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Raised concentrations of lipid peroxidation products (LPO) in pregnant women with impaired glucose tolerance

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Abstract

Introduction. Lipid peroxidation (LPO) results from oxidative damage to membrane lipids. Whereas LPO rises in normal pregnancy, the effect of gestational diabetes mellitus (GDM) on this process has not been clearly defined.

Materials and Method. Fasting blood concentrations of malondialdehyde+4-hydroxyalkenals (MDA+4-HDA), as LPO index, TNFα soluble receptors (sTNF-R1 and sTNF-R2), and soluble adhesion molecules (sICAM-1, sVCAM-1), were measured in 51 women at 28 weeks of gestation. The women were divided according to the results of 50.0 g glucose challenge test (GCT) and 75.0 g oral glucose tolerance test (OGTT): Controls (n=20), normal responses to both GCT and OGTT; Intermediate Group (IG) (n=15), abnormal GCT but normal OGTT; GDM group (n=16), abnormal both GCT and OGTT.

Results. Glucose concentrations in women diagnosed with GDM were within the range of impaired glucose tolerance. There were no significant differences in concentrations of either TNFα soluble receptors R1 and R2, or sICAM-1 or sVCAM-1. LPO concentrations [MDA+4-HDA (nmol/mg protein)] were significantly higher in women with GDM than in the other two groups [64.1±24.3 (mean±SD), 39.3±23.1, 47.0±18.1, for GDM, IG and Controls, respectively; $p<0.05$]. In multivariate analysis, the only significant independent correlation was between LPO level and glucose at 120 minutes of OGTT ($r_s=0.42$; $p=0.009$).

Conclusions. Oxidative damage to membrane lipids is increased in GDM and might result directly from hyperglycaemia. Physiological significance of this phenomenon remains to be elucidated.

Key words

gestational diabetes mellitus, lipid peroxidation, glucose tolerance, insulin resistance, TNF alpha soluble receptors

INTRODUCTION

Under physiological conditions, biological cells produce low or moderate amounts of reactive oxygen species (ROS) that are required for life processes. In basal conditions, ROS are continuously detoxified by antioxidant systems and, therefore, they are not toxic [1]. Overproduction of ROS, free radicals included, results in enhanced oxidative stress and may lead to several diseases [2]. Alternatively, pathological processes in organs or tissues may, in turn, lead to an increased formation of ROS and, in consequence, to increased damage to macromolecules, such as membrane lipids [2, 3]. Oxidative damage to membrane lipids results in lipid peroxidation (LPO). The placenta is a major source of oxidative stress during pregnancy. As placenta is rich in polyunsaturated fatty acids which are highly susceptible to attack by ROS, then increased LPO is expected during pregnancy, and that assumption has been already clinically proven [4].

In normal pregnancy, LPO rises until the middle of the 2nd trimester and generally returns to normal non-pregnant levels in early postpartum [5]. However, the concentrations of LPO products and their relationship with insulin resistance (IR) indices has not been validated in gestational diabetes mellitus (GDM), i.e., a condition characterized by hyperglycaemia and increased IR [6]. Pregnancy *per se* constitutes a pro-inflammatory condition associated with an inflammatory response characterized by leukocyte activation [7], while overproduction of LPO products might occur at sites of chronic inflammation [8]. Furthermore, endothelial dysfunction, IR and low-degree pro-inflammatory state are also features of GDM [9, 10].

Secretory products from adipocytes contribute to deterioration in glycaemic control and increased IR, with complications, such as type 2 diabetes and atherosclerosis [11]. Tumour necrosis factor alpha (TNFα) is implicated in the pathogenesis of complications of metabolic syndrome, including IR and post-ischemic myocardial dysfunction [12, 13]. After binding to its receptors, a proteolytic cleavage of the extracellular parts elicits the soluble forms of TNFα receptors, named sTNF-R1 (60 kDa) and sTNF-R2 (80 kDa) [14]. This process is known as shedding. The concentration of these soluble TNFα receptors (sTNFαRs) is proportional to previous TNFα action. In fact, sTNFαRs remain elevated in plasma for longer periods of time after the administration of TNFα and are thought to be a surrogate of previous TNFα effects [15, 16]. This is because the two soluble receptor forms – sTNF-R1 and sTNF-R2 – have longer half-lives

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than TNFα, and their concentration may reflect TNFα activity [17]. Furthermore, recent evidence suggests that the TNFα system and serum sTNF-R1 and sTNF-R2 might be associated with the rate of glucose and lipid oxidation during hyperinsulinemia in an opposite manner to adiponectin [18]. While serum TNFα concentrations were reported to be raised in GDM, in most [19, 20, 21, 22], though not in all studies [23], there are few data on concentrations of TNFα soluble receptors in women with GDM. Binding of monocytic cells to vascular endothelium, one of the earliest detectable events in atherosclerotic lesion development and in inflammatory processes, arises under the influence of adhesion molecules, such as soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) [24]. It has been shown that diabetic patients have an increase of soluble adhesion molecules (sICAM-1, sICAM-2, sVCAM-1, sE-selectin, sL-selectin, sP-selectin) considered an integral part of the inflammatory state [25]. Cellular forms of adhesion molecules mediate specific steps of leukocyte-endothelial cell interaction and have been implicated in the pathophysiology of pre-clampsia, endothelial dysfunction [26], as well as IR [25, 27].

Objective. The presented study aimed to test the hypothesis that concentrations of LPO products might be altered in GDM. A further aim was to assess any potential relationships between LPO products and IR indices and the components of TNFα system (i.e., TNFα soluble receptors R1 and R2), as well as soluble forms of adhesion molecules (sICAM-1 and sVCAM-1).

MATERIALS AND METHOD

This was a cross-sectional study performed at 28 weeks of gestation. The study group comprised 51 women who attended either Obstetric Clinics at the Royal Free Hospital in London, UK, or The Department of Endocrinology and Metabolic Diseases at The Polish Mother's Memorial Hospital Research Institute in Łódź, Poland, and were screened for GDM and evaluated with 50.0 g glucose challenge test (GCT) and 75.0 g oral glucose tolerance test (OGTT). Women with plasma glucose <7.8 mmol/l one hour after the GCT were regarded normal and subjected to routine antenatal care. GDM was diagnosed according to the WHO criteria [28]. The women were divided into three groups according to the results of GCT and OGTT: Controls (n=20) had normal responses to GCT and OGTT, Intermediate Group (IG) (n=15) had false positive GCT but normal OGTT, while the GDM group (n=16) had abnormal both GCT and OGTT. Demographic characteristics of study subjects are presented in Table 1. The study was approved by the Ethics Committees of The Royal Free Hospital in London, UK, and The Polish Mother's Memorial Hospital Research Institute in Łódź, Poland.

Measurements. The concentrations of malondialdehyde + 4-hydroxyalkenals (MDA + 4-HDA), as an index of LPO, were measured in serum using the LPO-586 kit purchased from Calbiochem (La Jolla, CA, USA). The serum (200 µl) was mixed with 650 µl of a methanol: acetonitrile (1: 3, v/v) solution, containing a chromogenic reagent, *N*-methyl-2-phenylindole and vortexed. After adding 150 µl of methanesulphonic acid (15.4 M), the incubation was carried out at 45 °C for 40 min. The reaction between MDA + 4-HDA and *N*-methyl-2-phenylindole yields a chromophore, which is spectrophotometrically measured at the absorbance of 586 nm, using a solution of 4-hydroxynonenal (10 mM) as the standard. The level of LPO was expressed as the amount of MDA + 4-HDA (nmol) per 1 ml of serum.

Having obtained ethical approval, glucose and insulin concentrations were measured at 0 minutes, and later at every 30 minutes, up to 120 minutes of OGTT. IR was assessed by HOMA [29] [where HOMA=fasting insulin (µU/ml) × fasting glucose (mmol/l)/22.5] and by the insulin resistance index (IRI) [30] based on glycaemia and insulinaemia during OGTT. The product of the glucose area under the plasma glucose curve and insulin area under plasma glucose curve is used as an index of IR. TNFα soluble receptors (sTNF-R1 and sTNF-R2), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured by commercial Quantakine Elisa assays (R and D systems), intra and inter-assay variation: 3.6%, 4.4%, 4.6 %, 3.5 % inter-assay variation 3.7, 3.2, 7.4%, 7.7%, for TNF alpha R1 and R2, and for sICAM-1 and sVCAM-1, respectively.

Statistical analysis. The data were analyzed by means of simple descriptive statistics and non-parametric tests of significance (since not all variables have normal distribution) – Mann-Whitney's U test for comparison of distributions in two independent groups, and the Kruskal-Wallis test in the case of more than two groups**.** Associations between LPO and other covariates of interest (demographic and clinical) were qualified by means of Pearson or Spearman rank correlations. In all the analyses, statistical significance was considered for $p \leq 0.05$. All the calculations were derived by means of Statistica v8.0 software.

RESULTS

There were no significant differences between the subgroups, regarding age and BMI, both before and during pregnancy (Tab. 1). According to the results of the OGTT, the principal differences between women with GDM and controls pertained to glucose levels after 120 minutes of OGTT (Fig. 1), while fasting glucose levels (albeit still higher than in controls, $p \leq 0.01$) were still within the reference range for all but one woman with GDM. In women with GDM, glucose levels at 120 minutes of OGTT were in the range between 8.0 mmol/l – 11.6 mmol/l, with only one subject exceeding glucose concentration of 11.1 mmol/l (i.e. the cut-off point between impaired glucose tolerance and diabetes mellitus in non-pregnant subjects). Worsening of glucose tolerance was characterised by an increase in fasting glucose in the GDM group, and fasting insulin and HOMA index in both

Table 1. Demographic characteristics (mean ± SD) of subjects participating in the study

Parameter	GDM (n=16)	IG (n=15)	CTRs (n=20)	*p-value*
Age [years]	32.6 ± 4.2	33.0 ± 4.3	31.9 ± 3.7	*0.65*
BMI before pregnancy [kg/m^2]	23.7 ± 3.2	23.5 ± 4.8	23.2 ± 4.2	*0.54*
BMI current [kg/m^2]	27.7 ± 3.6	26.8 ± 4.2	26.4 ± 4.2	*0.34*

P – value of the Kruskal-Wallis' test for comparison of distributions between three groups

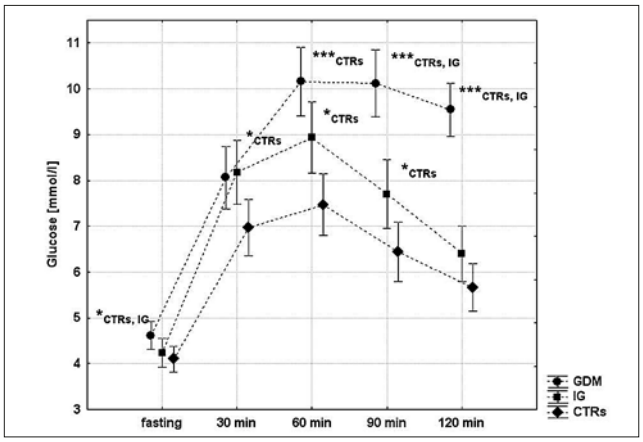

Figure 1. Glucose levels in glucose tolerance test (OGTT) in three groups of women: Gestational (GDM), Intermediate (IG) and Controls (CTRs). Vertical bars represent 95% confidence intervals for OGTT levels at different time points. Significant differences between groups, assessed by means of Mann-Whitney's U test, are indicated by asterisks: *($p \leq 0.05$); ***($p \leq 0.001$)

Intermediate (i.e., in patients with FPGCT) and in the GDM groups in comparison to Controls ($p<0.01$). However, there were no differences in fasting insulin, fasting glucose and HOMA index between the Intermediate and GDM groups ($p>0.10$ (Tab. 2). In contrast, there was no difference in the estimates of insulin resistance assessed by IRI between the Controls and Intermediate groups (0.68±0.25 *vs.* 0.93±0.29, $p=0.23$). There was, however, a marked difference in the value of IRI between the GDM and Intermediate groups (1.67±0.39 *vs.* 0.93±0.29, $p=0.015$), and between the GDM group and Controls ($p<0.001$).

Descriptive statistics for LPO concentrations [MDA+4-HDA (nmol/mg protein)] are presented in Table 2 and Figure 2. LPO concentrations were significantly higher in women with GDM than in the other two groups ($p<0.05$), but there were no differences in LPO concentrations between Controls *vs.* Intermediates. Concentrations of other measured parameters are also presented in Table 2. There were no

Table 2. Descriptive statistics of assessed variables for three groups of women: GDM Intermediate (IG) and Controls (CTRs). P-value of the Kruskal-Wallis' test for comparison of distributions of these characteristics in three independent groups. Significant differences

Variable	Group	n	Mean ± SD	Interquart. r.	Min	Max	*p-value*	
Glucose 0 min. [mmo/l]	GDM	16	4.6 ± 1.0	(4.2 ; 4.6)	3.6	8.0	↑$^{**}_{CTRs}$	*0.030*
	IG	15	4.2 ± 0.3	(3.9 ; 4.4)	3.7	4.7		
	CTRs	20	4.1 ± 0.4	(3.9 ; 4.3)	3.6	4.9		
Glucose 120 min. [mmo/l]	GDM	16	9.5 ± 1.2	(8.3 ; 10.6)	8.0	11.6	↑$^{***}_{CTRs,\ IG}$	*<0.0001*
	IG	15	6.4 ± 1.0	(5.3 ; 7.3)	4.4	7.6		
	CTRs	20	5.7 ± 1.2	(4.6 ; 6.6)	3.7	7.7		
Insulin 0 min. [mU/ml]	GDM	16	10.2 ± 4.1	(7.7 ; 13.2)	3.8	19.9	↑$^{***}_{CTRs}$	*0.0012*
	IG	15	10.6 ± 6.6	(6.0 ; 13.6)	4.2	27.2	↑$^{**}_{CTRs}$	
	CTRs	20	6.1 ± 3.9	(3.8 ; 6.5)	2.4	19.7		
Insulin 120 min. [mU/ml]	GDM	16	120.0 ± 70.4	(75.8 ; 145.1)	52.2	303.4	↑$^{***}_{CTRs}$	*0.0003*
	IG	15	80.9 ± 43.6	(54.5 ; 105.9)	17.7	180.3	↑$^{*}_{CTRs}$	
	CTRs	20	50.6 ± 23.1	(35.0 ; 72.8)	15.9	94.4		
HOMA [mU/ml · mmol/l]	GDM	16	2.22 ± 1.46	(1.46 ; 2.62)	0.61	7.07	↑$^{***}_{CTRs}$	*0.0014*
	IG	15	2.05 ± 1.36	(1.08 ; 2.84)	0.73	5.32	↑$^{**}_{CTRS}$	
	CTRs	20	1.15 ± 0.82	(0.67 ; 1.19)	0.38	4.11		
IRI	GDM	16	1,50 ± 0.38	(1.02 ; 1.82)	0.91	1.97	↑$^{***}_{CTRs,\ IG}$	*<0.0001*
	IG	15	0.93 ± 0.29	(0.81 ; 1.12)	0.31	1.38	↑$^{*}_{CTRs}$	
	CTRs	20	0.68 ± 0.25	(0.52 ; 0.92)	0.30	1.10		
sICAM1 [ng/ml]	GDM	16	364 ± 135	(291 ; 440)	136	606		*0.21*
	IG	15	312 ± 68	(262 ; 372)	202	438		
	CTRs	20	306 ± 94	(243 ; 344)	192	580		
sVCAM1 [ng/ml]	GDM	16	902 ± 267	(752 ; 1164)	608	2390		*0.11*
	IG	15	1066 ± 387	(878 ; 1274)	320	1826		
	CTRs	20	1048 ± 374	(842 ; 1169)	578	1516		
LPO [MDA+4-HDA (nmol/mg protein)]	GDM	16	64.1 ± 24.3	(44.0 ; 85.9)	36.2	102.3	↑$^{*}_{CTRs,\ IG}$	*0.033*
	IG	15	39.3 ± 23.1	(17.0 ; 60.8)	11.6	77.5		
	CTRs	16	47.0 ± 18.1	(34.1 ; 59.0)	23.0	79.0		
TNF-RI [pg/ml]	GDM	16	1293 ± 456	(1027 ; 1387)	884	2568		*0.64*
	IG	15	1271 ± 312	(1018 ; 1432)	824	1906		
	CTRs	20	1307 ± 336	(1110 ; 1414)	945	2246		
TNF-RII [pg/ml]	GDM	16	3478 ± 734	(2903 ; 4023)	2348	4857		*0.14*
	IG	15	3961 ± 693	(3420 ; 4700)	2576	4892		
	CTRs	20	3959 ± 1041	(3393 ; 4061)	2924	7532		

↑ or ↓) between two compared groups, assessed by means of Mann-Whitney's U test, are indicated by an asterisk: *($p \leq 0.05$); **($p \leq 0.05$); ***($p \leq 0.001$)

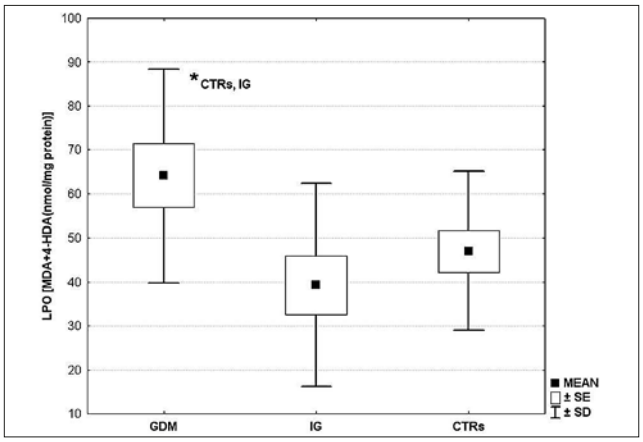

Figure 2. Box and whiskers plot for levels of LPO [MDA+4-HDA(nmol/mg protein)] in three groups of women: Gestational (GDM), Intermediate (IG) and Controls (CTRs). Significant differences between groups, assessed by means of Mann-Whitney's U test, are indicated by an asterisk: *($p \leq 0.05$). LPO concentrations were significantly higher in comparison to both Controls and Intermediate groups.

significant differences in concentrations of TNFα soluble receptors (sTNF-R1 and sTNF-R2), or IL-6, sICAM-1 and sVCAM-1 between the groups.

There was a significant correlation between concentrations of LPO products and glucose levels at 120 minutes of OGTT ($r = 0.45$; $p = 0.005$) (Fig. 3), but there was no significant correlation between LPO levels and age or BMI, or concentrations of other measured parameters. Glucose levels correlated with insulin levels ($r = 0.35$; $p = 0.014$), however, in the multivariate model of regression, with concentrations of insulin and glucose at 120 min as covariates, glucose was the only significant independent variable with partial correlation coefficient $r_p = 0.52$ ($p = 0.0012$).

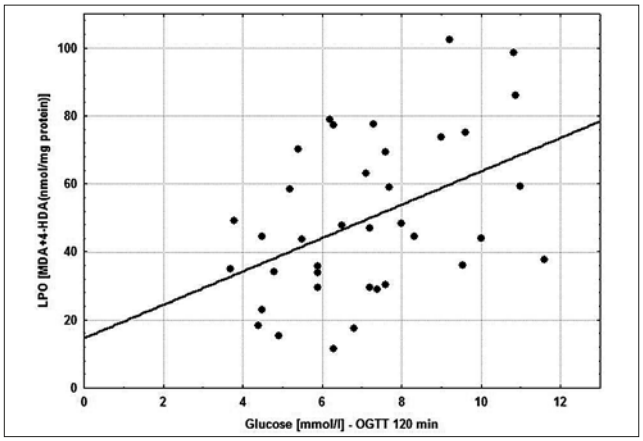

Figure 3. Correlation between LPO concentrations and glucose levels at 120 minutes of 75.0 g OGTT ($r = 0.45$, $p = 0.005$).

DISCUSSION

The main finding of the presented study was to demonstrate increased concentrations of LPO products in women with GDM in comparison to healthy pregnant controls, as well as with pregnant women with less pronounced abnormalities of glucose tolerance (i.e., false positive glucose challenge test, but normal results of 75.0 g OGTT). The main difference between women with GDM and those from the Control and Intermediate groups pertained predominantly to glucose levels at 120 minutes of OGTT (Fig. 1), while those from the Intermediate group were more insulin-resistant than controls (HOMA: 2.05±1.36 *vs.* 1.15±0.82, $p<0.01$).

As concentrations of LPO products did not correlate with the indices of insulin resistance (HOMA, IRI), but correlated independently with glucose concentration at 120 minutes of OGTT, then it is likely that glycaemia, rather than insulinaemia, might be the driving force behind raised concentrations of LPO products in women with GDM.

As mentioned above, in normal pregnancy LPO rises until the middle of the second trimester and generally return to non-pregnant levels in early postpartum [4, 5]; however, there are very scanty data for LPO levels in GDM. Dey et al. [31] reported a significant increase in the erythrocytic glutathione, serum total glutathione and protein thiols in GDM maternal blood when compared to controls, whereas erythrocytic superoxide dismutase exhibited a marked decrease in GDM. The authors, however, did not attempt to correlate LPO concentrations with glucose or insulin resistance indices, although they postulated that elevated glucose levels might induce oxidative stress in GDM mothers. Also, Karacay et al. [32] reported raised myeloperoxidase (MPO) in 27 women with GDM in comparison to 27 women with pre-clampsia and 29 controls, suggestive of raised LPO in GDM. These patients were tested for GDM at a later stage of pregnancy (up to 36 weeks). Again, however, there were no data on correlation with glucose, insulin, insulin resistance indices, as well as other parameters. Indeed, to the best of our knowledge, this is the first study, where concentrations of LPO products were tested for direct relationship with glucose and insulin resistance indices in pregnant women across the whole range of abnormalities of glucose intolerance (including those with false positive 50.0 g Glucose Challenge Test, i.e., our Intermediate group), as well as concentrations of soluble forms of adhesion molecules (sICAM-1 and sVCAM-1) and soluble TNFα receptors R1 and R2.

There are experimental data suggesting that glucose induces lipid peroxidation and inactivation of membrane-associated ion-transport enzymes in human erythrocytes *in vivo* and *in vitro* [33], although at concentrations higher than those observed in patients with GDM in the presented study. These data were later confirmed by other authors; for instance, Ahmed et al. [34] suggested that elevated levels of glucose induced oxidative stress that is ultimately reflected by the increased malondialdehyde (MDA) levels in erythrocyte membranes of diabetic patients. The authors also suggested that elevated concentrations of antioxidant enzymes may be considered as markers for vascular injury in patients with type 2 diabetes. Hyperglycaemia also induced an increase in antioxidant enzymes and a relationship seems to exist between diabetic complications and elevated levels of these enzymes.

There is also some evidence that oxidative stress may be involved in the progression and/or pathogenesis of GDM, as the release of 8-isoprostane (a marker of oxidative stress) was greater from placentas, subcutaneous adipose tissue, and skeletal muscles of women with GDM, in contrast to healthy pregnant controls [35]. Interestingly, elevated activity of butyrylcholinesterase, i.e. an enzyme involved in the reduction of oxidative stress, was also reported to be elevated in serum and placenta in gestational diabetes and in pregnant women with type 2 diabetes on insulin *vs.* women with diet-controlled GDM [36].

In contrast, data on the relationship between LPO and insulin resistance indices are less clear. For example, Facchini et al. [37] demonstrated a positive correlation between plasma lipid hydroperoxide concentrations and insulin resistance measured by the steady-state plasma insulin (SSPI) and glucose (SSPG) concentrations in response to a 180-min constant infusion of octreotide (r=0.42, p=0.01), but there was no correlation between HOMA and malondialdehyde (MDA) concentrations in women with impaired glucose tolerance [38], i.e., within the range of glucose concentrations similar to those observed in the presented study. It should also be noted that although LPO concentrations were reported to be raised in women with pre-clampsia [39], none of the women in the current study had any clinical features of pre-eclampsia at the time of testing, while pre-eclampsia subsequently developed in only one subject with GDM; therefore, the development of subsequent pre-eclampsia was unlikely to explain the elevated LPO concentrations in women with GDM.

Interestingly, the presented study failed to demonstrate differences in serum concentrations of TNFα soluble receptors in women with GDM *vs*. controls. This is in keeping with the results of Kinalski et al. [19, 40], but in contrast to the results of Winkler et al. [41] who reported higher serum concentrations of TNFα soluble receptors R1 and R2 in women with GDM. It must be appreciated, however, that regulation of the TNFα system in pregnancy is very complex, and that serum concentrations of TNFα soluble receptors reflect the contribution of various organs (including placenta) into the systemic circulation. Namely, components of the TNFα system may be released from placenta, adipose tissue, neutrophils and other sources [42]. There are data that in response to oxidative stress, GDM placenta releases less TNFα, in turn though, the GDM placenta is characterised by increased antioxidant gene expression, yet it appears to be less responsive to exogenous oxidative stress than tissues obtained from normal pregnant women [42]. On the other hand, high glucose concentrations induce TNFα release from the placenta and adipose tissue in women with GDM [43]. In such circumstances, the net release of TNFα and its soluble receptors from placenta may, at least in theory, depend on the balance between the severity of an exogenous oxidative stress and the degree of hyperglycaemia.

In summary, the presented study has demonstrated increased concentrations of LPO products in women with GDM, despite a relatively mild degree of glucose intolerance (if not pregnant, all but one subjects would be classified as impaired glucose tolerance only). Furthermore, the independent positive correlation with glucose levels at 120 minutes of OGTT suggests that the increased oxidative damage to lipids might result directly from hyperglycaemia. This hypothesis, however, still remains to be clinically and experimentally proven. The fact that the study failed to observe the expected differences in concentrations of other parameters (TNFα soluble receptors R1 and R2, sICAM-1, sVCAM-1) implies that an increase in lipid peroxidation might be a relatively early phenomenon in women with GDM, potentially antedating the change of concentrations of certain adipokines or inflammatory markers.

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