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Changes in serum lipid and lipoprotein concentrations and compositions at birth and after 1 month of life in macrosomic infants of insulin-dependent diabetic mothers

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Abstract The aim of this study was to determine whether macrosomia related to maternal diabetes alters lipoprotein metabolism and whether these abnormalities still persist or regress after 1 month of life. Serum lipoprotein compositions and concentrations as well as serum lipid fatty acid compositions were investigated in macrosomic infants (birth weight = 4840 ± 105 g at term) of insulin-dependent diabetic mothers at birth and after 1 month of life, and were compared to those of control infants (birth weight = 3400 ± 198 g at term) of healthy mothers. Compared to controls, at birth, macrosomic newborns had higher serum lipids, apolipoprotein A-I and B-100, and lipoprotein (very low density lipoprotein, low density lipoprotein, high density lipoprotein-2 and high density lipoprotein-3) levels. Higher percentages of C18:2n-6 in serum triacylglycerols, phospholipids and cholesteryl esters were also observed. At day 30, in macrosomics, serum triacylglycerol, apo B-100, very low density lipoprotein and low density lipoprotein levels were still significantly higher. C18:2n-6 and C18:3n-3 contents in serum phospholipids, triacylglycerols and cholesteryl esters were reduced while C20:4n-6 and C22:6n-3 contents in serum phospholipids and cholesteryl esters were enhanced, compared to control values.

Conclusion Macrosomia was associated with alterations in lipoprotein compositions and concentrations at birth, some of which persisted after 1 month of life, and might play a role in the pathogenesis of diabetes and atherosclerosis in adult life.

Key words Apolipoproteins · Diabetic mothers · Lipoproteins · Macrosomia · Serum fatty acids

Abbreviations *HDL* high density lipoprotein · *LCPUFA* long-chain polyunsaturated fatty acid · *LDL* low density lipoprotein · *VLDL* very low density lipoprotein

Introduction

Macrosomia is a common observation in diabetic pregnancies [3, 15, 30]. Several alterations in carbohydrate and lipid metabolism are observed in infants of diabetic mothers and are thought to be a consequence of maternal hyperglycaemia leading to fetal hyperglycaemia and hyperinsulinaemia [3, 6, 12, 25, 27].

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Macrosomic infants of diabetic mothers are prone to the development of obesity, diabetes mellitus and cardiovascular diseases in later life [5, 23, 33]. Obesity and diabetes mellitus in adulthood are associated with compositional changes in serum lipoproteins. Since obesity and hyperinsulinaemia begin early in life in macrosomic infants of diabetic mothers [5], it is of interest to determine whether these infants present "at-risk" lipoprotein profiles at birth and during the 1st month of life which might be indicative of later metabolic disease.

The fatty acid composition of the diet influences the plasma lipid and apoprotein concentrations during the 1st month of life [31]. In contrast to standard formula milks, breast milk contains long-chain polyunsaturated fatty acids (LCPUFA) which meet infant requirements. Because the infant's response to human milk is considered ideal, postnatal feeding with LCPUFA supplemented formulas in quantities similar to those found in breast milk might be appropriate.

The purpose of the present study was to determine whether macrosomia related to maternal diabetes alters lipoprotein metabolism and whether these abnormalities persist or regress after 1 month of life. In addition, the data should provide a better insight on the influence of LCPUFA supplementation on serum lipoprotein profiles and lipid fatty acid composition.

Materials and methods

Patients

The protocol was approved by the Tlemcen Hospital Committee for Research on Human Subjects. Subjects for this study were drawn consecutively from prenatal women evaluated at the Maternity Hospital of Tlemcen (Algeria). A total of 20 insulin-dependent diabetic pregnant women whose newborns were macrosomic at birth were selected. Maternal diabetic status was determined by medical history review. Gestational age was estimated by the last menstrual period and confirmed by ultrasound and newborn examination. Newborn weight was obtained immediately after delivery. Macrosomia was defined as birth weight >4000 g at term, which was more than 2 SD above the mean for gestational age. For comparison, a group of 50 control pregnancies was simultaneously studied. Control women were selected if they had no significant prior illness, no pregnancy related complications and no risk factor for gestational diabetes including normal glucose tolerance tests during the first and third trimesters of pregnancy. An attempt was made to match these women to diabetic subjects, at least regarding maternal age, height, parity, gestational age and mode of delivery. Both diabetic and control mothers were offered regular examinations of their offspring during the 1st month of life. Only 15 diabetic and 20 control mothers agreed. Therefore, only infants who underwent these examinations were included in the study. The infants belonged to one of the following groups:

1. Group 1 consisted of 15 macrosomic infants at term (birth weight $= 4840 \pm 105$ g, gestational age $= 39.2 \pm 1.2$ weeks, mean $\pm$ SD) born to poorly controlled insulin-dependent diabetic mothers. Eight of the mothers were White class B (duration of diabetes $= 4 \pm 0.4$ years) and seven White class C (duration of diabetes $= 11 \pm 1$ years). All diabetic mothers were non obese (pre-pregnancy body mass index $= 22.5 \pm 1.8$ kg/m^2), and were treated with insulin during pregnancy (self administration of multiple injections of short- or long-acting doses of insulin) but were poorly controlled as shown by their fasting glucose concentrations (Beckman glucose analyser, Palo Alto, Calif.) (8.7 ± 0.4 mmol/l in diabetics vs. 4.9 ± 0.2 mmol/l in normal pregnant women) and by their percentage glycosylated haemoglobin (Isolab Column Chromatography [16]) ($8.9 \pm 0.3\%$ in diabetics vs. $5.8 \pm 0.2\%$ in normal pregnant women). Macrosomic newborns had significantly higher cord serum insulin (measured by radioimmunoassay) and glucose levels compared to control newborns (40 ± 6.50 vs. 9.85 ± 1.76 mU/l for insulin and 8.12 ± 0.95 vs. 3.04 ± 0.73 for glucose, $P < 0.01$).

2. Group 2 consisted of 20 appropriate for gestational age infants (birth weight $= 3400 \pm 198$ g, gestational age $= 39.4 \pm 1.1$ weeks) born to healthy non obese (body mass index $= 21.8 \pm 2.3$ kg/m^2) and non diabetic mothers selected in the control group.

To reduce dietary influence on lipids, macrosomic and control infants were fed the same LCPUFA enriched formula (composition of formula: protein $= 14$ g/l, carbohydrate $= 56.50$ g/l, cholesterol $= 0.2$ g/l, fat $= 28$ g/l, milk fatty acid composition (as percentage of total fatty acids) C8:0, 0.8; C10:0, 1.2; C12:0, 8.5; C14:0, 4.3; C16:0, 26.3; C18:0, 3.9; C16:1, 1.5; C18:1, 38.5; C18:2n-6, 12.4; C18:3n-3, 2; C20:4n-6, 0.3; C22:6n-3, 0.3). All infants were followed up at 1 month after birth.

Blood samples

At delivery, cord blood samples were collected after umbilical cord clamping. At 1 month, blood was taken from peripheral veins of the same infants after an overnight fast of 6 h on the 30th day after birth. After clotting, sera were separated by centrifugation at 4°C and 600 *g* and preserved with 0.1% disodium EDTA and 0.02% sodium azide.

Laboratory methods

Lipoprotein isolation

Serum lipoproteins of density <1.21 g/ml were isolated by single ultracentrifugation flotation (Model LE 80 Ultracentrifuge, 50 Ti rotor, Beckman Instruments, Palo Alto, Calif.), according to Havel et al. [11].

Very low density lipoprotein (VLDL) ($1.006 <$ density < 1.019 g/ml), low density lipoprotein (LDL) ($1.019 <$ density < 1.063 g/ml) and high density lipoprotein (HDL) ($1.063 <$ density < 1.210 g/ml) were isolated from total lipoproteins by a single spin discontinuous gradient, according to Redgrave et al. [26].

HDL_2 ($1.063 <$ density < 1.125) were separated from HDL_3 ($1.125 <$ density < 1.210 g/ml) by 4 h centrifugation at 160,000 *g* [9].

Chemical analysis

Triacylglycerol contents of serum and each lipoprotein fraction were determined using a commercial kit (Boehringer Mannheim, Mannheim). Total cholesterol and unesterifed cholesterol assays were performed by gas liquid chromatography using epicoprostanol as internal standard, according to Gambert et al. [8]. Esterified cholesterol concentrations were obtained by difference between total cholesterol and unesterifed cholesterol values. Phospholipids in serum and lipoprotein fractions were assayed for phosphorus by the method of Bartlett [2]. Serum total lipids were extracted according to Folch et al. [7]. Triacylglycerols, phospholipids and cholesteryl esters were isolated by thin layer chromatography. Each lipid fraction was transmethylated and fatty acids were analysed by gas liquid chromatography [29], using a Becker gas chromatograph (Becker instruments, Downers

Grove, Ill.) equipped with a 50 m capillary glass column packed with carbowax 20 M (Spiral-RD, Couternon, France). Total protein contents of each lipoprotein were measured by the method of Lowry et al. [21], using bovine serum albumin as standard.

VLDL, LDL, HDL_2 and HDL_3 apolipoprotein separation and quantification

After concentration by partial lyophilisation and rapid diethyl-ether delipidation of VLDL, LDL, HDL_2 and HDL_3, apolipoproteins of each lipoprotein fraction were separated by sodium dodecyl sulphate-polyacrylamide gel electrophoresis, with 2.5%–20% acrylamide, at 25 V for 18 h, according to Irwin et al. [14] as previously described [22]. The data were expressed as arbitrary units per litre of serum. Immuno-electrophoresis using monoclonal antibodies and ready-to-use plates (Hydragel SEBIA kit, Issy Les Moulineaux, France) was performed to quantitate serum total apo A-I and B-100.

Statistical analysis

Results were analysed using standard statistical procedures with a commercial statistical software package (STATVIEW 512, Brain Power, Calabasas, Calif.). After verification of homogeneity of variances (Hartley test) and normality of distribution (Kolmogorov-Smirnov test), we used variance analysis and the unpaired *t*-test for comparing values of macrosomic and control groups, and the paired *t*-test for comparing cord blood and blood values at 1 month of life.

Results

Serum lipids, apolipoprotein and lipoprotein concentrations and compositions

At birth, compared with controls, macrosomic infants had significantly higher serum triacylglycerol, total cholesterol, apo A-I, apo B-100 and lipoprotein levels (Fig. 1). All VLDL and LDL lipids, HDL_2 and HDL_3 triacylglycerol contents were higher, while HDL_2 cholesteryl ester levels were lower in macrosomic than in control infants (Table 1). VLDL- and LDL-apo B-100, HDL_2- and HDL_3-apo A-I and apo A-II levels were higher in macrosomic than in control newborns (Table 2).

At day 30, serum triacylglycerol, apo B-100, VLDL and LDL concentrations were still significantly higher in macrosomic than in controls (Fig. 1). Macrosomic infants showed also higher VLDL and LDL apolipoprotein levels compared to control values (Table 2).

From birth to day 30, serum triacylglycerol, total cholesterol, apo A-I and apo-B-100, VLDL and LDL concentrations increased in control and in macrosomic infants. HDL_2 and HDL_3 amounts increased only in controls (Fig. 1), while HDL_2 cholesteryl esters were only increased in macrosomic infants (Table 1). All VLDL and LDL apolipoproteins, HDL_2- and HDL_3-apo A-I were raised, while HDL_2- and HDL_3-apo E were decreased in control and macrosomic infants (Table 1).

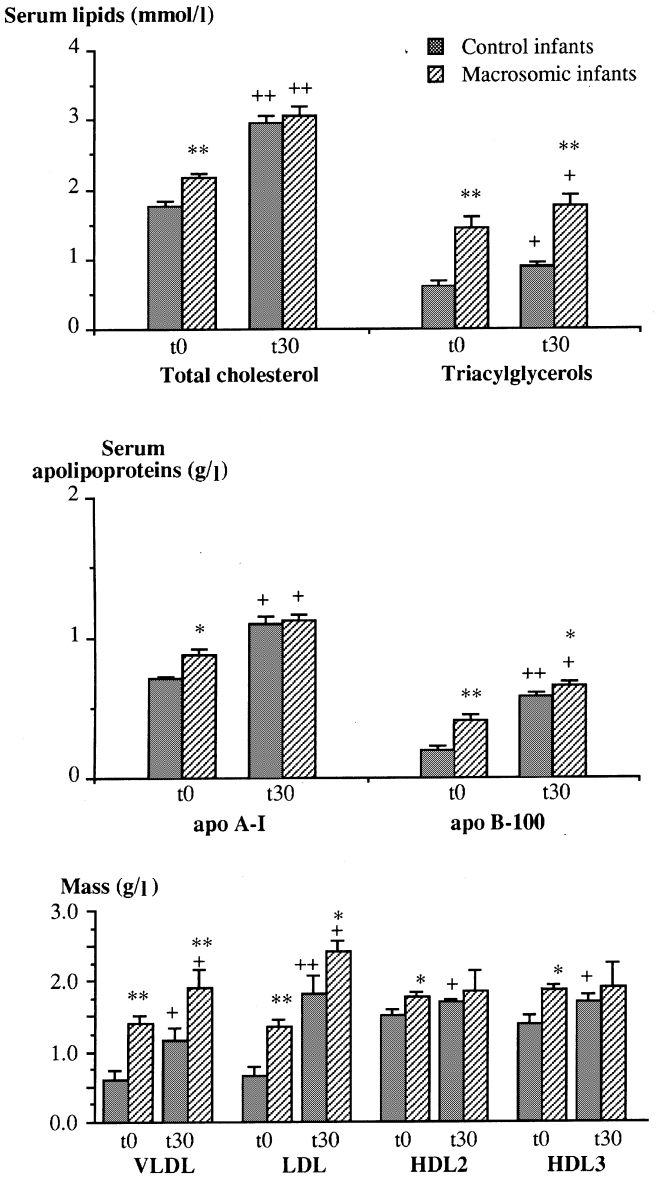

Fig. 1 Serum lipid, apolipoprotein (*apo A-I* and *B-100*) and lipoprotein (*VLDL*, *LDL*, *HDL_2* and *HDL_3*) concentrations in macrosomic and control infants at birth and after 1 month of life. Values are means ± SEM. Significant differences are indicated as: $^{*}P < 0.05$; $^{**}P < 0.01$ when macrosomic values were compared to control values. $^{+}P < 0.05$; $^{++}P < 0.01$ when t30 values were compared to t0 values in the same infant group (*t0* birth, *t30* 1 month of life). Lipoprotein mass is the sum of protein, triacylglycerol, phospholipid, cholesteryl ester and unesterified cholesterol contents of each lipoprotein

Composition of serum fatty acids

The most marked changes in fatty acid composition are shown (Fig. 2).

At birth, in serum triacylglycerols, cholesteryl esters and phospholipids, linoleic acid (C18:2n-6) was higher in macrosomic than in control infants. In serum phospholipids only, C20:4n-6 was higher, while saturated fatty

Table 1 Lipid compositions of serum lipoproteins in macrosomic and control infants at birth and after 1 month of life. Values are means ± SEM (*t0* birth, *t30* 1 month old)

	t0		t30	
	Control	Macrosomic	Control	Macrosomic
Triacylglycerols (mmol/l)				
VLDL	0.26 ± 0.02	0.6 ± 0.03**	0.42 ± 0.04^{+}	0.86 ± 0.06^{+**}
LDL	0.12 ± 0.01	0.26 ± 0.02**	0.22 ± 0.03^{+}	0.36 ± 0.02^{+*}
HDL_2	0.11 ± 0.01	0.28 ± 0.01**	0.12 ± 0.03	0.28 ± 0.04*
HDL_3	0.09 ± 0.02	0.30 ± 0.02**	0.10 ± 0.02	0.25 ± 0.04**
Unesterified cholesterol (mmol/l)				
VLDL	0.10 ± 0.01	0.16 ± 0.01*	0.24 ± 0.02^{++}	0.32 ± 0.03^{+*}
LDL	0.18 ± 0.03	0.32 ± 0.02**	0.44 ± 0.02^{++}	0.56 ± 0.02^{+*}
HDL_2	0.20 ± 0.05	0.29 ± 0.04	0.21 ± 0.06	0.24 ± 0.04
HDL_3	0.20 ± 0.04	0.21 ± 0.05	0.23 ± 0.03	0.23 ± 0.03
Cholesteryl esters (mmol/l)				
VLDL	0.14 ± 0.02	0.34 ± 0.04**	0.28 ± 0.03^{+}	0.40 ± 0.02*
LDL	0.26 ± 0.03	0.36 ± 0.02*	0.80 ± 0.04^{++}	0.96 ± 0.02^{++*}
HDL_2	0.47 ± 0.01	0.35 ± 0.03*	0.53 ± 0.06	0.50 ± 0.06^{+}
HDL_3	0.19 ± 0.02	0.15 ± 0.04	0.20 ± 0.04	0.20 ± 0.04

Significant differences are indicated as: * $P < 0.05$
** $P < 0.01$ when macrosomic values were compared to control values
$^{+}$ $P < 0.05$
$^{++}$ $P < 0.01$ when t30 values were compared to t0 values in the same infant group

Table 2 Serum VLDL-, LDL-, HDL_2- and HDL_3-apolipoprotein profiles (arbitrary units/l) in macrosomic and control infants at birth and after 1 month of life. Values are means ± SEM

	t0		t30	
	Control	Macrosomic	Control	Macrosomic
VLDL				
apo B-100	0.071 ± 0.019	0.189 ± 0.023**	0.130 ± 0.010^{++}	0.235 ± 0.012^{+**}
apo C-II	0.031 ± 0.009	0.043 ± 0.011	0.064 ± 0.010^{+}	0.090 ± 0.007^{+*}
apo C-III	0.029 ± 0.009	0.046 ± 0.012	0.061 ± 0.010^{+}	0.083 ± 0.010^{+*}
apo E	0.015 ± 0.007	0.030 ± 0.016	0.066 ± 0.011^{+}	0.093 ± 0.012^{+*}
LDL				
apo B-100	0.100 ± 0.030	0.220 ± 0.020*	0.460 ± 0.060^{++}	0.610 ± 0.040^{+*}
HDL_2				
apo A-I	0.325 ± 0.010	0.382 ± 0.016*	0.470 ± 0.025^{++}	0.485 ± 0.021^{+}
apo A-II	0.089 ± 0.006	0.106 + 0.007*	0.108 ± 0.011^{+}	0.110 ± 0.012
apo C-II	0.014 ± 0.008	0.021 ± 0.009	0.014 ± 0.005	0.023 ± 0.009
apo C-III	0.018 ± 0.006	0.016 ± 0.006	0.023 ± 0.012	0.021 ± 0.009
apo E	0.037 ± 0.010	0.033 ± 0.009	0.011 ± 0.006^{+}	0.011 ± 0.007^{+}
HDL_3				
apo A-I	0.35 ± 0.029	0.461 ± 0.017**	0.575 ± 0.021^{++}	0.600 ± 0.029^{++}
apo A-II	0.160 ± 0.012	0.229 ± 0.011*	0.191 ± 0.007^{+}	0.201 ± 0.037
apo C-II	0.029 ± 0.009	0.022 ± 0.018	0.028 ± 0.008	0.029 ± 0.010
apo C-III	0.062 ± 0.011	0.061 ± 0.011	0.088 ± 0.006^{+}	0.075 ± 0.015
apo E	0.041 ± 0.010	0.033 ± 0.011	0.010 ± 0.005^{+}	0.010 ± 0.060^{+}

Significant differences are indicated as: * $P < 0.05$
** $P < 0.01$ when macrosomic values were compared to control values
$^{+}$ $P < 0.05$
$^{++}$ $P < 0.01$ when t30 values were compared to t0 values in the same infant group

acids were lower in macrosomic compared with control infants (46.35 ± 1.98 vs. 42.27 ± 1.34, $P < 0.05$).

At day 30, in serum cholesteryl esters and phospholipids, C18:2n-6 was lower whereas C22:6n-3 was higher; in serum triacylglycerols, cholesteryl esters and phospholipids, α-linoleic acid (C18:3n-3) was diminished whereas C20:4n-6 was increased in macrosomic compared with control infants.

From birth to day 30, there was a rise in C18:2n-6 and a coincident fall in C20:4n-6 in serum lipids in control and macrosomic infants. C18:3n-3 was diminished whereas C22:6n-3 was raised in macrosomic infants, but no significant changes in controls.

Discussion

The epidemiological association described by Barker [1] between fetal lipid levels and adult cardiovascular disease has recently engendered great interest. However, these studies focus on the relationship between fetal undernutrition and later atherogenic risk, and pay only limited attention to overnutrition.

The present study was focused on determining whether lipoprotein metabolism alterations found in macrosomic infants of insulin-dependent diabetic mothers at birth persist after 1 month of life, and whether lipoprotein

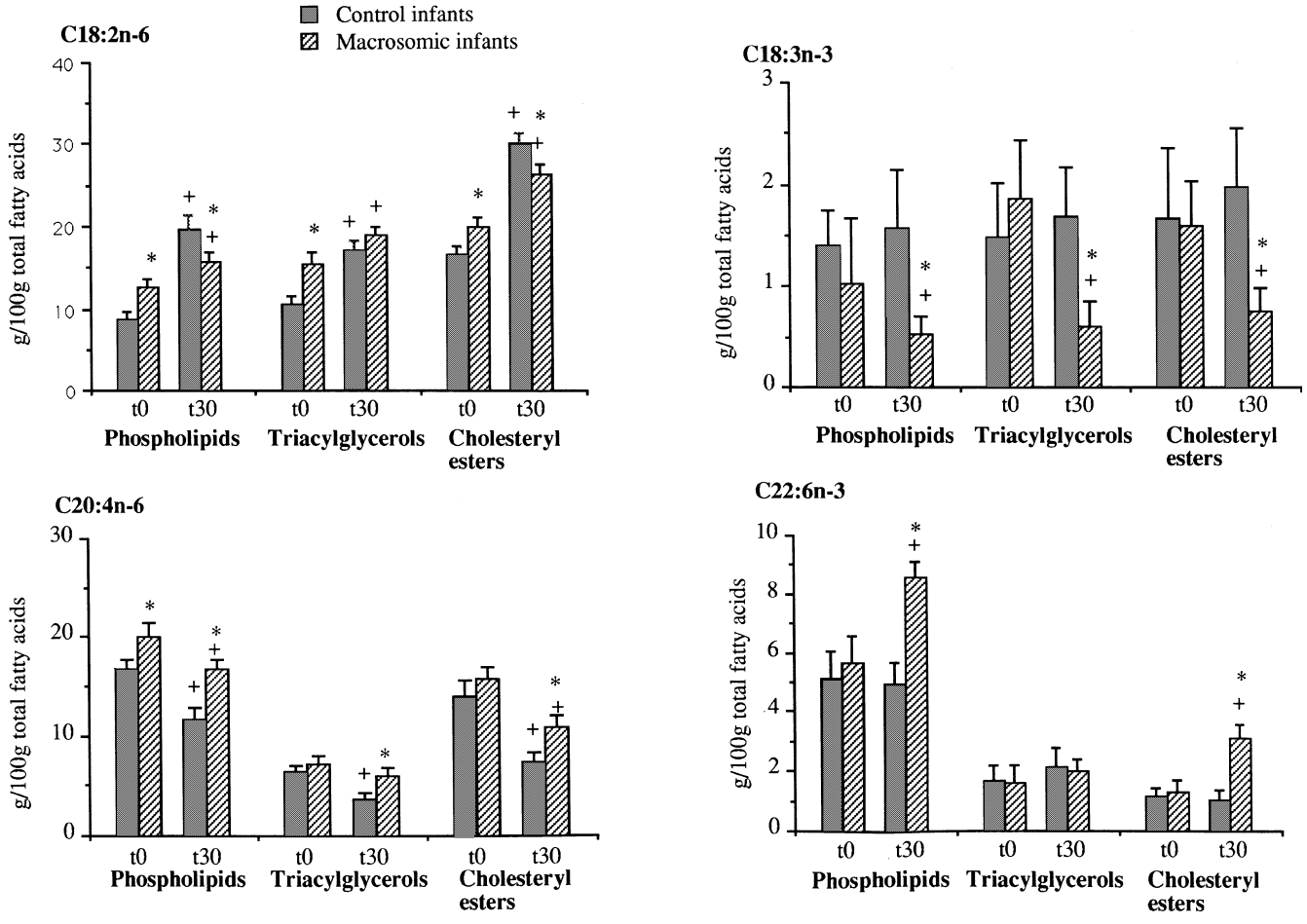

Fig. 2 Selected fatty acid compositions of serum lipids in macrosomic and control infants at birth and after 1 month of life. Values are means ± SEM. Significant differences are indicated as: $*P < 0.05$; $**P < 0.01$ when macrosomic values were compared to control values. $^{+}P < 0.05$; $^{++}P < 0.01$ when t30 values were compared to t0 values in the same infant group

abnormalities initiated in utero might be amplified or not with age. A 1-month postnatal life was chosen because at this age, serum lipid and lipoprotein profiles normally approach those of adults.

Our results showed that at birth, serum lipid and apolipoprotein contents were higher in macrosomic than in control newborns. At day 30, several lipid, apolipoprotein and lipoprotein differences disappeared while others persisted.

Fat and protein syntheses are increased in the fetus with overnutrition and our data are in agreement with earlier reports [3, 6]. The concomitant presence of excess substrates and hyperinsulinaemia enhances fetal lipid and protein syntheses [15, 30]. Insulin receptors may also play a role in the increased insulin effects in infants. Several authors have found evidence of defective down-regulation of insulin receptors in the hyperinsulinaemic fetus which may have increased insulin binding and thus its metabolic effects [20, 23]. In macrosomic infants, at birth and after 1 month of life, the high VLDL levels were accompanied with a concomitant increase in serum triacylglycerol and apo B-100. An increase in serum insulin concentrations could explain enhanced hepatic VLDL secretion and hypertriglyceridaemia in macrosomic newborns. In addition, macrosomic newborns (at t0 and t30) also showed higher LDL amounts resulting probably from high VLDL concentrations, since the majority of LDL particles are derived from VLDL after lipoprotein lipase action. These abnormalities are also common in adult diabetes and obesity [4, 10, 18].

Compared to controls, macrosomic newborns presented higher HDL_2 and HDL_3 levels accompanied by higher HDL-apo A-I and -apo A-II contents, suggesting an increase in the number of HDL particles resulting probably from their enhanced synthesis. This might reflect an insulin-induced increase in lipoprotein lipase activity. Further investigations on lipoprotein lipase activity in these infants are needed. Moreover, at birth and after 1 month of life, macrosomic as compared to control infants had higher VLDL and LDL cholesteryl esters and enhanced HDL_2 and HDL_3 triacylglycerols. These findings might be related to the excess transfer of cholesteryl esters from HDL to VLDL and LDL, and of triacylglycerols in the opposite direction, probably related to an increased cholesteryl ester transfer protein activity. High cholesteryl ester transfer protein activity leads to more atherogenic cholesteryl ester-rich VLDL which are catabolised in non hepatic sites such as arterial wall macrophages.

Consistent with previous reports [19, 28, 31], serum lipid and lipoproteins levels increased during the 1st month of life in control infants. These lipoprotein changes are due to increased lipid and apolipoprotein syntheses after birth [28, 31]. However, in macrosomic infants, despite a rise in apo A-I levels, HDL_2 and HDL_3 amounts increased only slightly during the 1st month of life.

An important result was the elevated serum apo B-100/apo A-I ratio in macrosomic infants (0.45 ± 0.03 vs 0.28 ± 0.02 and 0.60 ± 0.02 vs 0.52 ± 0.03) at birth and at 1 month of life, respectively. This is of considerable interest in view of the predictive value of this ratio for cardiovascular risk. Wang et al. [32] reported that infants with an initially high apo B-100/apo A-I ratio still had high values at the age of 8.5 months.

To obtain essential fatty acids, the fetus is dependent on their transport across the placenta from maternal circulation [13, 17]. In our study, macrosomic newborns showed high proportions of C18:2n-6 in serum triacylglycerol, cholesteryl ester and phospholipid fractions compared to control values. This could be accounted for by high maternal levels of this fatty acid with enhanced placental transfer. A higher C18:2n-6 percentage has been shown in serum lipids of diabetic subjects [24].

At 1 month of life, macrosomic infants as compared to controls, showed lower C18:2n-6 and C18:3n-3 contents in serum lipids accompanied by an increase in C20:4n-6 and C22:6n-3 levels in serum cholesteryl esters and phospholipids. C20:4n-6 and C22:6n-3 are chiefly the chain-elongated and desaturated products of C18:2n-6 and C18:3n-3, respectively. As the two groups of infants were fed the same formula milk, fatty acid abnormalities in macrosomic infants could be due to metabolism-induced rather than diet-induced changes. This might result from the enhanced conversion of essential fatty acids to their long-chain derivatives, probably related to a higher $\Delta 6$ desaturase activity. Insulin is known to induce $\Delta 6$ desaturation activity.

During the 1st month of life, in controls as well as in macrosomic infants, the main changes were an increase in the proportion of C18:2n-6 and a decrease in C20:4n-6 in serum triacylglycerols, cholesteryl esters and phospholipids, which agrees with previous works [28, 31]. However, the proportion of the decrease in C20:4n-6 was less in our infants than in those fed standard milk, but was similar to that in those fed breast milk [28, 31]. In our control newborns, at day 30, C22:6n-3 amounts were maintained at birth levels. In macrosomic infants, there was a significant rise in C22:6n-3 during the 1st month of life.

Postnatal feeding with formulas that lack C22:6n-3 leads to a decrease in plasma C22:6n-3 contents after birth [13, 31]. However, there was a degree of protection afforded by breast-milk, breast-fed infants having smaller decreases than in those fed standard formulas [13, 28]. In our study, C20:4n-6 and C22:6n-3 supplemented formula might assist in delivery of adequate levels of LCPUFA to developing organs.

Precise benefits of higher LCPUFA levels in macrosomic infants are difficult to predict. In adults, high dietary intake of LCPUFA is associated with low plasma lipids and C22:6n-3 consumption has been shown to have beneficial effects on cardiovascular disease.

Macrosomia is associated with changes in serum lipid and lipoprotein amounts and compositions. Persisting changes in insulin levels could explain fatty acid, lipid and lipoprotein alterations in macrosomic infants. Macrosomia should be considered as one of the potential risk factors for later metabolic diseases. Therefore, special health care for these macrosomic infants is recommended including regular examinations, and dietary guidelines.

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