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Similarities and differences in the pathophysiology of gestational diabetes between primigravidas and multiparas in the evaluation of the HOMA index
Part II: Evaluation of pancreatic β-cell function

Abstract

Background. Pancreatic beta-cell dysfunction is one of the most important pathogenetic mechanism in gestational diabetes mellitus (GDM). The relationship between this mechanism, multiparity and GDM has not been investigated. The aim of the study was to evaluate some of the clinical parameters and to asses beta-cell function in women with GDM diagnosed in a first pregnancy (primigravidas) and in a third or subsequent pregnancy (multiparas).

Material and methods. The study was performed in the same group of patients as the one presented in part one of this publication. Venous blood was collected after 12 hours of fasting to measure glucose and insulin levels. Beta-cell function was assessed using the HOMA-B index and in relation to insulin resistance (HOMA-B to HOMA-IR ratio).

Results. Both HOMA indexes, HOMA-B and HOMA-B/IR, were lower in multiparas (493.52 ± 653.78 and 567.83 ± ± 716.67, respectively; $P < 0.02$) than in primiparas (294.59 ± ± 583.53 and 302.76 ± 532.85, respectively; $P < 0.04$). There was a negative correlation between the parity and the HOMA indexes in the entire population ($P < 0.05$), between the HOMA indexes and BMI in both groups ($P < 0.05$), and between HOMA-B and age in primiparas ($P < 0.05$).

Conclusions. Beta-cell function, as evaluated by HOMA-B index and in relation to insulin resistance, is lower in multiparas than in primigravidas at the time of GDM diagnosis. Both indexes are related to parity and BMI. In primigravidas HOMA-B is related to age.

key words: gestational diabetes mellitus, parity, pancreatic beta-cell function, HOMA index

Introduction

Studies performed so far have indicated the presence of pancreatic beta-cell dysfunction in gestational diabetes mellitus (GDM) which makes it impossible for insulin to be secreted in relation to glycaemia [1] and the severity of insulin resistance [2]. It is possible that the more frequent occurrence of GDM in multiparas may be associated with an exacerbation and/or manifestation of a pre-existing pancreatic beta-cell dysfunction as a result of a recurrence of insulin resistance in subsequent pregnancies [3, 4]. The aim of the second part of the article was to evaluate the markers of pancreatic beta-cell function as the second pathogenetic mechanism of GDM in the population of primigravidas and multiparas at the time of GDM diagnosis.

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Material and methods

The study was performed in the same group of women recently diagnosed with GDM. The clinical characteristics of the patients has been presented in part

one of the article. Beta-cell function was evaluated in terms of the HOMA indexes according to Mathews and Hosker [5]. Beta-cell function was assessed on the basis of the HOMA-B index and in relation to the severity of insulin resistance using the HOMA-B to HOMA-IR ratio (HOMA-B/IR).

HOMA-B% = (20 × insulinaemia [μU/ml])/(glycaemia [mmol/l] – 3.5)

HOMA-B/IR = insulinaemia (μUm/l) × glycaemia (mmol/l/22,5/20 × insulinaemia (μU/ml)/glycaemia (mmol/l) – 3.5

Statistical analysis

The statistical analysis was performed using *Statistica for Windows* (StatSoft). The testing for normal distribution by the Shapiro-Wilk test demonstrated that the distribution of the variables did not overlap with the normal distribution. The significance of the differences between the groups was evaluated using the non-parametric Mann-Whitney U test, assuming the P values of ≤ 0.05 to be statistically significant. Spearman's correlation coefficients were assumed to be significant at the P values of ≤ 0.05.

Results

Table 1 presents the results of the comparison of HOMA-B and HOMA-B/IR in the study groups. The values of both indexes are lower in the group of multiparas. Tables 2 and 3 and Figures 1 and 2 present the coefficients of correlation between the HOMA indexes and the number of pregnancies, between the HOMA indexes and BMI in both groups and between the HOMA indexes and age. There were negative correlations between the HOMA indexes and the number of pregnancies, between HOMA-B/IR and BMI in both groups, and between HOMA-B and age in the group of primigravidas.

Table 2. Coefficients of correlation between the HOMA indexes and age and between the HOMA indexes and BMI

Parameter	Study group	Age	BMI
HOMA-B	1st pregnancy	–0.2486*	0.0319
	3rd or subsequent pregnancy	–0.0868	0.0240
HOMA-B/IR	1st pregnancy	–0.1487	–0.2794*
	3rd or subsequent pregnancy	–0.0123	–0.2747*

*p < 0.05

Table 3. Coefficients of correlation between the number of pregnancies and the HOMA indexes

	HOMA-B	HOMA-B/IR
Number of pregnancies	–0.1171*	–0.1090*

*p < 0.05

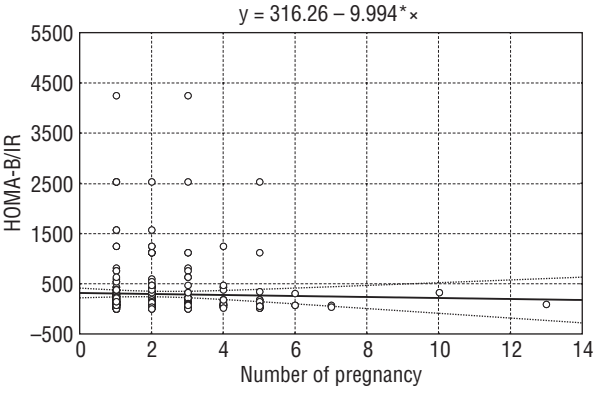

Figure 1. Scatter plot and the regression curve for the following variables: HOMA-B/IR and number of pregnancies in the entire population of the study

Discussion

Pancreatic beta-cell dysfunction is one of the main pathogenetic mechanisms of GDM [2, 6, 7]. Xiang et al. [7] evaluated the first phase of insulin secretion following

Table 1. Investigated parameters in the study groups

Parameter	1st pregnancy				3rd or subsequent pregnancy				P value
	N	M	SD	MIN MAX	N	M	SD	MIN MAX	
HOMA-B	144	567.83	716.67	0.88 4800.00	97	493.52	653.78	0.75 3764.00	**0.0289**
HOMA-B/IR	144	302.76	532.85	0.07 4249.29	97	294.59	583.53	0.05 4249.29	**0.0452**

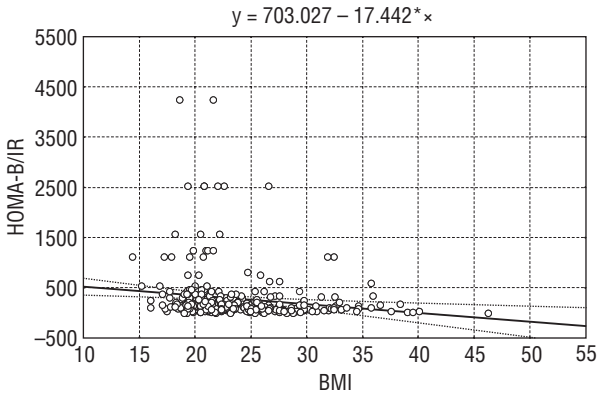

Figure 2. Scatter plot and the regression curve for the following variables: HOMA-B/IR and BMI in the entire population of the study

an intravenous dose of glucose and early secretion following an oral dose. They demonstrated approximately a 40% reduction in insulin secretion and a 67% reduction in relation to insulin resistance.

Our results suggest a lower function of pancreatic beta-cells as assessed by HOMA-B alone and in relation to insulin resistance (HOMA-B/HOMA-IR) at the time of GDM diagnosis in multiparas versus primigravidas. We demonstrated that in the entire population we investigated both indexes decrease in the subsequent pregnancies, which would suggest their dependence on the number of past pregnancies. Recurrent periods of insulin resistance in the course of pregnancies increase the function of beta-cells and may trigger the manifestation of pre-existing dysfunction [8]. In the interpretation of the lower values of the markers of beta-cell function in multiparas, one should take into consideration their older age, higher pregestational BMI and having at least two previous pregnancies. Clinical observations reveal a worsening of pancreatic beta-cell function with age [9]. It seems that the reduction of HOMA-B with age in the group of primigravidas may be a result of insulin resistance, pancreatic beta-cell dysfunction and pregnancy-induced metabolic alterations, which reveal the tendency towards a worse function of these cells with age already in the younger population.

In the case of both primigravidas and multiparas, the tendency towards increased function of beta-cells in response to increased insulin resistance, as assessed by HOMA-B/IR, depended on BMI. According to Homko et al. [2], the inability to sufficiently increase insulin secretion in response to the increasing insulin resistance in the late period of pregnancy is a manifestation of pancreatic beta-cell dysfunction in GDM. Our results point to the fundamental pathophysiological association between the value of HOMA-B/IR and the amount of body fat, as assessed by BMI, just before becoming pregnant. The mere fact that the mean pregestational BMI in primigravidas and multiparas fell within the normal limits is suggestive of the unfavourable effects of the differences in BMI on the values of HOMA-B/IR even in patients with normal body weight. The study by Metzger et al. [1] points to pregestational obesity and beta-cell dysfunction as two major risk factors of type 2 diabetes within several years of a pregnancy complicated by GDM. One cannot rule out that the untoward effects of adipose tissue on beta-cell function in these women may take place at lower pregestational BMI values than in obesity and persist throughout pregnancy. According to Catalano et al. [10], one of the mechanisms responsible for this process may be the increased serum concentration of free fatty acids as a result of decreased lipolysis. These findings are consistent with the observations by DeNino et al. [11], who demonstrated, in non-obese women, the effect of differences in abdominal fat on the changes in insulin resistance with age.

In summary, our results indicate a worsening of pancreatic beta-cell function, including the ability to overcome insulin resistance in subsequent pregnancies. Our study emphasises the importance of pregestational BMI values in this process. It therefore seems that the increased amount of adipose tissue before pregnancy, as assessed by BMI, decreases insulin secretion, including the ability of beta cells to overcome insulin resistance at the time of GDM diagnosis. It is possible that pregestational BMI may significantly determine the development of GDM by increasing insulin resistance and impairing insulin secretion before becoming pregnant.

It therefore seems that maintaining BMI in the low normal ranges may prove important for the prevention of GDM in all women, irrespective of the number of past pregnancies. This, however, is especially important in the case of women with at least two previous pregnancies, as their beta-cell function at the time of GDM diagnosis is already lower than beta-cell function in primigravidas. It is therefore especially important for the prevention of GDM in multiparas that the weight gain in subsequent pregnancies is controlled and normalised after deliveries. This may be a way to protect pancreatic beta-cell function already before the conception [12], thereby reducing the risk of GDM.

Conclusions

1. Pancreatic beta-cell function, as assessed by HOMA-B and in relation to insulin resistance, is lower in multiparas versus primigravidas at the time of diagnosis of gestational diabetes mellitus.
2. In both populations, pancreatic beta-cell function in relation to insulin resistance depends on pregestational BMI values.
3. In the group of primigravidas, HOMA-B is dependent on age.

References

1. Metzger B, Chon M, Roston S, Rodvany R. Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. Diabetes Care 1993; 16; 1598–1606.
2. Homko C, Sivan E, Chen X, Reece E, Guenther B. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. J Clin Endocrinol Metab 2001; 86: 568–573.
3. Shao J, Catalano P, Yamashita A et al. Decreased insulin receptor tyrosine receptor activity and plasma cell membrane glycoprotein over expression in skeletal muscle from obese women with gestational diabetes mellitus (GDM): evidence for increased serine/threonine phosphorilation in pregnancy and GDM. Diabetes 2000; 49: 603–610.
4. Shao J, Yamashito H, Giao L, Friedman J. Physiologic and molecular alterations in carbohydrate metabolism during pregnancy and gestational diabetes mellitus. Clin Obstet Gynecol 2000; 43: 87–98.
5. Mathews D, Hosker J. Homeostasis model assessment: insulin resistance and B-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–419.
6. Catalano P, Tyzbir E, Wolfe R et al. Carbohydrate metabolism during pregnancy in control subjects and woman with gestational diabetes. Am J Physiol 1993; 364: E 60-67.
7. Xiang A, Peters R, Trigo E et al. Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes. Diabetes 1999; 48: 848–854.
8. Kautzky-Willer A, Prager R, Waldhausl W et al. Pronounced insulin resistance and inadequate B-cell secretion characterize lean gestational diabetes during and after pregnancy. Diabetes Care 1997; 20: 1717–1723.
9. Basu R, Breda E, Oberg A et al. Mechanisms of age-associated determination in glucose tolerance, contribution of alterations in insulin secretion, action and clearance. Diabetes 2003; 52: 1738–1748.
10. Catalano P, Nizielski S, Shao J, Preston L, Qiao L, Friedman J. Down regulated IRS-1 and PPAR gamma in obese women with gestational diabetes: relationship to FFA during pregnancy. Am J Biol Endocrinol Metab 2002; 282: E522––E533.
11. DeNino W, Tchernof A, Dieme U et al. Contribution of abdominal adiposity to age-related differences in insulin sensitivity and plasma lipids in health nonobese woman. Diabetes Care 2001; 20: 925–932.
12. Buchanan T, Xiang A, Peters R et al. Preservation of pancreatic B-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high risk Hispanic women. Diabetes 2002; 51: 2796–2803.