Implication of lipids in macrosomia of diabetic pregnancy: can \( n \)-3 polyunsaturated fatty acids exert beneficial effects?

Hafida MERZOUK\(^*\) and Naim A. KHAN\(^†\)

\(^*\)Département de Biologie, Faculté des Sciences, Université de Tlemcen, Algeria, and \(^†\)UPRES 2422, Lipides et Nutrition, UFR Sciences de la Vie, 6 Boulevard Gabriel, Université de Bourgogne, Dijon 21000, France

**ABSTRACT**

Macrosomia or fetal obesity is a frequent complication of pregnancy in diabetes mellitus. Several alterations observed in carbohydrate and lipid metabolism in macrosomic infants of diabetic mothers are thought to be a consequence of maternal hyperglycaemia leading to fetal hyperinsulinaemia. Macrosomic infants of diabetic mothers are prone to the development of glucose intolerance, obesity and diabetes during childhood and adulthood. Furthermore, increasing evidence is accumulating regarding the importance of \( n \)-3 polyunsaturated fatty acids (PUFAs) in the reduction of plasma lipids and hyperglycaemia. In this review article, we shed light on the abnormalities in lipid metabolism in macrosomia. We also raise the question of the possible beneficial effects of \( n \)-3 PUFAs in diabetic pregnancy and in the prevention and treatment of long-term metabolic abnormalities associated with macrosomia.

**INTRODUCTION**

Fetal growth is a complex process involving the interaction of mother, placenta and fetus. The growth and development of the fetus depend upon nutrients such as glucose, lipids and amino acids as well as the genetic makeup and maternal and fetal endocrine status [1,2]. Several alterations in the metabolism of carbohydrates and lipids, observed in infants of diabetic mothers at birth, also persist postnatally [3–8]. The importance of the intrauterine and neonatal metabolic environment as possible teratogenic determinants for the predisposition of obesity, diabetes and cardiovascular diseases has been investigated in a number of studies [3–9,10]. Epidemiological, clinical and experimental studies have suggested that maternal diabetes during pregnancy is an important risk factor for fetal overnutrition and macrosomia [11,12], and for the development of an increased susceptibility to obesity and diabetes in the offspring [9–14]. Indeed, several factors have also been associated with fetal macrosomia such as a history of large babies, multiparity, maternal obesity and excessive weight gain during pregnancy and postmaturity [14–16]. Macrosomia has been defined as a birth weight greater than or equal to the 90th percentile birth weight for gestational age or infants who weigh > 4 kg at delivery, irrespective of gestational age or sex [4,14,17,18]. It seems that maternal hyperglycaemia leads to fetal hyperglycaemia, which stimulates pancreatic islet cells and, consequently, produces hyperinsulinaemia [12]. A positive relationship between maternal glucose levels and fetal macrosomia has been reported by several investigators [19–21]. The intrauterine hyperinsulinemic state results in increased fat tissue, liver glycogen,

**Key words:** diabetes, lipoprotein, macrosomia, polyunsaturated fatty acid (PUFA).

**Abbreviations:** ACAT, acyl Co-A cholesterol acyl transferase; apo, apolipoprotein; CETP, cholesteryl ester transfer protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; LDL-C, LDL-cholesterol; LPL, lipoprotein lipase; NEFA, non-esterified fatty acid; PUFA, polyunsaturated fatty acid; SREBP-1c, sterol-regulatory-element-binding protein-1c; TAG, triacylglycerol; HTGL, hepatic TAG lipase; VLDL, very-LDL.

**Correspondence:** Dr Naim A. Khan (e-mail Naim.Khan@u-bourgogne.fr).
content and total body size [22]. Furthermore, maternal plasma amino acids and lipids are also thought to be contributors to overgrowth of the fetus [11,12,23–25]. Macrosomic newborns incur a number of prenatal complications such as fetal distress, shoulder dystocia and a high incidence of Caesarean delivery [14]. During the neonatal period, macrosomic infants are at increased risk of hypoglycaemia, infant respiratory distress syndrome, hyperbilirubinaemia and hypertrophic cardiomyopathy [14]. Increased risks of maternal obstetrical complications and longer labour periods, especially in primigravid women, have been reported in mothers of macrosomic babies [15]. Consequently, fetal macrosomia is a risk factor for fetal injury and maternal morbidity in Type I, Type II and gestational diabetic pregnancies [14,18,19,26–28].

On the other hand, considerable interest has been generated over the last decade on the potential role of n-3 polyunsaturated fatty acids (PUFAs) in the prevention of diabetes and atherosclerosis. Several studies [29–31] have demonstrated favourable effects of n-3 PUFAs in the reduction of plasma lipids and hyperglycaemia, in addition to their anti-inflammatory, vasodilator, antihypertensive [29,30] and immunosuppressive effects [31]. The beneficial effects of n-3 PUFAs raise the question of their possible role in reducing the prevalence of macrosomia in diabetic pregnancy and in the prevention and treatment of long-term metabolic abnormalities associated with macrosomia.

The purpose is, therefore, to review the work already done on metabolic/lipid alterations and health benefits of dietary n-3 PUFAs in macrosomia.

**LIPID METABOLISM IN MACROSMIA**

**Clinical studies**

Diabetes has been considered as an important factor, altering maternal metabolism and complicating fetal development, regardless of diabetic type [32,33]. Changes in lipoprotein metabolism during normal pregnancy are reflected by increased serum concentrations of non-esterified fatty acids (NEFAs; free fatty acids), triacylglycerols (TAGs; triglycerides), cholesterol, phospholipids and apolipoproteins (apos) [34]. Diabetes mellitus is also associated with alterations in lipid levels and with changes in serum lipoproteins [35]. It may be hypothesized, therefore, that diabetes during pregnancy may alter lipoprotein metabolism further. Ohshima [36] has reported that very-low-density lipoprotein (VLDL)-TAG levels are enhanced in poorly controlled diabetic pregnancy. Koukkou et al. [37] have noticed an increase in total TAGs, but a decrease in low-density lipoprotein (LDL)-cholesterol (LDL-C) in women with gestational diabetes. The lipid profile in gestational diabetes is related to the level of insulin resistance, and the insulin sensitivity index is correlated negatively to TAG [38]. Decreased maternal insulin sensitivity in gestational diabetes may increase nutrient availability to the fetus, accounting for an increased risk of fetal overgrowth and adiposity [39]. In addition, Knopp et al. [40] have reported that neonatal birth weight is positively correlated with concentrations of TAGs and NEFAs, which readily cross the placenta in late pregnancy. Type I diabetic mothers with poor glycaemic control had increased serum TAGs, apoB100 and VLDL-TAG [4,32]. Type II diabetics had significantly higher TAG levels in all lipoprotein fractions than women with Type I diabetes or normal subjects [41]. Infants of diabetic mothers also showed lipoprotein changes. Some of the lipid abnormalities observed in macrosomic newborns are parallel with those found in their diabetic mothers [4]. Several investigators [5,32,42] have shown that, in macrosomic newborns of diabetic mothers, serum lipid, lipoprotein and apo concentrations are higher than in normal newborns of healthy mothers. These data indicate that the synthesis of fat and protein might have increased in these fetuses as a result of maternal overnutrition [42,43]. It seems that the concomitant presence of excess substrates and hyperinsulinaemia enhances fetal lipid and protein synthesis [22,23]. Insulin receptors may also play a role in the increased insulin effects in infants. Several authors [8,44] have found evidence of defective down-regulation of insulin receptors in hyperinsulinaemic fetus, which may have increased insulin-binding sites and, thus, its metabolic effects. The insulin concentrations in utero may also affect the induction and activity of various hepatic enzymes associated with fat and carbohydrate metabolism [22].

The role of sterol-regulatory-element-binding protein-1c (SREBP-1c) in the regulation of hepatic metabolism is now well established [45]. Indeed, insulin stimulates the synthesis of SREBP-1c [46]. SREBP-1c is a transcription factor that induces expression of genes involved in lipogenesis, especially fatty acid and TAG synthesis [47]. It has been shown [48] that this factor is active in fetal tissues and participates in the regulation of lipogenic genes during proliferation. Hence it is possible that SREBP-1c levels are increased in macrosomic fetuses; however, the correlation between high expression of SREBP-1c and high lipid metabolism in macrosomic newborns remains to be established experimentally.

**Alterations in lipid and lipoprotein levels**

Macrosomic infants have high serum VLDL levels accompanied by an increase in serum TAG and apoB concentrations [4,5,32]. An enhancement in glucose and NEFA transfer from the diabetic mother could explain raised hepatic VLDL secretion and hypertriglyceridaemia in macrosomic newborns, as glucose and NEFAs are major substrate determinants for hepatic secretion [49]. Indeed,
hyperinsulinaemia boosts lipid and protein synthesis [22]. Furthermore, significant positive correlations between maternal glycosylated haemoglobin (HbA1c) and TAG levels in late gestation and macrosomic neonate TAG and apoB100 concentrations support these findings [32]. Macrosomic newborns also possess high LDL levels as a result of high concentrations of VLDL, as most LDL particles are derived from VLDL by the action of lipoprotein lipase (LPL) [4,5,32]. Chan et al. [50] have reported that VLDL and LDL-C concentrations are significantly elevated in newborns of mothers with gestational diabetes. Increased LDL-C levels have been reported recently [51] in infants of Type I and gestational diabetic mothers as compared with levels in control infants. High activities of LPL and hepatic TAG lipase (HTAGL) have also been reported in infants of diabetic mothers [52,53]. Macrosomic newborns possess high levels of high-density lipoprotein (HDL), which are accompanied by high HDL apoA-I and apoA-II concentrations, suggesting an increase in the number of HDL particles, probably as a result of their enhanced synthesis [5,32]. Since HDL is primarily responsible for lipid transport during fetal life, elevated HDL particles might reflect an increase in the requirement for cholesterol and phospholipids for membrane, hormone and surfactant synthesis in macrosomic newborns. In these subjects, lecithin cholesterol acyltransferase (LCAT) activity is not significantly different from that found in control newborns, despite high concentrations of apoA-I [4]. In fact, LCAT activity is not correlated with apoA-I levels in newborns [54,55]. HDL2 and HDL3 particles are found enriched with TAGs, whereas amounts of HDL2-esterified cholesterol are low in macrosomic newborns [4,32]. A possible increase in the interchange of lipids between lipoproteins resulting from high choleseryl ester transfer protein (CETP) activity could contribute to the increase in HDL2 and HDL3 TAGs and the decrease in HDL2 cholesteryl ester levels. Plasma CETP activity could be enhanced in macrosomic newborns, as is found in obese adults [56], because adipose tissue is a major source of CETP [57]. Indeed, decreased HDL2-cholesterol (HDL-C) levels could be related to high HTAGL activity in infants of diabetic mothers [53]. In fact, a negative correlation between HTAGL activity and HDL2-C concentrations has been described in man [58]. These modifications in lipid metabolism of macrosomic infants are summarized in Table 1.

A perusal of Table 1 shows that the lipoprotein profile of macrosomic newborns of diabetic mothers is consistent with high atherogenic risk. In fact, the most useful marker ratios of atherogenic risk (apoB100/apoA-I; LDL-C/HDL-C; and HDL3-C/HDL2-C) are significantly higher in macrosomic newborns compared with controls [4]. Indeed, diabetes in pregnancy causes a tendency to hypercholesterolaemia in the offspring. Some of the alterations such as increased TAG, apoB100, VLDL and LDL levels in macrosomic newborns persist even after 1 month of life [5]. An important observation is the elevated serum apoB100/apoA-I ratio in these newborns at birth and at 1 month of life. Wang et al. [59] have also reported that infants with an initially high apoB100/apoA-I ratio still had high values at 1 year of age. This observation is of considerable interest in view of the predictive value of this ratio for cardiovascular risk. The epidemiological association described by Barker [60] between fetal lipid levels and cardiovascular disease has recently generated a great deal of interest. The maternal/fetal cholesterol hypothesis supports the basic assumption of the Barker hypothesis, i.e., conditions during fetal development profoundly influence atherogenesis in the latter [61]. Maternal hypercholesterolaemia during pregnancy is associated with greatly increased fatty streak formation in human fetal arteries and accelerated progression of atherosclerosis during childhood [61]. A good correlation exists between maternal and fetal plasma cholesterol levels in 5–6-month-old human fetuses [62]. Hypertriglyceridaemia has also been implicated in endothelial dysfunction [63]. Insulin, when occurring prenatally in elevated concentrations induced by gestational diabetes, may possibly act as an endogenous teratogen during critical periods of development, leading to permanent structural or functional organ changes and consequent reprogramming of metabolism [9]. However, long-term follow-up of the offspring of diabetic mothers will be necessary to assess whether fetal lipid alterations are associated with the development of obesity and diabetes and, thereby, pose an increased risk for atherosclerosis for advanced ages. Unfortunately, no studies have been done on this subject. In human beings, follow-up studies are difficult to undertake, in part, because of long periods of time and the influence of multiple factors affecting growth. Therefore there is a need to establish an animal model to investigate this issue.

### Table I Alterations in lipid metabolism in macrosomic infants of diabetic mothers

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<th>Lipid metabolism</th>
<th>Unchanged levels</th>
<th>Increased levels</th>
<th>Decreased levels</th>
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<td>HTAGL [53]</td>
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The reference numbers in the parentheses indicate the studies pertaining to the respective alterations in lipid metabolism.
Experimental studies

Experimental diabetes has been shown to impair maternal and fetal lipid metabolism [64,65]. The pregnant rat is a good experimental animal, because it shows a rise in VLDL-TAG during pregnancy similar to that seen in humans [64]. Streptozotocin has been used widely to induce not only diabetes, but also hyperglycaemia in pregnant rats [66–68]. Maternal streptozotocin administration before pregnancy affects fertility and impairs embryo development during the pre-implantation period [68]. However, administration of streptozotocin on day 5 of gestation exerts no effect on embryo development and, thus, avoids its lethal effects on the fetal pancreatic β-cells [66,67]. We have also used this animal model to explore the association between birth weight and the predisposition of macrosomic pups of diabetic dams to obesity development and the onset of adult diabetes [6,69–71]. In the diabetic pregnant rat, high levels of TAG and NEFAs in the maternal circulation create a steep concentration gradient across the placenta, which accelerate their transport and deposition as TAG in fetal tissues [65]. There is evidence for a role of insulin in regulating rat fetal growth [9,22]. Increases in total body proteins and lipids have been observed in hyperinsulinaemic newborns of diabetic rats [6,22,71]. These macrosomic rats maintain accelerated postnatal growth combined with high adipose tissue weight up to 12 weeks of age [6,11,66,67,72]. These animals exhibit several metabolic abnormalities that vary according to age and gender [6,69–71].

Modifications in lipid metabolism at different stages of development of macrosomic animals

At 1 month of age, serum lipid and lipoprotein concentrations in male and female macrosomic rats are similar to those of their respective controls [6,69–71]. However, adipose tissue LPL and HTGL activities are higher in macrosomic than in control rats [6]. Hence increased adipose tissue LPL activity could lead to enhanced fat storage and fat cell hypertrophy. In fact, the early elevation of adipose tissue LPL activity associated with normal muscle LPL activity has been shown [71] to be a contributory factor to the maintenance of obesity in offspring of the diabetic rat. Similar observations have been reported in Zucker obese (fa/ fa) rats in which adipose tissue LPL activity is high, whereas muscle LPL activity is normal, at 4 weeks of age [73–75]. High LPL and HTGL activities are normally associated with enhanced lipoprotein and remnant catabolism, resulting especially in low serum TAG and VLDL, and high LDL and HDL levels in the rats [76]. However, these correlations between lipolytic activities and circulating lipids are not found in macrosomic rats at 1 month of age. In these animals, the hyperinsulinaemic state observed at birth disappeared, and insulin concentrations are similar to those in controls. Nonetheless, an increase in tissue insulin sensitivity could be envisaged, as suggested by several authors [8,22]. Hence persistence of a high number of insulin receptors and/or greater insulin-binding affinity in the target tissue may contribute to enhanced anabolic effects, despite normal serum insulin levels in macrosomic rats at 1 month. In addition, liver cholesterol levels in these rats were also comparable with control values [69]. However, serum LCAT, hepatic 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (rate-limiting enzyme in the biosynthesis of cholesterol), cholesterol 7α-hydroxylase (enzyme that converts cholesterol into bile acids) and acyl CoA cholesterol acyl transferase (ACAT; an intracellular enzyme esterifying cholesterol) activities are higher in macrosomic animals than in controls [61]. Interestingly, insulin is one of the few hormones that has been shown [77] to play a critical role in the regulation of cholesterol synthesis through HMG-CoA reductase by modulating gene expression at the level of its mRNA and enzymatic protein synthesis. Indeed, insulin stimulates cholesterologenesis in hepatic and peripheral tissues [78]. Therefore the first month, a period related to an increase in tissue insulin sensitivity, is also characterized by an increase in hepatic HMG-CoA reductase and cholesterol synthesis in these animals. In addition, the increase in LCAT activity in these macrosomic rats could also be related to hyperresponsiveness of protein synthesis to insulin in hepatocytes. Another explanation for the increased synthesis of cholesterol in macrosomic rats at 1 month of age would be a high demand for cholesterol during the rapid growth phase [6,9,22]. Despite enhanced HMG-CoA reductase activity, a concomitant rise in hepatic and plasma cholesterol concentrations is not observed in macrosomic rats at 1 month of age. The amount of cholesterol in blood depends on the balance between removal from plasma, endogenous neosynthesis and its excretion. When abnormal cholesterol synthesis occurs in liver, neosynthesized cholesterol may have three metabolic fates: (i) storage in the liver; (ii) release into bile as free cholesterol or as bile acids; and (iii) excretion as plasma lipoprotein cholesterol. Macrosomic rats seem to respond to the increased cholesterol synthesis with a high rate of bile acid synthesis, as evidenced by increased cholesterol 7α-hydroxylase activity. Similar results were obtained in Yoshida and Wistar fatty rats [79,80]. Enhanced ACAT activity reflected higher esterification in macrosomic compared with control rats; however, despite high ACAT activity, hepatic cholesterol ester content is not increased in these obese rats at 1 month of age. Cianflone et al. [81] have suggested that cholesterol ester formation plays an important role in hepatic VLDL synthesis and secretion. Hence increased hepatic cholesterol ester incorporation into lipoprotein particles could occur in macrosomic rats and may be responsible for non-accumulation of liver
cholesterol at 1 month of age. However, VLDL, LDL, HDL, and HDL$_{2-3}$ cholesterol are not increased in these macrosomic rats. Increased expression of lipoprotein receptor, suggesting enhanced catabolism, in macrosomic rats might contribute to maintain normal lipoprotein cholesterol levels. Together, these results suggest a high cholesterol turnover in macrosomic rat, consistent with the observations in obese humans [82]. Indeed, in a recent study [83], despite similar serum total cholesterol levels, cholesterol synthesis was higher in obese subjects with diabetes than in controls.

At 2 months of age, the male macrosomic rats again show excess adipose tissue, high LPL, HTGL, LCAT, ACAT, HMG-CoA reductase and 7α-hydroxylase activities, whereas serum lipid and lipoprotein concentrations as well as liver lipid contents are similar to those in male controls. In obese females, in addition to these abnormalities, liver TAG concentrations are increased with a concomitant increase in serum VLDL and TAGs compared with female controls of the same age. An explanation for this discrepancy is not available; however, this could be the result of increased oestrogen levels in obese females compared with controls, as oestrogen is known to enhance hepatic TAG production and secretion [84]. Pronounced changes in the fatty acid composition of liver and VLDL lipids are also observed in the offspring of diabetic rats [70]. The changes in the lipid proportions in the suckling rats might be due to the alterations in dam’s milk. At 2 months of age, fatty acid composition of hepatic lipids is still altered in macrosomic rats, despite a similar diet [70]. These fatty acid changes are different from those observed at 1 month. Low α-linolenic acid (C18:3n-3) contents in hepatic TAGs and phospholipids, accompanied by higher docosahexaenoic acid (C22:6n-3) levels, imply an increase in elongase and desaturase activities of n-3 fatty acids in the liver of obese rats. It is clear that desaturation of n-6 fatty acids is counterbalanced by n-3 fatty acid desaturation, perhaps reflecting an hepatic regulation of PUFA metabolism. Indeed, at 2 months of age, the fatty acid composition of VLDL lipids is not modified in macrosomic rats, despite several changes in hepatic fatty acids [70].

At 3 months of age, the situation is somewhat different. Macrosomic rats (both males and females) are hyperinsulinaemic, with high lipid and lipoprotein concentrations. They also display significant increases in liver lipids, LCAT, LPL, HTGL, ACAT, HMG-CoA reductase and 7α-hydroxylase activities. Taken together, these results strongly suggest that the macrosomic rats developed insulin resistance in adulthood [66,67,85]. Moreover, it is well known that the development of obesity is linked to insulin sensitivity, whereas weight maintenance in the obese state is associated with insulin resistance [86,87]. At 3 months, adult macrosomic offspring of diabetic dams present both quantitative and qualitative abnormalities in different lipoproteins [71]. Adult obese rats have high VLDL concentrations accompanied by a concomitant increase in all VLDL-apoprotein and lipid components, suggesting elevated VLDL particle number. Overproduction of VLDL, a common feature of human and various experimental obesities, is a direct consequence of hyperinsulinaemia and hepatic hyperlipogenesis [35,73,75,88]. These adult obese rats also possess enhanced HDL$_{2-3}$ levels. A positive correlation between adiposity and HDL levels is seen in several animal models of obesity [89,90].

Adult obese offspring of diabetic dams also present compositional changes of HDL$_{2-3}$ particles, including enrichment in cholesterol [69,71]. Fatty acid composition of liver and VLDL-TAG lipids is also altered in 3-month-old obese rats [70]. The most interesting finding is a reduced arachidonic acid (C20:4n-6) level in the liver and VLDL-TAG and phospholipids. This phenomenon is important because it coincides with the development of insulin resistance. Similar changes in the fatty acid composition of plasma and liver lipids have been shown to occur in diabetes and obesity [91,92]. Indeed, it is found that the degree of complications in diabetes is inversely correlated with arachidonic acid (C20:4n-6) levels [93,94]. It is now known that decreased insulin sensitivity is associated with decreased arachidonic acid levels [92]. Therefore decreased arachidonic acid (C20:4n-6) amounts in liver and VLDL phospholipids of macrosomic rats might, in turn, impair insulin activity and aggravate insulin resistance in adulthood. In conclusion, fetal macrosomia in the offspring of diabetic mothers influences lipid and lipoprotein metabolism at birth and throughout adulthood.

In adulthood, macrosomic offspring display many of the metabolic characteristics that are typical of obese and diabetic subjects, including elevated VLDL concentrations and liver steatosis. Fatty acid composition of liver and VLDL lipids are also altered throughout adulthood, reflecting changes in insulin sensitivity in these obese offspring. It is, therefore, apparent that macrosomia in diabetic pregnancy may be considered as an important risk factor for adult obesity and diabetes and their metabolic complication, including essential fatty acid metabolism abnormalities and dyslipoproteinemia.

**n-3 PUFAs AND LIPID METABOLISM**

Dietary fatty acids are known to modulate the metabolism of lipids and lipoproteins [30,95–97]. Dietary PUFAs have been classified into two categories, belonging to n-6 and n-3 families (Figure 1). These fatty acids are indispensable for the animal cell to maintain its structure, fluidity and function. The n-6 PUFAs are synthesized from their precursor, linoleic acid (18:2n-6), through different steps involving a series of enzymes called desaturases and elongases. The n-6
The two major families of PUFAs

### n-6 Family

- **Linoleic Acid** (18:2 n-6)
  - Δ6
  - γ-Linolenic Acid (18:3 n-6)
    - elongase
  - Dihomo-γ-Linolenic Acid (20:3 n-6)
    - Δ5
  - Arachidonic Acid (20:4 n-6)
    - elongase
    - Δ5
    - 22:4 n-6
    - Δ4
    - 22:5 n-6
  - Docosahexaenoic Acid (22:6 n-3)

### n-3 Family

- α-Linolenic Acid (18:3 n-3)
  - Δ6
  - Eicosapentaenoic Acid (20:5 n-3)
    - elongase
    - Δ4
    - 22:5 n-3

**Figure 1** The two major families of PUFAs

n-6 and n-3 PUFAs are synthesized from their respective precursors, i.e., linoleic acid and linolenic acid respectively. The biosynthetic pathway is catalyzed by the reactions of two groups of enzymes, i.e., elongases and desaturases (Δ4, Δ5 and Δ6).

PUFAs are abundantly present in meat and vegetable oils. The most biologically active n-6 PUFA is arachidonic acid (C20:4 n-6), which is implicated in most cellular functions. Arachidonic acid (C20:4 n-6) is a substrate for the biosynthesis of physiologically active eicosanoids (prostaglandins, thromboxanes, leukotrienes and lipoxins). High contents of n-3 PUFAs, specifically docosahexaenoic acid (DHA; C22:6 n-3) and eicosapentaenoic acid (EPA; C20:5 n-3), are found in fish oil and marine algae. DHA is a significant structural component of membrane phospholipids in tissues throughout the body, particularly in retina, brain and spermatozoa. EPA gives rise, similar to arachidonic acid, to different biologically active metabolites via cyclo-oxygenase and lipooxygenase pathways [98]. Although both n-3 and n-6 PUFAs are metabolized by the same fatty acid desaturases (Figure 1), the affinity for the n-3 family is greater than for n-6 family.

**Clinical studies**

Recent studies [30,95,99,100] have demonstrated that increased intake of n-3 PUFAs, in particular EPA and DHA, may exert beneficial effects on serum lipids and platelet aggregation and, thus, could reduce risk of vascular diseases and thrombosis-linked complications. It has been suggested that a high dietary intake of fish oil, which is rich in n-3 fatty acid, may be a contributory factor to the low incidence of cardiovascular diseases in Eskimos [101]. Indeed, evidence has shown that n-3 fatty acids lower both plasma cholesterol and TAGs [99,100]. Fish oil has been shown to be useful in treating dyslipidaemia in diabetes [102,103]. Several studies have suggested that the hypotriglyceridaemic effect of n-3 fatty acids is due to reduced hepatic TAG output [104] or accelerated clearance of VLDL-TAGs [105]. In fact, n-3 PUFA supplementation increases the endogenous activities of LPL and HTGL [106]. However, the effects of n-3 PUFAs on lipolytic activities are divergent, with sometimes decreased or no effects [100]. Several mechanisms have also been proposed for the TAG lowering associated with n-3 PUFAs. These mechanisms include decreased delivery of fatty acids to the liver, accompanied by increased fatty acid oxidation and decreased fatty acid synthesis, resulting in decreased fatty acid availability for TAG synthesis [100]. Moreover, LDL levels are decreased, unchanged or increased with n-3 PUFAs [100,107]. Dietary supplementation with n-3 PUFAs induces the presence of large LDL particles, which might be expected to reduce atherogenic risk [107]. In addition, large amounts of EPA are found in LDL-esterified cholesterol, which lead to a marked disordering of lipid core and lowering of the LDL transition temperature [100]. Greater fluidity of the LDL core has been associated with reduced atherogenicity of the particle. In view of the well-known inverse relationship between plasma TAG levels and HDL-C, it is not surprising that fish oil treatment might increase HDL-C and HDL2 levels [100,106]. It is important to note that HDL2 levels are known to be antiatherogenic, as they protect LDL against oxidative modifications.

Glucose intolerance and insulin resistance are associated with a deviation from a traditional diet of fish (high in n-3 PUFAs) to commercial foods (low in n-3 PUFAs and high in saturated fats) in Eskimos [108]. Indeed, fish intake delays development of diabetes in glucose-intolerant individuals [109]. The effect of PUFAs on insulin sensitivity is well known. Increasing the contents of n-3 PUFAs within cell membranes in cultured cells increases membrane fluidity, the number of insulin receptors and the action of insulin [110]. In fact, compared with saturated fats, unsaturated fatty acids are more readily used for energy and mobilized by lipolytic stimuli [111,112]. They are preferentially incorporated into plasma membrane where they appear to have beneficial effects in relation to insulin action and metabolic rate [113]. n-3 PUFAs are also potent gene regulators, notably in regard to enzymes of endogenous lipid synthesis and adipocyte proliferation [111–113]. With respect to oxidative damage, n-3 PUFAs increase the tendency for LDL to be oxidized [114]. However, Kesavulu et al. [115] indicated that EPA and DHA decreased lipid peroxide levels and erythrocyte glutathione peroxidase activity with no changes in catalase and superoxide dismutase.

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activities in Type II diabetic patients. In addition, EPA improves endothelial function in hypertriglyceridaemic subjects, despite increasing VLDL oxidizability [116]. Taken together, these studies suggest that n-3 PUFAs may exert a beneficial role in prevention and therapy of both diabetes and obesity.

**Experimental studies**

Fish oil diets have also produced changes in lipoprotein composition in animal studies [100]. Fish oils lower TAGs by decreasing hepatic VLDL synthesis [117–119], LPL and HTGL activities are decreased in fish-oil-fed rats [120]. There is some experimental evidence that n-3 PUFA-enriched diets lead to changes in energy balance and in body weight, with n-3 PUFAs being less obesogenic [121,122]. Cunnane et al. [122] have shown in the ob/ob mice that, despite no significant change in food intake, there is less weight gain with a fish oil diet than with an equienergetic amount of n-6 fatty acids. Studies in rats have shown [121] that fish oil exerts beneficial effects on insulin resistance, since it completely prevents the development of insulin resistance induced by a diet rich in fat. These effects are linked to the incorporation of n-3 PUFAs in the phospholipids of skeletal muscles. In fact, insulin resistance in rats is inversely and significantly correlated with the n-3 PUFA content of their skeletal muscles [123]. PUFAs enhance peripheral glucose utilization in rats [124]. Hence one can envisage that all these beneficial effects of n-3 PUFAs also occur in macrosomia.

**PREVENTIVE STRATEGIES AGAINST MACROSOMIA**

In view of these findings, the perturbation in maternal glucose and lipid homoeostasis will have specific effects on fetal lipoproteins. Hyperglycaemia and hypertriglyceridaemia are major changes in diabetic mothers and in their macrosomic newborns. Macrosomia is a risk factor for later obesity, diabetes and dyslipoproteinaemia. Maternal diabetes should be carefully considered and
appropriate management should be organized, including not only glycaemic control during pregnancy, but also lipoprotein profile improvements. Dietary management has been proposed to prevent macrosomia [19,23,39,125–128]. These include maternal calorie restriction, low carbohydrate intake and low-fat diets [125–128]. In addition, it has been shown that maternal dietary fatty acids influence fetal lipid metabolism and contribute to postnatal metabolic changes [129–132]. As is evident from the studies reviewed here, n-3 PUFAs might be beneficial for many of the metabolic malfunctions associated with macrosomia (Figure 2). n-3 PUFAs might counteract maternal and fetal hypertriglyceridaemia and might decrease weight gain associated with macrosomia. These agents might also restrain the development of insulin resistance in adulthood. Indeed, if SREBP-1c is overexpressed in macrosomic fetuses, n-PUFAs might counteract this overexpression, since they have been shown to repress the maturation of SREBP-1c [133,134].

Unfortunately, no data are available on the effects of n-3 PUFAs in macrosomic newborns. Our preliminary study on n-3 PUFA-enriched diet during pregnancy showed that EPA and DHA reduced the incidence of macrosomia in streptozotocin-induced diabetic rats (H. Merzouk, A. Hichami and N. A. Khan, unpublished work). Further research is needed to determine the effects of n-3 PUFAs on macroomic lipoprotein metabolism, and to define the amount and duration of n-3 PUFA supplementation requirement to produce beneficial effects on lipoproteins and on glucose homoeostasis, with the aim of reducing the development of diabetes in macroomic offspring.

**CONCLUSIONS**

In this review, we have attempted to demonstrate that macrosomia is associated with abnormal metabolism of lipids and lipoproteins. The crucial question is whether n-3 PUFA supplementation can prevent or ameliorate lipoprotein status in macroomic offspring of diabetic mothers. Could supplementation of diet with n-3 PUFA during pregnancy and the early postnatal period exert beneficial effects in treating the complications of macrosomia? In the previous section, we have shown that several alterations in lipid metabolism in macrosomic offspring could be corrected by n-3 PUFA supplementation. Further research is needed to establish the beneficial effects of n-3 PUFA in macroomic offspring of diabetic mothers.

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