

Research Article

Insulin-like growth factor (IGF)-I, IGF-binding protein (IGFBP)-1, and fibroblast growth factor (FGF) 21 serum levels in Chinese women with and without gestational diabetes

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Abstract

Background: Although Asians are generally characterized by lower body mass index (BMI) compared to Caucasians, the prevalence of gestational diabetes mellitus (GDM) among Asian women is higher. Our previous studies found that, like the Caucasians, pregnant Chinese women show difference between GDM and non-GDM in the levels of total adiponectin. However, there is no difference in other inflammatory markers such as CRP, TNF α , IL-6 or MCP-1. The aim of the present study was to assess the IGF-I, IGFBP-1, and FGF21 levels in Chinese-American women with and without GDM.

Methods: The study involved 230 consecutively recruited pregnant subjects (191 without and 39 with GDM), 18-40 years of age and 24-28 weeks of gestation.

Results: GDM group had significantly higher levels of HbA_{1c}, 3-hour oral glucose tolerance test (3h-OGTT) and fasting insulin and no different BMI values when compared to Chinese women without GDM. Unadjusted comparisons demonstrated that IGF-I and FGF21 levels were significantly higher, and those of IGFBP-1 significantly lower in the GDM group compared to the non-GDM group. Adjusted analyses for age, BMI, HbA_{1c}, 1-hour glucose challenge test (1h-GCT), and insulin levels, confirmed the higher IGF-I levels in Chinese women with GDM supporting previous studies in Caucasian women.

Conclusions: These results demonstrate that, similarly to Caucasians, IGF-I may play a role in the pathophysiology of GDM in Chinese women.

Novelty statement

- Chinese women with gestational diabetes mellitus (GDM) demonstrate higher IGF-I blood levels compared to those without GDM.
- IGF-I may play a role in the pathophysiology of GDM.

Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. The prevalence of GDM varies between 2% and 17% among the different ethnic groups [2], with 5.0-7.4% prevalence among the Asian women [3] and 6.4% prevalence among the US Chinese women [4].

Previous studies showed that the white adipose tissue cytokine, adiponectin, and in particular its high-molecular circulating form, has insulin-sensitizing actions and is negatively associated with type 2 diabetes mellitus (T2DM) and GDM [5-8]. Our previous study in pregnant Chinese-American women showed that total adiponectin levels, rather than the high-molecular weight adiponectin levels, most consistently correlate with the insulin sensitivity parameters [9]. Women without GDM who had failed a 1-hour 50 gram oral glucose

challenge test (1h-GCT \geq 135 mg/dL) with or without one abnormal glucose value during the 3-hour 100 gram glucose tolerance test (3h-OGTT), exhibited lower levels of total adiponectin. In addition, total adiponectin negatively correlated with insulin resistance markers (insulin, 1h-GCT, HbA_{1c}, and BMI). In the current study, we analyzed the relationships between fibroblast growth factor (FGF)21, insulin-like growth factor-I (IGF-I), or insulin-like growth factor binding protein-1 (IGFBP-1) and markers of glucose tolerance (insulin, 1h-GCT, HbA_{1c}, BMI, and age) in Chinese-American pregnant women.

Insulin-like growth factor (IGF)-I, produced in the liver, acts as a primary mediator of the pituitary growth hormone (GH). It mimics the actions of insulin including stimulation of glucose uptake and

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inhibition of gluconeogenesis. IGF-I function is modulated by IGF-binding proteins of which IGFBP-1 is under inhibitory control of both insulin and IGF-I [10,11].

FGF21 is a protein that stimulates glucose uptake in adipocytes acting synergistically with insulin [12]. Studies have shown that treatment of diet-induced obese or leptin deficient (ob/ob) or leptin receptor deficient (db/db) obese mice obese mice with FGF21 or overexpression of FGF21 in transgenic mice resulted in reduced body weight and adiposity and improved insulin sensitivity [13-14]. Blood levels of FGF21 are elevated in T2DM patients [15,16], but the data for GDM patients are controversial, showing no different [12] or elevated [18] FGF21 blood levels. Indeed, recent studies demonstrated increased placental mRNA and protein FGF21 expression in GDM patients [17,18], but no difference in FGF21 cord blood levels [18].

Although Asian women are generally characterized by lower obesity rate, the GDM prevalence among Asians is approximately twice as high as that in Caucasian women (6.4% vs. 3.8%) [4]. The aim of this study was to evaluate the roles of IGF-I, IGFBP-1, and FGF21 in the pathogenesis of GDM in pregnant Chinese women in an effort to assess whether these markers relate differently to GDM in Chinese compared to the literature on Caucasians. To our knowledge, there have been no studies examining the involvement of these factors in the GDM in Asian populations.

Methods

Subjects

The study was approved by Mt. Sinai Beth Israel Hospital's Institutional Review Board. Chinese-American subjects were recruited by Drs. Stephen Wan and Doris Tan from their practices. Consent forms translated into Chinese were given and the consent was obtained from all women involved in the study. Inclusion criteria were as follows: women of Chinese ethnicity, 18 to 40 years of age and 24-28 weeks of gestation. Exclusion criteria were as follows: diagnosis of hepatitis B or other infectious diseases (Herpes virus, *Streptococcus B* carrier, *Chlamydia*, and *Candida*), thyroid dysfunction, thalassemia, and a history of miscarriages or infertility with use of *in vitro* fertilization (IVF).

Blood samples were obtained from subjects one hour after 50-gram oral glucose challenge test (1h-GCT). The serum samples were sent to Quest Diagnostics for glucose and HbA_{1c} analysis. Additional blood samples were collected at the same time, centrifuged at 2000 rpm for 10 minutes to separate serum from the cells, and the sera were stored at -80 °C for further biochemical marker measurements.

Identifying GDM

A 2-step test was used to diagnose GDM. 50 g glucose was administered and the serum glucose level was measured one hour later. The serum glucose value of 135 mg/dL was used as a threshold for 1h-GCT. If subjects failed the 1h-GCT (≥ 135 mg/dL), they underwent a 100-gram 3-hour oral glucose tolerance test (3h-OGTT) with capillary blood glucose levels measured at 0, 1, 2, and 3 hours. Glucose levels were measured by finger-stick HemoCue® Hb 201+ System glucometer (HemoCue, Brea, CA) since many study subjects refused to have blood drawn four times because of cultural beliefs about phlebotomy during pregnancy. The diagnosis of GDM was based on two or more glucose values at or above the threshold values: 0 hour (95 mg/dl), 1 hour (180 mg/dl), 2 hours (155 mg/dl), and 3 hours (140 mg/dl).

Enzyme-linked immunosorbent assay (ELISA)

Serum concentrations of biochemical markers (FGF21, insulin, IGF-I, and IGFBP-1) were measured using ELISA kits (ALPCO, Salem,

NH). The intra- and inter-assay coefficients of variability (CV) of the ELISA kits were as follows: IGF-I (5.1-6.67% and 2.3-6.8%), IGFBP-1 (2.5% and 4.9-7.4%), insulin (5.1% and 6.7%), FGF21 (4-5% and 3.5-10.2%).

Statistical analyses

230 consecutive patients were recruited and divided into two groups: GDM (191 patients) and non-GDM (39 patients). Demographic and clinical variables were compared (age, BMI, HbA_{1c}, 3h-OGCT, and insulin) using the two-sample *t*-test. Both the *t*-test and standard multiple linear regression were used to compare the two groups on each of the three markers (IGF-I, IGFBP-1, and FGF-21). The multiple regression method was used to compare markers after adjusting for age, BMI, HbA_{1c}, 1h-GCT, and insulin. Variable selection was determined using backward elimination, with group forced into the model. Results were considered significant if $p < 0.05$.

Results

The subjects' demographic and other variables (age, BMI, HbA_{1c}, 3h-OGCT, and insulin) are shown in Table 1. The two-sample *t*-test analysis showed that the GDM group, as expected, had significantly higher mean age ($p < 0.0029$), HbA_{1c} ($p < 0.0023$), 1h-GCT ($p < 0.0001$) as well as insulin levels ($p < 0.0001$). There were no statistically significant differences in BMI between the two subject groups (Table 1).

IGF-I, IGFBP-1, and FGF21 data are shown in Table 2. The unadjusted comparisons of these markers showed that the serum levels of IGF-I and FGF21 were significantly higher in the GDM group compared to non-GDM ($p < 0.0002$ and $p < 0.0098$, respectively). Conversely, the levels of IGFBP-1 were significantly lower ($p < 0.0144$) in the GDM group compared to the non-GDM group. After adjustment for age, BMI, HbA_{1c}, 1HGCT, and insulin levels, IGF-I level was still significantly higher ($p < 0.0332$) in the GDM group, however the levels of FGF21 and IGFBP-1 were no longer significantly different between the two groups (Table 2).

Discussion

Previous epidemiological studies demonstrated that ethnic background is an important factor in the development of GDM [19]. Asian and Pacific Islander women have higher predisposition to GDM compared to all other ethnic groups [4]. Compared to Caucasian women, the prevalence of GDM among Chinese women is approximately twice as high [4]. It is known that increased body weight before and during pregnancy [20-21] as well as higher weight gain velocity during pregnancy [22] are predisposing risk factors for the development of GDM. Importantly, this fact is inconsistent with the lower obesity rate among the Chinese, although previous reports

Table 1. Comparison on demographic and clinical variables.

Variable	Non-GDM (n)	GDM (n)	p value
Age [yrs]	30.27 ± 4.66 (191)	32.77 ± 5.09 (39)	0.0029
BMI [kg/m ²]	24.08 ± 2.84 (190)	24.95 ± 3.64 (39)	NS
HbA _{1c} [%]	5.16 ± 0.33 (178)	5.35 ± 0.31 (36)	0.0023
1h-GCT [mg/dl]	113.70 ± 22.75 (191)	161.05 ± 18.32 (37)	0.0001
Insulin [ng/ml]	55.32 ± 44.48 (191)	114.32 ± 92.88 (39)	0.0001

Table 2. Mean levels of candidate markers.

Variable	Non-GDM (n)	GDM (n)	p value
IGF-I [ng/ml]	178.19 ± 69.89 (180)	233.48 ± 102.20 (38)	0.0332
IGFBP-1 [ng/ml]	162.36 ± 105.82 (183)	141.23 ± 114.48 (38)	0.8338
FGF21 [pg/ml]	33.12 ± 21.90 (189)	48.84 ± 44.13 (38)	0.3475

showed that Asian women can develop insulin resistance at lower body mass index (BMI) values [23]. Our study did not show any statistically significant difference between the BMI values of non-GDM and GDM Chinese women, indicating that BMI may not be an important predictor of GDM among Chinese women. This phenomenon may be due to the higher body fat percentage among the Asians compared to Caucasians or the differences in the spatial distribution of the white adipose tissue depots. In fact, Asian women have a greater central adiposity than Caucasians, which could partially explain the higher prevalence of insulin resistance and diabetes [24,25].

Our previous studies suggested that both total and high molecular weight adiponectin may be important contributors to GDM in Chinese-American women, but unlike the Caucasians, Chinese women displayed no significant correlations between markers of glucose tolerance and inflammation [9]. The goal of this study was to compare FGF21, IGF-I or IGFBP-1 and markers of glucose tolerance (insulin, 1h-OGTT, HbA_{1c}, BMI or age) between pregnant Chinese-American women with or without GDM.

As expected, our data show that the GDM group had higher levels of HbA_{1c}, 1h-OGTT glucose and insulin levels compared to non-GDM group. Additionally, IGF-I levels were also elevated in the GDM compared to the non-GDM subjects. It is known that IGF-I mimics insulin in stimulating glucose uptake as well as in inhibiting gluconeogenesis [11]. IGF-I also plays an important role during gestation in placental development and function [26]. Elevated levels of IGF-I have been associated with septal hypertrophic cardiomyopathy [27]. The results from this study confirmed previous observations in Caucasian women that IGF-I levels with or without adjustment for age and BMI are higher in GDM [28].

Our unadjusted results also indicate that the levels of IGFBP-1 may be lower in GDM, supporting previous observations in Caucasians [29]. Previous studies showed that serum IGFBP-1 correlates negatively with circulating insulin levels, and it was suggested that IGFBP-1 may be a marker for hyperinsulinemia in obese menopausal women [30]. Although the role of IGFBP-1 in the development of GDM is not clear, lower IGFBP-1 levels may result in higher circulating free IGF-I levels, contributing to fetal macrosomia [31]. However, this hypothesis is not conclusive since, after adjusting for age and BMI, we did not find a statistically significant difference in the levels of IGFBP-1 between the two groups.

In this study we were also interested in assessing the association of FGF21 with GDM, since FGF21 was previously found to significantly correlate with markers of insulin resistance and dyslipidemia [32] and to play a role in the pathogenesis of T2DM [33]. Our data indicated significantly higher unadjusted serum FGF21 levels in GDM women compared to the healthy pregnant controls. After adjusting for age and BMI, however, the difference was no longer significant, suggesting that FGF21 may not play a role in the development of GDM in Chinese.

Our study has a number of limitations. The subjects without GDM were significantly younger than those in the GDM group. It is well known that age plays a major role in the development of glucose intolerance [34]. We were also not able to obtain data on the pre-gestational BMIs of our subjects, since they presented to the clinic for the first time at 8-14 gestational week.

We measured glucose values during the 3h-OGTT by using HemoCue® Hb 201+ System glucometer because of cultural beliefs, as described above. HemoCue® Hb 201+ System glucometer demonstrates negative bias of 8% when compared to Vitros 5,1 FS analyzer (Ortho

Table 3. Differences between Chinese and Caucasian women with GDM. ↑ - increased in GDM; ↓ - decreased in GDM; ↔ - no difference between GDM and non-GDM.

Risk Factor / Marker	Chinese (our studies)	Caucasians (literature)
Age	↑	↑
BMI	↔	↔
Free Adiponectin	↓	↓
Total Adiponectin	↓	↓
Insulin	↑	↑
IGF-I	↑	↑
FGF21	↔	↔
IGFBP-1	↔	↔

Clinical Diagnostics, Neckargemund, Germany) with within-run imprecision of 2.5-5.8% and between-run imprecision of 3.1-5.1%.

To our best knowledge this is the first study of the examined markers which involved pregnant Chinese women. That no Caucasian subjects were used as controls is another weakness of the study. Thus, the comparisons between the findings in Chinese and Caucasians were made based on the literature.

It is important to note that the findings from our study may not be representative of the general Chinese population in the United States or China, since we recruited the patients only from two obstetrics and gynecology clinics located in New York City's Chinatown area.

In summary, the results of our study demonstrate that, similarly to Caucasians, higher serum IGF-I levels are present in Chinese-American women with GDM compared to Chinese-American women without GDM (Table 3). Further studies are needed to better understand the role of IGF-I in the pathophysiology of GDM in both Asians and Caucasians.

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Disclosure

None of the authors have any financial conflict of interest in regard to the materials included in this manuscript.

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