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Urinary C-peptide secretion (UCPS): Can it be a new index to reflect insulin sensitivity and a predictor in pregnant women?

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Abstract

To investigate the correlation between urinary C-peptide secretion (UCPS) and insulin sensitivity in pregnant women, and to provide new ideas for the early detection of gestational diabetes, we recruited 166 women between 20 and 28 weeks of gestation. Their height and weight were measured to calculate the body mass index (BMI). 75g OGTT was carried out, to detect the serum glucose, serum insulin, and C-peptide levels. Besides, the homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β cell function (HOMA-β), the Matsuda index, and area under the serum C-peptide curve (CPauc) were calculated. Additionally, the fasting urine specimen and all urine samples within 2 hours after OGTT were collected to determine the urinary C-peptide and urine volume to calculate UCPS. We found that fasting serum insulin (Fins), fasting serum C-peptide (FCP), BMI, OGTT 2h, UCPS (UCPS120), CPauc, Matsuda index and HOMA-IR of GDM group were significantly higher than NGT group. FCP was positively correlated with UCPS0 (r=0.234, p=0.002) and HOMA-β (r=0.251, p=0.001). UCPS120 was positively correlated with CPauc (r=0.176, p<0.001), Matsuda index (r=-0.362, p<0.001) and HOMA-IR (r=0.336, p<0.001). The combination of BMI and UCPS120 was better than the other indices in predicting GDM, with a sensitivity of 72.0% and specificity of 70.7%. In conclusion, UCPS120 has the potential to be a new index to reflect insulin sensitivity in pregnant women. For screening the GDM, the combination of BMI and UCPS120 was better than other indices.

Keywords: Gestational diabetes mellitus, Urinary C-peptide secretion, Insulin sensitivity, BMI

Introduction

Gestational diabetes mellitus (GDM) is an increasingly serious global health problem, which is mainly caused by impaired insulin action and β-cell dysfunction [1]. With the progress of pregnancy, maternal insulin sensitivity decreases by about 60 percent [2], and increasing insulin antagonistic hormone will lead to maternal hyperinsulinemia [3]. GDM not only increases the risk for maternal and fetal complications during pregnancy, but also increases the risk of long-term complications in both mother and offspring [4,5]. Early identification of GDM in pregnant women is essential, as early appropriate treatment can reduce both mild and severe pregnancy-related complications. To diagnose GDM and evaluate the islet function of pregnant women, three or more points during the oral glucose tolerance test (OGTT) is usually used to detect serum glucose, insulin, and C-peptide [6,7]. Most methods to measure islet function require blood sampling, making them unsuitable in persons with difficult access to veins. Therefore, we propose a noninvasive, easily operative, and highly acceptable method to assess insulin sensitivity.

C-peptide is a part of proinsulin that is cleaved prior to co-secretion with insulin from pancreatic beta cells [7]. A fixed proportion of C-peptide is then excreted in urine, with excretion levels associated with insulin secretion and plasma insulin concentration under normal circumstances, making urinary C-peptide (UCP) a useful marker of insulin production in many clinical studies [8,9]. The objective of this study was to use postprandial UCP secretion (UCPS) to assess islet function in pregnant women between 20 and 28 weeks of gestation, and to investigate whether it can be used as a screening indicator for GDM.

Methods

1.1. Objects

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Pregnant Han nationality women at 20-28 gestational weeks (according to Chinese Diabetes Society 2017 guidelines) undergoing routine checks in the outpatient department of our hospital from January 2017 to December 2017 were selected. All of them were preliminarily screened the by 75g OGTT to collect fasting, 1 h and 2h plasma as well as urine specimens. All participants were then divided into GDM group and NGT group according to the serum glucose level. Those previously diagnosed with diabetes, combined with acute infection, taking glucocorticoids within the past 2 weeks, and combined with other chronic diseases were excluded. This study was approved by Ethics Committee, and all enrolled participants had signed the informed consent.

Diagnostic criteria of GDM: according to the recommendations of the guidelines from American Diabetes Association (2016): pregnant women conforming to any one of the following criteria could be diagnosed: FBG ≥5.1 mmoL / L (92mg/dL), 75g OGTT 1h serum glucose ≥10.0 mmoL/ L(180mg/dL) or 75g OGTT 2h serum glucose ≥8.5mmoL/ L (153 mg/dL).

1.2. Methods

General clinical data collection: age, family history of diabetes, history of GDM, previous medical history, gestational week (w), height (m), and current weight (kg) of all enrolled pregnant women were recorded. Meanwhile, the current body mass index (BMI, kg/m^2) was calculated.

Blood specimen collection and determination: for all enrolled pregnant women, 5ml fasting blood was collected at 8:00 in the morning after an 8h overnight fast, to determine the FBG, blood lipid, liver and kidney function, glycated hemoglobin (HbA1c), fasting insulin (FIns), and fasting C-peptide (FCP). After fasting blood collection, 75g OGTT was taken, and the venous blood was collected at 1h and 2h, respectively, to determine the serum glucose, serum insulin, and serum C-peptide at the corresponding time points.

Urine specimen collection and determination: fasting urine (participants should pass their overnight first void urine before OGTT, as well as urine at OGTT 2h (all urine should be collected until 2h after taking the glucose) were collected. No food was allowed during the OGTT, while water was allowed. The urine volume should be recorded each time, and 10 ml urine should be retained, which was transferred to 5 ml frozen tubes and preserved in the refrigerator at -80℃ until detection.

Determination of related indexes: Determination of serum insulin, serum C-peptide, and urine C peptide: chemiluminescent immunoassay (IMMULITE 2000 analyzer, Siemens); serum glucose determination: glucose oxidase method (AU5800 biochemical analyzer, Beckmann); HbA1c determination: high pressure liquid chromatography (HPLC) (Arkray HA-8180 full-automatic glycated hemoglobin analyzer, Arkray Kabushiki gaisha); and urine creatinine determination: picric acid method (AU5800 biochemical analyzer, Beckmann).

Computational formula: Matsuda index = 10000/squa [(18×FBG (mmoL/L) ×Fins (mU/L) ×OGTT the average serum glucose (mmoL/L) ×OGTT the average insulin (mU/L))]; HOMA-IR (homeostasis model of insulin resistance index) = Fins (mU/L) ×FBG (mmoL/L) / 22.5; HOMA-β (homeostasis model of insulin secretion index) = [20×Fins (mU/L)] / [FBG (mmoL/L) - 3.5]; UCPS (product of urine volume and urinary C peptide) (ug) = UCP (ng/mL) ×urine volume (mL) /1000.

1.3. Statistical analysis

Statistical analysis was performed using SPSS 13.0. A p value of < 0.05 was considered statistically significant. Measurement data were expressed as mean ± standard deviation, and inter-group comparison was carried out using t- test. For non-normal distribution data, Mann-Whitney U test was employed for comparison. The Pearson correlation coefficient and linear regression models were adopted for correlation analysis. Receiver operator characteristic curve (ROC) was used to assess the predictive ability for GDM of each index.

Results

The clinical and laboratory parameters of women with GDM and without GDM were compared and the results are displayed in Table 1. Data from 166 pregnant women were analyzed. The mean age was 28 years (range 21–40 years). Forty-one patients were diagnosed with GDM, of whom 21 had a family history of diabetes. There were no significant differences in age, gestational age and family history of diabetes between the two groups.

Table 1 also shows the results of univariate analysis of maternal characteristics and laboratory parameters. UCPS120 were found to be notably higher in women with GDM compared to those women without GDM (17.36±10.78 vs. 11.34±65.06 ng/ml, P < 0.05). Furthermore, we found a significant elevation in levels of serum insulin, FCP, CPauc, Matsuda index, and HOMA-IR of women with GDM in comparison with non-diabetic controls. As expected, FBG, BG60 and BG120, and HbA1C exhibited a notable elevation in women with GDM

as compared with healthy control women. There was no significant difference in Ins60 and Ins120 between both test groups.

Linear regression model was used to evaluate the relationship between UCPS and metabolic parameters. According to the results obtained from the analysis, we observed that UCPS0 levels showed a significantly positive correlation with FCP (r=0.243, p=0.002) and HOMA-β (r=0.251, p=0.001) (Figures 1A, 1B). Moreover, there was a positive correlation between UCPS120 and Matsuda index (r=-0.362, p<0.001), HOMA-IR (r=0.336, p<0.001) (Figure 2A, 2B) and CPauc (r=0.176, p<0.001) (Figure3).

To predict the GDM, we try to use the simple and non-invasive index, so BMI, UCPS120, HOMA-IR and Matsuda index are put into the model. The combination of BMI and UCPS120 was better than other index, with a sensitivity of 72.0% and specificity of 70.7% (Table 2, Figure 4).

Discussion

The present analysis of the collected data has shown that the UCPS120 levels were significantly higher after 20-28 weeks of gestation in the GDM women compared with controls. Furthermore, we found that UCPS120 was positively correlated with CPauc, Matsuda index, and HOMA-IR. We also observed that the combination of BMI and UCPS120 was better than the other indices, in predicting GDM. In conclusion, UCPS120 has the potential to be a new index to reflect insulin sensitivity in pregnant women.

Endogenous insulin levels are rarely measured in routine clinical practice, owing to practical limitations, including the need for rapid laboratory analysis of blood tests. Recently, a simple urine test, the urine C-peptide creatinine ratio (UCPCR), has been shown both in type 1 diabetes and type 2 diabetes, to be extremely well with the 'gold standard' measure of endogenous insulin secretion, the formal mixed-meal tolerance test, and a sensitive and specific test for absolute insulin deficiency [10]. UCPS is a new index adopted in this study, which reflects the total secretion of C-peptide in urine within a certain period of time, different from UCPCR [11]. In our study, UCPS0 was associated with FCP and HOMA-β, but the r value was low. In the other studies, they asked all the women to pass their overnight first void urine and collect the second void urine. We didn't emphasize to collect the second void urine; it may result in some discrepancy. UCPS120 of OGTT was correlated with CPauc, Matsuda index and HOMA-IR, and the Matsuda index had a strongest correlation. Previous study showed that Matsuda index had stronger correlation with hyperinsulinaemic euglycaemic clamp in pregnant women [12]. Although UCPCR120 only had weak correlation with Matsuda index, due to the small sample size, it still had the potential to be a new index to reflect insulin sensitivity in pregnant women.

Comparing the indexes of the two groups, it was found that the BMI, UCPS120, Fins, FCP, CPauc, Matsuda index and HOMA-IR of the GDM group were significantly higher than the NGT group. In all of these indexes, the calculation of CPauc, Matsuda index, and HOMA-IR requires more parameters. The determination of these parameters requires multiple blood tests. while BMI and UCPS120 are noninvasive ones. HOMA-IR and Matsuda index had better predictions for GDM in previous studies [13, 14]. Recently, researches showed that pregnant women with high BMI before pregnancy had significantly high risk for GDM [15]. And pregnancy high BMI may be an independent risk factor for GDM [16]. We hope to use effective, simple and best non-invasive index to predict the GDM. So, we choose BMI, UCPS120, HOMA-IR and Matsuda index. ROC curve analysis showed that to predict the GDM, the combination of BMI and UCPS120 was better than other indices, with a sensitivity of 72.0% and specificity of 70.7%. Many hospitals in China now advocate 75g OGTT for all pregnant women, but multiple blood collection during pregnancy may cause problems for some women. If non-invasive tests can be used to screen out high-risk groups, and then OGTT tests for high-risk groups, it may help to reduce the psychological pressure of pregnant women, but also to save medical resources.

There are still some limitations in this study, all women included were in the second trimester of pregnancy (20-28 weeks), and the sample size was small. The conclusion needs to be expanded to verify the sample size. Secondly, the women included in this study were all with normal renal function, and the effect of different renal function status on this index could not be determined. There is increasing evidence that lifestyle and therapeutic intervention after 18 weeks of pregnancy in at-risk women has little effect on preventing both GDM and fetal macrosomia [17-20]. Further studies with a larger scale are needed, such as women with different renal function states in the early stage of pregnancy, to evaluate whether UCPS can be applied to women in early pregnancy to facilitate early screening of high-risk populations and early intervention.

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Table 1. **Participants Characteristics and comparisons between two groups**

	Min	Max	NGT（N=125）	GDM（N=41）	*p*
Age（years）	21	40	27.70±3.66	28.20±3.84	0.462
Gestational age(weeks)	20	28	25.51±1.42	25.85±1.68	0.475
Family history of diabetes（%）	/	/	15(12.0%)	6(14.6%)	1.000
BMI（kg/m^2）	16.02	34.38	20.31±2.71	22.13±2.63	<0.001**
Fins（uU/mL）	2.04	46.04	7.42±3.22	10.40±6.84	0.014*
FCP（ng/mL）	0.72	6.14	1.87±0.67	2.51±0.84	0.001**
FBG（mmoL/L）	4.09	6.01	4.62±0.25	5.23±0.31	<0.001**
Ins60（uU/mL）	12.67	352.66	52.90±36.97	71.42±56.92	0.076
CP60（ng/mL）	3.59	35.62	9.94±3.73	12.20±5.02	0.016*
BG60（mmoL/L）	4.05	11.90	7.31±1.43	9.09±1.62	<0.001**
Ins120（uU/mL）	10.37	315.45	51.27±36.28	73.27±56.22	0.114
CP120（ng/mL）	4.61	22.97	10.95±4.00	12.70±4.60	0.135
BG120（mmoL/L）	3.95	9.32	6.55±0.94	7.68±1.26	<0.001**
UCPS0（ug）	0.36	27.86	4.76±4.57	5.74±4.19	0.510
UCPS120（ug）	1.19	51.37	11.34±65.06	17.36±10.78	0.033*
HbA1C（%）	3.90	5.60	4.82±0.25	5.09±0.22	<0.001**
HOMA-β	54.60	601.83	133.53±51.56	122.76±87.97	0.106
HOMA-IR	0.38	10.29	1.54±0.71	2.43±1.58	<0.001**
Matsuda	0.86	18.01	32.37±13.56	21.33±9.20	<0.001**
CPauc	446.40	2907.90	981.15±322.46	1187.69±400.53	0.014*
INSauc	1353.60	32004.30	4934.84±3125.91	6795.46±5057.21	0.058

*p<0.05; **p<0.01

BMI: body mass index;GDM: Gestational Diabetes Mellitus;HbA1c: Glycosylated hemoglobin;

Fins: Fasting Insulin; Ins60: OGTT 1-Hour Insulin; Ins120: OGTT 2-Hour Insulin;

FCP: Fasting C peptide; CP60: OGTT 1-Hour C peptide; CP120: OGTT 2-Hour C peptide;

FBG: Fasting Glucose; BG60: OGTT 1-Hour Glucose; BG120: OGTT 2-Hour Glucose;

UCPS0: Fasting UCPS; UCPS120: OGTT 2Hour UCPS;

HOMA-β: Homeostasis model assessment of beta cell function;

HOMA-IR: Homeostasis model assessment for insulin resistance;

CPauc: C peptide area under the curve; INSauc: Insulin area under the curve.

Table2. **ROC analysis to assess the predictive ability for GDM of each index**

variable	AUC	Standard error	P	95% credibility interval	
				lower	upper
BMI	0.713	0.043	<0.001	0.628	0.799
UCPS120	0.670	0.053	0.001	0.567	0.774
HOMA-IR	0.735	0.043	<0.001	0.651	0.819
Matsuda	0.752	0.042	<0.001	0.669	0.834
BMI+UCPS120	0.762	0.042	<0.001	0.679	0.846
BMI+HOMA-IR	0.763	0.039	<0.001	0.687	0.839
BMI+Matsuda	0.757	0.042	<0.001	0.676	0.839

BMI: body mass index;GDM: Gestational Diabetes Mellitus;UCPS120: OGTT 2Hour UCPS;

HOMA-β: Homeostasis model assessment of beta cell function;

HOMA-IR: Homeostasis model assessment for insulin resistance;