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Adverse effect of obesity on red cell membrane arachidonic and docosahexaenoic acids in gestational diabetes

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Abstract

Aims/hypothesis. Gestational diabetes is a metabolic disorder affecting 2–5% of women and is a predictor of obesity, Type 2 diabetes mellitus and cardiovascular disease. Insulin resistance, a characteristic of gestational diabetes and obesity, is correlated with the fatty acids profile of the red cell and skeletal muscle membranes. We investigated the plasma and red cell fatty acid status of gestational diabetes. The effect of obesity on membrane fatty acids was also examined.
Methods. Fasting blood obtained at diagnosis was analysed for the fatty acids in plasma choline phosphoglycerides and red cell choline and ethanolamine phosphoglycerides.
Results. There were reductions in arachidonic acid (controls 10.74±2.35 vs gestational diabetes 8.35±3.49, $p<0.01$) and docosahexaenoic acid (controls 6.31±2.67 vs gestational diabetes 3.25±2.00, $p<0.0001$) in the red cell choline phosphoglycerides in gestational diabetes. A similar pattern was found in the ethanolamine phosphoglycerides. Moreover, the arachidonic and docosahexaenoic acids depletion in the red cell choline phosphoglycerides was much greater in overweight/obese gestational diabetes (arachidonic acid=7.49±3.37, docosahexaenoic acid=2.98±2.18, $p<0.01$) compared with lean gestational diabetes (arachidonic acid=10.03±2.74, docosahexaenoic acid=4.18±1.42).
Conclusion/interpretation. Apparently normal plasma choline phosphoglycerides fatty acids profile in the gestational diabetic women suggested that membrane lipid abnormality is associated specifically with perturbation in the membrane. The fact that the lipid abnormality is more pronounced in the outer leaflet of the membrane where most of receptor binding and enzyme activities take place might provide an explanation for the increased insulin resistance in gestational diabetes and obesity. [Diabetologia (2004) 47:75–81]

Keywords Gestational diabetes mellitus · obesity · red cells · choline phosphoglycerides · ethanolamine phosphoglycerides · arachidonic acid · docosahexaenoic acid

Pregnancy is associated with increased insulin resistance. In order to maintain normal carbohydrate tolerance, both first and second phase insulin secretion increase [1]. A failure to respond to these changes leads to gestational diabetes mellitus (GDM) usually during the latter part of pregnancy [2]. In Western populations, GDM affects 2–5% of women, however the incidence rises considerably in certain ethnic communities where obesity is prevalent [3, 4]. Although GDM recedes after pregnancy, it is associated with an increased risk of obstetric complications and a predictor of obesity, Type 2 diabetes mellitus, and cardiovascular disease [5, 6, 7] and thus a prodromal of the 'Metabolic Syndrome' [8].

The pathogenesis of insulin resistance in GDM remains unknown. However, defective pancreatic beta-

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Abbreviations: AA, arachidonic acid; CPG, choline phosphoglycerides; DHA, docosahexaenoic acid; EPG, ethanolamine phosphoglycerides; FAME, fatty acid methyl esters; GDM, gestational diabetes mellitus.

cell function [1], impaired insulin receptor autophosphorylation [9], and CD36 deficit [10] have been proposed. Evidence is accumulating that the fatty acid composition of the membrane lipid is a critical cellular factor that influences both insulin secretion and its biological action [11, 12, 13, 14]. Arachidonic acid (20:4n-6, AA) and docosahexaenoic acid (22:6n-3, DHA), in particular, have been associated with insulin sensitivity [11]. Interestingly, insulin resistance was correlated with the fatty acids of the membrane choline phosphoglycerides (CPG) but not with those of ethanolamine phosphoglycerides (EPG) [15]; CPG and EPG are the predominant phospholipids of the outer and inner leaflet of the membrane lipid bilayer respectively [16].

One report [17] examined total red cell phospholipid fatty acid composition and found no difference between GDM and controls, but these women were studied at term and had all been treated to normalise their hyperglycaemia. Moreover, measuring total phospholipids obscures AA and DHA content by the sphingolipids with loss of sensitivity of the measurement.

Insulin resistance involves a loss of receptor and/or transporter efficiency in membrane. A change in membrane fatty acid profile would itself be expected to influence receptor function. Hence, we decided to study the membrane phospholipids fatty acids in control subjects and those women who developed diabetes during pregnancy. The role of pre-pregnancy BMI on membrane fatty acids was also investigated.

Subjects and methods

Subjects and sample collection. Women with singleton pregnancy were recruited during the 1st trimester at the antenatal clinic of Guy's and St Thomas' Hospital. A 75 g OGTT was carried out between the 28th and 34th gestation week in all women. If the blood glucose concentration at 60 min was less than or equal to 8.0 mmol/l they were considered normal. If at 60 min the blood glucose concentration was greater than 8 mmol/l a second sample was taken at 120 min. GDM was diagnosed if the blood glucose concentration at 120 min was equal to or greater than 9 mmol/l—EASD criteria 1979 [18]. Of the subjects, 61 were normoglycaemic (control) and 53 were identified as GDM. Venous blood was collected in heparin-treated tubes at the same time. Ethical approval was granted from The City Health Authority and Lambeth, Southwark and written informed consent was obtained from all participating women. This investigation was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Fatty acid analysis. The fatty acids of the plasma and red cell phospholipids were analysed as described [19]. Briefly, the total plasma and red cell lipid was extracted by a known method [20] and phosphoglycerides classes were separated by thin-layer chromatography on silica gel plates by the use of the developing solvents: chloroform/methanol/water (60:30:4 by volume). Fatty acid methyl esters (FAME) were separated using a gas-liquid chromatograph (HRGC MEGA 2 Series, Fisons Instruments, Milan, Italy) fitted with a BP20 capillary column (25 m×0.32 mm i.d., 0.25 μm film). Hydrogen was used as a carrier gas and the injector, oven, and detector temperatures were 250, 200, and 280°C, respectively. The FAME were identified by comparison of retension time with authentic standards. Peak areas were quantified by a computer chromatography data system (EZChrom Chromatography Data System, Scientific Software, San Ramon, Calif., USA). The fatty acids were expressed as a percentage of the total fatty acids.

Statistical analysis. The results are expressed as means ± SD. Two-tailed unpaired *t*-test was used to compare the difference in plasma and red cell fatty acid composition between the control and GDM. The women were subdivided according to their pre-pregnancy BMI (≤25 or >25). The effect of two factors, GDM and BMI, and its interaction on the red cell fatty acids was tested by two-way ANOVA. A post hoc test (Games-Howell test) for pair-wise comparisons was subsequently used to determine which group was different from each other. The data were analysed by the use of SPSS for Windows (version 10.0). A p value of less than 0.05 was considered to be statistically significant.

Results

The mean HbA_{1c} was 5.9% in GDM, range 4.8 to 7.8 (Table 1). Women diagnosed as GDM were heavier prior to pregnancy and at the time of OGTT compared with control subjects. Subsets of 50 control subjects and 45 GDM were selected based on pre-pregnancy

Table 1. Characteristics of the study population

	Control	GDM
n	61	53
Age (years)	28.4±5.5	30.6±4.6
Ethnicity		
Caucasian	24	12
Afro-Caribbean/African	17	31
Asian	9	5
Others	11	5
Parity (*n*)		
0	24	15
1	18	14
≥2	6	17
Unknown	13	7
Pre-pregnancy BMI (kg/m^2)[a]		
Mean	29.0±4.0	32.9±5.9†
Distribution (*n*)		
≤18.5	3	–
18.5–24.9	30	15
25–29.9	10	15
≥30	7	15
Wt. at recruitment (kg)	76.1±13.2	89.4±18.0*
Systolic BP (mm Hg)	114.8±13.7	123.8±15.8
Diastolic BP (mm Hg)	68.6±8.7	79.1±12.4
Serum glucose at 60 min (mmol/l)	6.13±1.37	12.14±2.06‡
Serum glucose at 120 min (mmol/l)	–	10.9±2.4
HbA_{1c} (%)	4.6±0.62	5.9±0.77‡

[a] The values were based on fifty controls and forty-five GDM
*, †, ‡ Significantly different from the controls at $p<0.05$, $p<0.01$, and $p<0.0001$ respectively

BMI. Of the subjects, 11 control women and eight GDM were excluded from the analysis due to unknown pre-pregnancy weight. Of the control subjects, 34 were of normal weight (BMI≤25, 68%) and 17 were overweight/obese (BMI>25, 34%). In GDM, 15 had a BMI of less than or equal to 25 (33.3%) and 30 had a BMI of greater than 25 (66.7%).

The subjects were recruited regardless of their ethnic background, consequently the distribution of ethnicity was different between the control and GDM subjects. However, the fatty acid profile of the plasma and red cell phosphoglycerides in the control Afro-Caribbean/African subjects did not differ from the control Caucasian subjects. Also the same pattern was observed amongst the GDM.

The fatty acid composition of plasma CPG showed no consistent changes (Table 2). However, an increase in palmitic acid (16:0) and AA (20:4n-6) and a decrease in oleic acid (18:1) and DHA (22:6n-3) were found in the GDM compared with the control subjects. In contrast, the fatty acid composition in the red cell was markedly changed in the CPG and less so in the EPG (Table 3). The total saturated fatty acids were increased, whereas both n-6 and n-3 series were decreased in GDM compared with the control subjects. The most striking changes were in the n-3 series with a 50% reduction in the GDM women.

Two-way ANOVA indicated that the effect of GDM and its interaction with BMI were significant on the red cell CPG AA, DHA, n-6 and n-3 fatty acids (Table 4). Pair-wise comparison on the selected CPG fatty acids of interest was given in Table 5. In women with a BMI of less than or equal to 25, GDM had comparable fatty acid profile compared with that of the controls. On the contrary, the overweight/obese GDM showed a substantial reduction in AA and DHA in the red cell CPG compared with the overweight/obese control women. The loss of n-6 and n-3 fatty acids was replaced by an increase in palmitic and oleic acids. Although the EPG fatty acids were not affected by BMI or GDM status, they followed a similar fatty acid distribution as the CPG (Table 6).

Table 2. Plasma choline phosphoglycerides (CPG) fatty acid composition of the controls (n=61) and GDM (n=53)

Fatty acids (%)	Control	GDM
16:0	30.49±2.64	31.84±2.19†
18:0	10.19±1.02	10.09±1.17
16:1	0.81±0.28	0.73±0.24
18:1	11.42±1.67	10.22±1.33‡
18:2n-6	23.39±2.75	22.61±2.80
20:3n-6	3.44±0.71	3.27±0.83
20:4n-6	8.50±1.58	10.27±2.11‡
22:4n-6	0.29±0.12	0.26±0.11
22:5n-6	0.46±0.25	0.38±0.26
18:3n-3	0.35±0.14	0.25±0.09‡
20:5n-3	0.80±0.73	0.90±0.95
22:5n-3	0.62±0.22	0.60±0.25
22:6n-3	4.53±1.70	4.55±1.15
20:3n-9	0.21±0.10	0.17±0.11
∑ Saturates	41.10±2.46	42.33±2.11†
∑ Monoenes	12.60±1.83	11.25±1.47‡
∑ n-6	36.70±2.85	37.29±2.19
∑ n-3	6.45±2.52	6.37±1.75

†, ‡ The values were significantly different from the corresponding level of controls at p<0.01 and p<0.0001 respectively

Table 3. Red cell (RBC) choline (CPG) and ethanolamine (EPG) phosphoglycerides fatty acid composition of the controls (n=61) and GDM (n=53)

Fatty acids	RBC CPG		RBC EPG	
(%)	Control	GDM	Control	GDM
16:0	23.49±4.86	30.64±5.57‡	17.45±3.22	19.33±3.64*
18:0	19.05±2.04	17.63±2.84*	7.16±1.48	7.82±2.11
16:1	0.48±0.23	0.54±0.22	0.47±0.19	0.49±0.23
18:1	12.63±2.54	15.29±3.25†	18.14±3.10	19.60±4.36
18:2n-6	13.32±1.91	13.80±3.32	5.05±0.91	5.05±0.94
20:3n-6	2.22±0.65	1.72±0.77†	1.11±0.24	0.84±0.24‡
20:4n-6	10.74±2.35	8.35±3.49†	14.97±2.19	13.69±3.91
22:4n-6	1.33±0.52	0.83±0.49‡	4.20±1.29	3.70±1.78
22:5n-6	0.63±0.30	0.60±0.51	0.97±0.51	0.95±0.95
18:3n-3	0.18±0.08	0.15±0.10*	0.21±0.14	0.24±0.19*
20:5n-3	0.61±0.62	0.36±0.23‡	0.92±0.44	0.79±0.52
22:5n-3	1.64±0.75	0.89±0.56‡	2.98±0.75	2.41±1.03†
22:6n-3	6.31±2.67	3.25±2.00‡	7.27±2.74	5.86±2.88*
20:3n-9	0.20±0.17	0.11±0.15	0.11±0.10	0.18±0.17
∑ Saturates	44.00±3.71	50.11±5.25‡	25.09±4.33	27.68±5.48*
∑ Monoenes	14.49±2.73	17.32±3.81†	19.62±3.37	21.43±5.12
∑ n-6	28.88±2.74	25.71±6.28*	26.71±3.13	24.66±5.91
∑ n-3	9.04±4.03	4.71±2.67‡	11.53±3.68	9.49±4.01*

*,†,‡ The values were significantly different from the corresponding level of controls at p<0.05, p<0.01, and p<0.0001 respectively

Table 4. Effect of gestational diabetes, body mass and its interaction on the red cell AA, DHA, n-6 and n-3 fatty acids[a]

Phosphoglycerides	Fatty acids	BMI	Control	GDM	Two-way ANOVA	(*p* value)
Choline	20:4n-6	≤25	9.72±1.99	10.03±2.74	GDM	0.019
		>25	11.77±1.97	7.49±3.37	BMI	0.014
					GDM×BMI	0.007
	22:6n-3	≤25	5.31±1.79	4.18±1.42	GDM	<0.0001
		>25	7.15±2.38	2.98±2.18	BMI	0.36
					GDM×BMI	0.011
	∑ n-6	≤25	27.87±2.58	28.92±3.00	GDM	0.148
		>25	29.75±2.39	24.53±6.64	BMI	0.029
					GDM×BMI	0.031
	∑ n-3	≤25	7.66±2.71	6.01±1.95	GDM	<0.0001
		>25	10.14±4.00	4.28±2.85	BMI	0.042
					GDM×BMI	0.013
Ethanolamine	20:4n-6	≤25	14.96±2.47	15.02±3.53	GDM	0.274
		>25	14.87±1.66	13.02±4.25	BMI	0.210
					GDM×BMI	0.243
	22:6n-3	≤25	6.79±2.93	6.95±2.39	GDM	0.094
		>25	7.99±2.32	5.51±3.05	BMI	0.156
					GDM×BMI	0.057
	∑ n-6	≤25	26.58±3.47	26.98±5.54	GDM	0.197
		>25	26.99±2.37	23.57±5.86	BMI	0.108
					GDM×BMI	0.103
	∑ n-3	≤25	11.00±3.96	11.02±3.49	GDM	0.088
		>25	12.24±2.90	8.94±4.34	BMI	0.193
					GDM×BMI	0.083

[a] Data shown are the means ± SD for Control ≤25 (*n*=34), Control >25 (*n*=17), GDM ≤25 (*n*=15), GDM >25 (*n*=30)

Table 5. Red cell choline phosphoglycerides fatty acids of the controls and GDM in relation to BMI: Results of post hoc test

Fatty acids (%)	BMI≤25		BMI>25	
	Control[a] (*n*=34)	GDM[b] (*n*=15)	Control[c] (*n*=17)	GDM[d] (*n*=30)
16:0	24.92±3.53[b,c]	28.17±4.66[a,d]	22.04±4.52[a]	31.62±5.76[b]
18:0	18.36±0.97[b,c,d]	17.74±4.02[a,c,d]	19.51±2.01[a,b,d]	17.72±2.49[a,b,c]
18:1	13.32±2.52[b,c,d]	14.55±2.34[a,c,d]	12.03±2.32[a,b]	15.52±3.50[a,b]
18:2n-6	13.72±1.58[b,c,d]	14.61±2.54[a,c,d]	12.76±1.37[a,b,d]	13.85±3.51[a,b,c]
20:3n-6	2.01±0.39[b]	2.11±0.63[a]	2.39±0.60[a,b]	1.50±0.57
20:4n-6	9.72±1.99[b,c,d]	10.03±2.74[a,c,d]	11.77±1.97[a,b]	7.49±3.37[a,b]
22:4n-6	1.15±0.34[b,c]	1.05±0.55[a,c,d]	1.46±0.44[a,b]	0.74±0.42[b]
22:5n-6	0.58±0.27[b,c,d]	0.67±0.58[a,c,d]	0.71±0.36[a,b,d]	0.59±0.52[a,b,c]
18:3n-3	0.17±0.09[b,c,d]	0.16±0.06[a,c,d]	0.19±0.05[a,b,d]	0.15±0.12[a,b,c]
20:5n-3	0.45±0.15[b,c,d]	0.43±0.20[a,c,d]	0.71±0.80[a,b,d]	0.32±0.24[a,b,c]
22:5n-3	1.36±0.47[b,c]	1.14±0.50[a,c,d]	1.76±0.78[a,b]	0.79±0.56[b]
22:6n-3	5.31±1.79[b,c]	4.18±1.42[a,d]	7.15±2.38[a]	2.98±2.18[b]
∑ Saturates	45.14±3.06[b,c]	47.34±3.09[a]	42.93±3.71[a]	51.37±5.46
∑ Monoenes	15.34±2.55[b,c,d]	16.26±2.40[a,c,d]	13.77±2.20[a,b]	17.69±4.15[a,b]
∑ n-6	27.87±2.58[b,c,d]	28.92±3.00[a,c]	29.75±2.39[a,b]	24.53±6.64[a]
∑ n-3	7.66±2.71[b,c]	6.01±1.95[a,c,d]	10.14±4.00[a,b]	4.28±2.85[b]

Means that do not share a superscript letter are significantly different at the 0.05 level

A heavier body mass, however, did not compromise the n-6 and n-3 fatty acid content in the red cell CPG of the control women. The relative percent of n-6 and n-3 series tended to increase and was significant (p=0.038) for AA in the overweight/obese controls in comparison with the lean control women.

Discussion

In this study we have shown that at diagnosis, women with GDM had reduced AA and DHA levels in the red cell CPG, the major phosphoglycerides of the outer leaflet of the membrane. A similar GDM-induced

Table 6. Red cell ethanolamine phosphoglycerides fatty acids of the controls and GDM in relation to BMI

Fatty acids (%)	BMI≤25		BMI>25	
	Control (*n*=34)	GDM (*n*=15)	Control (*n*=17)	GDM (*n*=30)
16:0	17.93±3.42	18.02±3.03	17.32±3.21	20.19±3.90
18:0	7.58±1.70	7.13±1.24	6.64±1.18	7.96±2.39
18:1	18.53±3.48	17.47±3.21	17.87±2.47	20.96±4.76
18:2n-6	5.16±0.77	5.13±1.06	5.01±0.97	5.07±0.97
20:3n-6	1.10±0.26	0.98±0.28	1.16±0.23	0.79±0.20
20:4n-6	14.96±2.47	15.02±3.53	14.87±1.66	13.02±4.25
22:4n-6	3.85±1.23	4.33±1.56	4.63±1.33	3.38±1.59
22:5n-6	1.08±0.57	1.07±1.05	0.91±0.46	0.95±0.99
18:3n-3	0.19±0.09	0.22±0.07	0.24±0.20	0.27±0.24
20:5n-3	0.95±0.43	0.86±0.44	0.82±0.29	0.73±0.57
22:5n-3	2.90±0.79	2.82±0.87	3.05±0.59	2.28±1.16
22:6n-3	6.79±2.93	6.95±2.39	7.99±2.32	5.51±3.05
∑ Saturates	26.05±4.81	25.56±3.99	24.32±3.90	28.66±6.15
∑ Monoenes	20.12±3.88	18.99±3.82	19.15±2.46	22.87±5.65
∑ n-6	26.58±3.47	26.98±5.54	26.99±2.37	23.57±5.86
∑ n-3	11.00±3.96	11.02±3.49	12.24±2.90	8.94±4.34

effect was also apparent in the EPG. Interestingly, the unfavourable effect of a high pre-pregnancy BMI on the red cell AA and DHA was found only in the GDM women.

The red cell cannot alter fatty acid chain length or the degree of unsaturation or synthesise phospholipids de novo [21] thus red cell CPG would be expected to reflect diet and plasma lipids to some extent. However, this was not the case as the plasma fatty acids composition of the GDM was comparable to that of the control subjects. In fact, the plasma AA level was higher in the GDM. Following the diagnostic OGTT only the GDM women were interviewed by a dietician but they were not given any particular advice on n-3 and n-6 fats. Nutrient intake was obtained subsequent to the OGTT from a sub-sample of women (control=10, GDM=13) by using a weighed three-day diet diary. Foodbase2000, nutrition analysis software developed by our institute and validated [22, 23, 24] was used to analyse the food composition. The results gave no evidence of differences in the dietary n-6 and n-3 fatty acids intake between the two groups. Moreover, there was no biochemical indication of dietary linoleic (18:2n-6) and alpha-linolenic (18:3n-3) acids or DHA deficiency measured by Mead acid (20:3n-9) [25], the Mead acid/AA ratio [26, 27], and docosapentaenoic acid (22:5n-6) in the plasma and red cell CPG. In contrast, others [28, 29, 30] have shown that GDM have a different fat intake (more saturated fat and less polyunsaturated fat) compared with control subjects. Although we did not have pre-diagnosis dietary information for these women, the fact that the plasma CPG and triglycerides (data not shown) were similar in the two groups suggests that dietary fat played a minor role in determining membrane fatty acids in the GDM.

The biosynthesis of AA and DHA requires delta-6 and delta-5 desaturase that are insulin dependent [31, 32, 33]. So far, there is no evidence that the activities of delta-6 and delta-5 desaturase are impaired in GDM. However, it is conceivable that its function could be depressed as seen in Type 2 diabetes mellitus [34] and obesity [35]. Yet, we found no difference in the ratio of AA (20:4n-6)/dihomo-gamma-linolenic acid (20:3n-6) in the red cell CPG, an indirect measure for delta-5 desaturase activity. This suggests that the pathology of glucose intolerance is associated with the incorporation of AA and DHA into membrane phospholipids.

A further analysis revealed that high pre-pregnancy BMI in GDM exaggerated the membrane lipid perturbation while lean GDM women managed to retain AA and DHA levels despite their equivalent hyperglycaemia (based on the glycaemic values at OGTT). Obesity is associated with glucose intolerance and reduced DHA in the skeletal muscle and red cells total phospholipid [36, 37]. Therefore, the overweight/obese control women were expected to follow a similar pattern to obese GDM. But unexpectedly, the overweight/obese control women had a higher AA and DHA compared with their leaner counterparts. We considered if it could be that the hyperglycaemia plays a pivotal role in determining membrane fatty acids. Although the glucose concentration at 120 min did not differ between overweight/obese and lean GDM women, the mean HbA_{1c} tended to be higher in overweight/obese (5.9%) than lean (5.6%) subjects. Thus glucose intolerance superimposed on obesity was associated with membrane lipid abnormality.

It is not clear whether the changes in membrane fatty acid composition alter the insulin action or the increased concentration of glucose and insulin leads to membrane lipid abnormality. There is clear evidence

of altered insulin binding [38] and its action [39] as a result of modification of fatty acids in the membrane phospholipids. Conversely, one study [15] showed that insulin resistance induced by nicotinic acid administration resulted in changes in fatty acid composition of the CPG in the muscle. An alternative explanation for membrane lipid abnormality in GDM could be structural change in membrane protein. Hydrophobic matching thickness of lipid bilayer (i.e. lipid acyl-chain length) and integral membrane proteins have been proposed as a determinator of the coupling between lipid and membrane proteins [40]. Protein prefers to be associated with the lipid species that is hydrophobically best matched. If the membrane protein structure changes by extracellular forces such as peroxidation and glycosylation, its folding property will alter, thereby its lipid composition may have to change to match. Abnormal glucose transporters [41], decreased insulin receptor binding protein [42], Ca^{++} transmembrane movement [43], alteration of uncoupling and remodelling of actin [44, 45] are examples of altered membrane protein function depressed in diabetes and obesity.

The red cell membrane is essentially an example of plasma membrane. Compositionally it is very similar to the vascular endothelium. This similarity could derive from the fact that the endothelial cell has the highest plasma membrane/cytoplasm ratio of any cell in the body. It is therefore likely that if the red cell membrane is selectively affected in diabetes or obesity, the endothelium could also be affected. The expected consequences would be vascular dysfunction. A loss of AA and DHA would reduce liquidity and the liberal mechanical properties normal to active cell membranes. Such a defect in the endothelial membrane could create susceptibility to vascular dysfunction as experimentally demonstrated in rats [46, 47].

At diagnosis, GDM was associated with AA and DHA reduction and increased palmitic acid in the red cell phosphoglycerides. The combination of glucose intolerance and obesity had unfavourable effects on membrane AA and DHA contents in overweight/obese GDM. The fact that the lipid abnormality was more pronounced in the outer leaflet of the membrane phospholipids, CPG where most of receptor binding and enzyme activities take place, might provide an explanation for the increased insulin resistance in GDM. It is conceivable that hyperglycaemia might cause the impairment in fatty acids incorporation into the red cell membrane. Or it could be that the genetically determined membrane protein causes reorganisation of lipid bilayer, subsequently affecting the structure or activities of membrane bound transporters or receptors.

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