this issue has not been fully investigated throughout pregnancy that is associated with expansion of adipose tissue.

In the present study, we failed to find an association between maternal serums TNF-α levels and insulin resistance. In a study by Bo et al. it has been reported that high maternal serum TNF-α levels were associated with insulin resistance.[19] However, this is not the consistent finings in all previous observations. Some investigations have found that high maternal serum TNF-α levels were inversely associated with insulin resistance.[19,20] Maternal obesity during pregnancy was associated with elevated levels of inflammatory factors.[21] In the current study, the mean BMI was near the normal ranges. This might help explaining the lack of relationship between serum TNF-α levels and insulin resistance. Clapp and Kiess reported that regular weight-bearing exercise during pregnancy suppressed the usual pregnancy-associated changes in the circulating levels of TNF-α.[22] In the current study, most of pregnant women lived in rural areas with high levels of physical activity. Furthermore, increased levels of several hormones including cortisol, catecholamine's and 1, 25 dihydroxy D3 during pregnancy might result in the inhibitory effect of maternal TNF-α production by monocytes and macrophages.[23]

We found a positive association between maternal serum hs-CRP levels and insulin resistance. Our findings are in agreement with several previous observations.[24,25] However, some studies have found that high serum hs-CRP levels during pregnancy were inversely associated with insulin resistance.[26,27] Existing evidence shows that a chronic inflammatory process represents triggering factor inducing insulin resistance.[28] CRP is synthesized by the liver in response to adipocytokines released from adipocytes.[29] Some adipocytokines like IL-6 and TNF-α are also produced predominantly by macrophages.[29] Elevated CRP levels have also been reported in obesity.[30] Taken together, these data suggest a model of obesity-driven systemic inflammation in pregnancy that leads to insulin resistance.

We failed to find a significant correlation between plasma TAC and serum 8-oxo-G levels, as indicators of oxidative stress, and insulin resistance. To our knowledge, this study is the first one examining the association between oxidative stress parameters and insulin resistance in pregnancy. However, earlier studies have reported the association of oxidative stress parameters and insulin resistance in obese subjects,[31] type 2 diabetics[32] and healthy obese men and women.[33] Kocic et al. showed a positive correlation between serum malondialdehyde (MDA) levels and insulin sensitivity index. However, they failed to find a significant association between total plasma antioxidant capacity, erythrocyte and plasma reduced glutathione levels and insulin resistance.[31] Tinahones et al. showed a close association between the degree of insulin resistance and biomarkers of oxidative stress in severely obese persons.[34] It has been argued that dietary factors are involved in the relationship between oxidative stress parameters and insulin resistance.[35] Given the blood sampling in winter and low consumption of fruits and vegetables in this season in the current study, the association between biomarkers of oxidative stress and insulin resistance might be confounded by other environmental factors.

Our study showed that insulin resistance is significantly correlated with serum total cholesterol levels, but we did not find a significant association with serum triglycerides and HDL-cholesterol levels. Our findings were in line with previous study reported high maternal serum total cholesterol levels as a determinant factor of insulin resistance.[36] Lampinen et al. showed that the waist-to-hip ratio and serum triglycerides affects the insulin sensitivity in the patients with pre-eclampsia.[37] There is a well-known association between triglycerides and insulin sensitivity due to vasodilation resulted from triglycerides.[37] Explanations accounting for the different findings include the environmental and genetic factors of our studied subjects that can alter the lipoprotein metabolism, resulting in insulin resistance. Dyslipidemia has frequently been reported in insulin resistance. It seems that several factors including decreased lipoprotein lipase activity (LPL) and peroxisome proliferator-activated receptor gamma (PPAR gamma) as well as increased acetyl-CoA synthetase (ACS) and microsomal triglyceride transfer protein (MTP) might provide some explanations.[38]

In conclusion, our findings showed that serum total cholesterol levels were independently correlated with HOMA-IR score at weeks 24-28 of gestation. Further studies are needed to confirm our findings.

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Conflict of Interests

Authors have no conflict of interests.

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