IMPACT OF BODY MASS INDEX ON INSULIN SENSITIVITY/ RESISTANCE IN PREGNANT WOMEN WITH AND WITHOUT GESTATIONAL DIABETES MELLITUS

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Summary. The aim of the present study was to evaluate the impact of body mass index (BMI) on homeostasis model assessment (HOMA) and insulin sensitivity, using the quantitative insulin sensitivity check index (QUICKI), and homeostasis model assessment value for insulin sensitivity (HOMA-S) in pregnant women with normal glucose tolerance (NGT) and gestational diabetes mellitus (GDM). A total of 102 pregnant women between 24-28 gestational weeks (53 with GDM and 49 with NGT) were included in the study. Age, body mass index (BMI), week of GDM diagnosis, fasting plasma glucose and insulin concentrations were measured in all women. HOMA indexes (insulin resistance – HOMA-IR and HOMA-B), QUICKI and HOMA-S indexes were calculated from fasting glucose and insulin concentrations. BMI was significantly higher in GDM patients (32.6 ± 4,39) compared to their NGT (26.83 ± 5.54) weight-matched group ($p < 0.011$). HOMA-IR in women with GDM was significantly higher than those in women with NGT ($p < 0.0001$). QUICKI-IS and HOMA-S were significantly lower in GDM group ($p = 0.001$; $p = 0.002$, respectively). The correlation between BMI and HOMA-IR were $r = 0.594$; $r = 0.485$, $p < 0.0001$ for GDM and NGT, between BMI and QUICKI ($r = -0.603$; $r = -0.458$); between BMI and HOMA-S ($r = -0.679$; $r = -0.467$ for GDM and NGT pregnant women). In our study, compared BMI of pregnant with NGT and GDM demonstrated that the OR of developing GDM was 1.099 (95% CI, 1.028-1.176, $p = 0.006$). According to our results, insulin sensitivities determined by QUICKI and HOMA-S are lower in GDM than NGT group, but GDM pregnant women have statistically higher HOMA-IR. We found higher positive correlation between BMI and HOMA-IR, and markedly negative correlation between BMI, QUICKI-IS and HOMA-S in preg-

nant women with GDM in comparison to NGT. Moreover, we observed that higher BMI decreased insulin sensitivity, increased insulin resistance and contributed to development of GDM.

Key words: *body mass index, gestational diabetes mellitus, homeostasis model assessment, quantitative insulin sensitivity check index*

INTRODUCTION

Normal pregnancy is accompanied by progressive insulin resistance that begins near mid-pregnancy and progresses through the third trimester to levels that approximate the insulin resistance seen in individuals with type 2 diabetes [1]. During gestation, there is a gradual decrease in insulin sensitivity. This insulin resistance is higher in women with gestational diabetes [2]. Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [4].

Numerous studies in the U.S. have reported an increased risk of GDM among women who are overweight or obese compared with normal-weight women [20]. The increasing prevalence of obesity in fertile age contributes to lower insulin sensitivity, and could stress β-cell function during pregnancy resulting in an increased risk of GDM [7]. Decreased insulin sensitivity or increased insulin resistance is defined as the decreased biological response of a nutrient to a given concentration of insulin at the target tissue, e.g. liver, muscle, or adipose tissue. Obesity is the most common risk factor related to decreased insulin sensitivity [8].

Homeostasis model assessment for insulin resistance (HOMA-IR) index is based on a single measurement of glucose and insulin in the blood, commonly used as a parameter of the severity of insulin resistance and it strongly correlates with direct assessment of insulin resistance using the euglycemic clamp technique [10]. The computer model can be used to determine insulin sensitivity (HOMA-S) from paired fasting plasma glucose and insulin concentrations across a range of 1-2,200 pmol/l for insulin and 1-25 mmol/l for glucose [18]. HOMA-S% was calculated using the validated calculator available at www.dtu.ox.ac.uk.

The quantitative insulin sensitivity check index (QUICKI) is based on a log transform of the insulin glucose product. Insulin sensitivity assessed with the QUICKI index showed the strongest correlation with direct measurements of insulin sensitivity using the glucose clamp [10]. In human pregnancy QUICKI has been found to be a good estimate of insulin sensitivity during both early and late pregnancy [12].

The aim of the current study was to evaluate the impact of BMI on insulin sensitivity and resistance, assessed using QUICKI-IS, HOMA-S and HOMA-IR, respectively, in pregnant women with NGT and GDM.

MATERIAL AND METHODS

A total of 102 pregnant women between 21-28 gestational weeks (53 with GDM and 49 with NGT) were included in the study. We assessed selected anthropometric, clinical, and pathophysiological parameters in all of them.

Exclusion criteria were chronic diseases, acute infection during pregnancy or at diagnosis, drugs that affect the carbohydrate metabolism or interfere with insulin sensitivity, multiple pregnancies, known diabetes, fetal malformation, or other severe maternal illnesses, aged < 18 or > 45 years.

All pregnant women with no previously diagnosed diabetes were offered screening for gestational diabetes mellitus (GDM) with a 2 h 75 g oral glucose tolerance test (OGTT) between 21 and 28 weeks of pregnancy. Diagnosis of GDM was in accordance with the recommendations of the International Diabetes in Pregnancy Study Group - fasting plasma glucose ≥ 5.1 mmol/L, 1 h ≥ 10.0 mmol/L, 2 h ≥ 8.5 mmol/L [9]. The OGTT stratified participants into two glucose tolerance groups: normal glucose tolerance (NGT group) and gestational diabetes mellitus (GDM).

The following data were collected for all women: age, pregnancy BMI at GDM diagnosis, gestational weeks, insulin at 0˘, fasting glucose and glucose at 2-h OGTT at the GDM diagnosis.

Blood samples for insulin and glucose measurements were drawn from subjects in a fasting state between 8.00 am and 9.00 am, after a 12-hour overnight fast. Plasma glucose was determined in the venous blood by the method of oxygen consumption (Analox GM9, Analox Instruments USA), (reference range 2.8-6.1 mmol/L) and the serum insulin concentration in the venous blood using the electrochemiluminescent immunoassay (ECLIA) (Elecsys 2010, Roshe Diagnostics), (reference range 2.6-24.9 μU/ ml).

All laboratory assays were performed at the Central Clinical Laboratory, University Hospital “Alexandrovska”.

HOMA-IR values were calculated from the concentrations of insulin and glucose using the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5. HOMA-B was calculated using the following formula: 20 × fasting insulin (μIU/ml)/fasting glucose (mmol/ml) − 3.5 [16].

QUICKI index was defined as follows: QUICKI=1/[(log(Ins0)+log(Glu0)], where Ins0 is the fasting plasma insulin level (μU/ml) and Glu0 is the fasting blood glucose level (mmol/l) [18].

We used the self-reported weight in kilograms (kg) and the height measured during the interview in squared metres (m2) to calculate maternal BMI (kg/m^2).

Statistical analysis

Data were analyzed using Statistical software for Windows 13.0 by SPSS – SPSS. The Shapiro-Wilk test was used to determine whether each variable had a normal distribution. These variables were expressed as means ± SD. The Kruskal-

Wallis test and the U Mann-Whitney test were used to compare selected groups. A $p < 0.05$ value was defined as significant. Comparisons between the subgroups were performed by one-way analysis of variance (ANOVA) with post-hoc analysis to locate the differences.

RESULTS

A total of 102 pregnant women were enrolled in the study (mean age 31.5, SD ± 4.55 years) and divided in two main groups based on the plasma glucose concentration and the IAPSD criteria for diagnosis of GDM: one group (n = 49) of subjects with NGT and second group with impaired glucose tolerance – pregnant with GDM (n = 53). Women in the NGT group were younger than those in the GDM group with statistically significant difference ($p < 0.003$). Women with GDM had a higher BMI with statistically significant difference ($p = 0.011$) (Table 1). The two groups were compared regarding the fasting glucose, fasting insulin, HOMA-IR, HOMA-B, HOMA-S and QUICKI-IS (Tabl. 2).

Table 1. Clinical characteristics of the participants

Characteristics	NGT group ($n_1 = 49$)	GDM group ($n_2 = 53$)	Statistical significance
Age (years)	30.51 ± 4.72	32.6 ± 4.39	$p < 0.003$
BMI (kg/m^2)	26.83 ± 5,54	30.56 ± 6.9	$p < 0, 011$
Gestational weeks	24 ± 4	24 ± 4	NS
Family history of diabetes T1DM (%) T2DM (%)	 $n_1 = 5$ (10,2%)	 $n_2 = 1$ (1,8%) $n_2 = 26$ (49%)	

GDM — gestational diabetes mellitus; BMI — body mass index.Values of parameters are presented as mean ± SD or count (percentage); T1DM-Type 1 Diabetes Mellitus; T2DM-Type 2 Diabetes Mellitus

Table 2. Characteristics of the patients' metabolic parameters

Characteristics	Pregnant with NGT ($n_1 = 49$)	Pregnant with GDM ($n_2 = 53$)	Statistical significance
Fasting glucose (mmol/l)	4.62 ± 0.28	5.93 ± 1.04	$P < 0.0001$
Fasting insulin mIU/l	11.35 ± 4.98	13.84 ± 8.43	$P = 0.02$
HOMA-IR	1.79 ± 1.08	3.8 ± 3.05	$P < 0.0001$
HOMA-S%	113.24 ± 64.7	81.15 ± 54	$P = 0.002$
QUICKI	0.65 ± 0.1	0.56 ± 0.11	$P = 0.001$
HOMA-B	126.48 ± 57.69	99.94 ± 41.51	$P = 0.017$

There was a statistically significant between-group difference in fasting glucose ($p < 0.0001$), fasting insulin ($p = 0.02$), HOMA–IR ($p < 0.0001$), HOMA-S% ($p = 0.002$), QUICKI–IS ($p = 0.001$) and HOMA–B ($p = 0.017$).

BMI showed positive correlation with HOMA–IR in both GDM and NGT groups ($r = 0.594$, $P < 0.0001$; $r = 0.485$, $P < 0.0001$, respectively). HOMA-S% index was strongly associated with BMI ($r = -0.467$; $r = -0.679$); QUICKI–IS had a negative correlation with BMI in GDM and NGT pregnant women ($r = -0.458$; $r = -0.603$, respectively).

DISCUSSION

Maternal obesity increases the risk of a number of pregnancy complications, including preeclampsia, gestational diabetes mellitus (GDM), and cesarean delivery [15]. Excessive weight gain during pregnancy and postpartum retention of pregnancy weight are significant risk factors for later obesity in women [17]. A number of surveys and meta-analyses, support the existence of independent connection between obesity and GDM.

BMI is a commonly used clinical criterion for obesity in pregnancy. Maternal overweight (BMI ≥ 25 kg/m²) has been shown to be the strongest risk factor for GDM: in two meta-regression analyses, the odds ratios for developing GDM were 1.97-2.14 in overweight (BMI ≥ 25 kg/m²), 3.01-3.56 in obese (most studies BMI ≥ 30 kg/m²) and 5.55-8.56 in severely obese (BMI ≥ 35-45 kg/m²) women compared with normal weight women [6]. In the Finnish obstetric population, the prevalence of overweight (BMI ≥ 25 kg/m²) increased from 18.8% in 1990 to 24.5% in 2000, and that of obesity (BMI ≥ 30 kg/m²) from 7.5% to 11.0%. They found an increasing trend in the risk of severe adverse obstetric outcomes, rising along with increasing maternal BMI [17].

We suspect that overweight and obesity, evaluated through BMI, are significant risk factors for GSD developing. Obtained results from our patients are as follows: in the GDM group overweight pregnant (BMI 25-30 kg/m²) women were n = 26 (49%), obesity pregnant women (BMI ≥ 30 kg/m²) were n = 22 (40.8%). In the NGT group women with normal BMI (19-25 kg/m²) predominated over overweight women (n = 20, 40.8% vs. n = 17, 34.6%). Our study confirmed that the prevalence of overweight and obesity before and during pregnancy are important risk factors for GDM developing.

Comparison between pregnant women with NGT and GDM (BMI 26.83 ± 5.54 and 30.56 ± 6.9, $p < 0.011$, respectively) demonstrated that the OR of GDM developing was 1.099 (95% CI, 1.028-1.176, $P = 0.006$). The increasing of BMI index with 1 kg/m² increased the risk of developing GDM with 9.9%.

Overweight and obese women in both NGT and GDM groups had lower insulin sensitivity than normal weight women. Despite of this fact, the both groups have a similar 50% insulin sensitivity reduction over the period of gestation [3]. Obese

women with GDM have a significant insulin response enhancement and insulin sensitivity decrease [5]. The mechanisms leading to increased insulin secretion in pregnancy, primary or compensatory to resistance, are not entirely known yet. They are partly related to metabolic effects of several hormones and cytokines which are elevated in maternal circulation during pregnancy [19]. Obese women are more likely to have decreased insulin sensitivity. The insulin sensitivity during pregnancy is related with the amount of maternal energy metabolism and visceral fat accumulation. Visceral fat volume in human`s body has important biological meaning, which is well illustrated during pregnancy. In this relation, the influence of visceral fat, respectfully BMI and insulin sensitivity is too important.

We found statistically significant differences in HOMA-S% between the NGT and GDM groups (P = 0.002). HOMA-S and BMI showed moderate inverse correlation in both NGT and GDM patient groups (r = -0.467 and r = -0.679, respectively). It was evident that the higher the BMI was, the stronger its influence on insulin sensitivity, expressed by HOMA-S% index, got.

The reverse correlation coefficient explicably was higher as an absolute value in pregnant women with GDM in comparison with healthy pregnant– the last ones had statistically lower BMI (P = 0.011). E. Kousta et al. (2007) got similar results when investigating a group of women from Europe with GDM history and availability of significant difference in relation to BMI. In the North Asia women group without difference in BMI, there was not a significant decrease of HOMA-S [13].

The values of QUICKI index in the two groups of pregnant women showed statistically significant difference (P = 0.001). When we evaluated the BMI effect over insulin sensitivity, we established a reverse correlation between QUICKI-IS and BMI in both of the groups (r = -0.458 for NGT and r = -0.603 for GDM). Our results were similar to published data from other authors. Yilmaz O. et al. (2010) announced diminished insulin sensitivity in pregnant women with GSD, expressed by the relation QUICKI index - BMI ($r = -0.384$, $P < 0.01$) [22]. Higher BMI, expression of higher visceral fat accumulation, suggested that enlarged fat cells are more responsive to the lipolytic effects of catecholamines and less sensitive to the antilipolytic action of insulin. The final result is related to induction of elevated insulin resistance, accumulation of visceral fat deposition and as a result of this – decreasing of insulin sensitivity [14].

According to the International Diabetes Federation criteria, the HOMA-IR cut-off point to differentiate between low and high insulin resistance is 2.38, several previous studies performed on smaller populations have demonstrated that HOMA-IR index assessed at diagnosis of GDM ranged from 1.6 to 25 [19]. In our research was specified that HOMA-IR values in pregnant women ranged between 0.7-6.8. HOMA-IR in women with GDM was significantly higher than those in women with NGT ($p < 0.0001$). There was a significantly positive relationship between BMI and HOMA–IR in the NGT and GDM groups ($r = 0.485$, $P < 0.0001$; $r = 0.594$, $P < 0.0001$ respectively).

Women with high BMI are obese, have decreased insulin sensitivity and higher insulin resistance. They are at increased risk for many adverse pregnancy outcomes for mother and children. For the overweight and obese women with subclinical decreased insulin sensitivity, pregnancy represents a metabolic stress test for disorders in pregnancy such as GDM and preeclampsia. These pregnant women are at increased risk for metabolic diseases in pospartum life, particularly if there is increased postpartum weight gain. Different data are also consistent with the underlying pathophysiology of GDM resulting in a 50-60% increase in type 2 diabetes in 10 years after the diagnosis of GDM [11].

In conclusion, we established that insulin sensitivity, determined by the QUICKI and HOMA-S, is lower in women with GDM than in pregnant women with NGT. We found higher positive correlation between BMI and HOMA-IR, and markedly negative correlation between BMI, QUICKI-IS and HOMA-S in pregnant with GDM in comparison to NGT. Thus, we observed that higher BMI decreases the insulin sensitivity, increases the insulin resistance and contributes to development of GDM.

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