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Fatty Acid Supply in Pregnant Women with Type 1 Diabetes Mellitus

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1. Introduction

Long-chain polyunsaturated fatty acids (LCPUFAs) play an important role in the human body in building up cell membranes and in regulating their fluidity. The most important fatty acids are the essential n-3 fatty acid, alpha-linolenic acid (C18:3n-3, ALA) and the essential n-6 fatty acid, linoleic acid (C18:2n-6, LA), and their most important metabolites, docosahexaenoic acid (C22:6n-3, DHA) and arachidonic acid (C20:4n-6, AA). LCPUFAs are precursors of different eicosanoids, and their availability may be disturbed in several diseases. As insulin is one of the most potent activators of △-6 desaturase enzyme, type 1 diabetes mellitus (T1DM) is characterised by the diminished levels of n-3 LCPUFAs (Decsi et al., 2002, 2007; Szabó et al., 2010b).

2. Role of polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are components of the lipid bilayer of cell membranes, where they also regulate membrane fluidity. Cell membranes containing more saturated fatty acids and cholesterol are more rigid, while PUFAs increase their fluidity as well as the number of receptors and their affinity to their substrates, like hormones and growth factors (Das, 2006).

PUFAs are also precursors of several second messengers. From the n-6 group, especially from AA proinflammatory eicosanoids are synthesized, while the n-3 fatty acids, especially eicosapentaenoic acid (C20:5n-3, EPA) are precursors of antiinflammatory eicosanoids.

The n-6 essential fatty acid (EFA), LA plays an important role in the maintenance of the epidermal water barrier (Koletzko & Rodriguez-Palmero, 1999), preventing thereby the transepidermal water loss and epidermal damage (Yen et al., 2008). There are data indicating that LA also lowers plasma total cholesterol levels (Nikkari et al., 1983). In an animal study the n-3 EFA, ALA lowered serum and liver triacylglycerol levels, while it increased serum HDL-cholesterol levels (Murano et al., 2007).

AA and DHA play an important role in the maturation of the developing nervous system: during the third trimester and in the first months of life there is an increased incorporation into the fetal/neonatal brain and retinal membranes (Farquharson et al., 1992; Martinez & Mougan, 1998).

Fish oil, containing EPA and DHA, may be beneficial not only during infancy, but also during adulthood. It may prevent the development of macula degeneration (Chua et al.,

2006), may lower the risk of developing dementia and Alzheimer-disease (Morris et al., 2003; Schaefer et al., 2006) and may be beneficial in bipolar depression (Noaghiul & Hibbeln, 2003). N-3 LCPUFAs play also an important role in the prevention of cardiovascular diseases: fish oil supplementation increased HDL-cholesterol levels, while decreased triacylglycerol levels (Laidlaw & Holub, 2003), reduced the progression of atherosclerosis (Erkkilä et al., 2004), the risk of coronary heart disease (Iso et al., 2006; Mozaffarian et al., 2005), fatal myocardial infarction (Yuan et al., 2001), sudden cardial death (Albert et al., 1998), incidence of atrial fibrillation (Mozaffarian et al., 2004) and the risk of stroke (Mozaffarian et al., 2005). In a longitudinal, observational study, fish oil supplementation reduced the risk of developing islet autoimmunity in children at increased genetic risk for T1DM (Norris et al, 2007).

Trans isomeric fatty acids increase serum lipoprotein(a), LDL-cholesterol, triacylglycerol (Katan et al., 1995) and total cholesterol levels (Louheranta et al., 1999), as well as significantly decrease the levels of HDL-cholesterol (Dyerberg et al., 2004; Louheranta et al., 1999; Sun et al., 2007); in summary, they increase the risk of cardiovascular diseases (Sun et al., 2007). In an animal study rats fed with *trans* fatty acid diet (similar to saturated fatty acid diet) had high levels of fasting plasma insulin and decreased adipocyte insulin sensitivity (Ibrahim et al., 2005). In contrast, in a human study *trans* fatty acid diet did not alter insulin sensitivity (Louheranta et al., 1999).

2.1 Biochemistry of fatty acids

The physiologically most important PUFAs contain 2-6 double bonds and have a chain length of 18, 20 or 22 carbon atom. The methyl end of the molecule is called the omega end. On the basis of the distance of the first double bond from the carbon atom at the omega end, three different groups of fatty acids can be distinguished: omega-3 (n-3), omega-6 (n-6) and omega-9 (n-9) fatty acids.

The human body is unable to establish double bond in the n-3 and n-6 position, so we have to ingest the EFAs, the n-3 ALA and n-6 LA with our diet. The most important dietary sources of these fatty acids are vegetables and vegetable oils.

From the essential n-6 LA, after △-6 desaturation γ-linolenic acid (C18:3n-6, GLA) and after elongation dihomo-γ-linolenic acid (C20:3n-6, DHGLA) is synthesised. After a △-6 desaturational step, the most important metabolite, AA is produced (Fig. 1).

The metabolism of the n-3 group is a longer, more complicated process. After elongation, △-5 and △-6 desaturation eicosapentaenoic acid (C20:5n-3, EPA) is formed. After chain elongation docosapentaenoic acid (C22:5n-3, DPA) is synthesised. The most important n-3 metabolite, DHA is produced after △-6 desaturation and peroxisomal β-oxidation (Fig. 1).

Although the same enzymes are involved into the metabolism of the n-3 and n-6 group, these fatty acids cannot be transformed into each other, because the molecule can only be activated from the carboxyl end. In the metabolism, the elongation is a quicker, while desaturation is a slower step, so these desaturational steps determine the speed of metabolism (i.e. these are the rate-limiting steps).

In the nature, PUFAs can be found predominantly as cis isomers, while *trans* fatty acids are produced in the stomach of ruminants and during the partial hydrogenation of vegetable oils. Cis double bond bends the molecule, while *trans* double bond straightens the fatty acid, so it is similar to saturated fatty acids. From this difference arise their different physiological effects: *trans* isomers are similar to saturated fatty acids, while cis isomers have more beneficial effects. As cis and *trans* fatty acids use the same enzymes during their metabolism, several studies

have indicated, that *trans* fatty acids may disturb the metabolism of the physiologically important n-3 and n-6 fatty acids (Szabó et al, 2007, 2010a; Vidgren et al., 1998).

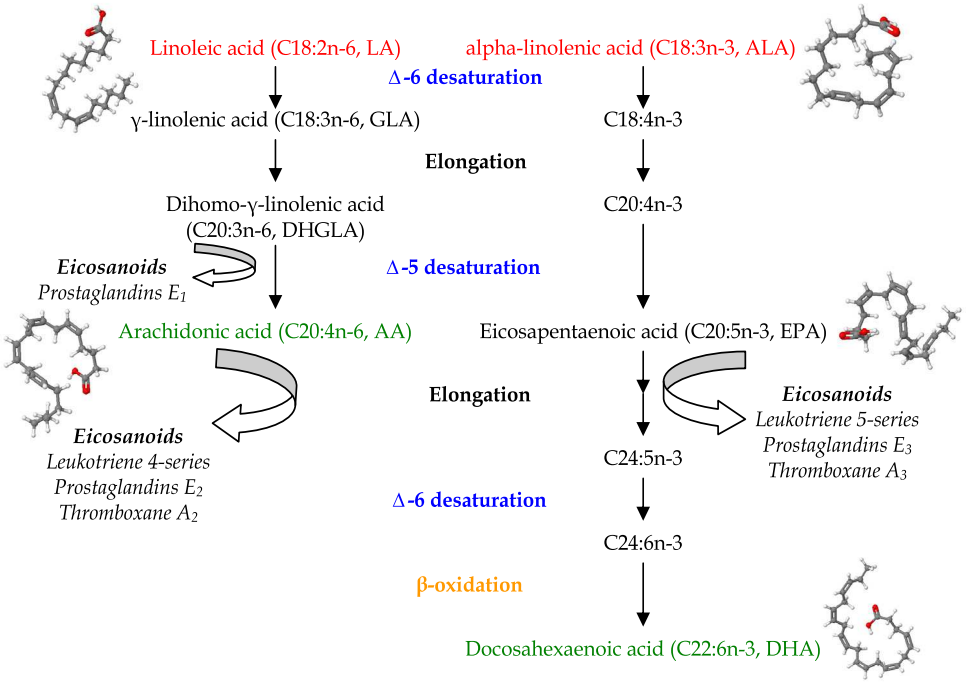

Fig. 1. Metabolism of n-6 and n-3 fatty acids
figure modified from http://www.lpi.oregonstate.edu; source of fatty acid figures: http://www.3dchem.com/index.asp

2.2 Dietary sources of fatty acids

The n-3 EFA, ALA is found in the highest quantity in linseed oil, and considerable amounts are found in hempseed oil (20%) as well (Erasmus, 1993); however, from the dietary point of view its most important sources are walnut and rapeseed oils (Beare-Rogers et al., 2001). The n-6 EFA, LA can be found in the highest proportion in primrose (81%; Erasmus, 1993) and grapeseed oils, but its most important dietary sources are sunflower, corn and pumpkin seed oils (Table 1; Beare-Rogers et al., 2001). Compared to vegetable sources, animal lipid sources contain smaller quantities of ALA and LA (Table 2).

Flesh of herbivorous animals is very rich in the most important n-6 metabolite, AA (Table 2). On the other hand, haslets of terrestrial animals, like liver and kidney contains DHA also in relative high concentrations.

The most important n-3 LCPUFAs, EPA and DHA can be found in fatty sea fishes (Table 3). The DHA content of sea fishes may vary according to season, area of catching and to age and gender of the fish (Racine & Deckelbaum, 2007). Marine fish contains higher levels of n-3 PUFAs, EPA and DHA, while lower n-6 PUFAs, LA and AA compared to freshwater species. In a Chinese study, the edible meat of cultured freshwater fish contained more n-3

PUFAs, EPA and DHA, than the meat of wild freshwater fish (Li et al., 2011). Fatty acid composition of fishes living in the Mediterranean Sea showed seasonal variation (mackerel: lowest in winter-14.44%, highest in spring-38.27%; European eel: lowest in autumn-7.88%, highest in spring-9.46%; Soriguer et al., 1997).

	LA	ALA
Corn oil*	39.4-65.6	0.5-1.5
Grapeseed oil*	58-78	<1.0
Linseed oil*	17-30	47-55
Olive oil*	3.5-20.0	0.0-1.5
Palm kernel oil*	6.5-12	<0.5
Pumpkin seed oil#	42-57	0-15
Rapeseed oil*	11-23	5-13
Sesame oil*	41.5-47.9	0.3-0.4
Soya bean oil	49.8-57.1	5.5-9.5
Sunflower oil (high LA content)*	65.7	–
Walnut oil*	52.9	10.4

* data modified from Beare-Rogers et al., 2001
# data modified from Erasmus, 1993

Table 1. Fatty acid composition (g fatty acid/100 g fat) of selected vegetable sources, fats and oils

	LA	ALA	AA	DHA
Chicken flesh	26.5	1.1	1.7	0.6
Duck flesh	13.9	1.5	–	–
Heart (beef)	20.9	10.5	0.5	–
Kidney (lamb)	9.7	3.4	6.4	1.5
Kidney (veal)	13.4	1.7	7.8	0.7
Lamb	6.2	0.7	0.7	–
Liver (chicken)	14.0	4.2	0.3	2.0
Liver (pork)	13.6	17.2	1.3	1.0
Milk (cow)	2.6	1.6	–	–
Rabbit	20.2	5.2	–	–
Turkey flesh	24.2	1.3	2.3	0.5
Veal	9.4	0.6	2.3	–
Venison	14.6	3.3	4.7	–

Table 2. Fatty acid composition (g fatty acid/100 g fat) of selected terrestrial animal lipid sources (data modified from Beare-Rogers et al., 2001)

	LA	ALA	AA	DHA
*High fat fishes (>8%)**				
Blue fish, mature (31.3%)*	2.2	n.d.	4.2	13.8
Horse mackerel (12.8%) *	1.1	n.d.	1.4	6.6
Rainbow trout (9.0%)#	5.4	1.4	0.8	10.8
Sardine (11.3%)*	2.2	1.4	2.6	14.7
Striped mullet (11.0%)*	2.7	0.73	3.1	11.7
*Medium fat fishes (4-8%)**				
Anchovy (7.1%)*	2.8	1.4	2.4	16.2
Atlantic mackerel (6.1%)*	2.1	0.68	2.8	25.3
Crucian carp, wild (6.02%)$	11.4	4.0	3.6	5.0
Mackerel (7.45%)#	1.9	2.3	1.7	15.9
Silver carp (5.36%)$	2.4	4.4	4.9	15.5
White herring (6.88%)$	1.2	3.6	2.8	11.8
*Low fat fishes (2-4%)**				
Anchovy (3.49%)#	1.5	2.2	1.4	25.5
Crucian carp, cultured (3.60%)$	17.0	2.6	4.0	6.7
Swordfish (1.93%)#	0.7	1.0	1.1	9.3
Tuna (1.16%)#	2.3	1.3	1.8	16.9

data modified from: * Tanakol et al., 1999 [Black & Marmara Sea]; # Soriguer et al., 1997 [Atlantic Ocean & Mediterranean Sea]; $Li et al., 2011 [East China Sea & Quiantang River]

Table 3. Fat content and fatty acid composition (g fatty acid/100 g fat) of selected sea fishes

2.3 Fatty acids during pregnancy

LCPUFAs play an important role in the maturation of the developing nervous system. AA and DHA are accreted in large amounts into the fetal nervous system: into the cortex and retinal cell membranes during the third trimester of pregnancy and in the first months of life (Farquharson et al., 1992; Martinez & Mougan, 1998). DHA can be predominantly found in the grey matter and retina (Horrocks & Yeo, 1999), while the highest AA content is in the amygdala (Brenna & Diau, 2007). In a primate study (Diau et al., 2005), the highest DHA content was found in globus pallidus (15.8%), while the lowest in the optic nerve (4.5%). AA content was the highest in the amygdale (13.7%) and the lowest in the optic tract (6.8%). Grey matter was richer is both AA and DHA, but there was a discontinuity between grey and white matter DHA concentration, while this great difference wasn't seen in AA concentrations.

The human body has the enzymes needed to synthesise LCPUFAs from their parent essential fatty acids, but the synthesis is a very slow, limited process. In vivo human studies showed that from ALA only a little part is metabolised into EPA and DHA: when supplementing ALA in low dose (<100 mg) only 1.5-7.0% EPA and max. 0.3% DHA were synthesised, while supplementing ALA in high dose (>100 mg) resulted in the synthesis of 0.2-9.0% EPA and 3.8-10.4% DHA. Hence, rise of EPA by 20-100% can be seen in a dose-dependent manner after the administration of ALA. In contrast, the change in DHA values is rather negligible in healthy

adults. Similarly, LA supplementation has little effect on AA supply, only ~0.1% of dietary LA is converted to AA in healthy adults (Plourde & Cunnane, 2007).

As AA and DHA play a key role in the fetal and neonatal brain and visual development, several authors investigated whether the fetus and/or the infant is capable to synthesise AA and DHA from LA and ALA, respectively. In an experimental study (Salem et al., 1996), in vivo conversion of EFAs in newborns was investigated. After the administration of deuterium-labeled LA and ALA, deuterium-labeled AA, EPA and DHA appeared in the neonatal blood. However, this capacity can hardly cover the LCPUFA requirement of the developing brain. Two groups of infants with sudden and unexpected death were studied (at the age of 2 to 48 weeks) and significantly higher AA and DHA values were found in erythrocyte and brain cortex lipids in breastfed infants than in infants fed formula that contained only LA and ALA, and the accretion of DHA was correlated with the length of breastfeeding (Makrides et al., 1994).

Since LCPUFA synthesis in the human organism is limited, the most important source of AA and DHA is diet. During pregnancy maternal diet covers the fetal requirements of these fatty acids, while after delivery either maternal diet (breastfeeding) or the independent diet of the infant (formula feeding). In an animal study (Diau et al., 2005), baboon neonates were fed either breastmilk or formula with or without AA and DHA. DHA supplementation restored the DHA supply in the grey matter to breastfed levels, while dietary AA had little effect on brain AA content. In other words: AA seems to be less sensitive to dietary manipulation than DHA.

Maternal diet and metabolism as well as maternal stores are the sources of fetal fatty acid supply. As the ability of the fetus to synthesise LCPUFAs is limited, placenta plays an important role in transferring AA and DHA from mother to the fetus. Several research groups (Berghaus et al., 1998; Gil-Sanchez et al., 2010; Ortega-Senovilla et al., 2009) investigated the differences in maternal and fetal (newborn) blood fatty acid composition and found a higher proportion of LCPUFAs, while lower proportion of the EFAs in the fetal circulation than in the mothers. This phenomenon is called "biomagnification" and may be related to the ability of the placenta to selectively transport LCPUFAs to the fetus. In an in vivo study (Larqué et al., 2003), pregnant women undergoing elective caesarean section received 4 h before delivery an oral dose of ^{13}C-labeled palmitic acid, oleic acid, LA and DHA. Venous blood was taken from the mothers every hour, and cord blood and placental tissues were also collected at delivery. All four fatty acids appeared in the placental tissues and cord blood triacylglycerol (TG) and non-esterified fatty acid (NEFA) lipids, and there was a preferential sequestration of DHA into the placenta. In a recent study (Gil-Sanchez et al., 2010), it was also shown that all labeled fatty acids were enriched in maternal plasma, as well as placental and cord blood lipids. This was the first study that showed a higher ratio of ^{13}C-labeled DHA in cord to maternal plasma. Unesterified fatty acids are transferred to the fetal circulation by both passive diffusion and through a complex, saturable, protein-mediated transport (Koletzko et al., 2007a). There are several fatty acid transfer proteins in the placenta, like fatty acid binding protein (FABP), that preferentially binds LCPUFAs, fatty acid translocase (FAT) and fatty acid transporter protein (FATP) located on both sides of trophoblast cells transporting fatty acids bidirectionally (Cetin et al., 2009). The plasma membrane FABP is located exclusively on the maternal side of membranes and might be involved in the preferential uptake of LCPUFAs by these cells (Koletzko et al., 2007a).

Fish or fish oil intake during pregnancy and lactation improves maternal fatty acid supply and, hence, may enhance fetal DHA concentrations. The increased DHA intake during pregnancy resulted in better visual and neural development in infants at the age of 18

months (Bouwstra et al., 2006), 3.5 years (Williams et al., 2001) and 4 years (Helland et al., 2003), while other studies failed to corroborate these findings (Bakker et al., 2003; Ghys et al., 2002). Because of the beneficial fetal/neonatal effects of n-3 LCPUFAs, for pregnant and lactating women, at least 200 mg/day DHA intake is recommended (Koletzko et al., 2007b).

3. Effect of type 1 diabetes mellitus on fatty acid supply

T1DM disturbs not only the carbohydrate, but also the lipid metabolism. The most extensively studied experimental animal model of T1DM is the alloxane or streptozotocin-induced diabetic rat or mouse. The results of animal studies are quite unequivocal: in diabetic animals significantly higher LA contents were found in liver, renal cortex and heart lipids (Ramsammy et al., 1993), in liver microsomes and erythrocyte membranes (Shin et al., 1995) as well as in plasma, liver and skeletal muscle phospholipids (Mohan & Das, 2001), while its most important metabolite, AA was significantly decreased in diabetic animals. These results can be explained with the diminished activity of △-5 (Ramsammy et al., 1993) and △-6 desaturase enzymes in T1DM (Ramsammy et al., 1993; Shin et al., 1995). On the basis of these animal studies, insulin is considered as the most potent activator of both △-5 and △-6 desaturase enzymes (Brenner, 2003).

Human studies are even less unambiguous than animal observations. Some studies found significantly higher LA values in diabetic patients (Decsi et al., 2002, 2007; Tilvis & Miettinen, 1985), while others found no significant differences (Ruiz-Gutierrez et al., 1993; Seigneur et al., 1994). On the other hand, most studies report significantly lower AA (Decsi et al., 2002; Ruiz-Gutierrez et al., 1993) and DHA values (Decsi et al., 2002; Ruiz-Gutierrez et al., 1993; Tilvis & Miettinen, 1985) in diabetic patients than in controls. In one study (Tilvis et al., 1986), diabetic patients treated with continuous insulin infusion therapy had significantly lower LA, and significantly higher AA and DHA values both in plasma and erythrocyte membrane lipids than patients with conventional insulin therapy. These results suggest that better diabetic control may improve the activity of △-6 desaturase enzyme.

After a longer period, hyperglycaemia and hypoinsulinemia may lead to several complications in diabetic patients. Several studies investigated the relationship between disturbed fatty acid status in diabetic patients and a number of complications, like diabetic neuropathy, nephropathy and retinopathy. These relationships and the potential role of n-3 fatty acid supplementation in diabetic patients are reviewed elsewhere (Szabó et al., 2010b).

3.1 Fatty acid supply during pregnancy in women with type 1 diabetes mellitus: Maternal effects

T1DM disturbs the fatty acid supply, therefore maternal LCPUFA stores may be compromised compared to healthy pregnant women. Disturbed fatty acid supply and metabolism may influence the course of pregnancy and delivery and may lead both to maternal and fetal complications. Nevertheless, we found only two human studies investigating the fatty acid supply during pregnancy in women with T1DM and four studies investigating fatty acid supply in cord blood lipids of newborns born from mothers with T1DM (Table 4).

Ghebremeskel et al. (Ghebremeskel et al., 2002) induced diabetes with streptozotocin in pregnant rats and investigated the liver fatty acid composition. They found significantly higher essential fatty acid values (ALA and LA) as well as n-3 and n-6 LCPUFA values (AA, EPA, DPA and DHA) in the TG and NEFA fractions. In an earlier study (Chen CH et al.,

1965), only LA was determined and no significant differences were found in plasma NEFA fraction between diabetic and control mothers.

Author	Number	Change in EFAs	Change in LCPUFAs
T1DM: maternal effects			
Chen CH et al., 1965	n = 3	pl. NEFA: LA ↔	no data
Min et al., 2005a	n = 32	pl. TG, CPG: LA, ALA ↔ RBC PC, PE: LA, ALA ↔	pl. CPG: DHA ↓ RBC PC: DPA, DHA ↓ RBC PE: DHA ↓
T1DM: fetal effects			
Chen CH et al., 1965	n = 4	pl. NEFA: LA ↔	no data
Ghebremeskel et al., 2004	n = 31	pl. CPG: LA, ALA ↑ pl. TG: LA, ALA ↓ pl. STE: LA, ALA ↔	pl. CPG: AA, DPA, DHA ↓ pl. TG: DHGLA ↓ pl. STE: AA, DHA ↓
Min et al., 2005a	n = 26	pl. TG: ALA ↓ pl. CPG: LA, ALA ↔ RBC PC, PE: LA, ALA ↔	pl. TG: DHGLA, DPA, DHA ↓ pl. CPG: AA, DHA ↓ RBC PC: AA, DHA ↔ RBC PE: DHA ↓
Winkler et al., 2008*	a.) n = 23 b.) n = 25	a.) RBC PC, PE: LA, ALA ↔ b.) RBC PE: LA, ALA ↑ RBC PC: LA, ALA ↔	a.) RBC PC: DPA ↓ RBC PE: AA, DHA ↔ b.) RBC PE: DHA ↓ RBC PC: AA, DHA ↔

* a.) = age of 3 months; b.) = age of 12 months
Abbreviations: AA: arachidonic acid, ALA: alpha-linolenic acid, CPG: choline phosphoglycerol, DHA: docosahexaenoic acid, DHGLA: dihomo-gamma-linolenic acid, DPA: docosapentaenoic acid, EFAs: essential fatty acids, EPA: eicosapentaenoic acid, LA: linoleic acid, LCPUFAs: long-chain polyunsaturated fatty acids, NEFA: non-esterified fatty acid, PC: phosphatidylcholine, PE: phosphatidylethanolamine, pl.: plasma, PL: phospholipid, RBC: erythrocyte, SM: sphyngomyeline, STE: sterol esther, T1DM: type 1 diabetes mellitus, TG: triacylglycerol

Table 4. Change in essential fatty acid and long-chain polyunsaturated fatty acid values compared to controls in pregnant women with type 1 diabetes mellitus and newborns from mothers with type 1 diabetes mellitus

Plasma and erythrocyte membrane fatty acid composition was studied in women with and without T1DM at midgestation (Min et al., 2005a). In the maternal plasma only choline phosphoglyceride (CPG) DHA was found to be decreased in diabetic patients, while in the erythrocyte membrane lipids more pronounced differences were found. Both the phosphatidylcholine (PC) fraction and in the phosphatidylethanolamine (PE) fraction significantly lower DHA values were found in mothers with T1DM than in healthy pregnant women. The authors hypothesised that this difference might be due to the synergistic effect of diabetes and pregnancy.

3.2 Fatty acid supply in newborns of mothers with type 1 diabetes mellitus: Fetal effects

AA and DHA play an important role in the maturation of the fetal nervous system. Although the developing fetus can synthesise AA and DHA from their precursors, this

synthesis is rather slow and can't meet the requirements of the fetus. As T1DM disturbs the fatty acid supply of pregnant women, newborns of mothers with diabetes may have inadequate in utero n-3 and n-6 LCPUFA supply. In contrast to the lack of data on maternal fatty acid supply, cord blood lipids in neonates of mothers with T1DM were published from several studies.

Chen CH et al. (Chen CH et al., 1965) found no differences between cord blood LA values between newborns of diabetic and control mothers. Cord blood of newborns from mothers with T1DM and healthy controls was analysed in detail in an English study (Ghebremeskel et al., 2004). In the plasma CPG fraction there were significantly higher LA and ALA values in cord blood of neonates from diabetic mothers, while their long-chain metabolites, AA and DHA were lower in both plasma CPG and sterin esther (STE) fractions, which may reflect impaired placental transfer of the n-3 and n-6 LCPUFAs. The authors speculated that the effect of T1DM and pregnancy-induced metabolic changes together with the Western diet might have resulted in decreased AA and DHA levels in pregnant women with T1DM.

In another study, cord blood samples of newborns of mothers with T1DM contained significantly lower ALA, DPA and DHA in the plasma TG fraction and significantly lower AA and DHA in the plasma CPG fraction (Min et al., 2005a). However, only DHA values were decreased in the erythrocyte PE fraction in the cord blood of the T1DM group.

In the BABYDIET study, newborns with increased genetic and familiar risk for T1DM were investigated (Winkler et al., 2008). Erythrocyte membrane PC and PE were determined in infants of mothers with and without T1DM at the age of 3 and 12 months. No differences were found in the values of the most important LCPUFAs, AA and DHA in the PC fraction, while significantly lower DPA values were found in the infants of diabetic mothers at the age of 3 months, than in those of the healthy controls. In contrast, comparing only the exclusively breastfed infants of mothers with and without T1DM, no differences were found in the values of n-3 and n-6 PUFAs. At the age of 12 months, infants from mothers with T1DM had significantly higher essential fatty acid (ALA and LA) values, but DHA values were decreased in the PE fraction.

As newborns of mothers with diabetes may have diminished AA and DHA supply, the neurodevelopment of these infants may also be affected. In an experimental animal study (Zhao et al., 2009), diabetes was induced in rats who were divided into two groups, one with good and one with poor diabetic control and were fed either with AA or control diet. After one week the animals were mated and the neurodevelopment of the pups was investigated. Maternal dietary AA supplementation through pregnancy and lactation resulted in improved sensorimotor and developmental performances of the offspring of both healthy controls and poorly controlled diabetic dams. Maternal AA supplementation also improved the AA supply of the offspring's liver, but not in the brain.

Maternal diabetes may disturb fetal fatty acid supply, however, from the epidemiological point of view the longer term effects are more important. Offspring of diabetic mothers may develop different malformations such as spina bifida, at birth they might be macrosomic and develop hypoglycaemia. The potential role of fatty acids in hyperglycaemia-induced teratogenesis was studied in an experimental animal model (Goldman et al., 1985). Diabetic pregnant rats without insulin treatment received subcutaneous AA injection during the period of organogenesis and although maternal glucose concentration didn't change, there was a significant decrease in the incidence of neural tube defects (from 11% to 3.8%), micrognathia (from 7% to 0.8%) and cleft palate (from 11% to 4%). These data suggest that beside good diabetes control also AA supplementation in diabetes might reduce the teratogenetic effect of hyperglycaemia.

4. Effect of gestational diabetes mellitus on fatty acid supply

Gestational diabetes mellitus (GDM) affecting 2-10% of pregnant women in the United States (National Diabetes Statistics, 2011) is associated with insulin resistance during pregnancy. Its prevalence is rising worldwide. Analysing the GDM screening results between 1994-2002 in Colorado state (Dabelea et al., 2005), the prevalence of GDM was increasing from 1994-1996 to 2000-2002 in all ethnic groups: Hispanic (2.8% to 5.1%), African American (2.5% to 4.6%), Asian (6.3% to 8.6%) and non-Hispanic white (1.9% to 3.4%). Women with GDM are at risk to develop type 2 diabetes mellitus either immediately after delivery (5-10%) or later, in 10-20 years (35-60%).

The risk factors of developing GDM during pregnancy are higher pre-pregnancy BMI, smoking, increasing maternal age and GDM during previous pregnancy. Western diet contains high fat intake with high n-6/n-3 fatty acid ratio, refined sugar, fried and snack foods with high *trans* fatty acid content; all these factors may play an important role in developing impaired glucose tolerance and, hence, GDM. Maternal high fat diet during pregnancy decreased EPA and DHA values in liver in newborn pups as well as in suckling pups born from both diabetic and control mothers (Ghebremeskel et al., 1999). In the Project Viva (Radesky et al., 2008), pregnant women with maternal age above 40 years (OR: 11.3), pre-pregnancy BMI above 30 kg/m^2 (OR: 3.44), GDM during prior pregnancy (OR: 58.3) and Hispanic ethnicity (OR: 3.19) had increased risk of developing GDM. However, dietary pattern during early pregnancy had no association with developing GDM.

4.1 Fatty acid supply during pregnancy in women with gestational diabetes mellitus: Maternal effects

As type 2 diabetes mellitus and obesity disturbs fatty acid supply, GDM may also have an effect on fatty acid metabolism in pregnant women. While only two studies were found investigating the effect of T1DM on maternal blood fatty acid composition, GDM was investigated in a number of studies. We found nine studies investigating the fatty acid supply during pregnancy in women with GDM and five studies investigating the fatty acid supply of newborns from mothers with GDM (Table 5).

In an early study (Chen CH et al., 1965), no difference was seen in LA values of mothers with GDM and controls at delivery. When in 2000 the diet and blood samples of pregnant women with GDM during the third trimester were analysed (Wijendran et al., 2000) women with GDM had significantly higher AA, EPA and DHA intakes than controls. Maternal erythrocyte PL contained more DHA, while other fatty acids didn't differ. The authors also determined the effect of fatty acid supply on plasma PL in these women at the 27-30th, 33-35th and 36-39th weeks of pregnancy (Wijendran et al., 1999). Although there were no significant differences in the LA and AA values between the two groups, values of DHGLA and C22:5n-6 were significantly lower at each investigated time points. In contrast, among the n-3 fatty acids, ALA and DPA were significantly lower, while DHA was significantly higher in women with GDM than in healthy controls. Wijendran et al. provided three possible explanations for the lower ALA and higher DHA values: 1. either increased desaturation and elongation of ALA to DHA may be responsible for these alterations, or 2. increased selective oxidation of ALA or 3. enhanced release of DHA into plasma PL. Both in controls and mothers with GDM, the n-3 and n-6 LCPUFAs decreased as the result of the physiologic adaptation in pregnant women to the increased fetal n-3 and n-6 LCPUFA requirement during the third trimester. The authors also investigated the correlations

Author	Number	Change in EFAs	Change in LCPUFAs
GDM: maternal effects			
Chen CH et al., 1965	n = 8	pl. NEFA: LA ↔	no data
Chen X et al., 2010	n = 49	pl.: LA, ALA ↑	pl.: AA, EPA, DHA ↑
Min et al., 2004	n = 53	pl. CPG: ALA ↓ RBC PC: ALA ↓ RBC PE: ALA ↑	pl. CPG: AA ↑ RBC PC: DHGLA, AA, EPA, DPA, DHA ↓ RBC PE: DHGLA, DPA, DHA ↓
Min et al., 2005b	n = 40	pl. TG: LA, ALA ↔ pl. CPG: ALA ↓ RBC PC, PE: LA, ALA ↔	pl. TG: AA, DHA ↔ pl. CPG: AA ↑ RBC PC: AA ↓ RBC PE: AA, DHA ↔
Min et al., 2006	n = 12	pl. TG: LA, ALA ↔ pl. PC: ALA ↓ pl. SM: LA ↔ RBC PC, PE: LA, ALA ↔ RBC SM: LA ↔	pl. TG: AA, DHA ↔ pl. PC: DHA ↑ pl. SM: AA, DHA ↔ RBC PC: AA ↓ RBC PE: AA ↓ RBC SM: AA, DHA ↔
Ortega-Senovilla et al., 2009	n = 15	pl.: LA, ALA ↔	pl.: AA, DHA ↔
Thomas et al., 2004	n = 44	pl. CPG: ALA ↓ pl. TG: LA ↑ pl. STE: ALA ↓	pl. CPG: AA ↑ pl. TG: DHA ↑ pl. STE: AA ↑
Wijendran et al., 1999	n = 15	pl. PL: ALA ↓	pl. PL: DHGLA, DPA ↓, DHA ↑
Wijendran et al., 2000	n = 13	RBC PL: ALA ↓	RBC PL: DHA ↑
GDM: fetal effects			
Chen CH et al., 1965	n = 9	pl. NEFA: LA ↔	no data
Min et al., 2005b	n = 40	pl. TG: LA, ALA ↓ pl. CPG: LA, ALA ↔ RBC PC, PE: LA, ALA ↔	pl. TG: AA, DHA ↔ pl. CPG: DHA ↓ RBC PC: DHA ↓ RBC PE: AA, DHA ↔
Ortega-Senovilla et al., 2009*	n = 15	a.) pl.: LA, ALA ↔ b.) pl.: LA, ALA ↔	a.) pl.: AA, DHA ↔ b.) pl.: AA, DHA ↓
Thomas et al., 2005	n = 37	pl. TG: ALA ↓ pl. CPG, STE: LA, ALA ↔	pl. CPG: DHGLA, DHA ↓ pl. STE: DHGLA ↓ pl. TG: AA, DHA ↔
Wijendran et al., 2000	n = 13	RBC PL: LA, ALA ↔	RBC PL: AA, DHA ↓

* a.) = umbilical vein; b.) = umbilical artery. Abbreviations: see Table 4.

Table 5. Change in essential fatty acid and long-chain polyunsaturated fatty acid values compared to controls in mothers with gestational diabetes mellitus and infants born from mothers with gestational diabetes mellitus (GDM)

between, on the one hand, maternal fatty acids and on the other hand, HbA_{1c} and prepregnancy BMI. Though there was an inverse association between plasma HbA_{1c} and

plasma PL AA also in the controls, this association was more pronounced in women with GDM. Similarly, positive correlation was found between mean fasting plasma insulin and plasma PL AA values. These correlations may indicate impairment in the transport of AA to the fetus. Prepregnancy BMI was correlated inversely to maternal DHA and positively to maternal AA values in the diabetic group. These findings suggest that maternal alterations in plasma PL DHA values may be more pronounced in obese women with GDM.

An English research group (Thomas et al., 2006) investigated the diet of pregnant women with and without GDM during the third trimester, and reported several differences. Diabetic women ingested less fat than controls, and the ratios of fatty acids in the diet were also different: diabetic women had lower saturated, monounsaturated and *trans* fatty acid intake, but higher PUFA intake. Interestingly, the distribution of PUFAs was largely similar in the two groups, only one fatty acid differed between the two groups: mothers with GDM ingested more DHA. They also investigated the effect of ethnicity on dietary fatty acid intake. Afro-Caribbean mothers with GDM had lower total fat, saturated, monounsaturated, *trans* fatty acid and PUFA intake than Caucasian mothers. The diet of the Afro-Caribbean GDM group contained lower LA, AA, n-6 PUFA and ALA values, while higher EPA and DHA compared to Caucasian mothers with GDM.

The same authors also compared the plasma fatty acid supply of these women at diagnosis (Thomas et al., 2004). Women with GDM had significantly higher LA values in the plasma TG fraction, higher AA values in the plasma CPG and STE fraction and higher DHA values in the plasma TG fraction than healthy controls, while ALA was significantly lower in plasma STE in women with GDM. These alterations may be explained by the high glucose concentration that led to the mobilisation of LA, ALA, AA and DHA from adipose tissue and liver. When comparing the fatty acid supply of both plasma and erythrocyte membrane lipids in these women at diagnosis (Min et al., 2004), in plasma CPG higher AA and lower ALA values were found in the mothers with GDM, while values of DHGLA, AA, C22:4n-6 as well as ALA, EPA, DPA and DHA was significantly lower in erythrocyte CPG lipids in the diabetic than in the control group. This discrepancy between plasma and erythrocyte membrane lipid composition may arise as an effect of GDM causing reduction of incorporation of these fatty acids into red blood cells and other tissues. As erythrocyte membrane lipid composition is very similar to that of the vascular endothelium, these alterations in erythrocyte membrane lipids may indicate that endothelium may be also affected in GDM.

In another study carried out in London, significantly lower ALA and higher AA in plasma CPG fraction was found in diabetic mothers than in healthy controls at delivery (Min et al., 2005b). However, AA was significantly lower in erythrocyte membrane PC fraction.

Min et al. carried out a pilot study in Korea, where the habitual diet contains higher n-3 fatty acid and lower total fat intake than the typical Western-type diet (Min et al., 2006). Women with GDM had lower ALA and higher DHA in plasma PC fractions at delivery, while values of AA was lower in erythrocyte PC and PE fractions in women with GDM than in controls. Comparing the AA and DHA values in GDM patients and controls living in Korea or in the UK, in both study groups lower AA and DHA values were found in erythrocyte PC lipids of the GDM groups than in the controls. However, Korean women (both diabetic and control) had higher DHA values than British women. This finding suggests that the reduction of erythrocyte membrane AA and DHA values in women with GDM might be attributed to effects of the disease itself regardless of ethnicity, obesity or diet. In contrast, there were no

significant differences in the fatty acid composition of plasma lipids between mothers with GDM and controls at delivery in an Italian study (Ortega-Senovilla et al., 2009).

As part of a prospective cohort study, a nested case-control study was carried out by Chen X et al. (Chen X et al., 2010) to investigate the differences in fatty acid status of women with impaired glucose tolerance, GDM and controls. In contrast to earlier studies (Wijendran et al., 2000; Thomas et al., 2006), this population had higher saturated fatty acid intake, while dietary LA, DHA and PUFA intakes were significantly lower in the diabetic group than in controls. At study entry (16th week) women who developed impaired glucose tolerance later, had higher plasma EPA absolute values; however, the percentage of PUFAs didn't differ significantly among the three groups. During the third trimester, mothers with GDM had higher AA, DHA and PUFA absolute concentrations, while women with impaired glucose tolerance had higher LA, ALA, EPA and DHA absolute values. Similarly to study entry, PUFA percents didn't differ among the groups. These data showed that not only GDM disturbs fatty acid supply of pregnant women, but impaired glucose tolerance as well. The authors also investigated the effect of BMI and found significantly higher concentrations of saturated and monounsaturated fatty acids and PUFAs in women with impaired glucose tolerance and BMI higher than 25 kg/m^2 at study entry than in normal weighted women with impaired glucose tolerance. During the third trimester, overweight and obese women with GDM had the highest fatty acid absolute concentration. These results indicate that the disturbance in the fatty acid metabolism is more pronounced when beyond the mild hyperglycaemia obesity is also present. Results of this study raised the possibility that reducing pregravid weight and modifying diet (increasing PUFAs and reducing saturated fatty acids) may reduce circulating free fatty acids, therefore decreasing insulin resistance and inflammation and lower future maternal risk of type 2 diabetes mellitus.

4.2 Fatty acid supply in newborns of mothers with gestational diabetes mellitus: Fetal effects

Macrosomia and lipid abnormalities are common complications associated with maternal diabetes during pregnancy. Offspring of diabetic mothers are prone to develop obesity, type 2 diabetes mellitus and cardiovascular diseases during adulthood. In an animal study (Soulimane-Mokhtari et al., 2008), diabetic and control rats were fed a control diet or diet rich in EPA and DHA. During pregnancy of the diabetic rats, VLDL- and LDL-cholesterol were significantly decreased in the intervention group. Moreover, similar changes were seen in the macrosomic offspring: maternal fish oil diet significantly decreased VLDL- and LDL-cholesterol. As n-3 LCPUFA supplementation during pregnancy restored tissue lipase activities to normal range and ameliorated long-term prognosis of macrosomia, n-3 fatty acid supplementation may be beneficial for mothers with GDM.

Maternal diabetes during pregnancy (characterised by hyperglycaemia, hyperlipidaemia, hyperlipoproteinaemia and altered T-cell function) may result in metabolic programming of the offspring causing obesity, impaired glucose tolerance, hyperlipidaemia and hyperlipoproteinaemia during adulthood (Khan, 2007). In Chinese children of mothers with GDM, significantly higher systolic and diastolic blood pressures and lower HDL-cholesterol levels were seen than in controls at the age of 8 years. High umbilical cord insulin was an independent risk factor of both abnormal glucose tolerance and obesity; hence, in utero hyperinsulinaemia and hyperglycaemia may have long-term effects on developing type 2

diabetes and metabolic syndrome (Tam et al., 2008). Type 2 diabetes was diagnosed at younger ages if the patients were exposed to maternal diabetes intrauterine, whereas this difference wasn't seen in the onset of type 1 diabetes (Pettitt et al., 2008). This finding suggests, that intrauterine hyperglycaemia predisposes to an earlier onset of type 2 diabetes, while type 1 diabetes is little influenced by the intrauterine milieu.

In the pioneer study published in 1965 by Chen CH et al. (Chen CH et al., 1965) newborns of mothers with GDM were also analysed and no differences were found in LA values between the diabetic and control groups. Wijendran et al. analysed not only the maternal diet and fatty acid composition of maternal erythrocyte PL, but also the fatty acid composition of cord blood erythrocyte membrane lipids (Wijendran et al., 2000). Though in the maternal blood only DHA differed between mothers with GDM and controls, in the cord blood several differences were found. Values of AA and n-6 PUFAs as well as DHA and n-3 PUFAs were significantly lower in the GDM group than in controls. The DHA sufficiency index calculated from DHA divided with C22:5n-6 was also decreased. This impaired AA and DHA supply in cord blood suggested the impaired fetal accretion of these LCPUFAs in pregnancy with GDM. The authors also correlated maternal and fetal fatty acids both in the GDM group and controls. Though in controls significant positive correlations were found between maternal plasma PL AA and DHA and cord blood plasma PL AA and DHA, these correlations were lost in the GDM group. In controls also an enrichment of AA and DHA in fetal erythrocyte was found, while in the GDM group fetal DHA was lower than maternal, and no difference in AA values were found. These alterations raised the possibility that placental transfer of maternal LCPUFAs during the third trimester may be altered in GDM. Maternal HbA_{1c} was also significantly and inversely correlated to fetal AA and DHA values. Although mothers had their HbA_{1c} values between 4-6%, these values were significantly higher than in controls suggesting a moderate impairment of glucose control. This altered glucose control may also have a negative impact on fetal LCPUFA accretion.

Min et al. (Min et al., 2005b) investigated cord blood samples of newborns from mothers with and without GDM in London and found significantly decreased ALA, LA, DHA and AA values in the plasma TG fraction. In contrast, in the plasma CPG fraction only DHA values were significantly lower in the diabetic group. Similarly, in the PC fraction of erythrocyte membrane lipids significantly decreased DHA values were found. This altered cord blood fatty acid supply may suggest the compromised placental fatty acid transport and/or fetal lipid metabolism.

In another English study (Thomas et al., 2005) also significantly lower DHA values were found in the cord blood plasma CPG lipids in the diabetic group. DHGLA was also decreased in plasma CPG and STE fractions. Values of LA, ALA and AA were not significantly different between the two groups in the plasma TG, CPG and STE fractions, but values of AA were reduced. Although mothers with GDM consumed more DHA, their neonates had reduced levels of both DHA and AA, suggesting that mothers with GDM have impaired placental transfer of LCPUFAs. Mead acid, which is considered as an indicator of shortage of EFAs, was increased in the plasma CPG and TG fractions. The elevated Mead acid values in the cord plasma TG and CPG fraction suggested fetal EFA deficiency.

In a recent study (Ortega-Senovilla et al., 2009) umbilical arterial and venous plasma fatty acid composition was analysed in women with GDM and controls who underwent elective caesarean section. While there were no significant differences in umbilical venous blood fatty acids between the two groups, in the umbilical arterial blood significantly lower AA, n-6 PUFA, DHA and n-3 PUFA values were found. Umbilical arterial and venous blood of both

GDM and control groups had lower LA and higher AA and DHA than their mothers. As umbilical venous blood comes from placental capillaries, these higher proportions of AA and DHA in umbilical venous than in maternal blood may indicate that the placental transfer remained unimpaired. However, the decreased n-3 and n-6 LCPUFA values might indicate enhanced utilization of these fatty acids.

4.3 Differences between fatty acid supply in pregnant women with type 1 diabetes mellitus and with gestational diabetes

We found ten studies about fatty acid supply of pregnant women with either T1DM or GDM. Five different research groups performed human investigations: Chen CH et al. from Cleveland, Chen X et al. from New Jersey, Min et al. from London (Min, Thomas), Ortega-Senovilla et al. from Madrid, finally Wijendran et al. from Hartford.

To the best of our knowledge, only one study investigated the LCPUFA supply in pregnant women with T1DM. In this study no differences were found in n-3 and n-6 EFA values, while the most important n-3 metabolite, DHA was lower in all lipid fractions. In GDM most of the studies found decreased or unchanged ALA values, while LA values remained in most cases stable. In case of LCPUFAs, the results are less unambiguous and there was a difference between plasma and erythrocyte LCPUFA values. In general we can say, that plasma LCPUFAs in most cases were higher in mothers with GDM than in controls or it remained unchanged. In contrast, in erythrocyte membrane lipids LCPUFAs were either lower or unchanged in women with GDM compared to healthy controls except for one study (Wijendran et al., 2000).

Although we found only one study about fatty acid supply of pregnant women with T1DM, it seems, that diabetes had no influence on the EFA supply in mothers. In contrast, GDM may diminish EFA supply during pregnancy. T1DM significantly lowered the LCPUFA values in both plasma and erythrocyte membrane lipids, while there was a discrepancy in the effect of GDM: in plasma lipids it rather increased while in erythrocyte membrane lipids decreased the availability of LCPUFAs.

4.4 Differences between fatty acid supply in neonates from mothers with type 1 diabetes mellitus and with gestational diabetes

There were seven human studies investigating the fatty acid supply in cord blood or blood from infants born from mother with either T1DM or GDM. Four different research groups have data about blood lipid fatty acid composition of these offspring: Min et al. from London (Ghebremeskel, Min, Thomas), Ortega-Senovilla et al. from Madrid, Wijendran et al. from Hartford, finally Winkler et al., from Munich.

In contrast to maternal data, four studies investigated the fatty acid composition of newborns or infants of mothers with T1DM. Findings of EFA values are rather unequivocal: values of LA and ALA are either higher or lower or remained unchanged in the T1DM group. However, result are more clear in the case of LCPUFAs, all three studies found significantly lower AA and/or DHA values in plasma lipids, while erythrocyte membrane DHA values were either lower or similar to AA values, they remained unchanged in the offspring of T1DM mothers.

Looking at the results about the effect of GDM, in most cases EFA values remained stable, while LCPUFAs, predominantly DHA was significantly lower in the GDM group. In cord blood there was no deviation between plasma and erythrocyte LCPUFA values: AA and

DHA were either lower or no significantly different in the offspring of GDM mothers than in controls.

To sum it up: T1DM has no clear effect on EFA status of the offspring, while GDM might lower it. In contrast, both T1DM and GDM lowered the availability of LCPUFAs in newborns and infants of diabetic mothers.

5. Conclusion

Data reviewed here indicate that both T1DM and GDM disturb the fatty acid supply in pregnant women and their offspring. Both types of diabetes during pregnancy may result in lower values of n-3 and n-6 LCPUFA in maternal erythrocyte lipids as well as in cord blood plasma and erythrocyte lipids. Therefore incorporation of fatty sea fishes rich in n-3 fatty acids into the diet (e.g. in the form of two 200 g pieces weekly) or other ways of n-3 LCPUFA supplementation during pregnancy may be beneficial.

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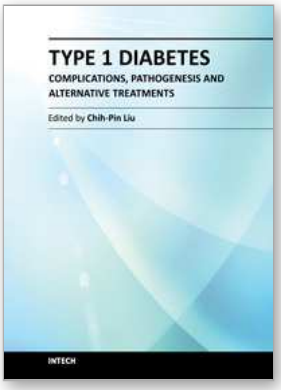

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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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