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An evaluation of selected lipid parameters in pregnancy complicated by gestational diabetes mellitus (Part 1)

Abstract

Background. The aim of the study was to evaluate selected parameters of lipid metabolism [total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglycerides (TG)] in women with gestational diabetes mellitus (GDM).
Material and methods. The study included 121 patients with GDM at the mean age of 30.5 ± 5.7 years and 36 healthy pregnant controls at the mean age of 25.3 ± 4.4 years. The lipid parameters of interest were determined at diagnosis in women with GDM and at the end of the 2nd trimester in healthy controls (baseline), and at the end of the 3rd trimester in both groups (T3).
Results. TG values were significantly higher at baseline in GDM versus control. TG change from baseline was significant in both groups, but higher in GDM, leading to the disappearance of the baseline differences between the groups at T3. TC values did not differ at baseline, while TC change from baseline was significant and higher in controls versus GDM. LDL-C and HDL-C values did not differ between the study groups at the time points of interest. In patients with GDM, HDL values at baseline and TC and LDL-C values at T3 were significantly lower in patients who were obese before the pregnancy versus patients with normal pregestational body mass. TG values did not differ significantly between the groups, although at baseline they had been significantly higher in overweight patients versus patients with normal pregestational body mass. With the advancement of pregnancy in GDM, a significant improvement of glycaemic control was achieved.
Conclusion. Elevated TG values were observed at the diagnosis of GDM. At the end of pregnancy, following antidiabetic treatment, TG values did not differ from those observed in healthy controls, although TC values were significantly higher.
key words: gestational diabetes mellitus, lipids

Introduction

Gestational diabetes mellitus (GDM), considered by some authors to be a risk factor for metabolic syndrome, may trigger irreversible vascular changes putting patients at a higher risk of cardiovascular disease [1]. In women with a history of GDM, endothelial dysfunction has been diagnosed as an exponent of vascular changes [2]. Development of diabetes mellitus during pregnancy may alter the metabolism of lipoproteins characteristic of uncomplicated pregnancy. The aetiology of GDM is very heterogenous, which may be the reason for the variety of data on the changes in lipid metabolism observed in the course of this disorder. The most commonly reported ones include elevated triglyceride (TG) levels and reduced total and LDL-cholesterol levels. There have also been reports of a lack of differences between healthy pregnant women and women with GDM [3–6].

The changes in lipoprotein metabolism found in normal pregnancy result from the effects of sex hormones. Of special importance is the elevation of chorionic gonadotropin and cortisol as well as oestrogens and progesterone, which augment insulin resistance and hyperinsulinism. Cholesterol is the substrate for steroid hormones produced by the placenta, and the changes in cholesterol concentration affect the levels of the various lipoprotein fractions. Changes in the concentrations of the individual types of lipoprotein in subsequent trimesters of pregnancy have been described elsewhere [7–9].

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We evaluated the type of changes in lipid metabolism in pregnant women with GDM versus healthy pregnant women. We also analysed factors which may additionally modify lipid metabolism.

Material and methods

The study included 121 women with GDM. Duration of pregnancy was estimated from the Naegele's rule, based on the first day of last menstrual period, and verified by ultrasound. Hypertensive patients, current smokers and patients taking pharmacologic agents which might affect lipid metabolism were excluded from the study.

The control group consisted of 36 pregnant women with normal 50 g oral glucose tolerance test. The study group characteristics are summarised in Table 1.

In all the subjects, total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and triglyceride (TG) levels were obtained at two time points: at presentation due to a referral for GDM and at the end of pregnancy (between 36 and 39 weeks of gestation). Blood samples were taken following 12 hours of night time fast, from the basilic vein, into tubes containing 3.2% sodium citrate at a 9:1 ratio. Citrated blood was centrifuged at 3000 rpm. Serum TC, LDL-C, HDL-C and TG levels were determined by the enzymatic method using BioMérieux kits, France (normal values were 50–200 mg/dL for TC, 0–130 mg/dL for LDL-C, 35–55 mg/dL for HDL-C and 50–200 mg/dL for TG), and lipoprotein electrophoresis was performed on a hydrogel using a Sebia electrophoresis system (France).

Glycaemic control was evaluated on the basis of glucose values obtained by the patients themselves every day: after an overnight fast (FBG, fasting blood glucose) and 1 and 3 hours after main meals. The correctness of the measurements was verified every 2 weeks by determinations performed at the laboratory using glucose oxidase and by determination of fructosamine and glycated haemoglobin (HbA_{1c}). Fructosamine was determined every 2 weeks by the colorimetric method using Roche kits (France) (normal laboratory range: 200–265 μmol/L) while HbA_{1c} was determined by immunoturbidimetry using Roche kits (France) (normal laboratory range: 4–6%). Glycaemic control parameters are summarised in Table 2.

The results were analysed statistically. The distribution of data was verified by the Kolmogorov-Smirnov test. Data with a near-normal distribution were analysed by the *t*-Student test, data for samples significantly different from the normal distribution were analysed by the rank sum test (Mann-Whitney U test) and data for matched pairs were analysed by the Wilcoxon test. Differences with a P value of < 0.05 were considered statistically significant. The relationship between selected factors and dependent variables was analysed by the multiple regression model.

Table 1. Study group characteristics (mean ± standard deviation)

Parameter (unit of measurement)	GDM	Control	P value
Number of patients (n)	121	36	
Age (years)	30.5 ± 5.7	25.3 ± 4.4	0.001
Week of gestation at the time of GDM diagnosis	29.6 ± 4.7	(–)	(–)
Pregestational BMI [kg/m^2]	25.5 ± 6.1	21.9 ± 4.1	0.01
Gestational weight gain [kg]	11.8 ± 5.3	16.1 ± 6.9	0.01
Due date (week)	39.7 ± 1.9	39.9 ± 1.0	NS

BMI — body mass index; GDM — gestational diabetes mellitus; NS — not significant

Table 2. Parameters of glycaemic control during pregnancy (mean ± standard deviation)

Parameter (unit of measurement)	Diagnosis of GDM	End of 3rd trimester	P value
FBG [mmol/L]	4.9 ± 1.1	4.3 ± 0.5	< 0.001
MBG [mmol/L]	6.0 ± 1.3	5.2 ± 0.5	< 0.001
Fructosamine [mmol/L]	2.0 ± 0.3	1.9 ± 0.2	< 0.001
HbA_{1c} (%)	4.9 ± 0.8	4.9 ± 0.8	NS

FBG — fasting blood glucose; GDM — gestational diabetes mellitus; MBG — mean blood glucose; NS — not significant

Results

Patients with GDM were significantly older and weighed significantly more before the pregnancy versus health controls, but gained significantly less weight during pregnancy. There were no significant differences in the due date between both groups, which approximated 40 weeks (Table 1). After the diagnosis of GDM, a gradual improvement of glycaemic control was noted, which was reflected by a significant reduction in FBG, mean daily glucose and fructosamine. No significant improvement of HbA_{1c} values was, however, observed (Table 2).

A significant increase of TG values was found at the end of pregnancy (T3) versus baseline (at the diagnosis of GDM) in patients with GDM, while the other lipid parameters did not change significantly. A significant increase of both TG and TC was observed in healthy controls during this time (Figure 1).

While TG levels were significantly higher in patients with GDM versus healthy controls at baseline, they did not differ significantly between the groups at T3. A significantly higher TC levels were, however, observed in healthy controls (Figure 1).

The multivariate analysis to evaluate the effect of selected factors [age, body mass index (BMI), HbA_{1c}, baseline glucose, presence of GDM] on lipoprotein levels revealed that the development of GDM affected the values of all the lipoproteins of interest with the greater effect observed for TG. Coefficient of regression was 47.26 ± ± 11.32 for the effect of GDM on TC, 10.04 ± 3.72 for the effect on HDL-C and 113.37 ± 13.96 for the effect on TG. No effect of age or HbA_{1c} on lipoproteins was observed in the study group, although increased BMI negatively affected TC and HDL-C (coefficients of regression: –0.54 ± ± 0.21 and –0.24 ± 0.08, respectively). There was also a negative association between baseline glucose and TC (coefficient of regression: –0.54 ± 0.21).

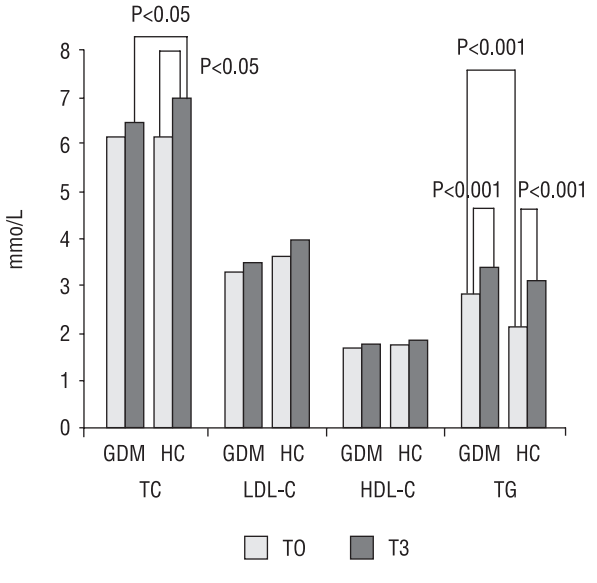

Figure 1. Changes in the lipid metabolism parameters in the course of pregnancy in women with gestational diabetes mellitus (GDM) and healthy controls (HC). T0 — diagnosis of gestational diabetes mellitus; T3 — end of the 3rd trimester of pregnancy; TC — total cholesterol; LDL-C — LDL-cholesterol; HDL-C — HDL-cholesterol; TG — triglycerides

In addition, in the GDM group, we analysed the study parameters with respect to their relationship to pregestational BMI, week of gestation when GDM was diagnosed and gestational weight gain. The results of this analysis are presented in Table 3.

Total cholesterol at the diagnosis of GDM was significantly lower in patients with: earlier diagnosis of GDM (≤ 28 weeks of gestation), patients who were obese versus normal-weight before pregnancy and patients with a slower weight gain during pregnancy (≤ 12 kg). At the end of the 3rd trimester significantly lower TC values were still observed in women with pregestational obesity.

LDL-cholesterol at the diagnosis of GDM was significantly lower in pregnant patients in whom GDM had been diagnosed before 28 weeks of gestation and in patients with normal body mass before pregnancy versus those with obesity. Significantly lower LDL-C values in obese versus non-obese patients is noteworthy. Also, at the end of pregnancy, LDL-C in obese patients was at its lowest, and significant differences were observed between obese versus non-obese patients before pregnancy. No differences in LDL-C levels were noted in relation to the degree of weight gain during pregnancy.

The highest HDL-C levels at the diagnosis of GDM were observed in patients with normal pregestational BMI and differed significantly from the values found in patients who had been obese before pregnancy. At T3, significantly higher HDL-C values were observed in patients with GDM diagnosed before 28 weeks of gestation. This parameter did not change throughout the pregnancy with the weight gain.

Baseline TG values were significantly higher in patients with GDM diagnosed after versus before 28 weeks of gestation. At the end of pregnancy significantly higher TG values were observed in patients overweight before pregnancy versus those with normal pregestational BMI values. In patients with pregestational obesity, TG levels at the time of GDM diagnosis and at T3 did not differ significantly from values observed in patients with normal body mass before pregnancy.

Discussion

Gestational diabetes mellitus is a syndrome of disturbed carbohydrate tolerance diagnosed during pregnan-

Table 3. Changes in the lipid parameters during pregnancy complicated by gestational diabetes mellitus in relation to various factors (mean ± standard deviations)

Parameter [mmol/L]		Pregestational BMI [kg/m^2]			Gestational weight gain [kg]		Week of gestation at the time of GDM diagnosis	
		< 25	25–30	> 30	≤ 12	> 12	≤ 28	> 28
TC	T0	**6.47** ± 1.06*	6.05 ± 1.30	**5.52** ± 1.25*	**4.98** ± 2.69**	**6.06** ± 1.30**	**5.79** ± 1.17**	**6.38** ± 1.21**
	T3	**6.67** ± 1.27*	6.23 ± 1.37	**5.79** ± 1.10*	6.48 ± 1.27	6.35 ± 1.36	6.32 ± 1.32	6.49 ± 1.29
LDL-C	T0	**3.76** ± 0.93•*	**4.30** ± 1.12•*	**2.91** ± 0.98*	3.37 ± 1.05	3.48 ± 0.99	**3.11** ± 0.98**	**3.62** ± 1.00**
	T3	**3.73** ± 1.15*	3.36 ± 1.20	**2.92** ± 0.98*	3.45 ± 1.21	3.48 ± 1.11	3.31 ± 1.13	3.59 ± 1.16
HDL-C	T0	**1.70** ± 0.41•	1,57 ± 0,35	**1.52** ± 0.34•	1.58 ± 0.39	1.66 ± 0.37	1.65 ± 0.43	1.61 ± 0.36
	T3	1.75 ± 0.53	1.37 ± 0.35	1.60 ± 0.30	1.69 ± 0.43	1.72 ± 0.50	**1.84** ± 0.54•	**1.62** ± 0.35•
TG	T0	2.64 ± 0.83	3.06 ± 1.01	2.94 ± 1.19	2.77 ± 1.02	2.81 ± 0.91	**2.49** ± 0.87**	**3.02** ± 1.00**
	T3	**3.19** ± 0.83•	**3.68** ± 1.11•	3.25 ± 1.05	3.19 ± 0.92	3.43 ± 0.99	3.09 ± 0.78	3.41 ± 1.04

Values between which significant differences were found have been printed in bold •P < 0.05; *P < 0.001, **P < 0.01; GDM — gestational diabetes mellitus; TC — total cholesterol; LDL-C — LDL-cholesterol; HDL-C — HDL-cholesterol; TG — triglycerides; T0 — diagnosis of GDM; T3 — 3rd trimester of pregnancy

cy. It is a heterogenous group of abnormalities which may encompass cases of type 1, type 2 or other forms of diabetes mellitus diagnosed in this period of a woman's life. Typical GDM develops in the second half of pregnancy as a result of gradually increasing insulin resistance. Some authors consider it an early marker of metabolic syndrome [1, 10, 11]. Obviously, as is the case with type 2 diabetes mellitus, the increasing insulin resistance must be accompanied by a factor that impairs insulin secretion by pancreatic beta cells, which is consistent with the fact that only several percent of pregnant women do develop GDM despite insulin resistance present in all of them [12, 13]. Diabetes mellitus as a complication of pregnancy may give rise to irreversible vascular changes that put the women at risk of increased cardiovascular morbidity [14–16].

The abnormalities of carbohydrate metabolism observed in GDM may lead to other abnormalities (most commonly the typical abnormalities seen in insulin resistance), especially lipid abnormalities. In our study, the typical change in the lipid profile observed in the GDM group at the moment of GDM diagnosis was elevated TG versus healthy controls, which was probably a result of a greater degree of insulin resistance in these patients. Normalisation of TG levels at the end of pregnancy was probably a result of the treatment [17].

We found significantly higher values of glycaemic control parameters, except for HbA_{1c}, in GDM patients versus healthy controls (Table 2). The lack of difference between the two groups with respect to HbA_{1c} may have been a result of too short a duration of hyperglycaemia before the diagnosis of GDM. While the correlation between TC and HbA_{1c} in type 1 and type 2 diabetes mellitus is well established, but in most cases this is observed in patients with much higher HbA_{1c} values than those achieved by patients during pregnancy [18, 20]. However, even a small increase of glucose levels may be associated with higher TG values (in proportion to glucose levels) [21, 22], which might have affected the elevated TG values we observed. It is important because according to some authors, elevated TG during pregnancy may result in foetal macrosomia irrespective of glucose levels [21, 23, 24].

At the end of pregnancy, TC levels in the GDM group were significantly lower than those observed in healthy controls. In addition to reduced TC, other studies have demonstrated reduced LDL-C as well in GDM patients, which was most likely a result of insulin therapy which inhibits lipolysis in the adipose tissue [10, 18]. The lower TC values in patients with GDM may also have been affected by lower HDL-C values, in proportion to the degree of insulin resistance, impaired glucose tolerance, increased lipolysis and ketogenesis [10, 19]. We did not observe any differences in pre- and post-treatment LDL-C or HDL-C levels. The evaluation of LDL-C does not, however, take into account changes in the composition of the particle itself (increased content of TG and cholesterol esters and reduced content of protein) leading to the formation of the small dense LDL fraction, typical of type 2 diabetes mellitus. The presence of atherogenic particles makes GDM similar to type 2 diabetes mellitus in terms of cardiovascular risk.

Similarly to other authors, we found that pregnant women with GDM were older and had higher BMI values before pregnancy but were slower to gain weight during pregnancy compared to healthy controls, most likely as a result of the dietary restrictions we had recommended [25].

Interestingly, in patients who were obese before pregnancy we found lower values of TC, LDL-C and HDL-C

than in the other groups. The reason for this finding is unclear. Obesity is characterised by increased production of TG in the liver leading to changes in the composition of VLDL and LDL particles, which by way of exchange with HDL particles, also change their composition leading to increased catabolism of changed HDL particles and reduced levels of HDL particles in the serum. In healthy patients, increasing obesity is paralleled by increased TG, reduced HDL-C and slightly elevated or unchanged TC. High-fat diet in obese persons leads to a smaller increase in TC and LDL-C than it does in non-obese persons, most likely as a result of increased energy expenditure [26]. The lipid profile in the study group might have also been affected by the diet during pregnancy. The higher risk of insulin therapy in obese pregnant women with GDM often is a significant motivation to conscientiously follow calorie-restricted diet.

Conclusions

1. The abnormality of lipid metabolism found in gestational diabetes mellitus versus healthy pregnant women is elevated triglycerides at the time of diagnosis.
2. Normalisation of triglycerides and achieving total cholesterol levels that are lower than in healthy pregnant women at the end of pregnancy might have resulted from antidiabetic treatment.
3. The group of pregnant patients with gestational diabetes who were obese before pregnancy, compared to women with normal body weight before pregnancy, demonstrated higher levels of total, LDL- and HDL-cholesterol.

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