Gestational diabetes as preexisting condition for type 2 diabetes and metabolic syndrome

Doctoral thesis

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INTRODUCTION

Gestational diabetes mellitus (GDM) defined as glucose intolerance that has its onset or first recognition during pregnancy. The incidence of gestational diabetes is not known recently. The frequency of GDM may vary among ethnic groups and with the use of different diagnostic criteria and screening method. According to previous Hungarian surveys, the prevalence of gestational diabetes mellitus ranges between 1.7-7.9%, while a more current, validated screening program reported that it affects 6.4% of all pregnancies. Most of these women (mainly due to their advanced age) do not belong to the low risk group for GDM. Several studies have suggested that gestational hyperglycemia is associated with adverse maternal and fetal outcomes. Gestational diabetes well established risk factor for the later development of type 2 diabetes and cardiovascular diseases.

Recent studies according to gestational diabetes reflect preventive aspects. GDM can serve as a model of a cohort with unfavorable cardiovascular risk profile without overt disease.

Recently the markers as disturbed carbohydrate metabolism, insulin resistance, obesity, and risk factors for cardiovascular morbidity and mortality are investigated intensively: Vitamin D deficiency, osteoprotegerin, TNF-alpha, adypocytokin (leptin adiponectin resistin, ghrelin) levels, and biological and biochemical predictors of atherosclerosis, (endothelial dysfunction, inflammatory and haemostatic system) in the group of prior GDM women.

Nowadays numerous randomized, controlled studies demonstrate that conversation of impaired fasting glucose and impaired glucose tolerance to type 2 diabetes can be prevented, or delayed with life style changes, weight gain and physical activity or/and drug (metformin, pioglitazone) therapy in former GDM women. Significant proportion of the female population with diabetes might have been detected earlier through the diagnosis of GDM, and women with GDM account for a large proportion of women with diabetes in the future. Therefore, effective preventive strategies directed at this group may have the capacity to expert a significant population heath impact.

AIMS

Our aim was to study to determine:

1. the prevalence of different degrees of glucose intolerance (type 2 diabetes, impaired glucose tolerance [IGT], impaired fasting glucose [IFG]);
2. pregnancy predictors of follow-up glucose intolerance
3. the prevalence of cardiovascular risk factors and the metabolic syndrome (according to the WHO, ATP III, IDF and the MDT MM criteria);
4. fasting leptin levels, and leptin changes after a 75g OGTT
5. fasting adiponectin levels and their associations with cardiovascular risk factors;
6. fasting resistin levels and their associations with cardiovascular risk factors;
7. fasting osteoprotegerin levels and their associations with cardiovascular risk factors

four years after a pregnancy complicated by gestational diabetes.

PATIENTS and METHODS

Patients

Data of 200 previous GDM women cared for at our institution during pregnancy between 1996 and 1998 was evaluated. GDM was diagnosed according to the WHO criteria at that time (WHO 1985): In 2000 all 200 women were invited to take part in a follow-up investigation. One hundred and five (52.5%) women sent back the questionnaire attached to the invitational letter inquiring about family, gynecological, and general medical history, current diseases (carbohydrate metabolism, hypertension), current medications, anthropometric characteristics (weight, height), the last measured blood glucose and HbA1c values, and about the child born at the and of the GDM pregnancy. From these 105 women 68 also participated in the clinical examination (34% of the original sample). All participants gave their informed consent before any study related procedures were performed. The investigational protocol was approved by the institutional ethical committee.

Thirty-nine women served as controls. Controls were recruited among hospital workers and their relatives, from the same age range as cases (23-46 years). Those with at least one previous delivery and a normal OGTT result during the last pregnancy were eligible as controls. Both cases and controls were investigated according to the same protocol.

During the clinical examination an assisted, more detailed questionnaire was completed, followed by a physical examination. During the latter height, weight, waist and hip circumference, blood pressure was measured.

Laboratory measurements

After a 12-hour fasting blood samples were drawn for the determination of blood glucose, HbA1c, serum insulin (*RK-400M, Izotóp Institute*, Budapest, Hungary), C-peptide *(BioChem ImmunoSystems,* Bologna, Italy*)*, blood lipids (cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride), creatinine, gamma-glutamyl transpeptidase (γGT), uric acid, fibrinogen, PAI-1, adipocytokines (leptin [LINCO, Research USA], resistin, adiponectin [both: Quantikine ELISA, R&D Europe Ltd.]), osteoprotegerin [Biomedica, Germany] and CRP. If the participant had no known diabetes a 75g oGTT was performed after the fasting blood tests to better characterize carbohydrate metabolic state. Albumin excretion was determined using a 24-hour collected urine sample. Homeostasis model assessment (HOMA) insulin sensitivity (HOMA2-%S) and HOMA β cell function (HOMA2-%B) were calculated

using the built-in equations of the HOMA2 calculator v2.2 (Diabetes Trials Unit, University of Oxford, Oxford, UK). To characterize insulin secretion we also calculated the insulinogenic index (II) as ($insulin_{30min}$-$insulin_{fasting}$) / ($glucose_{30min}$-$glucose_{fasting}$).

Definition of glucose tolerance categories. Diabetes was defined by a fasting glucose ≥7.0 mmol/l or a 2-hour postload glucose ≥11.1 mmol/l or reported doctor diagnosed diabetes or use of diabetes medication. Impaired glucose tolerance (IGT) was defined in the absence of known diabetes as a fasting glucose <7.0 mmol/l and a 2-hour postload glucose between 7.8 and 11.0 mmol/l. Impaired fasting glucose (IFG) was defined in the absence of known diabetes as a fasting glucose between 6.1 and.6.9 mmol/l and a 2-hour postload glucose between <7.8 mmol/l. We defined glucose intolerance as either diabetes or IGT or IFG.

Definitions of the metabolic syndrome. Since there is no uniform, well-accepted, worldwide definition of the metabolic syndrome nowadays, in our analysis of previous GDM and control women we utilized several criteria developed by widely known international bodies: WHO 1999, ATP III 2000, IDF 2005, and the criteria of Hungarian Diabetes Association (MDT MM). We modified the definition of insulin resistance in the WHO definition (originally measured by: hyperinsulinemic, euglycemic clamp - glucose uptake below the lowest quartile) as fasting serum insulin above the 3rd quartile of our control group.

Statistical analysis

Statistical analyses were undertaken using SPSS 14.0 software (SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables are presented as arithmetical means (± standard deviation), skewed variables as median [interquartile range], categorical variables as percentages. Variables were log-transformed as required. To compare two different groups 2-sample t-tests (after log-transformation for skewed variables), Mann-Whitney U-tests, chi^2 and Fisher-exact tests were utilized as appropriate. Since there was a significant age and BMI difference between prior GDM cases and controls, the comparisons were repeated after age and BMI adjustment using multiple linear regression (continuous outcomes) or binary logistic regression (categorical outcomes) with logarithmic transformations as required. If more than 2 ordinal groups were compared chi^2 for trend analysis was also performed. To describe risk factors for the development of type 2 diabetes mellitus after delivery (dependent variable), a multiple logistic regression model (stepwise forward method) was developed using the univariately associated ($P<0.1$) parameters as covariates (selected automatically). The association between the different risk factors and the development of type 2 diabetes mellitus is shown as odds ratios and 95% confidence intervals.

We used multilevel longitudinal modeling to describe determinants of fasting leptin levels and its change 90 minutes after glucose load. Data were structured so that the two leptin measurements were nested within subjects, and the standard errors were calculated by taking into account the non-independence of the observations, i.e. that the same individuals contributed to more than one observation in the dataset. All variables found to be independently related to fasting leptin were entered into the model as main effects. Since we had no a priori hypothesis on the determinants of leptin level changes after the OGTT, all variables were investigated individually as a time interaction variable. For the final model all variables were included that had a possible time interaction ($P<0.15$) in the individual models. Non-significant variables were then removed in a step-wise fashion to reach the most parsimonius model with the lowest information criteria. For the significant main effects all two-way interactions were tested, however they were all excluded due to non-significance.
Statistical significance was inferred at a 2-tailed $P<0.05$.

RESULTS

Participants compared to non-responders and responders

Altogether 200 women cared for GDM (96 [48%] insulin treated during pregnancy) at our institution were invited to fill in the mailed questionnaire and to take part in a follow-up investigation. The response rate was 52.5% (105 questionnaire were sent back), and 68 women participated in the clinical examination. There was no significant difference (all $P>0.05$) between the gestational parameters of responders and non-responders (age, gestational week at GDM diagnosis, diagnostic oGTT blood glucose values, BMI before pregnancy, weight gain during pregnancy, frequency of insulin treatment during pregnancy). We had no data regarding the current carbohydrate metabolism of the non-responders.
We found no significant difference between women participating at the clinical investigation (68/105) and those completing only the questionnaire (37/105) either in the above mentioned parameters (collected during pregnancy) or BMI and smoking habit at the time of the mailed questionnaire (all $P>0.05$). Participants had a higher average number of deliveries (2.1±0.9 vs. 1.8±0.9; $P=0.049$), and more frequently had a positive family history of diabetes mellitus (71 vs. 42%; $P=0.0006$).

Pregnancy predictors of follow-up glucose intolerance

At follow-up glucose intolerance and diabetes mellitus was found much more frequently among women who were insulin treated during pregnancy (N=32) compared to those who received dietary treatment (N=34) (OR: 5.0, 95% CI: 1.8-14.1; P=0.003, OR: 9.4, 95% CI: 1.9-46.5; P=0.004, resp.). Using multiple logistic regression the only independent predictor of follow-up glucose intolerance was fasting blood glucose during the diagnostic oGTT (OR: 2.74 per 1 mmol/l increase in fasting glucose, 95% CI: 1.17-6.38 P=0.02). Further parameters that were available for the model (P<0.1): 2-hour postload glucose during the diagnostic oGTT, insulin treatment during pregnancy, hypertension during pregnancy, and family history of diabetes mellitus.

Previous GDM women compared to healthy controls

Those 68 previous GDM women who participated in the clinical examination were somewhat older, had a shorter follow-up time since the index pregnancy compared to the 39 control women, who had normal glucose tolerance during pregnancy. While glucose intolerance (type 2 diabetes, IGT and IFG together) was almost 3 times more frequent in the previous GDM group compared to controls (42.6% vs. 15.4%; P=0.004), all type 2 diabetes cases were diagnosed among previous GDM women (21%). These differences remained statistically significant even after adjustment for age and BMI. Significantly higher serum fasting and 2-hr postload insulin levels as well as a lower HOMA insulin sensitivity index was obtained at the 75g oGTT during follow-up that corresponds to an increased insulin resistance of these women. No difference in HOMA β-cell function was found, while the more sensitive insulinogenic index tended to be lower among previous GDM women representing disturbed insulin secretion following a GDM pregnancy. These differences changed only minimally after adjustment for age and BMI (**Table 1**).

Previous GDM women had a worse cardiovascular risk profile compared to healthy controls. They had more pronounced obesity (measured as BMI, waist circumference, or waist to hip ratio), higher fasting plasma insulin, triglycerides, LDL-cholesterol, and blood pressure levels, although after adjustment for age and BMI only the differences in waist to hip ratio, diastolic blood pressure, and triglycerides remained significant (P<0.05).

Table 1. **Carbohydrate metabolism and cardiovascular risk factors in prior GDM compared to control women at follow-up**

	Prior GDM	Control	P	P*
N	68	39		
Age (yrs)	36.1±6.0	33.6±5.9	0.043	
Follow-up time (yrs)	3.5±0.6	8.2±5.1	0.0001	
BMI (kg/m^2)	26.1 [7.7]	22.9 [4.8]	0.001	
Waist (cm)	85 [20]	75 [14]	0.001	0.26
Waist to hip ratio	0.83±0.07	0.77±0.07	0.0001	0.003
Glucose intolerance (%)	42.6%	15.4%	0.005	0.044
Glucose tolerance categories			0.003	0.005
Normal glucose tolerance (%)	57.4%	84.2%		
Impaired fasting glucose (%)	5.9%	0		
Impaired glucose tolerance (%)	16.2%	15.8%		
Diabetes mellitus (%)	20.6%	0		
HbA1c (%)	5.8±1.0	5.4±0.5	0.017	0.25
Fasting insulin (pmol/L)	229 [111]	111 [97]	0.0001	0.0001
2-hr postload insulin (pmol/L)	611 [313]	368 [425]	0.007	0.002
HOMA2-%S (%)	24 [12]	47 [38]	0.0001	0.0001
HOMA2-%B (%)	184±72	166±84	0.24	0.20
Insulinogenic index	109 [126]	143 [150]	0.051	0.033
Systolic blood pressure (mmHg)	114±13	108±11	0.019	0.40
Diastolic blood pressure (mmHg)	74±9	68±7	0.001	0.017
Hypertension (%)	17.6%	0	0.004	
Triglycerid (mmol/l)	1.0 [0.7]	0.7 [0.4]	0.001	0.042
LDL-cholesterol (mmol/l)	3.34±0.67	3.01±0.86	0.027	0.18
HDL-cholesterol (mmol/l)	1.31±0.28	1.42±0.37	0.087	0.68
Gamma GT (U/l)	18 [16]	19 [13]	0.48	0.56
Uric acid (mmol/l)	198±51	184±49	0.15	0.89
Urine albumin excretion (mg/24h)	7 [8]	8 [6]	0.34	0.34

Data are shown as mean±SD, median [IQR], or n (%).
IFG: Impaired fasting glucose according to WHO definition
IGT: Impaired glucose tolerance according to WHO definition
HOMA2-%S - Homeostasis model assessment (HOMA) insulin sensitivity (HOMA2-%S).
HOMA2-%B - HOMA β cell function.
Insulinogenic index – ($insulin_{30min}$-$insulin_{fasting}$) / ($glucose_{30min}$-$glucose_{fasting}$).
See details on calculations in the text.
* - P-value for the difference between cases and controls after adjustment for age and BMI.

Prevalence of the metabolic syndrome at follow up.

Using any of the criteria of the metabolic syndrome (WHO: 28 vs. 0%, ATP III: 27 vs. 9%, IDF: 37 vs. 14%, MDT MM: 38 vs. 8%) its prevalence was increased among previous GDM women compared to controls (all $P<0.05$).

Using any of the above criteria for the diagnosis of the metabolic syndrome, we could prove a positive association between the degree of obesity (normal weight BMI < 25 kg/m^2, overweight BMI 25-30 kg/m^2, obese BMI > 25 kg/m^2) and the risk of the metabolic syndrome in the previous GDM group using chi^2 for trend analysis. We could prove such association in the control group only according to definition of MDT MM, probably due to a lack of statistical power related to the lower number of controls and a lower prevalence of the metabolic syndrome.

We found a significant positive association between the degree of glucose intolerance and the risk of the metabolic syndrome according to the WHO criteria in the previous GDM group: its prevalence was 26% among normal glucose tolerant, 47% among IGT and IFG, and 57% among type 2 diabetic women (P=0.024).

In addition to the obvious difference in the components of the metabolic syndrome, women with prior GDM and the metabolic syndrome (according to WHO definition) were significantly heavier before pregnancy (80.7±21.8 vs. 62.5±9.5 kg; P = 0.003), however gained less weight during pregnancy (4.9±7.0 vs. 10.6±5.4 kg; P=0.0001) than prior GDM women without the metabolic syndrome at follow-up. They were less frequently engaged in vigorous physical activity (≥1.5 hours of vigorous physical activity/week: 0 vs. 26.1%, P=0.014), they had an increased uric acid (233±53 vs. 186±45 mmol/l; P = 0.001), and gamma-glutamyl transpeptidase level (31 [22] vs. 16 [14] U/l; P < 0.0001) compared to prior GDM women without the metabolic syndrome.

Leptin

GDM women who took part in the follow-up examination were older (age at delivery 32.4± 6.1 vs. 30.5±5.8 years, P=0.04) but otherwise similar to the non-participants (all P>0.05) regarding their pre-pregnancy weight (67 [13] vs. 71 [24] kg), and gestational week (28 [12] vs. 29 [10]), fasting and 2-hour postload blood glucose (5.3 [0.8] vs. 5.1[1.0] and 9.1 [1.9] vs. 9.4 [1.9] mmol/L resp.) at GDM diagnosis. They showed a similar frequency of insulin treatment during pregnancy (49 vs. 47%, P=0.88).

Women with a prior diagnosis of GDM had a higher body mass index, fasting and postload glucose, lower HOMA insulin sensitivity, higher triglyceride, higher diastolic blood pressure, and higher fasting and postload leptin levels than control women (all $P<0.05$). Women with prior GDM were significantly more frequently diagnosed with glucose intolerance at the follow-up examination in 2000 and hypertension during pregnancy and were less frequently present smokers (all $P<0.05$).

Associations of fasting leptin levels with the investigated variables after BMI adjustment

Since BMI was the most important determinant of fasting leptin levels among the investigated variables, explaining 55% of the variation, all the analyses of the possible predictors of fasting leptin levels were adjusted for BMI. After the back-transformation of the model coefficients from Table 2 an 11% (95% confidence interval [CI] 9-13%) increase in leptin levels / 1 kg/m2 increase in BMI was found. According to the regression models with log-transformed fasting leptin as the outcome, fasting leptin was negatively associated with HOMA insulin sensitivity (0.4% decrease, 95%CI 0.2-0.7% / 1% increase in HOMA insulin sensitivity), LDL-cholesterol (13% increase, 95%CI 0.3-27% / 1 mmol/L increase in LDL-cholesterol), current smoking (32% lower levels, 95%CI 17-44%), prior GDM status (24% higher levels, 95%CI 3-48%, all $P<0.05$).

Postload changes in leptin levels

Since fasting and postload (90 minute) leptin levels were exceptionally highly interrelated ($r=0.936$, $P<0.0001$), no separate model was developed for postload leptin as an outcome.

According to the multilevel models with log-transformed leptin as the outcome, the amount of postload change in leptin (13% decrease, 95%CI 8-18%) was associated with presence of glucose intolerance (16% less decrease, 95%CI 4-28%), HOMA insulin sensitivity (0.2% larger decrease, 95%CI 0-0.3% / 1% increase in HOMA insulin sensitivity), prior GDM status (11% less decrease, 95%CI 0.4-22%, all $P<0.05$).

We used multilevel modeling to determine which variables were independently associated with fasting leptin levels and postload changes in leptin levels. All variables independently related to fasting leptin were entered into the model as main effects, and all variables where there was a possible time interaction ($P<0.15$) were included in the individual models. According to the most parsimonious model with the lowest information criteria fasting leptin levels were associated with BMI (10.1% increase, 95%CI 8.1-12.1%/1 kg/m^2 increase), HOMA insulin sensitivity (0.4% decrease 95%CI 0.2-0.7%/1% increase insulin sensitivity),

glucose intolerance (24% decrease 95%CI 8-37%), and smoking (31% decrease 95%CI 16-44%).

In comparison to the fasting values postload (90 minute) leptin levels decreased significantly in women with normal glucose tolerance by 13% (95%CI 8-18%). As there was no significant change in leptin levels among women with glucose intolerance (16% less [meaning 16% - 13% = 3% increase], 95%CI -4-29%) the slopes for women with normal glucose tolerance and glucose intolerance are significantly different.

As a sensitivity analysis we ran the above model after the exclusion of the controls, and found that the effect sizes were similar to the ones reported in Table 3, however current smoking lost its significance (data not shown).

Adiponectin and resistin

Sixty women with prior GDM and 30 age matched healthy subjects had both resistin and adiponectin values. Prior GDM women presented more frequently with glucose intolerance including impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (42 vs. 18%; P=0.027). Furthermore diabetes mellitus (20% vs. 0% P=0.005) and hypertension (18 vs.0% P=0.008) has been found exclusively in this group. Prior GDM women were overweight, according to their body mass index (27.2±6.9 vs. 23.7±3.8 kg/m^2; P=0.002), waist to hip ratio (0.83±0.07 vs. 0.77±0.07; P=0.001), body fat content (30.4±8.2 vs. 25.3±6.6%; P= 0.004). They had significantly higher triglycerides (1.2±0.7 vs. 0.9±0.6 mmol/l; P=0.037), LDL-cholesterol (3.3±0.7 vs. 2,9±0.9 mmol/L P=0.017), lower HDL-cholesterol (1.3±0.3 vs. 1.5±0.4 mmol/L; P=0.048), fasting serum insulin (32.8±16.1 vs. 17,6±9,9 microU/ml; P=0.0001) and HOMA (9.2±5.8 vs. 4.1±2.3; P=0.0001) values. The prevalence of the WHO metablic syndrome was higher in women with prior GDM (29% vs. 0%; P=0.001).

Elevated fasting resistin (25.4±9.8 vs. 17.6±6.7 ng/mL; P=0.0001) and decreased adiponectin level (9.1±5.1 vs. 14.33±5.5 ng/mL; P=0.0001) was detected in women with prior GDM.

Within prior GDM group, higher fasting resistin values were univariately associated with higher HDL-cholesterol (r=0.265; P=0.032), higher CRP (r=0.494; P=0.005) and higher fibrinogen (r=0.38; P=0,002).

Lower fasting adiponectin values were univariately associated with higher body mass index (r=-0.433; P=0.0001) higher body fat content (r=-0.368; P= 0.002), higher waist circumference (r=-0.448; P=0.0001) and waist to ratio (r=-0.453; P= 0.0001) higher systolic (r=-0.284; P= 0.021) and diastolic (r=-0.355; P= 0.003) blood pressure, higher uric acid (r=-

0.334; P=0.006) and higher fibrinogen (r=-0.257; P=0.037), and lower HDL-cholesterol (r=0.564; P=0.0001). Lower adiponectin associated with presence of metabolic syndrome independently of its criteria: WHO (6.3±3.6 vs. 10.1±5.3 ng/mL; P=0.002); ATP (5.9±2.4 vs. 10.3±5.3 ng/mL; P=0.0001) or IDF (6.2±3.5 vs. 10.9±5.1 ng/mL; P=0.0001), current diabetes mellitus (6.9±3.2 vs. 9.5±5.0 ng/mL; P=0.03) and hypertension (6.0±2.0 vs. 9.8±5.3 ng/mL; P=0.0001).

Osteoprotegerin

In this part of our study we evaluated the data of 30 former GDM and 14 control subjects. Glucose intolerance (diabetes mellitus and. IGT) was observed 18/30 (60%) in prior GDM subjects vs. 2/14 (14%) in control group. Impaired fasting glycemia was not found in any of the groups. Prior GDM women were overweight, they had a higher HOMA insulin resistance, and lower fasting C-peptide levels compared to control subjects. (Table 1) There was no difference in osteoprotegerin (OPG) levels between prior GDM and control subjects (3.35±1.42 vs. 3.82±1.38 pmol/L). Henceforward, the data of prior GDM and control subjects was analyzed together.

Higher serum OPG levels were found in patients with present glucose intolerance (4.04±1.34 vs. 3.05±1.32;pmol/L P=0.018). Serum OPG showed a significant association with higher age (r=0.33; P=0.031), triglycerides (r=0.38; P=0.012), fasting C-peptide (r=0.50; P=0.0001), GGT (r=0.52; P=0.0001), presence of glucose intolerance (r=0.36; P=0.018), and lower HDL-cholesterol (r=-0.31; P=0.004) and serum calcium (r=-0.503; P=0.028). No associations were found with body mass index, waist to hip ratio, total cholesterol, fibrinogen, presence of hypertension, or positive family history of either diabetes or cardiovascular disease.

Serum OPG levels were independently associated (r=0.76 for the whole model; P<0.0001) with γGT (β=0.3; P<0.0001), fasting serum C-peptide (β=0.014; P=0.014) and current glucose intolerance (β=0.231, P=0.037). Age, fasting C-peptide, triglycerides, HDL cholesterol, serum calcium were also available for selection to the model.

NOVEL FINDINGS and CONCLUSIONS

1. While glucose intolerance (type 2 diabetes, impaired fasting glucose and impaired glucose tolerance) was almost 3 times more frequent in he previous GDM group compared to controls (OR 4,10, 95%CI 1,51-11,05), type 2 diabetes was found exclusively among previous GDM women.
2. The only independent predictor of follow-up glucose intolerance was the fasting blood glucose measured during the diagnostic oGTT during pregnancy.
3. Previous GDM women had a worse cardiovascular risk profile compared to healthy subjects. They had more pronounced obesity (measured as body mass index, waist circumference, waist to hip ratio), higher fasting plasma insulin, triglycerides, LDL-cholesterol, and blood pressure levels. Using any criteria to diagnose the metabolic syndrome (a cluster of cardiovascular risk factors), its prevalence was increased among previous GDM women compared to controls. We described first, that the most suitable international criteria of metabolic syndrome is the definition of WHO to determine the prevalence of the metabolic syndrome among prior GDM women. We described first the prevalence of metabolic syndrome among former GDM women according to the definition of MDT MM.
4. We found higher circulating fasting leptin and resistin levels, and lower adiponectin values in women with previous gestational diabetes. We described first, that leptin levels significantly decreased 90 minutes after an OGTT in women without glucose intolerance, while this decrease was significantly lower (and not different from 0) in women with present glucose intolerance, independently of prior GDM status.
5. .Decreased adiponectin level was detected in women with prior GDM. Lower fasting adiponectin values were associated with higher body mass index, higher body fat content, higher waist circumference and waist to ratio higher blood pressure, higher uric acid higher fibrinogen), and lower HDL-cholesterol. Lower adiponectin associated with presence of metabolic syndrome independently of its criteria.
6. We described first elevated fasting resistin levels four years after a GDM pregnancy. Within prior GDM group, higher fasting resistin values were univariately associated with higher HDL-cholesterol, higher CRP and higher fibrinogen.
7. According to our novel observation, OPG levels (a marker of both bone metabolism and atherosclerosis) were independently associated with current glucose intolerance, higher gamma-glutamyl transferase and fasting serum C-peptide levels.

PUBLICATIONS

Publications Relevant to Current Work

1. **Madarász E,** Tabák GyÁ, Speer G, Lakatos P, Kerényi Zs, Tamás Gy. Abnormal glucose tolerance is associated with diminished postload change in leptin levels in women. Diabetes Metab. Res. Rev. DOI: 10.1002/dmrr.1001, 2009. **IF**:**3,149**
2. **Madarász E**, Tamás Gy, Tabák GyÁ, Kerényi Zs. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diab. Res. Clin. Pract. 85:197-202, 2009. IF: **1,888**
3. **Madarász E**, Tamás Gy, Tabák GyÁ, Speer G, Lakatos P, Kerényi Zs. Osteoprotegerin levels in women with prior gestational diabetes mellitus. Diabetes Care 32(1):e5, 2009.
4. **Madarász E,** Tamás Gy, Tabák GyÁ, Szalay J, Kerényi Zs**.** Metabolikus szindróma gesztációs diabéteszt követően: négyéves utánkövetés. Orv. Hetil. 149**:**831-838, 2008.
5. **Madarász E,** Tamás Gy, Kerényi Zs. A gesztációs diabétesz, mint a metabolikus szindróma egyik előfutára. Családorvosi Fórum 5:20-23, 2007.
6. **Madarász E**, Tamás Gy, Tabák GyÁ, Bosnyák Zs, Tóth K, Szalay J, Csákány MGy, Kerényi Zs. 2-es típusú diabetes, szénhidrátanyagcsere-zavar és cardiovascularis rizikófaktorok előfordulása korábbi gesztációs diabetest követően: négy éves utánkövetés. Diabetol. Hung. 14:153-162, 2006.
7. Kerényi Zs, Stella P, Tabák ÁGy, Nádasdi Á, **Madarász E**, Bosnyák Zs, Baranyi É, Csákány MGy, Karádi I, Tamás Gy. Gestational diabetes mellitus: early manifestation or predictor of the metabolic syndrome. Diabetol. Hung. 10 (S2):32-36, 2002.

Other Publications

1. Kerényi Zs, Tamás Gy, Kivimaki M, Péterfalvi A, **Madarász E**, Bosnyák Zs, Tabák GyÁ. Maternal glycemia and risk of large for gestational age babies in a population-based screening. Diabetes Care DOI: 10.2337/ DC09-1088, 2009. IF: **7.349**
2. Tabák GyÁ, Tamás Gy, Péterfalvi A, Bosnyák Zs, **Madarász E,** Rákóczi I, Kerényi Zs. The effect of paternal and maternal history of diabetes mellitus on the development of gestational diabetes mellitus. J. Endocrinol. Invest. DOI: 10.3275/6293, 2009. **IF: 1,888**
3. Tabák GyÁ, Kerényi Zs, Nagy E, Bosnyák Zs, **Madarász E**, Tamás Gy. Height and gestational diabetes mellitus. Diabet. Med. 19:344-345, 2002. **IF*:* 2,172**

4. Bosnyák Zs, Kerényi Zs, Stella P, **Madarász E**, Tóth K, Tabák GyÁ, Tamás Gy. Hypertonia gestatiós diabetesben: előfordulása a terhesség során és utánkövetéskor. Hypertonia és Nephrologia 4:198-209, 2000.

Abstracts

1. **Madarász E,** Kerényi Zs, Zsirai L, Wudi K, Tabák GyÁ, Tamás Gy. Inzulinpumpa alkalmazás és hagyományos inzulinkezelés összehasonlítása 1-es típusú diabéteszes terhességben. Diabetol. Hung. 16(S1):76-77, 2008.
2. **Madarász E**, Tamás Gy, Tabák GyÁ, Kerényi Zs. Kardiovaszkuláris rizikófaktorok (metabolikus szindróma?) együttes előfordulása gesztációs diabéteszt követően. Diabetol. Hung. 14(S2):104-105, 2006.
3. **Madarász E**, Kerényi Zs, Tabák GyÁ, Speer G, Lakatos P, Tamás Gy. Az adiponectin szerepe korábban gesztációs diabéteszes asszonyokban. Diabetol. Hung. 13(S1):22, 2005.
4. **Madarász E,** Tabák GyÁ, Bosnyák Zs, Kerényi Zs, Tamás Gy. Gestatios diabetest (GDM) követő hypertonia előfordulása és terhesség alatti prediktorai. Diabetol. Hung. 12(S1):20, 2004.
5. Kerényi Zs, Péterfalvi A, Bosnyák Zs, **Madarász E,** Tabák GyÁ, Szánthó J, Rákóczi I, Tamás Gy. A gestatios diabetes incidenciája validált teljes körű szűrés alapján. Diabetol. Hung. 12(S1):12, 2004.
6. Kerényi Zs, Péterfalvi A, Bosnyák Zs, **Madarász E,** Tabák ÁGy, Szánthó J, Rákóczi I, Tamás Gy. Incidence of gestational diabetes mellitus: results of a validated universal screening. Diabetologia 47(S1):A104, 2004. **IF: 5,689**
7. **Madarász E**, Kerényi Zs, Tabák GyÁ, Nádasdi Á, Bosnyák Zs, Baranyi É, Csákány MGy, Tamás Gy. Characteristic features of the metabolic syndrome 3 and 8 years after a GDM complicated pregnancy. Diabetes 52 (S2):A567-567, 2003. **IF: 8,298**
8. Tamás Gy, **Madarász E**, Tabák GyÁ, Speer G, Szalay J, Lakatos P, Kerényi Zs. Serum osteoprotegerin levels in prior gestational diabetic women. Diabetes 52 (S2):A168, 2003. **IF:8,298**
9. Bosnyák Zs, Tamás Gy, Földesi I, **Madarász E**, Kerényi Zs. Do mainly nonmodifiable risk factors predict gestational diabetes in a relatively lean population? - A community-based perspective. Diabetes 52(S2):A407, 2003. **IF:8,298**

10. **Madarász E**, Kerényi Zs, Tabák GyÁ, Speer G, Lakatos P, Szalay J, Tamás Gy. Osteoprotegerin vérszintek korábban gesztációs diabéteszes és egészséges kontroll asszonyokban. Diabetol. Hung. 11(S1):33, 2003.
11. Breyer H, Tamás Gy, Wudi K, Stella P, Tabák GyÁ, **Madarász E**, Gyarmati I, Kerényi Zs. Első tapasztalataink folyamatos szöveti glukózméréssel. Diabetol. Hung. 11(S1):23, 2003.
12. Tamás Gy, Tabák GyÁ, **Madarász E**, Speer G, Bekő G, Lakatos P, Kerényi Zs. A metabolikus szindróma jellegzetességei korábban gestatiós diabeteszes asszonyokban: a vér leptinszintje oGTT során. Diabetol. Hung. 10(S1):76, 2002.
13. Nagy E, Wudi K, Stella P, **Madarász E**, Bosnyák Zs, Péterfalvi A, Tabák GyÁ, Tamás Gy, Kerényi Zs. A gestatiós diabetes gondozása: 3 év tapasztalatai. Diabetol. Hung. 10(S1):52, 2002.
14. **Madarász E**, Kerényi Zs, Nagy-Szabó J, Baranyi É, Tabák GyÁ, Csákány MGy, Szalay J, Lakatos P, Tamás Gy. Korábban gestatiós diabetes miatt kezelt asszonyok korai utánvizsgálata. Diabetol. Hung. 10(S1):49, 2002
15. Kerényi Zs, Tabák GyÁ, Bosnyák Zs, **Madarász E**, Nagy E, Szánthó J, Rákóczi I, Tamás Gy. A gestatiós diabetes szűrésének módszertani problémái. Diabetol. Hung. 10(S1):38, 2002.
16. Tabák GyÁ, Tamás Gy, **Madarász E**, Nádasdi Á, Bosnyák Zs, Baranyi É, Csákány MGy, Stella P, Kerényi Zs. Csökkent inzulinérzékenység és metabolikus szindróma gesztációs diabéteszt követően. Magyar Belorv. Arch. 55(S3):128-129, 2002.
17. **Madarász E,** Tamás Gy, Tabák GyÁ, Speer G, Lakatos P, Kerényi Zs. The determinants of fasting leptin levels and the characteristics of the leptin curves following a 75g oGTT in women with previous gestational diabetes mellitus (GDM). Diabetologia 45(S2):237, 2002. **IF: 5,136**
18. Tamás Gy, **Madarász E**, Tabák ÁGy, Szalay J, Speer G, Lakatos P, Kerényi Zs. Leptin és hypertonia: A metabolikus szindróma jellemzői korábban gesztációs diabéteszes asszonyokban. Hypertonia és Nephrológia 6:28, 2002.
19. Kerényi Zs, Tabák ÁGy, **Madarász E**, Speer G, Nagy-Szabó J, Lakatos P, Tamás Gy. A986s polymorphism of the calcium-sensing receptor, insulin secretion and metabolic syndrome in women with prior gestational diabetes. Diabetologia 44(S1):332, 2001. **IF: 6,299**
20. Tamás Gy, Tabák ÁGy, **Madarász E**, Speer G, Bekő Gy, Nagy-Szabó J, Lakatos P, Kerényi Zs. Characteristic features of the metabolic syndrome in women with prior

GDM: circulating leptin concentrations during oGTT. Diabetologia 44(S1):946, 2001. **IF: 5.700**

21. Kerényi Zs, Tabák ÁGy, Bosnyák Zs, **Madarász E**, Nagy E, Szánthó J, Rákóczi I, Tamás Gy. Universal vs. Selective screening for gestational diabetes: are Caucasian women really at low risk? Diabetes 50(S2):A385, 2001. **IF: 7.700**
22. **Madarász E**, Kerényi Zs, Nagy-Szabó J, Speer G, Nádasdi Á, Bekő G, Tabák GyÁ, Csákány MGy, Baranyi É, Lakatos P, Tamás Gy. Korábban gesztációs diabétesz miatt kezelt asszonyok korai utánvizsgálata - első eredmények. Diabetol. Hung. 9(S1):31 2001.
23. Tűű L, **Madarász E**, Vitályos T, Budai G, Kerényi Zs. Guillain-Barré-szindróma 2-es típusú cukorbetegségben szenvedő betegben. Diabetol. Hung. 9(S1):46 2001.
24. Kerényi Zs, Tabák GyÁ, Stella P, Bosnyák Zs, **Madarász E**, Nádasdi Á, Tóth K, Baranyi É, Csákány MGy, Tamás Gy. Gestatiós diabetes mellitus: Reklasszifikáció, utánkövetés, gondozás - a multimetabolikus X-syndroma lehetséges primer prevenciója? Diabetol. Hung. 8(S1), 2000.
25. Kerényi Zs, Tabák GyÁ, Stella P, Bosnyák Zs, Nádasdi Á, **Madarász E**, Baranyi É, Csákány MGy, Tamás Gy. Gestational diabetes mellitus: reclassification, follow-up, and care - primary prevention of the metabolic syndrome? Diab. Res. Clin. Pract. 50:S426, 2000. **IF: 0.982**
26. **Madarász E**, Tóth K, Kerényi Zs, Tamás Gy. A gesztációs diabétesz diagnózisa, kezelése, szövődményei és a terhesség kimenetelének tükrében. Diabetol. Hung. 7(S1):20, 1999.
27. Bosnyák Zs, Kerényi Zs, Stella P, **Madarász E**, Tóth K, Tamás Gy. Hypertonia gesztációs diabéteszben: előfordulása a terhesség során és utánkövetéskor. Diabetol. Hung. 7(S1):19, 1999.
28. **Madarász E**, Kerényi Zs, Tabák GyÁ, Tóth K, Bosnyák Zs, Baranyi É, Csákány MGy, Mészáros J, Tamás Gy. A hypertonia előfordulási gyakorisága gesztációs diabéteszben. Hypertonia és Nephrologia. 3(S1):57,1999.
29. Bosnyák Zs, Kerényi Zs, Stella P, Tabák GyÁ, **Madarász E**, Tóth K, Tamás Gy. Hypertonia gesztációs diabéteszben: a későbbi magasvérnyomás betegség előjelzője? Hypertonia és Nephrologia 3(S1):58 1999.
30. Kerényi Zs, Tabák GyÁ, Bosnyák Zs, **Madarász E**, Tóth K, Baranyi É, Csákány MGy, Tamás Gy. Gestationsdiabetes und Hypertonie: Frühmanifestation oder Prädiktor des kardiovaskulären Insulinrezistenzsyndroms? Diabetes und Stoffwechsel 8(S4):16, 1999.

31. Kerényi Zs, Tabák GyÁ, Bosnyák Zs, **Madarász E**, Tóth K, Baranyi É, Csákány MGy, Tamás Gy. Prior Gestational Diabetes: Hypertension During Pregnancy and at follow up - early manifestation of a complex metabolic cardiovascular syndrome Diabetologia 41(S1):A8, 1998. **IF:4,986**
32. Kerényi Zs, Stella P, Tabák GyÁ, Bosnyák Zs, **Madarász E**, Tóth K, Tamás Gy. Előzetes gesztációs diabetesz és hypertonia: a multimetabolikus szindróma korai manifesztációja vagy prediktora? Hypertonia és Nephrologia 5(S2):248, 1998.

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