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Research Article
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The Association of Glycemic Markers with Plasma Adipocytokine Levels in Women with Gestational Diabetes

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Abstract

Introduction: Alterations in the synthesis of cytokines have been demonstrated in gestational diabetes (GDM), but the association of cytokines with short- and long-term glycemic markers has not been defined clearly. In this study, the variations in the plasma levels of visfatin, TNF-α, IL-1β, IL-6, and IL-10 were investigated and theirassociations with glycemic markers -HbA1C, fructosamine, 1,5-anhydro-D-glucitol (1,5-AG), and continuous glucose monitoring system (CGMS) parameters were evaluated.

Material and methods: 33 pregnant women with GDM, and 20 pregnant women without any maternal and fetal disorder were comprised in the study. Three of the 33 women diagnosed with GDM required insulin therapy were excluded from the study. The visfatin, TNF-α, IL-1β, IL-6 and IL-10 and 1,5-AG were determined by ELISA. HbA1C% and fructosamine were also evaluated. Continuous glucose monitoring system (CGMS) was applied to the women with GDM.

Results: Serum IL-6 and IL-1β levels were significantly high in GDM compared to controls (p=0.039, and p=0.04, respectively). An increase in TNF-α level by approximately 33% did not reach significant level. No significant interactions between BMI and cytokines were found. Visfatin levels were correlated with 1,5 AG (r=0.557, p=0.001) and TNF-α concentration was correlated with HbA1C (r=0.341, p=0.050). IL-1β was associated with both MAD% and average glucose which are indices of CGMS (p=0.004 and p=0.008).

Conclusions: Increased IL-6, IL-1β, and TNF-α, and their correlation with short- or longterm glycemic markers present an evidence for the roles of these cytokines and visfatin on carbohydrate metabolism in the course of gestational process and gives a priority to proinflammatory cytokine profile in gestational diabetes.

Keywords: Gestational diabetes mellitus; Dipocytokines; 1,5-anhydro-D-glucitol (1,5-AG); Continuous glucose monitoring system; HbA1c

Introduction

Gestational diabetes mellitus (GDM) is a result of carbohydrate intolerance which occurs during pregnancy. In one third of patients, it returns to normal glucose tolerance after delivery. Alterations in maternal metabolism occur during normal pregnancy in order to provide the needs for fetus and placenta and insulin secretion increases 2-2.5 fold to maintain the euglycemic state. A pregnancy accompanied by hyperinsulinemia represents a causative factor for insulin resistance and leads to vascular dysfunction via inflammatory mediators. Insulin sensitivity also is decreased progressively owing to the diabetogenic effects of gestational hormones and proinflammatory cytokines have been attributed to be causative factors of insulin resistance [1,2].

Gestational diabetes associates with low grade inflammatory response and dysregulated synthesis or function of pro-inflammatory cytokines, i.e. interleukin (IL)-6, IL-1β, IL-10, tumor necrosis factor (TNF)-α, and visfatin. These compounds together with inflammatory cells such as macrophages participate the initiation and progression of insulin resistance, GDM and diabetes mellitus [3,4]. The infiltration of macrophages in pancreatic and adipose tissue causes enhanced production of proinflammatory cytokines while other immune cells can also contribute the infiltration [5]. This massive exposure of pancreatic β- cells results in low insulin synthesis and apoptosis, thus causing high blood glucose levels [6,7].

High glucose level directly affects islet cells inducing pro-apoptotic receptor FAS on β-cells, leading to IL-1 β activation as a final effector way [8]. Several cytokines-TNF- α, IL-6- and some chemokines are found in plasma of the patients have been shown IL-1 dependent [9]. TNF, IL-1 β and IL-6 have been reported to promote insulin resistance and reflect the innate immune system activation [10]. TNF-α affects on glucose metabolism by either inhibiting insulin signaling or reducing the expression of regulatory molecules [11,12]. The roles of TNF- α and IL-1 β as well as IL-6 have been emphasized in the pathogenesis of insulin resistance and gestational diabetes [13-15]. On the other hand, IL-10 is an anti-inflammatory cytokine specifically counteracting with the responses mediated by TNF-α [16,17]. IL-10 works as a modulator of maternal immune response against fetal allograft, and its level increases during pregnancy [18]. Low concentrations of IL-10 in

plasma have been found to associate with gestational diabetes [15,19]. Intensity of hyperglycemic situation has been shown to alter both TNF- α and IL-10 levels leading to higher TNF- α/ IL-10 ratio [20]. An adipocyte-derived protein, visfatin is known to be mediated by glucose and insulin levels. Although plasma levels of visfatin have been found increased in cases with type 2 diabetes, metabolic syndrome and obesity [21-23], opposite findings have also been reported [24].

In women with GDM, variations in plasma cytokine levels have previously been demonstrated [25,26]. However, the association of cytokines with short- and long-term glycemic markers has not been defined clearly. HbA1C is a glycation product of hemoglobin defined as a long-term glycemic marker, representing the glycemic changes over 90 days. It is known that a considerable lag-time exists between actual glycemic changes and HbA1C response. Therefore, the improvement or deteriation of blood glucose level in short period are not reflected exactly with HbA1C. However, fructosamine levels indicate all glycated proteins including albumin, lipoprotein and globulin and has been reported to show larger intra-individual variability compared with HbA1C [27]. Serum protein concentrations and dilutional anemia which may develop during pregnancy can affect fructosamine levels [28].

1,5-Anhydroglucitol (AG), a sensitive very short-term marker, reflects glycemic status during 24 h period and responses rapidly to changes in plasma glucose concentrations [29]. Serum 1,5-AG has been reported to exhibit postprandial hyperglycemia more accurately than HbA1C [30]. Therefore, the assessment of metabolic control in GDM patients is recommended to accomplish with measuring 1,5 AG together with HbA1C [31].

In the present study, the variations in the plasma levels of visfatin, TNF-α, IL-1β, IL-6, and IL-10 were investigated and their associations with glycemic markers -HbA1C, fructosamine, 1,5-anhydro-D-glucitol (1,5-AG)-, and continuous glucose monitoring system (CGMS) parameters were evaluated.

Materials and Methods

Patients

The study group consisted of 33 pregnant women diagnosed with gestational diabetes (median age 32, range 20-47) and pregnant women without any maternal and fetal disorder (n=20, median age 28, range 18-37) served as controls. Median gestational age was 36 weeks.

All pregnant women attending to the Istanbul Faculty of Medicine, Department of Gynecology and Obstetrics are screened for GDM between 24th and 26th weeks by a two-step GDM screening test according to American Diabetes Association (ADA) [32]. The glycemic control of women diagnosed with GDM was provided only by diet and exercise. Three of the 33 women diagnosed with GDM required insulin therapy were excluded from the study together with the patients with renal failure, hepatic insufficiency, severe anemia. The treatment protocol was planned to maintain normoglycemic state throughout the pregnancy. Control subjects were compared with the women with GDM for maternal age, parity, gestational age at delivery, birth weight, and family history of DM. All women delivered a live birth.

Venous blood samples were collected in vacutainer serum separator tubes (Becton Dickinson, Plymouth, UK), centrifuged at +4°C for 15 minutes, at 1000×g. Serum aliquots were stored at -80°C for the measurements of TNF-α, IL-10, IL-1β, IL-6 and 1,5-AG levels. Serum fructosamine, HbA1C levels were carried out on the same day. For HbA1C assay, blood samples were collected in vacutainer tubes containing K2-EDTA. Continuous glucose monitoring system (CGMS) was applied for 72 h to the women with GDM.

The study was approved by the Ethical Committee of Istanbul University (project # 2014/399). An informed consent was taken from each patient.

Methods

HbA1C levels were determined using cation- exchange high performance liquid chromatography [HPLC] with Bio-Rad Turbo II (Bio-Rad, Richmond, California, USA) and fructosamine levels were measured with colorimetric method using Roche modular system (Roche, Mannheim, Germany) within four hours following blood drawn.

Serum visfatin, IL-6, TNF-α, IL-10, IL-1β concentrations were determined by the enzyme-linked immunosorbent method (ELISA, Assaypro, St Charles, USA) with intra-assay coefficient of variation (CV) were below 5%, and interassay CV<8%. Serum visfatin level was measured using ELISA kit (Sunred Biological Technology, Shanghai, China) with intra- and inter-assay CVs being 9.0% and 11%, respectively. 1,5 AG levels were measured with ELISA technique with intra-assay CV% 2.5 and inter-assay CV 5.0% (Cusabio, Wuhan, China). Reference values of 1,5-AG was 14.4-30.2 mg/L in healthy subjects [33].

The results of CGMS were analyzed for 72h period before blood collection for 1,5-AG and HbA1C measurement in 33 women. Mean glycemia and its standard deviation, mean maximum and minimum glucose levels and the percentage of mean absolute difference (MAD%) were calculated using CGMS software using 12 measurements through 72 hours (Medtronic, Minneapolis, MN, USA).

Demographic values (weight, height and waist/hip circumferences) were measured and BMIs of subjects were calculated as the ratio between weight and height squared (kg/m^2).

Statistical analysis

Data were analyzed using SPSS 15 (SPSS, Chicago, IL, USA). The results were expressed as mean ± SD and median [range]. The normality of the data distribution was evaluated by the Kolmogorov-Smirnov test. Mann–Whitney U-test was performed to compare the data between the groups. Correlation analyses were carried out by the Pearson test. Interaction effect between BMI and cytokine levels was tested with a two-way ANOVA model. Statistical significance was defined as $p<0.05$.

Results

Baseline demographic characteristics of the subjects are shown in Table 1. There was no significant difference between the groups with respect to age, weeks of gestation, average weight gain during pregnancy, parity, or family history of type 2 diabetes. Only BMI of two groups were significantly different (p=0.006).

Data obtained from the women with GDM were compared with those in the control group (Table 2). Serum IL-6 and IL-1β levels were found significantly high in the former (p=0.039, and p=0.04, respectively). An increase in TNF-α level by approximately 33% was observed, but the difference did not give a statistical significance.

Visfatin levels in GDM group showed a slight decrease, while IL-10 levels were similar in both groups. No significant interactions were found between maternal BMI and cytokines, therefore the analyses on IL-6 (p=0.03) and IL-1 β (p=0.04) were not adjusted for BMI.

Demographic characteristics	GDM [n=30]	Control group [n=20]
Age [years]	32 [20-47]	28 [18-37]
Parity	3 [1.0-6.0]	1.0 [1.0-3.0]
BMI [kg/m^2]	26.4 [17.3-44.1]	24 [21-26]
Gestational weeks at delivery	36 [35-38]	35 [34-38]
Birth weight [g]	3190 [2390-3800]	3177 [2150-3500]
Family history of DM [n]	20	8

Table 1: Demographic characteristics and birth outcomes of the study groups. Median [range].

	GDM	Control	p
Visfatin [ng/mL]	3.8 ± 2.9	4.97 ± 5.47	0.426
IL-6 [pg/mL]	3.1 ± 0.9	2.7 ± 0.7	0.04*
TNF-α [pg/mL]	6.61 ± 7.53	4.41 ± 3.03	0.59
IL-1β [pg/mL]	1.62 ± 0.4	1.39 ± 0.2	0.04*
IL-10 [pg/mL]	88.3 ± 66.5	71.8 ± 13.8	0.73
TNF-α/ IL-10	0.08 ± 0.1	0.06 ± 0.05	0.56
1,5 AG [mg/L]	17.2 ± 4.3	20.0 ± 5.8	0.06
HbA1C % [mmol/mol]	5.1 ± 0.3 [32 ± 4]	4.9 ± 0.17 [30 ± 2]	0.11
Fructosamine [μmol/L]	2.1 ± 0.3	-	-
Average glucose [mg/dL]	86.1 ± 0.7	-	-
Min. glucose [mg/dL]	54.7 ± 11.9	-	-
Max. glucose [mg/dL]	131.4 ± 23.2	-	-
MAD%	6.84 ± 3.06	-	-

Table 2: Adipocytokine, glycemic markers, and CGMS indices in women with gestational diabetes [means ± SD].

Significant correlations between glycemic markers and cytokines were obtained in the GDM group. Visfatin levels were correlated with 1,5 AG (r=0.557, p=0.001) and TNF-α concentration was correlated with HbA1C (r=0.341, p=0.050). When the indices of CGMS were evaluated, mean glucose concentration was 85.1 (10.7) mg/dL, minimal glucose level was 54.7 (11.9) mg/dL, and maximum glucose level was 131.4 (23.3) mg/dL. IL-1β was significantly asso0ciated with both the percentage of MAD% and average glucose level (r=0.524, p=0.004 and r=0.488 and p=0.008, respectively). No significant association was found between fructosamine levels and any of the cytokines. Significant associations were also obtained between proinflammatory cytokines; visfatin levels were associated with IL-10 [r=0.565, p=0.001], TNF-α was associated with IL-6 (r=-0.318, p=0.032) and IL-10 (r=0.588, p=0.000). IL-1β concentrations were correlated with TNF-α /IL-10 ratio (r=-0.350, p=0.01).

Discussion

Pro- and anti-inflammatory cytokines secreted from placenta contribute to normal fetal growth and development and they also take part in maternal immunity. The balance between pro- and anti-inflammatory cytokines shows variations during different gestational stages. The regulatory function of IL-10 in this delicate equilibrium has been emphasized in the course of normal pregnancy [18].

In the present study, plasma levels of adipocytokines (visfatin, IL-6, TNF-α, IL-1 β- and IL-10) were determined in GDM patients and the relation between cytokine levels and long- and short-term glycemic markers was evaluated. IL-6 and IL-1β levels were found elevated in GDM patients. Although TNF-α levels showed 33% increment, the difference between groups did not reach a significant level. During pregnancy, increased TNF-α and decreased IL-10 levels have been observed in the late term [13,15,19]. However, some researchers did not find any differences with respect to the stages of pregnancy [19]. Our findings were in agreement with the latter. In GDM patients, Moreli et al. have reported increased levels of TNF-α in placenta and maternal plasma, together with decreased IL-10 levels in plasma, and introduced the precedence of an altered cytokine profile in hyperglycemic pregnancies [20]. Despite the increase in placental TNF-α, its plasma levels may not alter due to the presence of various factors which is known to affect the transition of placental secretion through the circulation. Among these factors, hypoxia resulted from hyperglycemic environment and pre-existing inflammatory condition should be taken into account [34,35]. Previous studies with regard to IL-10 levels in GDM are not concordant [15,19,25,26,36]. Our results are in good agreement with the researchers who reported no difference in maternal IL-10 levels during GDM [26,36,37].

When the association between glycemic markers and cytokines were investigated, IL-1β levels were associated with average glucose level and MAD% which are indices of CGMS and reflect the fluctations of glucose levels in short-term. This association may be explained by the ongoing inflammatory condition which is triggered due to excess glucose. It has been shown that IL-β system is induced by hyperglycemia [5]. Other cytokines and inflammatory mediators are accepted to be IL-1 dependent [9]. On the other hand, no association was obtained between 1,5 AG and IL-1 β. This short-term marker was correlated only with visfatin levels. 1,5 AG level has been reported to demonstrate negative correlation with high glucose levels in poorly controlled diabetes [38]. It has been shown that visfatin stimulates glucose uptake and inhibits glucose release from the hepatocytes by inducing the expression of peroxisome-proliferator-activated receptor-γ (PPAR-γ) which might be involved in developing insulin resistance [39]. Our findings support an auxiliary action of visfatin for glucose homeostasis in accordance with a previous study [40].

TNF-α levels were associated only with HbA1C which is long-term glycemic marker, while no association was obtained with 1,5 AG and MAD%. In a previous study, it has been reported that increases in plasma TNF- α levels associated with the glycated hemoglobin in GDM patients [41]. IL-6 has been shown to exert inflammatory properties and being secreted under hyperglycemic conditions [42]. Nevertheless, the roles of IL-6 in insulin resistance is controversial. While IL-6 secreted from liver and adipocytes have been related with insulin resistance, IL-6 derived from skeletal muscle has opposite effect

[43,44]. In our study, IL-6 levels were found increased. There are several studies reported high levels of IL-6 and decreased levels of IL-10 in GDM patients [45,46], whereas some others did not confirm these results [37,47]. In our study, we could not find any association among IL-10 and IL-6 levels with any of the glycemic markers.

Our study has some limitations. First, the study population is limited. Second, our study was performed in GDM patients close to term. Measurements of cytokine levels together with glycemic markers at several terms of the gestational period would have given a better understanding about the impact of cytokines on carbohydrate metabolism.

The increased levels of proinflammatory cytokines, IL-6, IL-1β, and TNF-α, and their correlation with short- or long-term glycemic control markers present an evidence for the roles of these cytokines and visfatin on carbohydrate metabolism in the course of gestational process and gives a priority to proinflammatory cytokine profile among laboratory tests in GDM patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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