Relationship between Gestational Diabetes Mellitus and Type 2 Diabetes: Evidence of Mitochondrial Dysfunction

Rob N.M. Weijers1* and Dick J. Bekedam2

Background: We examined the pathogenesis of gestational diabetes mellitus (GDM) in a large Dutch multiethnic cohort.

Methods: We used a 2-step testing procedure to stratify 2031 consecutive pregnant women into 4 groups according to American Diabetes Association criteria: (a) normal glucose tolerance (NGT), (b) mild gestational hyperglycemia (MGH), (c) GDM without early postpartum diabetes within 6 months of delivery (GDM1), and (d) GDM with early postpartum diabetes (GDM2). Antepartum and postpartum clinical characteristics and measures of glucose tolerance were documented.

Results: Overall, 1627 women had NGT, 237 had MGH, 156 had GDM1, and 11 had GDM2. Prepregnancy body mass index values progressively increased from NGT to MGH to GDM1. The fasting plasma glucose concentration, the 100-g oral glucose tolerance test (OGTT) area under the curve, and the mean glucose concentration during the OGTT all increased progressively among the 4 groups. The fasting C-peptide concentration displayed an inverted-U pattern, with a maximum at a mean plasma glucose concentration during the OGTT of 9.6 mmol/L in the transition from GDM1 to GDM2. The fasting C-peptide/glucose concentration ratio decreased by 42% in GDM patients compared with NGT patients, whereas the ratios in MGH and NGT women were similar.

Conclusions: Progressive metabolic derangement of glucose tolerance 1st detected during pregnancy mimics the pathogenesis of type 2 diabetes. In addition, our results imply an impaired basal glucose effectiveness in the early prediabetic state. To explain the parallel in both metabolic derangements, we postulate that GDM, like type 2 diabetes, is attributable to the same inherited mitochondrial dysfunction.

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This report continues our analyses (1, 2) of the clinical and biochemical characteristics of gestational diabetes mellitus (GDM)3 without early postpartum diabetes within 6 months of delivery (GDM1) and with early postpartum diabetes (GDM2) in a large Dutch multiethnic cohort. We describe our characterization of the entire cohort to detail the pathogenesis of GDM and compare it with the pathogenesis of type 2 diabetes.

Detailed studies of women with glucose intolerance, which is 1st detected during pregnancy, provide 3 types of information regarding the relationship between GDM and type 2 diabetes. First, virtually all women with GDM appear to have a large β-cell defect against a background of chronic and exaggerated resistance to insulin’s ability to stimulate glucose utilization (3). Insulin-secretion rates in response to moderate hyperglycemia are reduced in these women, not only compared with nondiabetic pregnant women but also relative to their degree of insulin resistance; consequently, the insulin sensitivity–secretion curve is ~50% lower than for nondiabetic women (4).

Several mechanisms for the progression to chronic insulin resistance in GDM have been proposed: abnormal subcellular localization of glucose transporter protein-4 (GLUT4) (5), alterations in the insulin-signaling pathway (6, 7), reduced expression of PPARγ (6), increased expression of the membrane glycoprotein PC-1 (7), and reduced insulin-mediated glucose transport (5). Second, a GDM
diagnosis may impart a risk for type 2 diabetes in addition to that typically identified by the oral glucose tolerance test (OGTT) in nonpregnant individuals. Long-term follow-up studies, recently reviewed by Kim et al. (8), reveal that most women with GDM do progress to diabetes at some time after the index pregnancy; GDM is therefore considered a prediabetic state because of its high conversion rate to type 2 diabetes (9). Finally, recent studies demonstrated an ~30% reduction in basal rates of muscle mitochondrial ATP synthesis (due to reduced mitochondrial numbers and/or function) in a group of healthy, young, lean, and insulin-resistant offspring of parents with type 2 diabetes (10, 11). These data indicate that diminished rates of ATP synthesis may be responsible for the onset of the prediabetic state that finally leads to type 2 diabetes.

We examined the relative importance of the various mechanisms leading to GDM and its progression to type 2 diabetes after pregnancy by investigating the progressive and substantial decrease in glucose tolerance in association with C-peptide concentration among 4 diagnostic categories of pregnant women: with normal glucose tolerance (NGT), mild gestational hyperglycemia (MGH), GDM1, or GDM2. We discuss our findings of the parallel between GDM and type 2 diabetes in metabolic derangements in the context of published results and mitochondrial function in GDM and type 2 diabetes.

Participants and Methods

Study Population and Diagnosis

We have previously described the data set (1, 2), and we briefly review it. We conducted this cross-sectional study between October 1998 and April 2003 with 2031 consecutive pregnant women referred to the obstetrics and gynecology outpatient clinic of the Onze Lieve Vrouwe Gasthuis, a teaching hospital in a multiethnic town borough in the Amsterdam-East region. A substantial part of the population (~23%) consists of 1st- and 2nd-generation immigrants from northern Africa and Hindustani and Creole people from the former Dutch colony of Surinam. We screened all women for GDM at the initial antepartum visit at 16–33 weeks gestation (rather than the usually recommended GDM screening of 24–28 weeks gestation) with a 50-g 1-h glucose-challenge test (GCT) performed in the morning after a 12-h overnight fast (12). Women with a 1-h capillary whole-blood glucose value ≥7.8 mmol/L underwent a 100-g 3-h OGTT within the next 2 weeks. Measurement of the fasting glucose concentration in venous whole blood was followed by capillary whole-blood glucose measurement at 1, 2, and 3 h after administration of 100 g glucose. GDM was diagnosed when 2 or more whole-blood glucose values met or exceeded 4.6, 9.6, 8.2, and 7.3 mmol/L, respectively, as recommended by the Fourth International Workshop-Conference on Gestational Diabetes Mellitus (13). Capillary and venous whole-blood glucose values were compared after conversion to plasma glucose values according to published data (14). All women were followed up postpartum within 6 months of delivery. NGT was defined as a fasting plasma glucose concentration <6.1 mmol/L (15). The diagnosis of diabetes was based on 75-g OGTT results or a fasting plasma glucose concentration ≥7.0 mmol/L at any 2 prior examinations (16). Any type 2 diabetes diagnosis immediately after or within 2 months of delivery was carefully examined after a washout period of 2 months. We used the GCT and OGTT results and the presence or absence of early postpartum diabetes to divide the study participants into 4 diagnostic categories: (a) women with NGT, (b) women with MGH (a positive GCT result and a subsequent negative OGTT result), (c) women with GDM1 (a positive GCT result and a subsequent positive OGTT result), and (d) women with GDM2.

Data Collection

Maternal, antepartum, postpartum, and neonatal data were collected prospectively and entered into a standardized database. Maternal and historical variables were age and gestational age at study entry, obstetric history and family history of diabetes, prepregnancy body mass index, pregnancy-induced hypertension, ethnicity (Caucasian vs non-Caucasian), parity, neonatal data, fasting C-peptide and glucose concentrations, and onset of early postpartum diabetes. Patients with polycystic ovary syndrome (n = 1), hyperthyroidism (n = 1), or prepregnancy diabetes mellitus (n = 22) were excluded from analysis. All individuals provided informed consent before participation, and the hospital’s ethics committee approved the study.

Definitions

Definitions for family history of diabetes, pregnancy-induced hypertension, body mass index before pregnancy, polycystic ovarian syndrome, and ethnicity have been described (2). Because the 5 non-Caucasian subgroups (sub-Saharan African, Northern African, Armenian, Asian, and other) were too small for valid comparisons, we combined them into a single non-Caucasian group.

Analytic Methods

Whole-blood glucose was measured by the hexokinase method [EBIO model 6666; Eppendorf (17)]. Serum C-peptide concentration was measured with an RIA reagent set (Immulate C-peptide; EURO/DPC) (18).

Statistical Methods

Relevant analytic variables included age and gestational age at entry into the study, prepregnancy body mass index, ethnicity, C-peptide concentration, and glycemic variables. We analyzed continuous variables for the 4 diagnostic groups with the Kruskal–Wallis test and compared pairs of groups with the Mann–Whitney U-test when the Kruskal–Wallis test revealed significant differences. Adjustment for prepregnancy body mass index did
not change the statistical results. *P* values for nominal variables were calculated with the *χ*² test. Values > 3 times the interquartile distance above the 75th percentile or below the 25th percentile were considered outliers. Women with outlying values (11 with NGT) were excluded from the analysis, but their inclusion had no effect on the study’s statistical outcomes. A *P* value of 0.05 for 2-sided tests was taken as the level of statistical significance. All statistical procedures were performed with SPSS version 9.0 for Windows (SPSS).

The positively skewed distribution of insulin values required In-transformed data before statistical analysis. We calculated the total glucose area under the 3-h OGTT curve with the trapezoid method.

Bivariate analysis was used to calculate the parameter values of the 95% isodensity ellipse of the distribution of the combination of fasting plasma glucose and C-peptide concentrations, the slope of the linear relationship between C-peptide and glucose concentrations, and the absolute correlation coefficient between these variables. Calculation was done according to Tatsuoka, with EVAL-kit software (CKCHL Twee Steden Ziekenhuis).

**Results**

Of the 2031 eligible women who gave informed consent to participate in the study, 11 women had a diagnosis of GDM2, 156 women had GDM1, and 237 women had MGH. From the 1627 remaining women with a negative GCT result, we randomly selected 476 women as control individuals. The final study population of 880 women entered the study between 16 and 33 weeks of gestation.

Table 1 highlights relevant anthropometric and clinical characteristics of the 4 groups. Age at entry into the study was substantially higher in women with MGH and GDM1 than in NGT participants. No appreciable differences in the mean gestational age were seen among the 4 groups. The prepregnancy body mass index increased progressively from MGH to GDM1 to GDM2. The C-peptide concentration decreased thereafter (Fig. 1). With the mean plasma glucose concentration during the OGTT as a variable, the fasting C-peptide concentration showed an inverted-U pattern, with a maximum at a mean plasma glucose OGTT value of 9.6 mmol/L at the transition from GDM1 to GDM2.

Bivariate statistical analyses for fasting plasma glucose and C-peptide (Fig. 2) showed that the fasting C-peptide/glucose concentration ratio (the slope of the major axis of the ellipse, an index of sensitivity to insulin) was significantly reduced in GDM women compared with NGT individuals [0.53 (0.37) and 0.91 (0.30), respectively]. Fasting glucose concentrations remained higher in the MGH group than in the NGT group [4.5 (0.6) mmol/L vs 4.1 (0.5) mmol/L, *P* < 0.001], but the fasting C-peptide/glucose concentration ratios in the MGH and NGT groups were similar [0.90 (0.31) and 0.91 (0.30), respectively].

**Discussion**

Cross-sectional analyses of 75-g 3-h OGTT results for a large sample of Caucasians and populations with an exceptionally high prevalence of type 2 diabetes revealed inverted-U plots of insulin vs glucose in plasma (known as the Starling curve of the pancreas) (19). After glucose ingestion, glucose and insulin concentrations in the plasma of healthy individuals and individuals with impaired glucose tolerance are positively related to a mean plasma glucose concentration of ~10 mmol/L during the OGTT. The peak of the inverted-U curve coincides with

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**Table 1. Relevant characteristics in patients with NGT, MGH, GDM1, and GDM2.**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>NGT</th>
<th>MGH</th>
<th>GDM1</th>
<th>GDM2</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>33.5 (7.4)</td>
<td>35.2 (8.3)</td>
<td>35.0 (6.1)</td>
<td>33.4 (8.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gestational age at entry, weeks</td>
<td>25.0 (3.5)</td>
<td>25.3 (3.8)</td>
<td>24.8 (4.6)</td>
<td>24.4 (11.3)</td>
<td>0.779</td>
</tr>
<tr>
<td>Ethnicity (Caucasian/non-Caucasian), n</td>
<td>250/226 (53/47)</td>
<td>121/116 (51/49)</td>
<td>47/109 (30/70)</td>
<td>1/10 (9/91)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prepregnancy body mass index, kg/m²</td>
<td>23.0 (5.4)</td>
<td>24.6 (2.4)</td>
<td>28.1 (7.0)</td>
<td>26.3 (8.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fasting C-peptide, nmol/L</td>
<td>0.64 (0.30)</td>
<td>0.79 (0.42)</td>
<td>0.96 (0.48)</td>
<td>0.90 (0.30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>4.1 (0.5)</td>
<td>4.5 (0.6)</td>
<td>5.1 (1.0)</td>
<td>6.1 (2.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3-h OGTT glucose area, mmol·h·L⁻¹</td>
<td>—</td>
<td>21.2 (2.7)</td>
<td>27.2 (3.9)</td>
<td>38.2 (3.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean glucose during OGTT, mmol/L</td>
<td>—</td>
<td>6.5 (0.8)</td>
<td>8.3 (1.2)</td>
<td>11.5 (1.1)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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*Continuous data are represented as the median (interquartile range). Nominal data are represented as the number of patients (percent).*

* P ≤ 0.005, vs NGT.

* P < 0.001, vs MGH.

* P < 0.01, vs NGT.

* P < 0.001, vs NGT.

Not measured.
this value—the renal threshold for glucose—and marks the conversion of impaired glucose tolerance to type 2 diabetes. In this cross-sectional study, we demonstrated that the C-peptide concentration also shows an inverted-U profile, rising through NGT, MGH, and GDM1 to a maximum at a mean plasma glucose value of 9.5 mmol/L during the OGTT and declining in GDM2 women. This value is consistent with observations in nonpregnant individuals, for whom the peak of the inverted-U curve consistently coincides with the renal threshold for glucose despite differences in type 2 diabetes prevalence among populations (20, 21). Because the characteristics of the curve for the pregnant individuals in our study mirrored those of nonpregnant individuals in spanning the range of glucose tolerance from normoglycemic to overtly diabetic, our data strongly suggest that progressive deterioration of glucose tolerance 1st detected during pregnancy mimics the pathogenesis of type 2 diabetes, i.e., the temporal sequence in which these metabolic abnormalities appear in the stages of disease development. Several issues are specific to these data. First, the small number of women in our cohort who had diabetes within 6 months of pregnancy limits the power of the study. Nonetheless, the complementarity of our diagnostic OGTT data for women with and without early postpartum diabetes to data from other groups validates our evaluation of the mutual relationships and ranking of classifying values (22, 23).

Second, a positive GCT value primarily depends on decreased insulin sensitivity, which is more pronounced at a positive 100-g diagnostic OGTT value, whereas an increased fasting glucose value primarily depends on decreased glucose effectiveness. Because these variables measure different alterations, they are useful in combination (i.e., a 100-g diagnostic OGTT glucose area result or a mean glucose concentration during a diagnostic OGTT). Finally, the evidence that the cutoff values for the 50-g 1-h GCT and the 100-g 3-h OGTT yield considerable differences in fasting C-peptide concentration, fasting glucose concentration, and diagnostic OGTT glucose area among the 4 groups reflects the discriminating capacity of the 2-step testing procedure.

To our knowledge, our report constitutes the 1st description of how the major axis of the isodensity ellipse for the fasting plasma glucose and fasting C-peptide concentrations for the NGT group parallels that of the MGH group (Fig. 2). Because the angle between the major axis and the x-axis is a measure of insulin's ability to stimulate glucose utilization, these data suggest that NGT and MGH women have similar insulin sensitivities in the fasting state. Nevertheless, MGH women had considerably higher fasting plasma glucose concentrations than NGT women. The Bergman concept, which distinguishes insulin-dependent and insulin-independent components of glucose clearance (indicated by insulin sensitivity and glucose effectiveness, respectively), may resolve these apparently discrepant results (24). In the basal state, healthy individuals had insulin oscillations with a regular 14-min periodicity of amplitude 1.8 mU/L (25). Thus, for an insulin sensitivity value of $3.1 \times 10^{-4} \text{ min}^{-1} \cdot (\text{mU/L})^{-1}$, the fractional glucose turnover of 2nd-trimester NGT and MGH women is 0.056% of the glucose space per minute (26). Glucose-effectiveness values of 0.016 min$^{-1}$ and 0.010 min$^{-1}$ in nondiabetic and diabetic individuals, respectively (27), indicate that 1.6% and 1.0% of the body's extra cellular glucose pool will disappear per minute at the basal insulin concentration; thus, ~95% of the glucose-restoration rate at basal insulin concentration

![Fig. 1. Best-fit relationship between fasting C-peptide concentration and fasting plasma glucose concentration in women.](image)

Women with NGT (triangle), MGH (circle), GDM1 (diamond), and GDM2 (square). Data for both variables are expressed as the median; bars represent interquartile ranges.

![Fig. 2. Plots of the standard principal component, generated by bivariate analysis of fasting plasma glucose concentration and C-peptide concentration among women with NGT, MGH, or GDM1.](image)

The major axis of the 95% isodensity ellipse for the 3 groups (NGT, MGH, and GDM1) had the following equations (where x is the glucose concentration): \[ \ln(\text{C-peptide})_{\text{NGT}} = -4.19 + 0.91x (r = 0.39; S_x = 0.30); \ln(\text{C-peptide})_{\text{MGH}} = -4.28 + 0.91x (r = 0.30; S_x = 0.31); \ln(\text{C-peptide})_{\text{GDM1}} = -2.75 + 0.53x (r = 0.23; S_x = 0.37). \]
in NGT and MGH women in the 2nd trimester is determined by the ability of glucose to stimulate its own uptake. The appreciably higher basal glucose concentration in MGH women than in NGT women may therefore indicate a lower glucose effectiveness in the former. This observation is consistent with results of a prospective study on the development of diabetes in normoglycemic offspring of parents with type 2 diabetes, which found diminished glucose effectiveness during the prediabetic state of type 2 diabetes (28). Moreover, the impairment in the ability of glucose to promote glucose clearance in people with diabetes indicates that decreased glucose effectiveness plays a pivotal role in the development of type 2 diabetes (24, 29). Because MGH is an early phase in the prediabetic period, decreased glucose effectiveness may be a key feature of this period.

Because of its hydrophilic nature, glucose cannot penetrate the lipid bilayer surrounding cells of muscles and other tissues; thus, specific GLUTs are required to facilitate its diffusion into cells. A hallmark of facilitated diffusion is saturation behavior, that is, if the glucose-transport rate is measured as a function of the difference in glucose concentration across the membrane driving the transport, a limiting rate is approached when all GLUTs are busy. The erythrocyte membrane, which has~500,000 GLUT1 copies, best demonstrates these mechanisms. For glucose concentrations within the normoglycemic range, 1 GLUT1 molecule is available for 1200 glucose molecules (data not shown); that is, transport velocity is limited only by conditions (temperature and pH) and by the number of transporter molecules. Thus, the high-affinity transporters (GLUT1 and GLUT3) with Michaelis–Menten constants between 1 and 2 mmol/L function at rates close to maximal velocity, and degrees of cell surface expression greatly influence the rate of glucose uptake into cells (30). In other words, the effective diffusion coefficient of the glucose transported across the membrane is lower in prediabetic and diabetic individuals than in nondiabetic individuals. Therefore, we hypothesized that a lower increment in glucose disappearance in response to an increase in glucose concentration may occur in MGH women because the basal number of GLUTs is lower than in NGT women.

The mechanisms that decrease glucose’s ability to enhance its own clearance in MGH women are not known; however, extensive work has shown an inherited reduction in the mitochondrial content in skeletal muscle of insulin-resistant prediabetic offspring of parents with type 2 diabetes, and this reduction may be responsible for decreased oxidative phosphorylation, decreased lipid oxidation, and lipid accumulation (10, 11, 31, 32). These phenomena could lead to a continuing tendency toward both weight gain and excess intraorgan lipid concentrations. Consistent with these findings, we found that the prepregnancy body mass index increased progressively from NGT to MGH to GDM1 and was a determinant of MGH as well as GDM (1). In addition, reduced β-oxidation of free fatty acids (FFAs) may produce a decreased cis-FFA/total FFA ratio over several years. For example, arachidonic acid and other polyunsaturated fatty acids are primarily processed to so-called local hormones, including prostaglandins, thromboxanes, leukotrienes, and other hydroxyeicosanoic acids, whereas saturated FFAs are taken up and stored as triacylglycerols by adipocytes, which in turn release the original saturated FFAs in response to hormone messengers. The fatty acid profile of serum lipids, especially phospholipids, reflects the fatty acid composition of cell membranes (33). Thus, long-standing decreases in mitochondrial activity may ultimately contribute to an increase in the percentage of saturated fatty acids or a decrease in the percentage of (poly)unsaturated fatty acids in membrane phospholipids. This concept is consistent with the results of Min et al., who studied the membrane phospholipid fatty acids in control individuals and women who developed diabetes during pregnancy, because insulin resistance, a characteristic of gestational diabetes, is correlated with the fatty acid profile of the erythrocyte and skeletal muscle cell membranes (34). These investigators found that appreciable reductions in arachidonic acid and docosahexaenoic acid were associated with a substantial increase in saturated fatty acids in erythrocyte membrane phosphatidylcholine and phosphatidylethanolamine of GDM women, compared with control individuals (34).

Double bonds in fatty acids are nearly always in the cis configuration, which produces a bend in the fatty acid chain. This bend has important consequences for the structure of biological membranes. Saturated fatty acid chains can pack closely together under certain conditions to form ordered and rigid arrays, whereas unsaturated fatty acids prevent such close packing and produce flexible, fluid aggregates. In this context, an accumulation of saturated fatty acids in membrane phospholipids is likely to disrupt the organization of lipid microdomains in cellular membranes.

We introduce the membrane-flexibility ratio (MFR), the number of cis-fatty acid molecules per total number of fatty acid molecules in a phospholipid bilayer of defined membrane structure, as a measure of membrane flexibility. From the data of Min et al. (34), we calculated a significant decrease in the erythrocyte MFR in GDM women compared with control individuals; that is, GDM women had a markedly lower MFR for phosphatidylcholine and phosphatidylethanolamine fatty acids in the erythrocyte membrane [0.49 (0.09) vs 0.54 (0.07) (P <0.0001) and 0.67 (0.13) vs 0.70 (0.09) (P <0.05), respectively]. These calculations suggest that the pathology of glucose intolerance is associated with the percentage of unsaturated fatty acids incorporated into membrane phospholipids. A decrease in unsaturated fatty acids would reduce the liquidity and flexible mechanical properties typical of active cell membranes and in turn reduce the number of GLUT1 and GLUT3 molecules. On the other hand, the lipid composition of membranes, along
with proteinaceous regulatory factors, has an important role in the budding of transport vesicles (35), suggesting that a decreased MFR may also be a primary cause of defects in the machinery for insulin-mediated docking and fusion of vesicles containing GLUT4 molecules (36) and lead to a decrease in insulin sensitivity. This supposition is in line with the report of Garvey et al. (37), who demonstrated a defect in basal GLUT4 trafficking and targeting that led to transporter accumulation in a dense membrane compartment. The transporters could not be recruited to cell surface membranes of insulin-resistant individuals with and without diabetes. It is interesting that FFA-induced insulin resistance produces decreased glucose-transport activity (38) and that glucose transport is the rate-controlling step in insulin-stimulated muscle glycogen synthesis in patients with diabetes (39).

One of the characteristics of the 2nd half of pregnancy is an appreciable increase in the plasma concentration of FFA, which has the beneficial effect of preserving glucose for the growing fetus (40). This observation suggests the presence of 2 types of MFR decreases in women with GDM: the typical decrease in MFR of late pregnancy and a more chronic decrease in MFR, as seen in people with an inherited defect in mitochondrial oxidative phosphorylation. Under conditions of progressing membrane inflexibility due to an inherited decrease in mitochondrial activity, superposition of both MFR decreases during a pregnancy may lead to an increase in metabolic abnormalities characterized as MGH or as GDM1 or GDM2 (Fig. 3). We also observed a time-dependent increase in metabolic abnormalities in pregnant women who returned for specialist antenatal care with a 2nd pregnancy.

In conclusion, we suggest that the progressive deterioration of glucose tolerance 1st detected during pregnancy parallels the pathogenesis of type 2 diabetes and postulate a pathway for the underlying mechanisms: Cell surface expression of GLUTs greatly influences the rate of glucose uptake, which depends on the MFR, which in turn is influenced by the amount of unsaturated fatty acid in membrane phospholipids. In a prediabetic state, the total MFR of a pregnant woman may be specified by both a temporary decrease due to pregnancy and by a chronic decrease due to an inherited defect in mitochondrial oxidative phosphorylation and may determine the metabolic abnormality characterized as MGH or as GDM1 or GDM2.

References


