47 Fatty Acid Metabolism in Diabetes

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CONTENTS

I. INTRODUCTION

The two major abnormalities in both insulin-dependent diabetes mellitus (IDDM, type 1) and noninsulin-dependent diabetes mellitus (NIDDM, type 2) are hyperglycemia and dyslipidemia.

In normal as well as many pathological conditions, the metabolism of carbohydrates, especially glucose, is closely linked to the metabolism of lipids. Insulin is intimately involved in the control of carbohydrate and lipid metabolism. There is either an absolute (in IDDM) or relative (in NIDDM) deficiency of insulin in diabetes or peripheral resistance to insulin, particularly in obese NIDDM subjects. Thus, in untreated as well as poorly controlled diabetic subjects, hyperlipidemia is often associated with hyperglycemia. Close relationship has also been reported for fasting plasma glucose and fasting and meal-stimulated free fatty acid (FFA) levels (Coates et al., 1994). Newgard and McGarry (1995) recently advanced the concept that important signal for insulin secretion may reside at the linkage between glucose and lipid metabolism, namely the generation of malonyl coenzyme A (CoA) that promotes fatty acid esterification and inhibits oxidation. The treatment of hyperglycemia by both diet and exercise, oral agents (sulfonylureas, biguanides, thiazolidinediones), or insulin often also results in the partial reduction of hyperlipidemia.

A major proportion of fatty acids are present in the esterified form as a component of phospholipids, triglycerides, or cholesterol esters. In contrast, only a small fraction of total fatty acids in the body (plasma and tissues) is in the free form (nonesterified or FFAs). The metabolism of fatty acids is intimately linked to the metabolism of lipids and lipoproteins. The differences in the composition of lipids and lipoproteins between control and diabetic subjects are both quantitative and qualitative. In diabetes the most common abnormalities in lipid metabolism, and therefore of fatty acids, are elevated triglycerides (TGs) and very-low-density lipoproteins (VLDL), altered lipogenesis, and accelerated lipolysis (Randle, 1963; Tarrant et al., 1964; Fredrickson et al., 1967; Saudek and Eder, 1979; Brown et al., 1982; Dunn, 1988, 1990; Garg and Grundy, 1990; Fagot-campagna et al., 1997). An increase in small dense low-density lipoprotein (LDL), an integral part of insulin resistance syndrome, has been recognized as an independent risk factor for coronary heart disease (CHD) and may be a predictor of NIDDM (Austin et al., 1995, 1996). The increased VLDL levels are due to increased production as well as decreased clearance. As a consequence, there is an increase in FFA in the plasma of diabetic subjects. Increased levels of plasma TG, total and LDL-cholesterol, apolipoprotein B (apo B), apolipoprotein A-IV (apo A-IV), and phospholipids are also observed in poorly controlled IDDM subjects (Attia et al., 1997). The increased level of lipoproteins containing apoprotein B appears to be due to increased secretion rather than intracellular degradation due to increased FFA flux from liver (Ginsberg, 1996). In poorly controlled diabetic patients there is also an increased nonenzymatic glycosylation of LDL apoprotein B (Steinbrecher and Witztum, 1984; Taskinen, 1987), increased oxidation of LDL lipoproteins (Dimitriadis et al., 1996) and apo A-IV levels (Verges et al., 1994) and decreased high-density lipoprotein (HDL) and HDL_2-cholesterol (Verges et al., 1994). The low levels of HDL are due to a decreased production (Golay et al., 1987) and an increased catabolism due to the increased hepatic TG lipase activity (Kasim et al., 1987). Autoantibodies to LDL are also increased in NIDDM subjects with and without atherosclerosis and are accompanied by high levels of polyunsaturated fatty acids (PUFAs) in LDL (Griffin et al., 1997). Abnormalities in lipid metabolism have been reported in animal models of diabetes, namely, streptozotocin-treated rat, d*b*/d*b* mouse, and in newer models of NIDDM, the obese SHR/N-cp rat and obese WKY/N-cp rat (Hennig and Dupont, 1983; Cunnane et al., 1985; Michaelis et al., 1986; Bhathena et al., 1989a). The abnormalities of lipid metabolism also accompany various complications of diabetes, namely retinopathy, nephropathy, peripheral neuropathy, coronary arterial disease, microangiopathy, lipodystrophy, and ketoacidosis (Vannini et al., 1984; Appel et al., 1985; Winocour et al., 1987; Stacpoole et al., 1988; Vandongen et al., 1988). The vascular complications of diabetes may be in part due to increased lipoperoxidation of LDL in erythrocytes and other cell membranes (Rabini et al., 1994).

This chapter covers only the alterations in plasma and tissue fatty acid composition, the role of dietary fatty acids in different types of diabetes and its complications, the metabolism and hormonal regulation of fatty acids in diabetes, and how the control of diabetes by diet and exercise, oral hypoglycemic and hypolipidemic agents, and insulin affects fatty acid metabolism. Though earlier studies will be referred to, this chapter concentrates more on the studies carried out in the past 10 years. Only a few references are cited; several more could have been easily added.

II. FATTY ACID COMPOSITION OF TISSUE LIPIDS

Dietary fatty acids have been shown to influence the fatty acid composition of lipids in plasma and tissues in normal as well as in pathological conditions such as diabetes (Horrobin, 1989; Popp-Snijders and Blonk, 1995; Berry, 1997). The trend in past 40–50 years indicate increased consumption of saturated fats, *trans* fatty acids (TFA), vegetable oils rich in linoleic acid and decreased consumption of long-chain PUFA (arachidonic acid, AA; eicosapentaenoic acid, EPA; and docosahexaenoic acid, DHA) leading to increased incidence of NIDDM and related disorders (Simopoulos, 1994).

The fatty acid composition of cholesterol esters appear to be related to the risk of development diabetes. The risk is increased when cholesterol esters are rich in saturated fatty acid, palmitoleic acid, γ-linolenic acid (GLA), and dihomo-γ-linolenic acid (DHLA), and low in linoleic acid (Vessby et al., 1994). The prevalence of diabetes may also be correlated with the dietary ratio of ω6–ω3 fatty acids (Berry, 1997). Besides diet, genetic factors may also play a role in altering fatty acid composition of cholesterol esters (Vessby et al., 1994). Feeding very long-chain fatty acids (C24–C34) increases these fatty acids in phosphatidyl choline but not in other phospholipids of some organs such as rod of outer segments in normal as well as diabetic rats (Suh et al., 1994).

In untreated and poorly controlled diabetic subjects, desaturases involved in the metabolism of fatty acids are decreased (see below) and 18-carbon fatty acids with a low number of double bonds predominate both in plasma and in tissues. Thus, even though the composition of fatty acids in plasma reflects that in the diet, metabolites may be different. Mikhailidis et al. (1986) fed DHLA to controls and IDDM subjects. In controls there was an increase in DHLA as well as its metabolite AA in erythrocyte lipids, but in IDDM subjects there was no proportionate increase in AA in erythrocyte lipids, indicating a possible defect in Δ5 desaturase. Similarly, conversion of DHLA to prostaglandin E_1 (PGE_1) was also inhibited in IDDM subjects but not in controls (Mikhailidis et al., 1986). Decreased AA in plasma and 6-keto-$PGF_{1\alpha}$ in urine have been reported in IDDM (Pottathil et al., 1985). Bassi et al. (1996) reported decrease in plasma phospholipid ω6 fatty acids in IDDM subjects with mild ketosis, which was primarily due to decrease in AA. There was also an increase in 20:4 to 20:3 ratio indicating decreased Δ5 desaturase activity during mild ketosis. Fatty acids in platelets from control nondiabetic subjects showed a significant inverse correlation between linoleic acid and AA. No such relationship was observed in IDDM and NIDDM subjects, indicating that both Δ5 and Δ6 desaturases are impaired in the diabetic state (Jones et al., 1986). Diabetic children in good control showed a direct correlation between apo A-I and PUFAs and the ratio of PUFA/saturated fatty acids in TGs, while APO A-II correlated with the ratio of DHLA and AA (Ewald et al., 1982).

Some differences have been observed in the fatty acid compositions of plasma lipids between IDDM and NIDDM subjects (Seigneur et al., 1994). A decrease in EPA was observed in the livers of diabetic subjects (Singer et al., 1980) but, in another study, EPA in liver TGs was high (greater than 30%) in diabetic subjects without hyperlipoproteinemia (Singer et al., 1984). In another study, no significant differences were observed in plasma concentrations of AA, EPA, DHA or the saturated fatty acids (palmitic and stearic) between normal and poorly controlled diabetic Melanesian subjects (Rao and Erasmus, 1996). In red blood cells of IDDM (van Doormaal et al., 1984) as well as NIDDM (Prisco et al., 1989a) subjects, phospholipids have significantly higher saturated fatty acids and decreased PUFA. A similar fatty acid profile was observed in plasma of IDDM subjects (van Doormaal et al., 1984; Juhan-Vague et al., 1986), which was normalized when diabetes was improved by insulin infusion (van Doormaal et al., 1984). However, in another study insulin treatment had no significant effect on the fatty acid composition of erythrocyte membrane phospholipids (Persson et al., 1996). In NIDDM subjects with hyperlipidemia, there is an increase in saturated fatty acid and monounsaturated fatty acid (MUFA) in plasma lipids and a decrease in ω6 PUFA metabolites and C_{20}–C_{22} PUFA (Bohov et al., 1997). Diabetic subjects with macroangiopathy had significantly lower EPA and DHA acid but higher AA in platelet phospholipids than diabetic subjects without macroangiopathy and control subjects (Morita et al., 1983; Prisco et al., 1989b). Increased AA has also been observed in LDL and in erythrocyte membrane phospholipids of diabetic subjects

compared to controls (Rabini et al., 1994). Similarly, in patients with diabetic nephropathy, levels of DHLA, α-linolenic acid (ALA) and DHA are low in plasma phospholipids compared to control subjects (Das, 1995). Alteration in fatty acid composition is also observed in milk of diabetic mothers, especially lower levels of long-chain PUFA (Jackson et al., 1994), indicating altered metabolism in the mammary gland (Bitman et al., 1989).

Since hyperlipidemia and other abnormalities of lipid and lipoprotein metabolism associated with coronary artery disease are usually present in diabetic subjects, especially obese NIDDM, they are prudently recommended to consume diets low in total fat and saturated fatty acids and high in PUFA (Mann et al., 1976; American Heart Association, 1986; American Diabetes Association, 1987; Kissebah and Schectman, 1988; Margolis and Dobs, 1989; Clandinin et al., 1993). It is therefore not surprising to find higher levels of linoleic acid, GLA, and AA as well as EPA and DHA and lower levels of saturated fatty acids in plasma and tissues of well-controlled diabetic subjects (Ewald et al., 1982; O'Dea and Sinclair, 1985; Mann, 1986). Increased levels of EPA have been observed in plasma (Glauber et al., 1988; Landgraf-Leurs et al., 1990), red blood cells (Glauber et al., 1988), erythrocyte membranes (Kamada et al., 1986), platelets (Tilvis et al., 1987; Landgraf-Leurs et al., 1990), and pancreatic B cells (Lardinois, 1987) in diabetic subjects given a daily supplement of fish oils. Since fatty acids from the ω-3 family compete with those from the ω-6 family (Holman, 1986), feeding fish oil decreases linoleic acid and AA from tissue lipids, especially phospholipids (Dang et al., 1989; Landgraf-Leurs et al., 1990).

As stated earlier, atherosclerosis is a common abnormality of diabetes. Thickness of carotid intima-media is one of the predictor of atherosclerosis. In a population-based study, Ma et al. (1997) observed positive correlation between saturated fatty acid and MUFA composition of plasma phospholipids and cholesterol esters and carotid artery intima-media thickness. There was a negative correlation for PUFA and carotid artery intima-media thickness. This study further indicates the benefit of reducing dietary intake of saturated fatty acids to reduce the incidence of cardiovascular complications in diabetic subjects. The importance of MUFA in addition to ω3 fatty acids in reducing cardiovascular risk in Asian Indian diabetic subjects has been stressed (Peterson et al., 1994).

In animal models of diabetes, a somewhat different picture is observed. Most of the data on the fatty acid composition of various tissues in the diabetic state have come from animal studies. Significant changes in fatty acid composition of lipids, especially phospholipids, have been observed in many but not all tissues. In streptozotocin diabetic rats, the incorporation of palmitate, oleate, and linolenate into erythrocyte membrane phospholipids is reduced but arachidonate incorporation is not affected (Arduini et al., 1995). This is partially reversed by the treatment with propionyl-L-carnitine treatment (Arduini et al., 1995). In alloxan diabetic sheep (Henderson et al., 1982) and streptozotocin diabetic rat (Takahashi et al., 1987), there is a decrease in saturated fatty acids and an increase in PUFA in liver TGs, which are the major lipids. TG levels are also elevated in the hearts of diabetic animals (Denton and Randle, 1967; Murthy and Shipp, 1977; Paulson and Crass, 1982; Murthy et al., 1983), and the level of linoleic acid is increased (Gudbjarnason et al., 1987). Increased levels of TGs in the hearts of diabetic animals are due to both stimulation of esterification (synthesis) (Murthy and Shipp, 1977; Paulson and Crass, 1982) and an inhibition of lipolysis (Paulson and Crass, 1982; Murthy et al., 1983). In phospholipids, however, there is a significant decrease in PUFA in diabetic animals (Henderson et al., 1982; Takahashi et al., 1987), indicating a shift in PUFA from phospholipids to TGs. Similar decreases in AA and other PUFAs have been observed in whole liver (Holman et al., 1983) and in mitochondrial and microsomal lipids from diabetic rats (Labonia and Stoppani, 1988; Burke and Fenton, 1989; Dang et al., 1989). There was however, an increase in DHA in mitochondrial and microsomal membranes (Labonia and Stoppani, 1988; Burke and Fenton, 1989). Modulation of adipose tissue fatty acid by dietary fatty acids has been reviewed by Clandinin et al. (1993). Lipid changes in the heart in diabetes have been reviewed by Dhalla et al. (1992). Decreases in PUFA, especially AA, are also observed in adipocytes and from streptozotocin diabetic rat (Field et al., 1988, 1989, 1990; Clandinin et al., 1993) and in heart muscle of alloxan (Gudbjarnason et al., 1987) as well as streptozotocin (Holman et al., 1983) diabetic rat compared

to controls. The levels were normalized when the diabetic rats were fed diets with high PUFA/saturated fatty acid ratios (Field et al., 1988, 1990).

Dietary fatty acids produced no significant change in brush border membrane phospholipids (Keelan et al., 1987) or cholesterol esters in controls as well as the streptozotocin diabetic rats. Lack of alteration in lipid composition by dietary fatty acids in intestinal brush border membrane as opposed to a significant effect in liver and adipose tissue may be due to the fact that both the liver and adipose tissue are actively involved in lipid metabolism as opposed to the intestine. Also, unlike liver and adipose tissue, the intestine is not insulin sensitive (Shiau and Holtzapple, 1980) and therefore is less likely to show metabolic responses to dietary fatty acids. Abnormalities of PUFA metabolism were also observed in T cells (Singh et al., 1988), glomeruli (Kanzaki et al., 1987), testes (Wilder and Coniglio, 1984), and diaphragm and renal cortex (Chorvathova and Ondreicka, 1983) of streptozotocin diabetic rats. In the streptozotocin diabetic rat, dietary fatty acids did not alter AA content in plasma phospholipids, but in aortic phospholipids there was a significant decrease in AA, which was increased by feeding diets high in ω-6 fatty acids (Takahashi et al., 1988). In genetically diabetic *db/db* mice, decreases in AA in phospholipids in the pancreas and in TGs in the liver have been observed and were normalized by dietary essential fatty acids (EFAs) (Cunnane et al., 1985).

Thus, most tissues show a decreased level of AA in phospholipids in streptozotocin-treated animals, even when they are fed diets high in linoleic acid and GLA such as soybean oil and evening primrose oil, clearly indicating a defect in Δ5 and Δ6 desaturases. Streptozotocin produces hypoinsulinemia by destroying pancreatic B cells resembling IDDM in humans with absolute insulin deficiency, and insulin is required for normal functioning of desaturases.

III. METABOLIC EFFECTS OF DIETARY FATTY ACIDS IN DIABETES

A. Unsaturated Fatty Acids

There are at least four families of unsaturated fatty acids. However, fatty acids from only two families, ω-6 and ω-3, are considered essential. The two most common EFAs are linoleic acid (18:2ω6) and ALA (18:3ω3). They are required for normal growth and other biological processes and cannot be synthesized in humans owing to the lack of specific desaturases required to insert double bonds at the correct positions. Both acids, linoleic and ALA, as well as oleic acid are involved in cholesterol transport and oxidation. Most of the other biological effects of both of these fatty acids appear to be through their conversion to longer chain, more unsaturated fatty acids, such as GLA and AA from linoleic acid and EPA from ALA. GLA, in fact, is 170 times as active as linoleic acid in lowering cholesterol levels (Horrobin and Manku, 1983). High cholesterol-lowering activity has also been reported for AA (Kingsbury et al., 1961). These fatty acids are precursors for leukotrienes (LTs) and prostanoids that are biologically active. In addition, AA is a major component of cellular membrane structure, and the nature and unsaturation of the membranes determine the biological function (see below). The importance of EFA in human and animal nutrition has been reviewed by Sinclair (1984). It has been shown that dietary PUFA also regulate transcription of genes thereby influencing the metabolic directions of fuels (Clarke et al., 1997). Though precise mechanism of how PUFA regulate gene transcription is not known, it may be via modulation of transcription factor peroxisome proliferator-activated receptor (PPAR) action.

In diabetes, in general there is increased concentration of saturated fatty acid and MUFA and decreases in PUFA (see above). EFAs of both families have been shown to have several beneficial effects in normal and diabetic subjects. Complications of diabetes, namely, retinopathy, nephropathy, and peripheral neuropathy, may occur in chronic EFA deficiency (Sinclair, 1984). However, some deleterious effects of EFA have also been observed. Dietary fish oils contain proportionately higher concentrations of EPA and DHA. Their role in diabetes will be discussed separately.

B. ω-6 Fatty Acids

Most studies in human diabetic subjects used vegetable oils rich in linoleic acid. Few studies have used dietary AA and evening primrose oil that contain appreciable amounts of GLA as well as linoleic acid. In IDDM and NIDDM the beneficial effects include decreased cholesterol and TG levels especially with high doses of GLA (Chaintreuil et al., 1984); reversal of abnormalities in lipid metabolism caused by very low-fat diet (Piper et al., 1986); improved platelet function (Monnier et al., 1983), possibly by increased prostanoid and LT synthesis and secretion; enhanced erythropoiesis and decreased glycosylated hemoglobin levels (van Doormaal et al., 1988); and increased bleeding time (O'Dea and Sinclair, 1985), thereby reducing the risk of coronary artery disease. In addition, linoleic acid has been shown to have a protective effect in diabetic retinopathy (Houtsmuller et al., 1980; Howard-Williams et al., 1985), and GLA has beneficial effect in the prevention and treatment of diabetic polyneuropathy (Jamal and Carmichael, 1990; Keen et al., 1993). The beneficial effect of GLA on neurophysiological parameters in diabetic subjects has been reviewed by Horrobin (1997). Similarly, increased linoleic acid in LDL- and HDL-cholesterol in NIDDM subjects appear to protect against the oxidation of LDL (Dimitriadis et al., 1996). An epidemiological study in Australian aborigines also reported a beneficial effect of diets low in fat but high in PUFA in preventing the development of diabetes and cardiovascular diseases (Naughton et al., 1986). Diabetic subjects also showed a greater insulin response to PUFA compared to saturated fat.

Yam et al. (1996) reported increased incidence of NIDDM, cardiovascular diseases, hypertension, and obesity with hyperinsulinemia and insulin resistance as the underlying causes in Israeli population, which has the highest consumption of PUFA to saturated fatty acid ratio in the world. Thus, instead of being beneficial, high consumption of PUFA may have serious long-term effects. In animal studies, high PUFA intake has been shown to increase incidence of variety of tumors. Higher concentrations of long-chain PUFAs, especially C_{20}–C_{22} in muscle membrane phospholipids are shown to reduce insulin resistance, while linoleic acid appears to increase insulin resistance (Simopoulos, 1994).

Most of the studies in animals have been carried out in streptozotocin diabetic rats. Beneficial effects of PUFA have been observed after both short- and long-term feeding (Keelan et al., 1989). Diabetic rats fed PUFA had lower plasma and urinary glucose (Rajotte et al., 1988), lower glycosylated hemoglobin (Rajotte et al., 1988; Keelan et al., 1989), lower relative decline in glucose after intravenous glucose load, lower cholesterol and TG levels, and near-normal microsomal glucose-6-phosphatase activity (Keelan et al., 1989). However, in another study no improvement was seen during oral and intravenous glucose tolerance tests (Rajotte et al., 1988). In diabetes there is an increase in passive transport of both glucose and lipids. Saturated fatty acids further increase passive transport of lipids (Thomson et al., 1988). PUFAs decrease the enhanced glucose (Thomson et al., 1987a,b) and galactose (Thomson et al., 1987a) transport, possibly by increasing intestinal brush border membrane alkaline phosphatase activity (Thomson et al., 1987b), and also by enhancing lipid transport (Thomson et al., 1988). Others have not observed the beneficial effect of PUFAs on intestinal glucose uptake (Keelan et al., 1989).

As seen in human diabetic subjects, EFAS, especially GLA, improves nerve conductance in streptozotocin diabetic rats and improves symptoms of diabetic polyneuropathy (Julu, 1988; Tomlinson et al., 1989; Cameron and Cotter, 1994; Dines et al., 1995). Ascorbyl GLA appears to be more effective in improving neurovascular defect in diabetic rats than GLA, ascorbate or the combination of the two (Cameron and Cotter, 1996a). Similar synergistic effect was observed when GLA was given in combination with antioxidant (Cameron and Cotter, 1996b) or the aldose reductase inhibitors (Cameron et al., 1996; Cameron and Cotter, 1997). The beneficial effect of GLA may be in part due to increased prostacyclin production. A beneficial effect of AA on diabetes-related embryopathy has also been reported (Pinter et al., 1988). Reece et al. (1996) reported *in vivo* decreased incidence of neural tube defect in diabetic rats fed safflower oil. The effect was attributed to the conversion of linoleic acid to AA. In human skin fibroblast cultured in the presence of lipoprotein-deficient

serum, linoleic acid and AA increased carbohydrate oxidation as measured by increased pyruvate dehydrogenase activity (Loriette et al., 1987).

Dietary PUFA has been reported to increase glucose utilization (Awad, 1981; Field et al., 1990) along with increased insulin binding (Field et al., 1988) and improved insulin sensitivity (Field et al., 1990). Others, however, have reported increased insulin resistance in liver and muscle in diabetic rats fed linoleic acid and saturated fatty acids (Storlien et al., 1987). In obese as well as insulin-treated diabetic rats, PUFA from corn oil appears to suppress lipogenic enzyme gene expression stimulated by insulin (Iritani et al., 1995; Iritani and Fukuda, 1995). PUFAs compared to saturated fat, decreases insulin binding, autophosphorylation of the receptor and the kinase activity in liver, which are partially reversed by pioglitazone (Iritani and Fukuda, 1995). In streptozotocin diabetes, T-cell-dependent immune function is decreased. Although dietary linoleic acid did not improve the T-cell function, diets low in linoleic acid further decreased the immune function (Singh et al., 1988). In diabetic mice, dietary linoleic acid increases the incorporation of AA in phospholipids of the pancreas and liver (Cunnane et al., 1985).

Several studies in animal models of diabetes have reported detrimental effects of EFA and beneficial effects of feeding EFA-deficient diets. Thus, in diabetes prone BB rats, feeding an EFA-deficient diet, which lowers the concentrations of AA, decreased the incidence of spontaneous diabetes (Lefkowith et al., 1990). It is possible that AA or its eicosanoid metabolites may be responsible for the inflammatory injury in this model of autoimmune diabetes (Lefkowith et al., 1990), which resembles human IDDM. In this regard, it is interesting to note that injection of arachidonate in BB rats increased the concentrations of thromboxane B_2 (TXB_2) and trioxilin A_3 and decreased 6-keto-$PGF_{1\alpha}$ (Pace-Asciak et al., 1988). This increased ratio of TXB_2 to 6-keto-$PGF_{1\alpha}$ is in line with the prothrombotic nature of platelets associated with diabetes (Pace-Asciak et al., 1988). Similarly, in nonobese diabetic mice, EFA deficiency decreases the incidence of diabetes and has the protective effect on autoimmunity (Benhamou et al., 1995). There is an increase in splenocyte interleukin-4 production and a reduction in interferon-γ production, while in macrophages there is an increase in tumor necrosis factor-α (TNF-α) and interleukin-1 and a reduction of PGE_2 indicating altered eicosanoid metabolism (Benhamou et al., 1995). The beneficial effect of EFA deficiency was also observed in low-dose streptozotocin-treated diabetic mice, possibly by decreasing the lipid mediators of autoimmunity such as prostaglandin and LTs (Wright et al., 1988). The destruction of pancreatic B cells was also low in EFA-deficient mice (Wright et al., 1988; Fraser et al., 1997). EFA deficiency also prevents diabetes in low-dose streptozotocin mice treated with cyclosporin A (Wright et al., 1995), the later is known to increase the severity of diabetes in streptozotocin-treated mice. Also streptozotocin- and alloxan-treated diabetic rats were less EFA deficient than control rats when fed diets deficient in EFA (Riisom et al., 1981). The levels of AA in liver and heart phospholipids were higher in diabetic rats than in controls fed an EFA-deficient diet (Riisom et al., 1981). The reason for this is not clear. It could be that the concentration of AA in phospholipids is well preserved in diabetes or that a specific phospholipase (phospholipase A_2) may be less active. It is also possible that processes of desaturation and elongation of fatty acids are less affected in diabetes. The latter possibility is less attractive because desaturases have been shown to be decreased in diabetes.

C. ω-3 Fatty Acids and Fish Oils

In diabetic subjects, dietary supplementation of long-chain PUFAs present in fish oils has been studied more extensively than that of other fatty acids. The two predominant PUFAs in fish oils are EPA and DHA. In nondiabetic but hyperlipidemic subjects, fish oil feeding has been shown to have more beneficial effects, especially in reducing the risk of heart disease, and few deleterious effects, as reviewed by Mueller and Talbert (1988), Gibson (1988), Margolis and Dobs (1989), Harris (1989), Nestel (1990), Flaten et al. (1990), and Kinsella et al. (1990). In a prospective study with Physicians, moderate consumption of fish had no effect on lowering the risk of cardiovascular disease (Morris et al., 1995). In diabetic subjects, however, supplementation with fish oils has not produced beneficial

TABLE 47.1
General Effects of Dietary Fish Oils in Normal and Diabetic Subjects

Reduce risk of heart disease
Lower TGs and lipoproteins
Increase HDL-cholesterol (HDL_2 and HDL_3)
Reduce thrombogenicity of platelets in microcirculation
Reduce platelet aggregation
Decrease incidence of NIDDM
Increase insulin secretion and insulin sensitivity
Prevent insulin resistance caused by high fat and saturated fat diets
Improve fluidity of cell membranes in IDDM but not NIDDM subjects
Decrease blood pressure in hypertensive individuals
Decrease as well as increase plasma or blood viscosity
Increase total and LDL-cholesterol
Increase fasting and postprandial blood glucose
Increase hepatic glucose output
Impair insulin secretion (in diabetic patients)
Increase nonenzymatic glycosylation
Altered eicosanoid production
Increase bleeding time
Impair red cell deformity
Decrease vitamin E absorption
Increase caloric intake and hence weight gain
Cause stomach and intestinal irritation

effects to the extent seen in nondiabetic subjects. The role of dietary fish oils in diabetic subjects has been reviewed by Axelrod (1989), Sorisky and Robbins (1989), and Vessby (1989). Fish oil concentrate K-85, containing 92% of total fatty acids as ω3 fatty acids has been shown to lower serum TG and VLDL in nondiabetic hypertriglyceridemic subjects (Mackness et al., 1994). Its effect in diabetic subjects however, needs to be explored. ω3 Fatty acids also have antihypertensive effects (Knapp, 1996). The known metabolic and biological effects of fish oils in nondiabetic and diabetic subjects are summarized in Table 47.1.

In diabetic subjects, the most consistent beneficial effect of dietary fish oils is the lowering of plasma TG levels (Popp-Snijders et al., 1986, 1987; Schectman et al., 1988, 1989; Borkman et al., 1989; Mori et al., 1989; Rillaerts et al., 1989; Schmidt et al., 1989; Stacpoole et al., 1989; Bagdade et al., 1990; Landgraf-Leurs et al., 1990; Rivellese et al., 1996; Sirtori et al., 1997), though in one study no significant lowering of TG was observed in NIDDM (Kasim et al., 1988). Singer et al. (1984) observed a negative correlation between TG and EPA in the liver of diabetic subjects. In most studies (Haines et al., 1986; Schectman et al., 1988; Vandongen et al., 1988; Mori et al., 1989; Stacpoole et al., 1989) but not all (Borkman et al., 1989; Rillaerts et al., 1989), total cholesterol and LDL-cholesterol were increased. However, this deleterious effect was negated by increases in HDL-cholesterol (especially in HDL_2 and HDL_3 subfractions) (Vandongen et al., 1988; Mori et al., 1989; Rillaerts et al., 1989; Schectman et al., 1989; Schmidt et al., 1989; Bagdade et al., 1990). There was also a lowering of the cholesterol/phospholipid ratio (Kamada et al., 1986) and the cholesterol/HDL-cholesterol ratio (Rillaerts et al., 1989; Schmidt et al., 1989), which is a measure of atherogenic index. Decrease in plasma VLDL TG and FFA and increase in long-chain ω3 fatty acids in erythrocyte phospholipids have been observed after 6 months of feeding fish oil to NIDDM subjects (Rivellese et al., 1996) but had no significant effect on blood glucose control in these subjects. Fish oil increases lipoprotein lipase (LPL) activity in NIDDM (Kasim et al., 1988) but has no effect in IDDM (Bagdade et al., 1990). In a study comparing ω3 fatty acids from fish oil (EPA + DHA) with that from linseed oil (linolenic acid), fish oil decreased plasma TGs in NIDDM subjects but

linseed oil was without effect (Goh et al., 1997) indicating that preformed long-chain ω3 fatty acids are more effective in lowering lipid levels in diabetic subjects than linolenic acid. ω3 Fatty acids are also more readily incorporated in brain and other tissues as compared to those from vegetable oils. Recognizing the need for preformed long-chain PUFA for brain development and function, infant milk formulas are now being supplemented with fish oil (Clandinin et al., 1992; Carlson, 1994). This has led to improved brain and visual function in infants (Makrides et al., 1994; Uauy et al., 1994). The beneficial effects of fish oil on lipid metabolism in NIDDM subjects are potentiated by high-fiber intake (Sheehan et al., 1997).

Dietary fish oils have several deleterious effects on carbohydrate metabolism in diabetic subjects. There is an increase in fasting and postprandial glucose (Glauber et al., 1988; Kasim et al., 1988; Schectman et al., 1988; Borkman et al., 1989; Friday et al., 1989; Vessby, 1989), increased levels of glycosylated hemoglobin (Schectman et al., 1988), increased hepatic glucose output (Glauber et al., 1988), but unaltered glucose disposal (Glauber et al., 1988; Friday et al., 1989) and thus worsened glycemic control. However, in a multicenter study, ethyl ester of ω3 fatty acid did not worsen the glycemic control (Sirtori et al., 1997). In another study, fish oil improved glucose homeostasis in some but not all subjects (Zak et al., 1996). Short-term feeding of fish oil was shown to increase gluconeogenesis from glycerol but not the overall glucose production or the glycemic control (Puhakainen et al., 1995). Owing to the increase in gluconeogenesis from glycerol, long-term feeding of fish oil is anticipated to deteriorate glucose control. Insulin secretion is also impaired by fish oil feeding (Glauber et al., 1988; Lardinois et al., 1988), but plasma insulin levels are generally not altered (Borkman et al., 1989; Friday et al., 1989). In some diabetic subjects, fish oil feeding also increases the daily insulin requirement for metabolic control (Stacpoole et al., 1989). Dietary fish oil, however, prevents insulin resistance caused by a high-fat diet or by saturated fat (Storlien et al., 1987; Borkman et al., 1989) and improves insulin sensitivity (Popp-Snijders et al., 1987; Vessby, 1989). Beneficial effects of dietary ω-3 fatty acids have been observed in a diabetic subject with acanthosis nigricans and lipodystrophy (Sherertz, 1988); however, this needs to be confirmed. ω3 Fatty acids also increased fluidity of erythrocyte membranes in IDDM (Kamada et al., 1986; Tilvis et al., 1987), but no change was seen in NIDDM subjects (Popp-Snijders et al., 1987; Rabini et al., 1993). Dietary fish oil affects several hormones besides insulin. Thus, fish oil feeding decreased glucagon and somatomedin-C (Bhathena et al., 1991) and β-endorphin (Bhathena et al., 1993).

In diabetic subjects there is a decrease in thromboxane but normal prostacyclin production (Tilvis et al., 1987), and increased platelet aggregation (Landgraf-Leurs et al., 1990). ω-3 Fatty acids further lower thromboxane production *in vitro* in platelets stimulated with collagen or adenosine diphosphate (Haines et al., 1986; Tilvis et al., 1987; Landgraf-Leurs et al., 1990), but thromboxane production from exogenous AA is increased (Tilvis et al., 1987). Fish oil feeding either decreased platelet aggregation (Landgraf-Leurs et al., 1990) or prolonged the lag phase before aggregation (Haines et al., 1986). Harris et al. (1997) reported that antiatherogenic effect of fish oil may also be in part due to enhance arterial nitric oxide (NO) production, which has vasodilatory effects. Other beneficial effects of dietary ω-3 fatty acids in diabetic subjects include decreased blood viscosity (Rillaerts et al., 1989), lowering of blood pressure (Kasim et al., 1988), and increased neutrophil but not monocyte chemotaxis (Schmidt et al., 1989). The formation of eicosanoids and their effects in diabetes are discussed later in this chapter.

ω-3 Fatty acids in fish oils are highly unsaturated and are easily oxidized. Vitamin E decreases this peroxidation, and hence in some diabetic subjects, especially children, high intake of fish oil causes vitamin E deficiency, which may lead to neurological disturbance when severe malabsorption problems exist (Margolis and Dobs, 1989). The apparent differences in the observed fish oil effects in different studies are partly due to different doses of fish oil concentrate as well as the length of feeding.

Very few studies on the effects of dietary fish oils have been carried out with animal models of diabetes. In diabetes-prone BHE rats fed fish oil, thyroxine increased fatty acid synthesis in liver and adipose tissue (Pan and Berdanier, 1990). In low-dose streptozotocin-treated mice, fish oil decreased elevated blood glucose and improved immune function (Linn et al., 1989) but increased the development of retinopathy (Hammes et al., 1996). In streptozotocin-treated rats, ω-3 fatty acids had no

effect on glucose, TG, or cholesterol levels, but the development of cardiomyopathy was partially blocked, possibly by improving Ca^{2+} transport activity in cardiac sarcoplasmic reticulum (Black et al., 1989). However, in diet induced, insulin resistant mildly diabetic rats, fish oil did reduce plasma TG and cholesterol and corrected hyperinsulinemia (Luo et al., 1996). Infusion of perilla oil rich in ALA compared to soybean oil in streptozotocin-treated diabetic rats increased the proportion of EPA and decrease AA in serum and liver phospholipids accompanied by a decrease in TXA_2 production (Ikeda et al., 1995). These changes were independent of plasma insulin levels. In hepatic microsomes, ω-3 fatty acids decreased the incorporation of AA acid in phospholipids and also decreased Δ5 desaturase activity. There was a corresponding increase in DHA in hepatic microsomes (Dang et al., 1989), indicating a competition between ω-3 and ω-6 fatty acids. ω3 Fatty acids also increase cholesterol to phospholipid ratio in liver microsomal membranes of normal as well as experimental diabetic rats (Igal and de Gomez Dumm, 1997). In β-TC3 insulinoma cell line, EPA-potentiated glucose-stimulated insulin secretion without affecting glucose metabolism (Konard et al., 1996).

From human studies, it is thus clear that in diabetic subjects ω-3 fatty acids appear to have some beneficial effects on lipid metabolism and may decrease the severity of cardiac disorder and lower the incidence of coronary artery disease. However, ω-3 fatty acids have detrimental effects on carbohydrate metabolism and worsen glycemic control even though insulin sensitivity is improved. Also, the beneficial effects on lipid metabolism cannot be sustained by prolonged fish oil treatment and are reversed when fish oil feeding is stopped. Thus, on the basis of the present knowledge, it is not prudent to supplement high doses of ω-3 fatty acids for a prolonged time to diabetic subjects. The beneficial effect of lowering hypertriglyceridemia in diabetic subjects can be achieved by substituting starch for simple sugars in the diet. The consumption of fish is more beneficial than fish oil for diabetic individuals. The reasons for this are beyond the scope of this chapter.

D. Saturated Fatty Acids

Several studies have shown that saturated fat intake is a risk factor for hyperinsulinemia. Folsom et al. (1996) observed a positive correction between saturated fatty acid percentage in plasma phospholipids and insulin levels. Rasmussen et al. (1996) compared the effect of butter and olive oil in NIDDM subjects and showed that saturated fat increase insulin response more than MUFAs.

Saturated fatty acid (palmitate) also increases glucose-induced insulin release but not basal release, which is reversed by epinephrine. Palmitate appears to act via increasing calcium flux and the mobilization of intracellular calcium (Warnotte et al., 1994). Though saturated fatty acids stimulate glucose transport in isolated rat adipocytes acutely, prolonged treatment induces insulin resistance via postreceptor defect (Hunnicutt et al., 1994). The stimulation of glucose transport by saturated fatty acids in adipocytes is via stimulation of insulin receptor autophosphorylation (Hardy et al., 1991).

E. *Trans* Fatty Acids

The average estimated consumption of TFA in the United States is 6%–8% of total daily intake (Senti, 1988). Most of it comes from margarines and other hydrogenated oils used for frying (Enig et al., 1990), from milk (Parodi, 1976), and in small quantities from some green vegetables. In humans and animals, dietary TFAs are readily and reversibly incorporated into plasma and tissue lipids, especially TGs, and to a small extent in phospholipids (Moore et al., 1980; Vidgren et al., 1998). TFAs have also been found in human milk after feeding diets high in TFA (Aitchison et al., 1977). In phospholipids TFAs are normally incorporated in position 1, where saturated fatty acids are also preferentially incorporated. Mitochondrial enzymes can metabolize TFAs via 2-*trans*-enoyl CoA or 3-*trans*-enoyl CoA depending on the position of the double bond (Schettler, 1986).

The biological effects of TFAs are not fully understood. Compared to oleic acid, TFAs have been shown to elevate serum TG (Anderson et al., 1961; Mensink and Katan, 1990), total cholesterol (Vergroesen, 1972; French et al., 2002), and LDL-cholesterol (Laine et al., 1982; Mensink

and Katan, 1990), and to lower HDL-cholesterol (Mensink and Katan, 1990). Mattson et al. (1975), however, did not observe the elevation in cholesterol or TG. The TFAs also elevate apo B and lower apo A-I compared to oleic acid (Mensink and Katan, 1990). Thus, the effects of TFAs on lipid and lipoprotein metabolism are worse than those of saturated fatty acids (Mensink and Katan, 1990). The TFAs of the ω-9 family (18:1ω9) inhibit Δ6 desaturase involved in the conversion of linoleic acid to GLA in the liver and heart but have no effect on Δ5 desaturase in the ω-6 family. They also decrease Δ9 desaturase (Hill et al., 1982). In monkeys, Barnard et al. (1990) reported that, unlike *cis* isomers, TFAs had no effect on erythrocyte membrane fluidity but affected insulin receptors by decreasing the number and increasing the affinity, an effect similar to that observed with saturated fatty acids (Ginsberg et al., 1979; Gould et al., 1982; Berlin et al., 1989). In brain TFAs are less potent in inhibiting binding of opiates to their receptors and in decreasing membrane viscosity compared to corresponding *cis* fatty acids (Remmers et al., 1990). They also alter the concentration of dopaminergic neurotransmitters in brain (Acar et al., 2003).

It is important to note that these studies were carried out in normal humans and animals. No studies on the effects of TFA in diabetic subjects have been reported. Since in most studies, TFAs have been shown to be as atherogenic as saturated fatty acids (and certainly more than unsaturated fatty acids) and also to lower insulin receptor number, it is possible that, compared to unsaturated fatty acids, TFAs will have deleterious effects in diabetic subjects. It is therefore advisable for diabetic individuals to restrict their intake of fats containing TFAs. Studies on the effects of TFAs on lipid profile, glucose homeostasis, and insulin and other hormones in diabetic subjects are long overdue.

F. Free Fatty Acids

One of the complications of lipid metabolism in diabetes is the increased lipolysis, which results in the increased plasma concentration of FFAs. Thus, increases in plasma FFAs have been observed in both IDDM and NIDDM subjects with or without ketoacidosis (Liewendahl and Helenius, 1976; Yue et al., 1981; Linfoot et al., 2005). Intra abdominal fat appears to be the precursor for increased lipolysis (Kissebah, 1996). In control subjects as well as in NIDDM subjects elevated levels of FFA inhibits insulin-stimulated glucose uptake in skeletal muscle by suppressing glycolysis and increasing insulin-stimulated glycogen synthesis (Kim et al., 1996) and hence may play a significant role in the pathogenesis of insulin resistance in NIDDM (Reaven and Chen, 1988; Randle et al., 1994; Boden, 1996; Charles et al., 1997). In NIDDM subjects, cigarette smoking further aggravates insulin resistance by increasing plasma FFA and decreasing lipid peroxidation (Targher et al., 1997). Elevated levels of FFA are also observed in the myocytes of diabetic animals (Kenno and Severson, 1985). FFAs can be both oxidized and re-esterified within tissues without oxidation (Felber et al., 1987). Increased availability of FFA increases fat oxidation (Lillioja et al., 1985; Felber et al., 1987). Elks (1990) suggested that increased availability of FFA for oxidation by muscle and other tissues may lead to the impairment of carbohydrate oxidation, thereby leading to the glucose intolerance seen in obese diabetic subjects. However, rate of lipid oxidation by muscle is reduced in NIDDM subjects (Kelley and Simoneau, 1994). Glucose-fatty acid cycle appears to act via inhibition of PDH complex by acetyl CoA and NADH (Wieland, 1983). In diabetes PDH level falls significantly and glucose utilization by inhibiting fatty acid oxidation is much less in diabetic monocytes than that of normal cells (Abdel-aleem et al., 1995). Increased activity of carnitine palmitoyltransferase-I (CPT-I) and carnitine acetyl transferase and decreased activity of PDH complex is also observed in diabetic d*b*/d*b* mice leading to increased oxidation of fatty acid and decreased oxidation of glucose (Makar et al., 1995). Glucose-fatty acid cycle may also operate in patients with insulin resistance and hyperlipidemia (Kumar et al., 1994). FFAs appear to stimulate insulin release (Crespin et al., 1973) and inhibit glucagon release (Madison et al., 1968) from pancreatic islets. However, long-term exposure of islets to high levels of FFA results in beta cell dysfunction and diminishes glucose-induced insulin secretion (Zhou and Grill, 1994; Girard, 1995; Newgard and McGarry, 1995; Hirose et al., 1996).

In pubertal IDDM subjects insulin has no significant effect on plasma FFA (Caprio et al., 1994). Higher concentrations of FFA in blood are associated with morphological changes in the arteries of diabetic rats (Reinila, 1981), which may be due to their high-detergent activity (Shaw, 1985). Elevated FFA in plasma in diabetes and other disorders result in hypercorticoidism and initiates a positive feedback loop between adipocytes and hypothalamic-pituitary-adrenal axis (Widmaier et al., 1995). In the fasting state and in diabetes, high levels of FFA increase platelet aggregation (Gjesdal et al., 1976; Mikhailidis et al., 1981), possibly by inhibiting vascular adenosine diphosphate activity and thereby decreasing the concentration of adenosine, an inhibitor of aggregation and a vasodilator as compared to adenosine diphosphate, which stimulates platelet aggregation (Barradas et al., 1987). Another mechanism may involve inhibition of prostacyclin (PGI_2) synthesis and acceleration of its degradation. Significant decreases in PGI_2 have been observed in the aorta and bladder of streptozotocin diabetic rats (Colwell et al., 1983; Jeremy et al., 1986, 1987). Recently NO has been suggested to play a role in FFA-induced insulin secretion since, islets from prediabetic Zucker fatty diabetic rats, FFA-induced significant rise in NO and reduced insulin secretion (Shimabukuro et al., 1997b).

IV. METABOLISM OF FATTY ACIDS IN DIABETES

The metabolism of fatty acids includes synthesis, desaturation and elongation, oxidation, and formation of eicosanoids. Desaturation and elongation of EFA is necessary for the synthesis of AA, which is generally not obtained from the diet and is required for eicosanoid formation (see below). AA is also a vital component of phospholipids of cellular membranes. Alteration in AA would lead to abnormal membrane formation and result in altered unsaturation and fluidity of the membranes.

A. Desaturation

There are four specific microsomal desaturases that are involved in the desaturation of fatty acids (Sinclair, 1984; Holman, 1986; Axelrod, 1989). Δ9 desaturase is involved only in the ω-9 and ω-7 series and converts palmitic acid to palmitoleic acid and stearic acid to oleic acid. Δ6, Δ5, and Δ4 desaturases are involved in the desaturation of fatty acids of all four families. Though not clearly demonstrated, it is presumed that the same desaturase is involved in the insertion of double bonds in specific positions in fatty acids of different families, that is, that there is only one each of Δ9, Δ6, Δ5, and Δ4 desaturases. Thus, there is interaction and competition between fatty acids of different families for the desaturase. This interaction has been reviewed by Holman (1986). Usually fatty acids with greater unsaturation are preferentially desaturated. Thus, fatty acids of the ω-3 family would be preferentially desaturated compared to other families, and fatty acids of the ω-7 and ω-9 families will be desaturated more only when the availability of EFAs is diminished.

In human diabetic subjects and experimental diabetic animals, the activity of all four desaturases is decreased. Though desaturase activity is present in liver microsomes, the alteration in fatty acid composition in diabetes, especially low levels of AA, in several tissues such as platelets, kidney, heart, testes, and plasma indicate that desaturation possibly occurs in these tissues as well. It is important to note that Δ5 and Δ6 desaturases are not present in human skin (Chapkin et al., 1986). The decrease in all four desaturases explains higher levels of fatty acids with 16- and 18-carbon atoms and lower levels of fatty acids with 20- and 22-carbon atoms in diabetic subjects and experimental diabetic animals (see above) except those fed fish oil, which supplies preformed EPA and DHA.

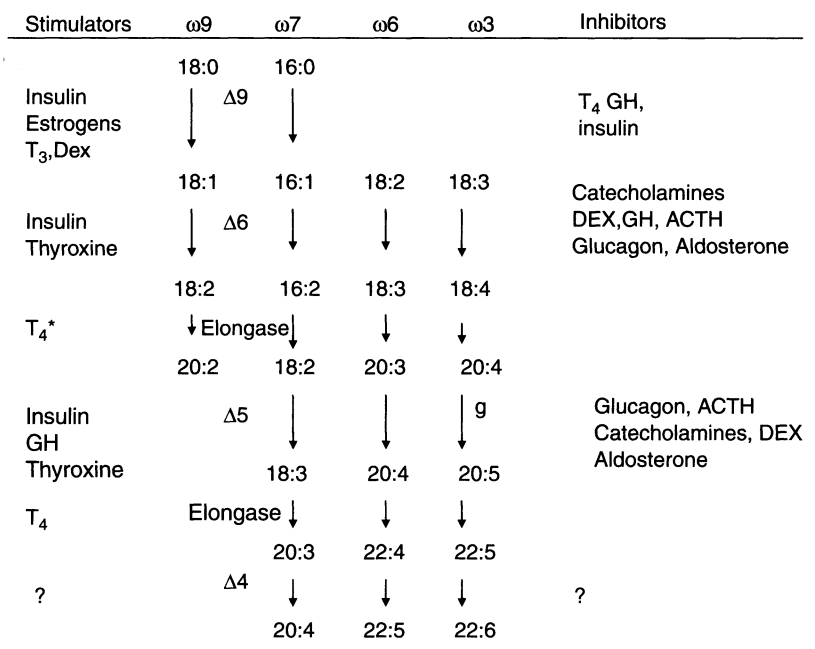
A decrease in Δ9 desaturase has been reported in diabetic rats (Friedmann et al., 1966; Gellhorn and Benjamin, 1966; Mercuri et al., 1974; Eck et al., 1979; Faas and Cater, 1980; Garg et al., 1986; Dang et al., 1988). Since it is not involved in the metabolism of EFA, Δ9 desaturase is of less importance. On the basis of direct *in vitro* studies in liver microsomes as well as on altered fatty acid composition, decreased Δ9 desaturase activity has been observed in liver, platelets, aorta, and plasma (Faas and Carter, 1980; Garg et al., 1986; Dang et al., 1988). Dietary carbohydrates

also modulate the desaturases in the normal as well as the diabetic state (Worcester et al., 1979). Different sugars have quantitatively different effects on Δ9 desaturase in liver and adipose tissue. In liver, dietary fructose stimulates Δ9 more than glucose in normal as well as diabetic rats (Mercuri et al., 1974; Worcester et al., 1979). Prasad and Joshi (1977) reported 20-fold stimulation of hepatic Δ9 desaturase by fructose in diabetic rats. In adipose tissue, fructose produced less stimulation of Δ9 desaturase than glucose (Worcester et al., 1979). Of all the four desaturases, Δ9 desaturase is most affected in diabetes (Gellhorn and Benjamin, 1964; Friedmann et al., 1966; Eck et al., 1979). Studies on the activity of Δ9 desaturase in human diabetic subjects are lacking. It is, however, possible that the decrease in Δ9 desaturase may also occur in diabetic humans especially in poorly controlled IDDM subjects, since insulin plays an important role in desaturation (see below).

A decrease in Δ6 desaturase has been suggested on the basis of fatty acid composition as well as direct measurement of the enzyme in diabetic humans (Tilvis and Miettinen, 1985; Jones et al., 1986; Tilvis et al., 1986; Keen et al., 1993). The enzyme is also decreased in experimental diabetic animals (Friedmann et al., 1966; Eck et al., 1979; Faas and Carter, 1980; Dang et al., 1988; Shin et al., 1995) and is increased after insulin treatment (Shin et al., 1995). It is a rate-limiting enzyme in the conversion of linoleic acid to AA (Marcel et al., 1968). Decreased Δ6 desaturase activity or its fatty acid metabolic products have been shown in several tissues including liver, kidney, aorta, platelets, testes, and plasma (Faas and Carter, 1980; Dang et al., 1988). Erythrocytes appear to be devoid of this enzyme (Shin et al., 1995). Riisom et al. (1981) reported increased Δ6 desaturase activity in liver microsomes of alloxan- and streptozotocin diabetic rats fed EFA-deficient diets compared to control rats fed the same diet. They also observed higher levels of AA in liver and heart phospholipids in diabetic rats than in control rats. It is important to note that in this model, EFA deficiency actually reduced the severity of diabetes and that diabetic rats were less EFA deficient than control rats. Therefore, increased Δ6 desaturase activity is not unexpected. The fatty acid composition in liver and heart, however, did not parallel the activity of desaturase in liver microsomes. It is possible that AA is better preserved in phospholipids or that lipolysis is decreased when diabetes is accompanied by EFA deficiency.

Decreases in Δ5 desaturases in several tissues have also been shown or suggested in diabetic humans (Stone et al., 1979; Tilvis and Miettinen, 1985; Jones et al., 1986; Tilvis et al., 1986; El Boustani et al., 1989; Bassi et al., 1996) and experimental animals (Holman et al., 1983; Wilder and Coniglio, 1984; Dang et al., 1988). Studies on the activity of Δ4 desaturase in humans and animals are lacking. Studies reporting changes in desaturases on the basis of fatty acid composition should be viewed with caution. Besides desaturases, fatty acid concentration in tissue and plasma can be changed because of utilization, oxidation, and membrane lipid degradation and synthesis.

The activity of desaturases, especially Δ6 and Δ5, is modulated by several factors. Two important factors are diet and hormones. Cholesterol feeding has been shown to decrease Δ5 and Δ6 desaturase activity in rats (Huang et al., 1985, 1990; Garg et al., 1986). However, dietary cholesterol stimulates Δ9 desaturase (Garg et al., 1986). This would tend to increase concentration of unsaturated 18-carbon fatty acids including oleic acid. No direct study of dietary cholesterol on desaturases has been carried out in humans, but increased levels of linoleic acid and decreased levels of AA observed in some hypercholesterolemic subjects may indicate a decrease in desaturase activity. Similarly, studies in diabetic animals with cholesterol feeding have not been done. Primrose oil, which is relatively high in GLA, may be beneficial in diabetic subjects because it bypasses the critical step in the formation of AA. TFAs have been reported to decrease desaturase activity (Brenner, 1981; Hill et al., 1982; Holman, 1986). High-fat diets also decrease the activity of Δ9, Δ6, and Δ5 desaturases (Garg et al., 1986). PUFAs increase Δ6 and Δ5 desaturases (Pugh and Kates, 1984; Garg et al., 1986). Both increases (Pugh and Kates, 1984) and decreases (Garg et al., 1986) have been observed in Δ9 desaturase by dietary PUFAs compared to saturated fats. Theoretically, fish oils, which are rich in EPA and DHA, are clearly beneficial for diabetic subjects because they need not be desaturated or elongated. However, high doses of fish oil compete with AA for the formation of eicosanoids. Eicosanoids formed from EPA have effects on platelet function diametrically opposite to those formed from AA (see below) and hence may not be of advantage for diabetic subjects.



* In microsomes but not in mitochondria

FIGURE 47.1 Hormonal control of fatty acid desaturation and elongation. The stimulatory and inhibitory effects of various hormones on different desaturases and elongase are shown. Note that the hormonal control of Δ4 desaturase is not yet defined. *Abbreviations:* T_3, triiodothyronine; T_4, thyroid hormone; Dex, dexamethasone; GH, growth hormone; ACTH, adrenocorticotropic hormone. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

Like lipases, desaturases are also controlled by hormones. There is indirect, as well as, direct evidence that hormones control desaturation of fatty acids. Indirect evidence comes from the alteration of fatty acid composition in diabetic, thyroidectomized, hypophysectomized, and adrenalectomized animals where one or more hormone is lacking. Figure 47.1 summarizes the stimulatory and inhibitory effects of various hormones on desturation and elongation. Insulin plays an important role in fatty acid desaturation. Insulin treatment in humans (Tilvis et al., 1986; El Boustani et al., 1989) as well as experimental diabetic animals (Gellhorn and Benjamin, 1964; Prasad and Joshi, 1977; Eck et al., 1979; Faas and Carter, 1980) stimulates desaturases. Faas and Carter (1980) reported that insulin increased Δ6 desaturase levels, yet AA decreased in the liver, which they suggested could be due to increased utilization in excess of increased synthesis by desaturase. Glucagon and catecholamines, which antagonize the effect of insulin, decrease desaturase activity (de Gomez Dumm et al., 1975, 1976a,b; Brenner, 1981). Thus, decreased insulin and elevated glucagon in diabetic subjects would account for decreased desaturase activity in diabetes. Desaturase activity is also influenced by lipid-lowering agents. Using a ratio of 20:4 to 20:3 as an index of Δ5 desaturase activity, Matsui et al. (1997) showed that bezafibrate increases Δ5 desaturase activity and thereby improving insulin sensitivity.

Insulin has been shown to stimulate as well as inhibit Δ9 desaturase. Estrogens, triiodothyronine and synthetic glucocorticoid, dexamethasone, stimulate Δ9 desaturase (Marra and de Alainz, 1995; Stanton et al., 2001), while thyroid and growth hormones inhibit it (Gueraud and Paris, 1997). In obese women insulin stimulates Δ5 desaturase (Medeiros et al., 1995). Insulin and thyroxine also stimulate Δ5 and Δ6 desaturases while catecholamines, glucagon, aldosterone, adrenocorticotropic hormone (ACTH) and dexamethasone inhibit both desaturases. Thus, decreased insulin and increased glucagon in diabetic subjects would account for decreased desaturase activity in diabetic state. However, Liu et al. (2000) reported increased Δ6 desaturase activity in diabetes.

Testosterone, aldosterone, and corticosterone inhibit Δ6 desaturase in HTC cells (Marra et al., 1988). The hormonal control of Δ4 desaturase is not well defined. Δ4 Desaturase is also involved in the conversion of EPA to DHA in brain (Anderson et al., 1990). However, it is not clear whether any hormone or neuropeptide play a role in its modulation in brain. The TFAs of the ω9 family (18:1ω9) inhibit Δ6 desaturase involved in the conversion of linoleic acid to GLA in the liver and heart but have no effect on Δ5 desaturase in the ω6 family. Others have reported that TFAs also inhibit Δ5 desaturase and can also inhibit cyclooxygenase and lipooxygenase and thereby decrease eicosanoid production. They also decrease Δ9 desaturase (Hill et al., 1982). The effects of TFAs on desaturases in diabetes have not been elucidated.

B. Elongation

Elongation of fatty acids is carried out in the endoplasmic reticulum and in microsomes. Studies on the conversion of 18-carbon fatty acids to 20- and 22-carbon fatty acids have concentrated more on desaturases. Chain elongation is catalyzed by discrete enzymes using CoA derivatives as substrates (Sprecher, 1982). The elongases act much faster than desaturases (Sinclair, 1984). As observed for desaturation, there is also competition for elongation between the families of fatty acids. Thus, GLA is elongated to a greater extent than ALA. Unsaturated fatty acids of the ω-6 family increase elongation while saturated fatty acids decrease elongation of fatty acids of both families (Christiansen et al., 1968). No specific defect has been reported to occur in elongation of fatty acids in diabetes. Thyroxine has been shown to stimulate elongase in liver microsomes but not in mitochondria. The effects of other hormones on elongases have not been reported in normal or diabetic state.

C. Oxidation of Fatty Acids in Diabetes

Fatty acids are normally oxidized in liver mitochondria via β oxidation to acetyl CoA and then to CO_2 via the citric acid cycle. Short- and medium-chain fatty acids enter the mitochondria where they are esterified to CoA before oxidation. Long-chain fatty acids, however, are first esterified in the cytosol and then transported across mitochondrial membrane by CPT-I and CPT-II (McGarry et al., 1989) where they undergo β oxidation via fatty acyl-CoA dehydrogenase. The oxidation of short, medium-, and long-chain fatty acids is catalyzed by three isoenzymes. In general, unsaturated fatty acids are more readily oxidized than saturated fatty acids and hence saturated fatty acids are stored in tissue lipids more than unsaturated fatty acids. In human muscle, oxidation of long-chain fatty acids is controlled by glucose plus insulin via regulation of entry into mitochondria. However, mitochondrial uptake and oxidation of medium-chain fatty acids is not dependent on glucose and/or insulin (Sidossis et al., 1996). In diabetes, owing to the lack of insulin, oxidation of glucose is reduced and is compensated by increased oxidation of fatty acids. The ratio of fatty acid oxidation to esterification is higher in streptozotocin diabetic rats than in control animals and is not significantly affected by insulin treatment (Moir and Zammit, 1994). β oxidation of fatty acids in heart can be down regulated by intra mitochondrial acetyl CoA derived from carbohydrate oxidation (Lopaschuk and Gamble, 1994). The formation of ketone bodies occurs when production of acetyl CoA exceeds the capacity of the citric acid cycle to metabolize acetyl CoA to CO_2 and H_2O as seen in the case of IDDM subjects with severe insulin lack (see below). DHA, oleic acid, and its *trans* isomer inhibit β oxidation in mitochondria because of the accumulation of 2, 4-di- or 2, 4, 7-trienoyl CoA. In diabetes, these fatty acids have less inhibitory effect on β oxidation, since 2, 4-dienoyl CoA can be readily oxidized, as mitochondria from diabetic rats have increased 2, 4-dienoyl CoA reductase activity (Osmundsen and Bjornstad, 1985).

In the heart of diabetic rats oxidation of fatty acids is increased more than glucose oxidation during heavy work load (Christe and Rogers, 1995) and in the absence of palmitate, both, TG lipolysis and endogenous palmitate oxidation rates are higher in the heart of diabetic rats (Saddik and Lopaschuk, 1994). The increased palmitate oxidation in diabetic rats may be due to decreased activity of PDH and acetyl CoA flux through the Krebs cycle (Abdel-aleem et al., 1997). In untreated diabetic rats, hepatic mRNA levels of acetyl CoA carboxylase (ACC) and fatty acid synthase (FAS)

are reduced. Vanadate treatment restores mRNA and the activities of these enzymes in liver but not in adipose tissue. The action appears to be via improvement of thyroid function (Brichard et al., 1994). In pancreatic islets ACC is abundant but FAS is poorly expressed. Fatty acid oxidation in islets appears to be regulated by malonyl CoA (Brun et al., 1996).

In addition to β oxidation, fatty acids can also be oxidized via ω oxidation in microsomes, though to a much lesser extent. In diabetic subjects (Lippe et al., 1987) as well as in experimental diabetic animals (Bjorkhem, 1973; Wada and Usami, 1977; Kam et al., 1978; Hemmelgarn et al., 1979), the rate of ω oxidation of fatty acids is increased compared to controls and accounts for almost 15% of overall fatty acid oxidation. The increased ω oxidation of fatty acids in diabetes can be advantageous for both carbohydrate and lipid metabolism. Dicarboxylic acids formed via ω oxidation are further metabolized by β oxidation to form succinyl CoA (Hemmelgarn et al., 1979), which leads to decreased glucose formation (Kam et al., 1978; Hemmelgarn et al., 1979). Second, increased ω oxidation also decreases the incorporation of fatty acids into phospholipids (Wada et al., 1971) and hence lowers lipid synthesis. The administration of long-chain dicarboxylic acids to diabetic rats also decreases the concentration of ketone bodies in the blood (Wada et al., 1971). Shimabukuro et al. (1997a) reported increased FFA oxidation in cultured islets by leptin. However, in islets of obese, mildly diabetic Zucker rat leptin had no effect possibly due mutation of leptin receptor. The Zucker diabetic fatty rats also have increased fatty acid transport by adipocytes as measured by the uptake of oleate (Berk et al., 1997).

It is not clear whether insulin or other hormones have significant effects on β or ω oxidation of fatty acids. However, increased ω oxidation in diabetes indicates that the lack of insulin may be responsible. By reducing lipolysis and glycogenolysis, insulin enhances the relative contribution of carbohydrate oxidation and reduces fat oxidation in resting state as well during exercise in diabetic rats (Houwing et al., 1995). The hormonal control of fatty acid oxidation in diabetes needs to be addressed.

D. Binding Proteins and Fatty Acid Oxidation

Fatty acid-binding proteins (FABP) play an important role in the fatty acid oxidation. In streptozotocin diabetic rat, fatty acid oxidation in liver homogenate increases significantly but the FABP content decreases. FABP also decreases in the aorta of streptozotocin diabetic rats and is reversed by insulin treatment (Sakai et al., 1995). In heart, fatty acid oxidation is unaltered but FABP content is increased (Glatz et al., 1994). Thus, changes in fatty acid oxidation capacity do not appear to correlate with FABP content during the development of diabetes (Veerkamp et al., 1996). This indicates that though FABP in different tissues are structurally identical, there is differential regulation of FABP in different tissues in diabetes. In muscle of streptozotocin diabetic rats, heart-FABP (H-FABP) level and mRNA are increased but the transcription rate was unchanged indicating that the regulation of expression of H-FABP in muscle may not be at the level of transcription (Carey et al., 1994). In streptozotocin diabetic rat fatty acid binding characteristics of myocardial plasma membrane FABP are altered in that there is a decrease in the affinity for the binding of saturated fatty acids but not for unsaturated fatty acids as indicated by the decreased affinity of *trans*-parinaric acid (Heylinger et al., 1995).

In Pima Indians, intestinal FABP with threonine at codon 54 instead of alanine has been shown to result in higher insulin resistance and increased fat oxidation *in vivo* and threonine-containing protein had twofold greater affinity for long-chain fatty acids than the alanine-containing protein indicating increased absorption and/or processing of dietary fatty acid by the intestine and thus increased fat oxidation (Baier et al., 1995; Tataranni et al., 1996).

In adipocytes, FABP has been shown to be a glycoprotein IV or CD36. CD36 is also responsible for fatty acid building in erythrocytes and platelets. It is strongly expressed in cardiac and skeletal muscle and adipose tissue but not in liver, pancreas, and brain (Greenwalt et al., 1995). It is up regulated in diabetes and by high fat feeling (Greenwalt et al., 1995). Type of fatty acids appears to modulate RNA for CD36 protein. In capillary endothelial cells CD36 expression appears to be

correlated with parenchymal cell fatty acid utilization (Greenwalt et al., 1995). CD36 transfers bound fatty acid to the fatty acid acyl-CoA enzyme on the inside of the membrane (Sfeir et al., 1997). Two other proteins have also been shown to have the same function, namely membrane-bound aspartate aminotransferase ($FABP_{pm}$) with a molecular weight of 43 kDa (Berk et al., 1990) and fatty acid transport protein (FATP) with a molecular weight of 63 kDa (Schaffer and Lodish, 1994). It is not clear whether FABP present in enterocytes, heart, mammary cells, adipocytes, and blood cells are same or different proteins. It has been suggested that FABP2, or a tightly linked gene may be associated with insulin resistance (Mitchell et al., 1995).

E. Conversion of EFAs to Eicosanoids

Formation of eicosanoids is another important biological function of EFAs. Eicosanoids can be formed only from fatty acids with 20-carbon atoms and at least three double bonds. There are three different pathways involving different enzyme systems. Microsomal cyclooxygenase converts fatty acids to prostanoids (prostaglandins, prostacyclins, and thromboxanes); lipoxygenase gives rise to hydroperoxyeicosatetraenoic acids, which are quickly converted to LTs, and cytochrome p450 monooxygenase which leads to formation of epoxides and hydroxyeicosatetraenoic acids. The three important fatty acids involved in eicosanoid production are DHLA, AA, and EPA. As they have different numbers of double bonds, they each give rise to a different series of eicosanoids. Thus, prostanoids of 1-series and LTs of 3-series are formed from DHLA. AA produces prostanoids of 2-series and LTs of 4-series, while EPA is converted to prostanoids of 3-series and LTs of 5-series. The two families of fatty acids, ω-3 and ω-6, compete for the same enzymes, and hence, depending on the availability of fatty acids, products of different series are formed. Thus, EPA inhibits the production of prostaglandins (cyclooxygenase pathway) from AA (Culp et al., 1979; Corey et al., 1983). The products formed from AA and EPA are biologically more active and more important. These fatty acids are usually derived from phospholipids by the action of phospholipase A_2. Prostanoids are produced in most tissues, whereas LTs are generally formed in different blood cells, pancreatic islets, and glomerular cells. Kinsella et al. (1990) have reviewed the conversion of fatty acids to eicosanoids.

In platelets, AA forms TXA_2 whereas EPA forms TXA_3. In endothelial cells of blood vessels, the major product of AA is prostacyclin PGI_2 and that of EPA is PGI_3. TXA_2 has potent platelet-aggregating activity; TXA_3 either has weak activity or is inactive. Both PGI_2 and PGI_3 have strong antiaggregating activity and are vasodilators. They prevent platelet clumping and increase bleeding time. PGE_1 derived from DHLA also has antiaggregating activity. LTs, on the other hand, cause chemotaxis in neutrophils and eosinophils, and stimulate cyclic adenosine monophosphate (cAMP) production and the release of lysosomal enzymes from polymorphonuclear cells. LTC_4 and LTD_4 are humoral agents and promote smooth muscle contraction.

In diabetes, AA in membrane phospholipids is decreased (see above). This is caused by decreases in Δ5 and Δ6 desaturases and in lipase activity. As a result there is decreased formation of TXA_2 and PGI_2 in diabetic subjects (Nordoy, 1981; Goodnight et al., 1984; Mikhailidis et al., 1986; Tilvis et al., 1987; Prisco et al., 1989b). There is also an increase in PGH_2 (Shimizu et al., 1993) and $PGF_{2\alpha}$ (Harrison et al., 1978) in vascular tissues. In IDDM subjects, DHLA is also decreased, leading to decreased PGE_1 formation (Mikhailidis et al., 1986). There is also a decrease in PGI_2 synthesis in IDDM as measured by the urinary 6-keto-$PGF_{1\alpha}$. These changes explain the increased adhesiveness and aggregation of platelets observed in IDDM subjects (Bern, 1978; Waitzman, 1979; Colwell and Halushka, 1982; Ewald et al., 1983; Mikhailidis et al., 1986). The role of different prostaglandins in platelet function in diabetes has been reviewed by Colwell and Halushka (1982).

In streptozotocin diabetic rats, PGI_2 synthesis in the aorta is decreased (Jeremy et al., 1987). The decrease in PGI_2 formation increases with the duration rather than the severity of diabetes. However, in the bladder there is increased PGI_2 formation, possibly due to distention (Jeremy et al., 1986). Fujii et al. (1986) observed a slight increase in PGI_2 and a greater increase in TXA_2

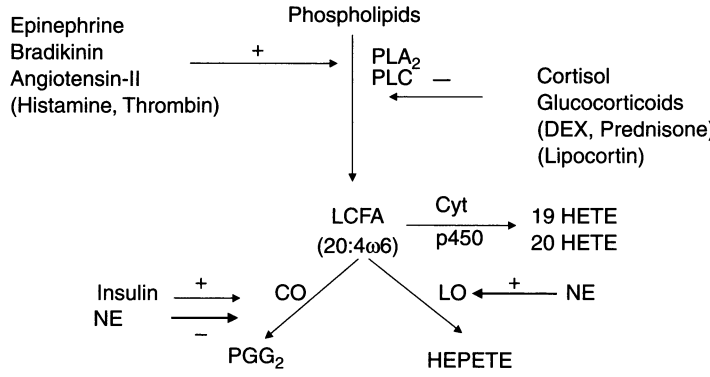


FIGURE 47.2 Role of hormones in eicosanoid formation. Most hormones affect eicosanoid formation by controlling lipolysis of phospholipids. Insulin and nor epinephrine act on the cyclooxygenase and lipooxygenase. The different PLA_2s involved are $cPLA_2$, cytosolic PLA_2 which is Ca^{2+} dependent; $IPLA_2$, cardiac PLA_2 which is Ca^{2+} independent; and $spPLA_2$, sarcoplasmic PLA_2. *Abbreviations:* PLA_2, phospholipase A_2; PLC, phospholipase C; Dex, dexamethasone; LCFA, long-chain fatty acids; cyt p450, cytochrome p450; CO, cyclooxygenase; LO, lipooxygenase; PGG_2, prostaglandin G_2; NE, norepinephrine; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

(as measured by its inactive metabolite TXB_2) and PGE_2 synthesis in the mesenteric vascular bed of streptozotocin-treated diabetic rats compared to control rats. Thus, there was a decrease in the PGI_2/TXA_2 ratio, indicating a tendency for increased platelet aggregation. In streptozotocin-treated diabetic rat, mRNA for cyclooxygenase is decreased in sciatic nerve and aorta but not in kidney and retina (Fang et al., 1997). Evening primrose oil increased mRNA for cyclooxygenase in nerve and retina indicating a tissue specific effect. Aldose reductase inhibitor, on the other hand, had no effect on cyclooxygenase expression (Fang et al., 1997).

Various hormones are involved in eicosanoid formation (Figure 47.2). The hormonal control occurs during the conversion of long-chain PUFA by phospholipases and also at the level of cyclooxygenase and lipooxygenase. Epinephrine, bradikinin, and angiotensin II stimulate phospholipase A_2 and phospholipase C (Vane, 1976; Van Den Bosch, 1980; Shukla, 1982) while cortisol and synthetic glucocorticoids, dexamethasone, and prednisone, inhibit the lipases (Blackwell et al., 1980). They appear to act via lipocortin. Histamine and thrombin also stimulate these lipases (Van Heugten et al., 1996). Insulin acts directly on cyclooxygenase and stimulates the conversion of AA to PGG_2, which is then converted to various prostanoids. TNF has also been reported to stimulate prostaglandin synthesis (Burch and Tiffany, 1989). The interactions between hormones and prostanoids have been reviewed by Myers et al. (1989).

Prostaglandins also play a role in insulin secretion. Sodium salicylate, which inhibits cyclooxygenase and thereby decreases prostaglandin synthesis, increases basal as well as glucose-stimulated insulin secretion in diabetic subjects indicating involvement of prostaglandin. Robertson and Chen (1977) infused PGE_2 in normal humans and inhibited acute insulin response to glucose. In addition, prostaglandins are also involved in abnormal collagen metabolism in diabetes (Yue et al., 1985). Bradykinin has been shown to stimulate phospholipids to release AA which is then metabolized via cyclooxygenase, lipooxygenase, and cytochrome p450 to yield vasoactive products (Quilley et al., 1994).

LTs formed by lipoxygenase are also biologically active. LT_5 formed from ω-3 fatty acids is more active in immune functions in humans (Kelley et al., 1991). Neutrophils and monocytes increase LT formation from EPA more than from AA (Lee et al., 1985). This explains the beneficial effects of fish oil on immune function in low-dose streptozotocin diabetic mice in which fish oil decreased the number of class II antigen-expressing cells in pancreatic islets (Linn et al., 1989).

F. Hormones, Eicosanoids, and Platelet Aggregation in Diabetes

Increased plasma glucose appears to be a factor in platelet aggregation in diabetes. In control animals, glucose infusion increases TXA_2 production and decreases the ratio of PGI_2/TXA_2. Insulin treatment reverses the ratio (Fujii et al., 1986). Glucose also decreases prostacyclin-stimulating activity in cultured aortic endothelial cells. This activity is increased by LDL and linoleic acid (possibly by conversion to AA), but insulin has no effect on the activity (Umeda et al., 1990). Thus, increased plasma glucose levels in diabetic subjects may be partly responsible for decreased PGI_2 levels and hence increased platelet aggregation. Alteration in platelet phosphoinositide has also been reported in streptozotocin diabetic rats (Jethmalani et al., 1994).

In diabetic subjects who consume large quantities of fish oil, the situation is different. There is an increase in TXA_3 and PGI_3 synthesis and decreased TXA_2 and PGI_2 owing to the decreased availability of AA and the competition of the ω-3 fatty acids from fish oil. Thus, because of the decreased TXA_2 and PGI_2 and the increased PGI_3 and inactive TXA_3, there is less platelet aggregation, which is beneficial for diabetic subjects with coronary artery disease and hypertension (Leaf and Weber, 1988; Knapp and Fitz-Gerald, 1989; Kasim, 1993; Nishikawa et al., 1997). Figures 47.3 and 47.4

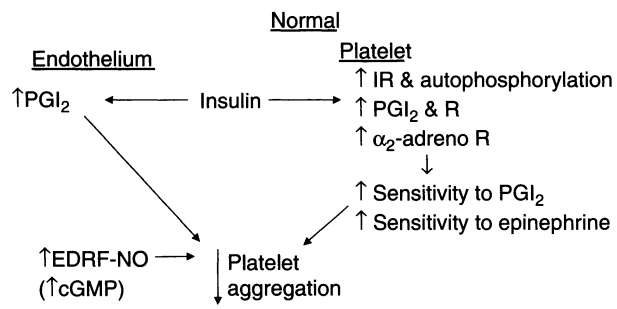


FIGURE 47.3 Role of insulin and prostanoids in platelet aggregation in normal state. Under physiologic (normal) condition, insulin stimulates prostacyclin in endothelium and in platelets which in turn inhibit platelet aggregation. *Abbreviations:* PGI_2, prostacyclin I_2; IR, insulin receptor; α_2-adreno R, α_2 adrenergic receptor; NO, nitric oxide; EDRF, endothelium-derived relaxing factor. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

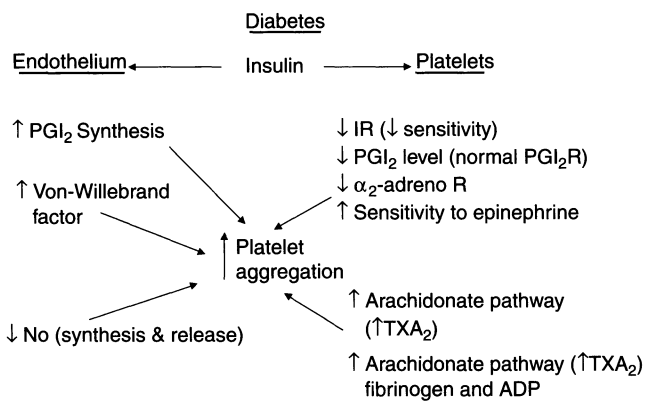


FIGURE 47.4 Role of insulin and prostanoids in platelet aggregation in diabetes. In diabetic state, decreased availability of insulin leads to decreased prostacyclin in endothelium and platelets which results in increase platelet aggregation. *Abbreviations:* PGI_2, prostacyclin I_2; IR, insulin receptor; α_2-adreno R, α_2 adrenergic receptor; NO, nitric oxide; TXA_2, thromboxane A_2; ADP, adenosine diphosphate. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

summarize the role of hormones, hormone receptors, and prostanoids in platelet aggregation in normal and diabetic states.

V. HORMONAL CONTROL OF FATTY ACID METABOLISM IN DIABETES

The hormonal control of fatty acid metabolism is summarized in Figure 47.5 and has been reviewed in normal and diabetic subjects (Liljenquist et al., 1974; Storlien et al., 1997; Saleh et al., 1999; Bhathena, 2006). The metabolic processes, lipogenesis and lipolysis, which control fatty acid concentration in plasma and tissues, are under hormonal control. The principal hormones involved in lipid metabolism are insulin, glucagon, catecholamines, cortisol, and growth hormone. Many other hormones also affect fatty acid metabolism as shown in Figure 47.5. The levels of these hormones are altered in diabetes, which explains altered lipid metabolism in diabetes. Insulin has multiple effects on lipid metabolism. Though insulin stimulates lipogenesis (Beynen et al., 1982; McTernan et al., 2002), its major effect is antilipolytic, especially the inhibition of hormone-stimulated lipolysis (Jungas and Ball, 1963; Mahler et al., 1964; Fain and Shepherd, 1979; Cavallo-Perin et al., 1992; Suda et al., 1993; Linfoot et al., 2005). Glucagon, catecholamines, cortisol, and growth hormone, which are counterregulatory hormones to insulin, have predominantly lipolytic activity (Ball and Jungas, 1963; Gerich et al., 1976; Rosen et al., 1981; Goodman and Grichting, 1983). However, glucagon (Wu et al., 1990a), growth hormone (Davidson, 1987), and catecholamines (Wahrenberg et al., 1989) also have antilipolytic activity. In humans, glucagon has only a marginal effect on LPL, but it has a much stronger effect in young animals. The lipolytic activity of catecholamine is mediated via β-adrenoreceptors and the antilipolytic effect is mediated through α-2-adrenoreceptors

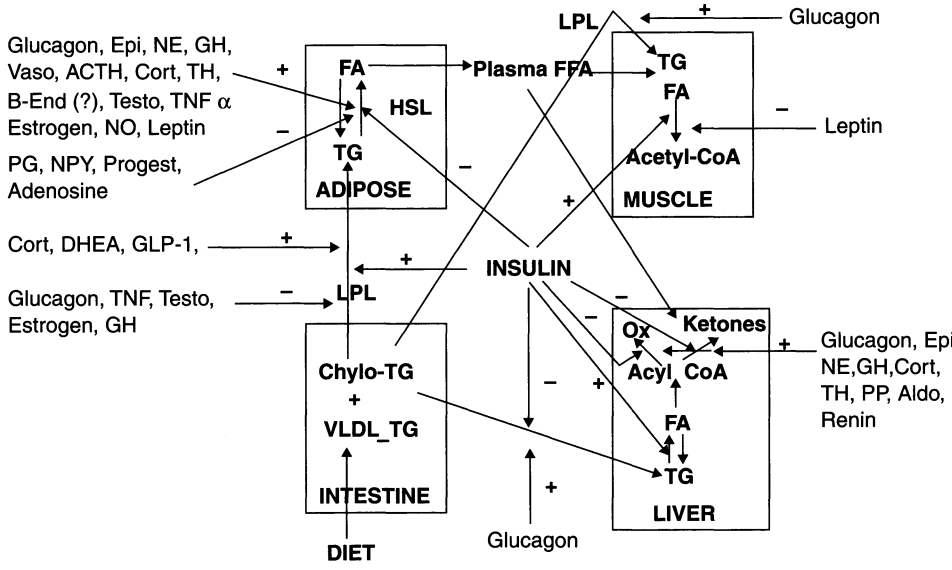


FIGURE 47.5 Hormonal control of fatty acid metabolism. Schematic diagram showing how different hormones control fatty acid metabolism in intestine, adipose tissue, muscle, and liver. "+" indicates stimulatory (positive) effect and "—" indicates inhibitory (negative) effect on different processes. *Abbreviations:* HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; Epi, epinephrine; NE, norepinephrine; GH, growth hormone; Vaso, vasopressin; ACTH, adrenocorticotropic hormone; Cort, cortisol; TH, thyroid hormone; β-end, β-endorphin; Testo, testosterone; TNF-α, tumor necrosis factor-α; NO, nitric oxide; PG, prostaglandins; NPY, neuropeptide Y; Progest, progesterone; DHEA, dehydroepiandrosterone; GLP-1, glucagon-like peptide 1; PP, pancreatic polypeptide; Aldo, aldosterone. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

(Leibel and Hirsch, 1987; Pecquery et al., 1988). The effects of these hormones on lipolysis occur through hormone-sensitive lipase that is activated by cAMP. Glucagon, catecholamine, cortisol, and growth hormone all increase cAMP formation by activating adenylate cyclase and hence stimulate lipolysis.

Insulin stimulates phosphodiesterase, which catabolizes cAMP and decreases cAMP level, thereby inhibits lipolysis. LPL present in adipose tissue, muscle, and heart, is responsible for the lipolysis of TG-rich lipoproteins (Nicoll and Lewis, 1980) and for the production of HDL-cholesterol (Nikkila et al., 1978), while TG lipase present in liver increases the catabolism of HDL-cholesterol (Kuusi et al., 1980). The effect of type of dietary fatty acids on insulin action is reviewed by Storlien et al. (1997). High intake of saturated fat appears to produce hyperinsulinemia and increases risk of diabetes. PUFAs appear to have the opposite effect. The role of insulin in controlling fatty acid metabolism is reviewed by Dutta-Roy (1994).

In diabetes, the counterregulatory hormones are generally elevated while either insulin is decreased or there is peripheral resistance to insulin. In IDDM, plasma norepinephrine is decreased. Also, the antilipolytic effect of catecholamines is normal, but the lipolytic effect is increased 10-fold (Wahrenberg et al., 1989). Thus, these changes in hormones favor increased lipolysis, and hence elevated levels of FFAs are observed in IDDM as well as NIDDM. Unsaturated fatty acids as well as glucose play an important role in these processes. Thus, the increased concentration of unsaturated FFAs stimulates the lipogenic effect of insulin on adipocytes (McTernan et al., 2002). In muscle, however, FFAs are antagonistic to insulin (Randle et al., 1963). In humans, glucose potentiates the antilipolytic effect of insulin on isolated adipocytes (Arner et al., 1983). In poorly controlled diabetic subjects, however, the antilipolytic activity of insulin is decreased (Trevisan et al., 1986; Jensen et al., 1989) because of the reduced insulin sensitivity. In rats, glucose has no effect on insulin-stimulated antilipolysis (Thomas et al., 1979) but inhibits the antilipolytic effect of catecholamine-stimulated lipolysis (Desai et al., 1973). In diabetic subjects, TG lipase is inversely proportional to HDL-cholesterol, being higher in subjects with low HDL-cholesterol and lower in those with elevated HDL-cholesterol (Kasim et al., 1987). In streptozotocin diabetic rats, TG lipase activity is decreased (Jansen and Hulsmann, 1975; Elkeles and Hambley, 1977), but this is reversed by PUFA (Hulsmann et al., 1977). Unlike TG lipase, insulin stimulates LPL (Garfinkel et al., 1976; Sadur and Eckel, 1982). In NIDDM subjects, LPL activity is decreased in adipose tissue and skeletal muscle (Taskinen and Nikkila, 1979). Insulin also stimulates phospholipase C in adipose tissue (Farese et al., 1986). In livers of diabetic mice insulin increases transcription of FAS (a key enzyme in lipogenesis) gene (Paulauskis and Sul, 1989). In human adipocytes, LPL is suppressed by TNF in the presence of insulin and dexamethasone (Fried and Zechner, 1989) but not in the absence of insulin (Kern, 1988). TNF decreases LPL mRNA levels, rates of LPL synthesis, and the LPL activity. Thus, TNF may be important in the pathogenesis of hypertriglyceridemia (Feingold et al., 1989; Fried and Zechner, 1989). It is important to note that TNF is involved in the pathogenesis of diabetes, and its administration to diabetic animals increase blood glucose levels without changes in insulin concentration (Feingold et al., 1989). Farese (1990) has reviewed the role of insulin in phospholipid metabolism. In line with its lipogenic activity, insulin stimulates phospholipid synthesis in adipocytes (Farese et al., 1982; Pennington and Martin, 1985), hepatocytes (Cooper et al., 1990), and diaphragm and skeletal muscle (Ishizuka et al., 1990). Various actions of insulin on fatty acid metabolism in adipose, liver, and muscle are summarized in Table 47.2.

Insulin also plays a role in cholesterol synthesis by controlling hydroxymethylglutaryl CoA reductase, a key enzyme in cholesterol biosynthesis. Insulin stimulates the activity of the enzyme *in vitro* and hence cholesterol synthesis (Bhathena et al., 1974; Geelen et al., 1980). It is important to note that owing to lack of insulin, lipogenesis in insulin-sensitive tissues is decreased but lipogenesis is normal in the intestine, which is insulin insensitive. Lipogenesis in the intestine is dependent on substrate availability, and in diabetes, because there is an increase in substrate availability, fatty acid and TG synthesis are elevated (Popper et al., 1985; Feingold et al., 1990). Thus, de novo intestinal synthesis partly accounts for the increased TG in VLDL in diabetes. However, Jiao et al. (1989)

TABLE 47.2
Insulin and Fatty Acid Metabolism

Adipose	
↓	HSL (↓ rate of lipolysis, ↓ plasma FFA)
↑	FA and TG synthesis (re-esterification)
↑	Fatty acyl-CoA and fatty acyl transferase
↑	LP lipase (↑ uptake of TG from plasma)
Liver	
↑	FA and TG synthesis (de novo lipogenesis from glucose)
↑	VLDL formation (↑ FAS and ACC)
↑	Cholesterol synthesis
↓	Rate of FA oxidation and ketone formation (↓CAT-1)
Muscle	
↓	Rate of FA oxidation (↓ malonyl CoA)
↓	Ketogenesis

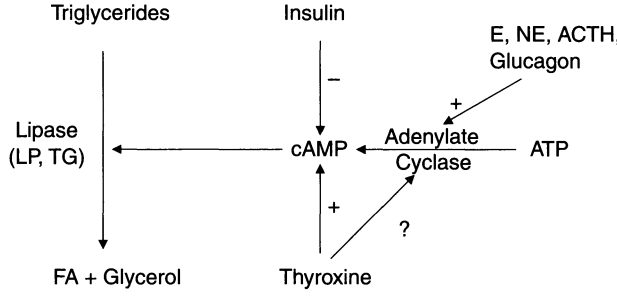


FIGURE 47.6 Hormonal control of fatty acid synthesis in adipose tissue. Note that insulin and counter-regulatory hormones control fatty acid synthesis via cAMP. "+" indicates stimulatory effect and "—" indicates inhibitory effect. "?" indicates the effect is not clearly established. *Abbreviations:* E, epinephrine; NE, norepinephrine; ACTH, adrenocorticotropic hormone; LP, lipoprotein lipase; TG, triglyceride lipase. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

reported inhibition of cholesterol synthesis and esterification in cultured human intestinal cell line Caco-2.

In diabetes there is an increase in lipid peroxidation as measured by free and total malondialdehyde (MDA). Insulin treatment reduces free MDA but not total MDA (Peuchant et al., 1997) indicating a partial protection against elevated lipid peroxidation in diabetes. Although insulin therapy in NIDDM subjects with secondary failure to oral agents increases GLA in TG and cholesterol esters, it does not alter the platelet function in these subjects (Rodier et al., 1995).

Figure 47.6 summarizes the hormonal control of fatty acid synthesis in adipose tissue. Glucagon has multiple effects on lipid metabolism. It stimulates lipolysis by activating lipase (see above). The action is via stimulation of adenylate cyclase. It also stimulates LPL in muscle but not in adipose tissue (Geelen et al., 1980). In liver, glucagon stimulates fatty acid oxidation (McGarry and Foster, 1981) and suppresses fatty acid synthesis (Allred and Roehrig, 1972; Bricker and Levey, 1972; Goodridge, 1973; Watkins et al., 1977). Glucagon also inhibits cholesterol synthesis (Geelen et al., 1980). In diabetes, increased lipolysis is also observed in the heart (Kenno and Severson, 1985) and is stimulated by epinephrine to the same extent as in controls (Rosen et al., 1981), but not by isoproterenol (Kenno and Severson, 1985). Many of the effects of hormones on lipogenesis have been studied in rats or in isolated cells *in vitro*. It is important to note that in humans lipogenesis occurs

predominantly in the liver, whereas in rats both liver and adipose tissue are involved. Although the intestine is insensitive to insulin *in vivo*, in isolated intestinal cells insulin has an inhibitory effect on cholesterol synthesis.

A major consequence of increased FFA in diabetes in the face of decreased insulin is ketoacidosis. Increased glucagon and decreased insulin will stimulate lipolysis in adipose tissue, producing FFA in plasma that is transported to liver. Decreased availability of insulin reduces lipogenesis, and hence FFAs are converted to ketone bodies (acetoacetate and β-hydroxybutyrate). Glucagon plays a critical role in ketoacidosis. In normal subjects, infusion of glucagon stimulates insulin secretion, and no rise in ketones occurs. However, in diabetic subjects deficient in insulin (IDDM), glucagon infusion produces a rise in ketones (Liljenquist et al., 1974). The role of glucagon in ketogenesis in diabetes has been shown by many others (Gerich et al., 1975; Schade and Eaton, 1975; McGarry and Foster, 1979). Ketogenesis by increased glucagon and decreased insulin has been shown to occur also in experimental animals and isolated cells (Keller et al., 1977; Woodside, 1979). McGarry and Foster (1981) suggested the following mechanism for ketogenesis in diabetes. Glucagon acutely suppresses fatty acid synthesis by blocking the formation of malonyl CoA (a key metabolite in lipogenesis from glucose), which in turn causes depression of carnitine acyltransferase I and activates fatty acid oxidation, leading to accelerated production of ketone bodies. Schade and Eaton (1979) also reported that other hormones counterregulatory to insulin, such as catecholamine, also stimulate ketogenesis. However, an elevated ratio of glucagon to insulin is the primary factor for accelerated ketogenesis in diabetes (McGarry and Foster, 1977, 1981) as shown in Figure 47.7. In diabetic ketoacidosis, saturated unbranched fatty acids, succinic and adipic, are predominantly excreted in the urine and can be used as a marker of the ketoacidotic state (Liebich et al., 1980).

Elevated FFA in plasma in diabetes and other disorders results in hypercoticoidism and initiates a positive feedback loop between adipocytes and hypothalamic-pituitary-adrenal axis (Widmaier et al., 1995). Abnormality in thyroid function and altered thyroid hormone levels have been reported in diabetic subjects and that dysfunction of the hypothalamic-pituitary-thyroid axis may be involved (Suzuki et al., 1994). Fluctuations in estrogens and insulin-like growth factor-II (IGF-II) have been reported to contribute to the pathogenesis of NIDDM and that IGF-II and insulin may be inversely regulated in NIDDM (Holden, 1995). Recently leptin has been reported to increase fatty acid oxidation and decrease fatty acid incorporation into TGs in soleus muscle and thus oppose the lipogenic effect of insulin (Muoio et al., 1997). Leptin also increases fatty acid oxidation in cultured pancreatic islets (Shimabukuro et al., 1997a). In healthy subjects no correlation was observed between plasma leptin levels and plasma glucose, insulin, TG or FFA (Pratley et al., 1997). Similarly, in obese, mildly diabetic Zucker rat, leptin had no effect possibly due to mutation of the leptin receptor.

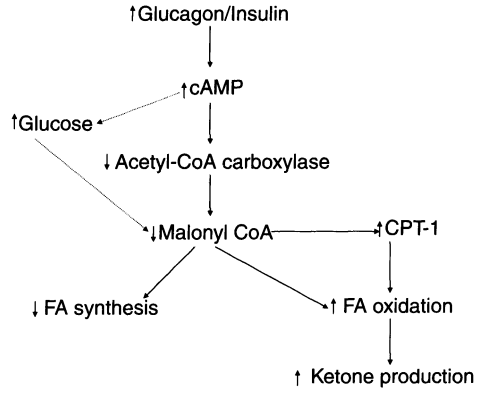


FIGURE 47.7 Hormonal control of fatty acid metabolism in liver in diabetes. Increased glucagon/insulin ratio in diabetic state leads to stimulation of cAMP in liver leading to increased fatty acid oxidation and increase ketone production. *Nutritional Neurosc.* 9:1–10, 2006. With permission.

VI. EFFECT OF TREATMENT OF DIABETES ON FATTY ACID METABOLISM

Hyperglycemia of diabetes is normally controlled by (1) diet and exercise, (2) oral agents, and (3) insulin. Diabetes in many cases is also associated with other complications such as hypertension, polyneuropathy, nephropathy, retinopathy, obesity, insulin resistance, and in most instances, hyperlipidemia, especially in NIDDM subjects. Until recently most drug therapy for diabetes was geared toward reducing hyperglycemia and correcting insulin responsiveness with less emphasis on correcting lipid abnormalities. Normalizing blood sugar levels by any means also partially lowers hyperlipidemia. However, more attention should be given to reduce lipid abnormalities in diabetes and the associated metabolic disorders. The reduction of elevated FFA levels and hyperlipidemia will help glucose-fatty acid cycle which is operative in many tissues by shifting the oxidation of FFA in favor of oxidation of glucose. The effects of insulin in the management of diabetes have been discussed throughout this chapter. The management of dyslipidemia of secondary complications of diabetes has been briefly reviewed by Garg and Grundy (1990). This section therefore deals primarily with the effect of diet, exercise, oral agents (hypoglycemic and hypolipidemic), and metal ions on fatty acid metabolism.

A. Diet and Exercise

The importance of dietary carbohydrate and lipid sources in the management of diabetes and their effects on fatty acid metabolism has been discussed throughout this chapter. Recently, several studies in humans and animals have shown beneficial effects of soybean and flaxseed meal in diabetes (Kaminskas et al., 1992; Nestel et al., 1997; Hermansen et al., 2001; Bhathena and Velasquez, 2002; Jayagopal et al., 2002; Torres et al., 2005). In addition to modulating hyperglycemia, soy protein reduces hyperlipidemia and hyperinsulinemia. In streptozotocin diabetic rats, soy protein compared to casein, lowered EPA and increased AA, which resulted in decreased ratio of aortic prostacyclin production to TXA_2 (Ikeda and Sugano, 1993). Soy protein along with its associated isoflavones and fiber reduces total cholesterol, LDL-cholesterol, VLDL-cholesterol, apolipoprotein B100, FFAs and TGs but has no significant effect on HDL-cholesterol, glucose or HbA1c (Hermansen et al., 2001). Zhan and Ho (2005) carried out meta-analysis of 23 human studies and found that soy protein with intact isoflavones was associated with significant decrease in serum total cholesterol, LDL-cholesterol, and TGs and significant increase in serum HDL-cholesterol. In another meta-analysis similar results were seen namely soy protein isolate with high isoflavones lowered serum LDL-cholesterol (Zhou et al., 2004). The hypocholesterolemic effect of isoflavones appears to be due in part to the modulation of steroid hormones involved in lipid metabolism (Ali et al., 2004). In contrast, recently, Sacks et al. (2006) analyzed data from 22 randomized trials and found no significant effect of soy protein with isoflavones compared to milk or other proteins on lipid parameters. Soy isoflavones also had no significant effect. It is possible that soy protein or isoflavones may not affect lipid parameters in normal subjects when lipid levels are in normal range, but may affect lipid levels when they are elevated as in diabetic subjects. Soy protein also reduces insulin/glucagon ratio which in turn down regulates the expression of hepatic sterol regulatory element-binding protein (SERBP-1) that results in decreased lipogenic enzymes leading to decreased LDL- and VLDL-cholesterol and TG (Torres et al., 2005). ω6 Fatty acids in soybean oil and ω3 fatty acids in flaxseed oil also activate SERBP-1 (Rodriguez-Cruz et al., 2005). They also activate alpha and gamma PPAR leading to increased lipid oxidation and hepatic steatosis.

The beneficial effects of flaxseed on lipid parameters in diabetes appear to be due to the presence of ω3 fatty acids. Flaxseed oil improves insulin sensitivity, decreases LDL oxidation and increases HDL-cholesterol (Nestel et al., 1997). In hypercholesterolemic rabbits, lignan present in flaxseed, secoisolariciresinol diglucoside, also lowers serum total- and LDL-cholesterol (Prasad, 1999). Secoisolariciresinol diglucoside also reduces the incidence of diabetes in both, type 1 and type 2

diabetic rats (Prasad, 2000, 2001; Prasad et al., 2000). The beneficial effects of isoflavones and lignans on tissue lipids may be due in part to their antioxidative actions since oxidative stress has been shown to be one of the causes of both type 1 and type 2 diabetes.

The beneficial effects of exercise on fatty acid metabolism, especially in NIDDM subjects, is primarily due to decreased body weight, increased insulin sensitivity, and lowered blood glucose level (National Institutes of Health, 1987). Improved insulin response to exercise is only acute and reverses after inactivity. Strenuous and prolonged exercise increases the rate of FFA metabolism in muscle and other tissues. There is a moderate fall in insulin, increased insulin sensitivity, increased insulin clearance and increases in glucagon, catecholamines, growth hormone, and cortisol (Keller et al., 1977; Schade and Eaton, 1979; Gray et al., 1980; Horton, 1988; Wasserman et al., 1989; Tuominen et al., 1997). As a consequence, there is an increase in lipolysis and increased ketone body production in the liver, which can be used for energy by muscle. In several prospective studies, exercise has been shown to reduce plasma TG and total and LDL-cholesterol and to increase HDL-cholesterol. The beneficial effects of light to moderate exercise on ischemic heart disease in diabetes are also suggested by epidemiological evidence (Leon, 1988). Exercise also improves altered immune function in obese diabetic rats (Plotkin and Paulson, 1996). The role of exercise training in NIDDM has been reviewed by Horton (1996) and Ivy (1997). Benefit of moderate exercise is also seen in IDDM subjects, where glucose uptake and oxidation is lower and fat oxidation is enhanced (Raguso et al., 1995). It is important to note that in poorly controlled IDDM subjects, strenuous exercise may not be beneficial because it can increase lipolysis, ketogenesis, and blood glucose levels due to insulin deficiency. Similarly, in well-controlled IDDM subjects, the dose of insulin should be reduced or extra carbohydrate should be given to prevent hypoglycemia.

In diabetic rats exercise causes increase in FFA more than in control rats. This mobilization appears to be due to reduced inhibition of lipolysis by the relative lack of insulin since insulin levels that are already low are unaltered (Houwing et al., 1997).

B. Oral Hypoglycemic Agents

The two classes of oral agents most frequently used in glycemic control are sulfonylureas and biguanides. A residual pancreatic insulin secretion is a prerequisite for the use of oral agents. The rationale for their use and the mechanisms of their actions have been extensively reviewed by Krall (1991), Lebovitz (2001, 2004), Ferner (1988), and others (Olefsky, 1985). The most widely used sulfonylureas are first-generation tolbutamide, second-generation glyburide (glibenclamide), and now third-generation glimepiride. The mechanisms of their action include increased glucose-stimulated insulin secretion and increased insulin responsiveness (decreased resistance) and action in target tissues due to increased insulin receptor number (Bhathena, 1987). They also decrease hepatic gluconeogenesis. In diabetic subjects, sulfonylureas also inhibit platelet aggregation *in vivo* (Sagel et al., 1975).

The commonly used biguanides are metformin and phenformin. Unlike sulfonylureas, they are not known to stimulate insulin secretion, but they do potentiate insulin action and increase insulin binding to hepatocytes and adipocytes and increases tyrosine kinase activity (Rossetti et al., 1990). More importantly, they inhibit glucose absorption and increase glucose utilization by the liver and muscle. They may also inhibit gluconeogenesis and hepatic glucose output in diabetic subjects thereby preventing hyperglycemia from occurring (Bailey, 1992). Phenformin causes increased lactic acidosis and is now used less frequently. Its use is banned in the United States but that of metformin has increased.

Both groups of compounds affect lipid metabolism. Stone and Brown (1966) reported that tolbutamide has antilipolytic activity. Thus, in IDDM subjects, injection of tolbutamide decreased plasma FFA concentration. *In vitro* studies in adipocytes from fasted nondiabetic rats, tolbutamide, but not phenformin, induced a significant decrease in FFA and glycerol release (Stone et al., 1966). This effect of tolbutamide may be related to decreased hyperglycemia, since sodium sulfadiazine,

another sulfonylurea that is nonhypoglycemic, had no effect on lipolysis. In NIDDM subjects, glibenclamide decreased plasma FFA and lactate concentrations (Jeng et al., 1989) but had no effect on apolipoproteins (Billingham et al., 1989). Insulin, however, reversed the apolipoprotein changes. In NIDDM subjects, metformin decreased serum total- and LDL-cholesterol. The effect persisted for a long time (Rains et al., 1989). Metformin also decreases fatty acid oxidation, reduces hepatic synthesis of VLDL TGs (Muntoni, 1974; Fedele et al., 1976) and reduces plasma FFA (Riccio et al., 1991; Perriello et al., 1994) and this may be in part responsible for its antidiabetic property (Gregorio et al., 1997). In short-term (21-day) treatment in IDDM subjects, metformin had no significant effect on plasma cholesterol, TG, glucose level, or glycosylated hemoglobin, but decreased maximum platelet aggregation stimulated by low-dose adenosine diphosphate (Gin et al., 1989). The site of action of metformin appears to at muscle, liver, and adipose tissue. It is important to note that insulin is more effective than oral agents in raising HDL-cholesterol levels in NIDDM subjects. In nondiabetic obese subjects, however, short-term (15-day) treatment with metformin decreased plasma TG and insulin concentrations. In muscle metformin has been shown to activate 5′-AMP-activated protein kinase which lowers lipid synthesis and increases oxidation of fatty acids. In type 2 diabetes atypical protein kinase C is defective and long-term metformin treatment in type 2 diabetic subjects improves basal as well as insulin-stimulated atypical protein kinase C in muscle (Luna et al., 2006). Metformin also lowered the elevated levels of plasminogen activator inhibition activity and increased the depressed euglobin fibrinolytic activity (Vague et al., 1987; Nagi and Yudkin, 1993). This indicates that biguanides may have a role in platelet function. The effects of oral hypoglycemic agents on platelet function in diabetic subjects needs to be explored further. The metabolic effects of metformin including its effect on fatty acid and lipid metabolism, have been reviewed by Wu et al. (1990b); Del Prato et al. (1995); Bailey and Turner (1996); Davidson and Peters (1997); and Raptis and Dimitriadis (2001).

C. Oral Agents to Treat Lipid Disorders

In the past two decades new classes of compounds has been introduced to treat lipid disorders of diabetes. The effects of some of them on fatty acid metabolism are briefly described. They are reviewed by Ilarde and Tuck (1994); Rachman and Turner (1995); Lefebvre and Scheen (1995); Dagogo-Jack and Santiago (1997); Raptis and Dimitriadis (2001); and Stumvoll (2003).

a. Insulin Sensitizers

Thiazolidinediones: The commonly used thiazolidinediones are rosiglitazone, pioglitazone, and troglitazone. They also affect fatty acid mobilization and oxidation. They lower blood glucose level without stimulating insulin secretion but increase insulin effectiveness (Chaiken et al., 1995) indicating that their action is peripheral. The effect appears to be due to lowering of plasma FFA levels (Miles et al., 1997). They also inhibit gluconeogenesis at the level of pyruvate carboxylase and glyceraldehyde 3-phosphate dehydrogenase reaction (Fulgencio et al., 1996) and stimulate glucose uptake by the muscle (Miles et al., 1997). Thiazolidinediones inhibit oxidation of long-chain fatty acid (18:1) but not the medium-chain fatty acid (octanoate). The inhibition of oxidation is via the inhibition of mitochondrial and microsomal long-chain acyl-CoA synthase activity but have no effect on mitochondrial CPT-I. In liver they increase insulin-stimulated conversion of glucose into fatty acids.

Thiazolidinediones are high-affinity ligands of PPAR-γ, a key factor for adipocyte differentiation. In preadipose cells they exert potent effect on the expression of genes encoding proteins involved in fatty acid metabolism such as FAS and phosphoenolpyruvate carboxykinase (Ibrahimi et al.,1994; Hallakou et al., 1997), LPL and hormone-sensitive lipase (Teruel et al., 2005). In adipose tissue thiazolidinediones act to conserve lipid by reducing lipid supply and subsequent utilization (Oakes et al., 1997). Troglitazone lowers serum FFA and TG concentrations by inhibiting TG synthesis and raises HDL-cholesterol level (Mimura et al., 1994; Kumar et al., 1996) but has no effect on

phospholipid synthesis. Plasma LDL-cholesterol increases with doses up to 600 mg/day but not at 800 mg/day of troglitazone. The possible side effect appears to be reduction in neutrophil counts at high doses of troglitazone (Kumar et al., 1996). In type 2 diabetic subjects rosiglitazone decreases postprandial FFA concentration (Boden et al., 2005; Van Wijk et al., 2005) and TG concentration (Tan et al., 2005) and increases oxidation of FFA in muscle (Wilmsen et al., 2003), total body fat, and oxidative phosphorylation (Boden et al., 2005). It also enhances downstream insulin receptor signaling in muscle (Miyazaki et al., 2003).

b. Fatty Acid Oxidation Inhibitors

Bromopalmitate and methylpalmoxirate (fatty acid derivatives) are fatty oxidation inhibitors. In 3T3-L1 adipocytes, 2-bromopalmitic acid, and 4-bromocrotonic acid inhibited basal as well as isoproterenol and dibutyryl cAMP-stimulated lipolysis (Fong et al., 1997). The effect of 4-bromocrotonic acid appears to be due to inhibition of hormone-sensitive lipase (Fong et al., 1997).

Dexfenfluramine, increase FFA turn over and oxidation rates in obese NIDDM subjects. It also reduces serum glucose but has no effect on insulin secretion (Greco et al., 1995).

c. Inhibitors of Lipolysis

Acipimox, a nicotinic acid analog, is an inhibitor of lipolysis. In lean and obese NIDDM subjects it decreases plasma FFA, glycerol and ketone levels and muscle lipid peroxidation, and increases insulin levels and insulin sensitivity (Vaag et al., 1991; Fulcher et al., 1992; Kumar et al., 1994; Piatti et al., 1996). In normal rats it decreases plasma FFA, inhibits lipolysis and hepatic gluconeogenesis and enhances the ability of insulin to suppress hepatic glucose production and peripheral glucose utilization (Al-Shurbaji et al., 1990; Lee et al., 1996). It may be used to treat lipid disorders in diabetes in combination with hypoglycemic agents.

Adenosine A1 agonist SDZ WAG944 is a potent inhibitor of adenosine deaminase-induced lipolysis. In diabetic rats it decreases plasma FFA and TG concentration. Antilipolytic agent *N*-{(1s, *trans*)-2 hydroxycyclopentyl} adenosine (GR 79236) reduces plasma FFA concentration and improves ketoacidosis in diabetic rats (Thompson et al., 1994). Inhibitor of hepatic fatty acid oxidation, B-aminobetaine is a carnitine analog and inhibits CPI-1 in hepatocytes but may induce fat deposition in the liver (Kashiwagi, 1995).

d. Lipid-Lowering Agents

Bezafibrate normalizes fatty acid changes in skeletal muscle TG of rats fed high fructose + lard (Matsui et al., 1997), which tend to produce insulin resistance. Whether bezafibrate has similar effect in diabetic animals or humans with insulin resistance and altered lipid and fatty acid composition needs to be evaluated. It also increases Δ5 desaturase activities.

Gemfibrozil decreases plasma FFA, TG, and phospholipids in elderly diabetic subjects. There is also a decrease in long-chain saturated fatty acids in phospholipids suggesting an impairment of chain elongation of fatty acid in liver microsomes (Brosche and Kipfmuller, 1996). However, in another study in NIDDM subjects it increased plasma FFA and LPL activity but it decreased insulin sensitivity (Ohrvall et al., 1995). It also decreased VLDL-cholesterol and TG.

Pravastatin, a HMG CoA-reductase inhibitor, is effective in patients with hypercholesterolemia secondary to diabetes and renal diseases (Haria and Mctavish, 1997). Hence it may be useful in combination therapy in diabetic patients who are at high risk of cardiovascular morbidity. Simvastatin, another HMG CoA-reductase inhibitor, also decreases LDL-cholesterol, and LDL/HDL ratio in NIDDM subjects with hyperlipoproteinemia (Ohrvall et al., 1995). Simvastatin has been shown to increase (Paolisso et al., 1991) as well as decrease (Ohrvall et al., 1995) insulin sensitivity. Its use in the treatment of NIDDM is not very effective, but may be used in conjunction with other treatments.

D. Metal Ions

The commonly used metal ions to treat diabetes and having an effect on fatty acid metabolism are chromium, vanadium, and molybdenum.

a. Chromium

The role of chromium in improving diabetes and its effect on lipid metabolism has been reviewed by Anderson (1995). In humans and diabetic animals chromium has been shown to have beneficial effects on glucose homeostasis and on lipid metabolism. Chromium appears to act via potentiating the effects of insulin by increasing insulin binding to cells (Anderson et al., 1987). Trivalent chromium in organic form appears to be a biologically active form. Chromium has been shown to decrease total cholesterol, LDL-cholesterol and TG, and increase HDL-cholesterol in subjects with IDDM as well as NIDDM (Canfield, 1979; Nath et al., 1979; Mossop, 1983; Evans, 1989; Anderson et al., 1997). In streptozotocin diabetic rats, glucose tolerance factor (GTF), a chromium-containing compound, reduces TG and FFA levels but has no effect on total cholesterol or HDL levels (Mirsky, 1993). In genetically diabetic mice, GTF decreased plasma TG and cholesterol levels (Tuman and Doisy, 1977).

b. Vanadium

In streptozotocin diabetic rats, vanadium compounds have beneficial effects on glucose and lipid metabolism. Vanadium lowers serum glucose level, decreases serum FFA and normalizes epinephrine-stimulated FFA release from adipose tissue (Brichard et al., 1994; Nakai et al., 1995; Sakurai et al., 1995). Vanadium appears to act via incorporation into adipose tissue (Nakai et al., 1995) and by improving low thyroid hormone status (Sakurai et al., 1995). Vanadium also partially increases mRNA and activities of key lipogenic enzymes, ACC and FAS in liver but not in adipose tissue (Brichard et al., 1994). Recently, new vanadium and zinc complexes have been synthesized (Yamaguchi et al., 2006). Vanadium compounds appear to have more insulin-mimetic activity than zinc compounds as measured by the effect on FFA release from rat adipocytes treated with epinephrine (Yamaguchi et al., 2006). Similarly, in streptozotocin diabetic rat macrocyclic binuclear oxovanadium complex lowered the elevated levels of lipids in plasma and tissue to near normal levels. It lowered the levels of LDL-cholesterol and increased the HDL-cholesterol levels and also normalized the altered fatty acid composition in liver and kidney (Ramachandran and Subramanian, 2005). The insulin-mimetic activity and the molecular mechanisms of various vanadium complexes had been reviewed by Scior et al. (2005). Wang et al. (2006) reported that in streptozotocin-treated mice, zinc supplement prevents diabetic cardiomyopathy via increased cardiac metallothionein.

c. Molybdenum

In streptozotocin diabetic rats, molybdenum decreased hyperglycemia and glucosuria and corrected the elevation of plasma FFA. Molybdenum also reversed low expression and activity of ACC and FAS in liver but not in adipose tissue (Ozcelikay et al., 1996). Thus, both vanadium and molybdenum, mimics certain insulin actions.

E. Other Agents

Probucol, an antioxidant, appears to decrease the oxidation of LDL in diabetic subjects. Addition of MUFA further decreases LDL oxidation, especially of dense LDL, which is more susceptible to oxidation (Reaven et al., 1996) and is more atherogenic.

Hydralazine, an antihypertensive drug, decreases serum TG and cholesterol in streptozotocin diabetic rats without affecting hyperglycemia. It also increases the binding of fatty acids by myocardial plasma membrane FABP (Heylinger et al., 1995).

Pyrazinoylguanidine reduces serum FFA, glucose and TG in hypertensive diabetic subjects and reduces glycosuria (Vesell et al., 1994). Thus, this drug appears to be beneficial for treatment of glucose as well as lipid abnormalities. Whether it is effective in treating diabetic subjects without hypertension remains to be studied.

β_3 *Adrenergic receptor* (β3AR) agonist treatment has been reported to normalize blood glucose, and decrease insulin and FFA levels in obese (ob/ob) mice (Arbeeny et al., 1995). Since similar defects are present in diabetes, β3AR agonists may also have therapeutic value in the treatment of NIDDM. Thus, a decrease in basal level of mRNA for the β3AR in brown adipose tissue in obese mice compared to lean controls has been observed.

Ascorbic acid supplementation alleviates hyperlipidemia in streptozotocin diabetic rats without affecting hyperglycemia or hypoinsulinemia (Dai and McNeill, 1995) suggesting that combination treatment of hypoglycemic and hypolipidemic agents may be beneficial.

Indobufen is an antiaggregatory agent and inhibits platelet aggregation by interfering with cyclooxygenase enzymes in platelets. In diabetic subjects it significantly lowers lipid peroxidation without affecting fatty acid composition of platelet phospholipids (Dmoszynska et al., 1995).

L-Propionylcarnitine (LPC) has beneficial effect in the heart of streptozotocin diabetic rats. It increases the rates of glucose and palmitate oxidation by heart (a favorable shift in glucose and fatty acid metabolism) and prevents the depression of cardiac mitochondrial respiration seen in diabetes (Broderick et al., 1996). LPC also has beneficial effect on neuropathy and retinopathy (Hotta et al., 1996).

Etomoxir, an inhibitor of CPT-I and fatty acid synthesis, has been reported to reduce high serum TG, FFA, and cholesterol in streptozotocin diabetic rats. It had no effect on low serum insulin or triiodothyronine (T_3) (Rupp et al., 1994). In NIDDM subjects it decreased blood glucose and improved lipid parameters, namely decreases in TG and cholesterol (Ratheiser et al., 1991).

Enprostil, a synthetic dehydoprostaglandin E_2, treatment for 1 week significantly reduced postprandial plasma FFA and TG and slightly decreased in cholesterol in NIDDM patients (Reaven et al., 1988). Thus, it may be useful in treating lipid disorders in type 2 diabetic subjects.

NO lowering agents such as nicotinamide and aminoguanidine may also be considered for diabetic treatment.

VII. CONCLUSIONS AND AREAS FOR FURTHER STUDY

In diabetes, fatty acid metabolism is altered qualitatively as well as quantitatively. Dyslipidemia appears to be due to altered lipogenesis as well as lipolysis, possibly due to hormonal imbalance. The desaturases that are responsible for synthesis of PUFAs are decreased in diabetes. This leads to more saturated fatty acid and less PUFA, especially AA in tissue phospholipids and other lipids. As a consequence, membrane fluidity is altered and eicosanoid production of 2-series is decreased. Dietary fish oils have several beneficial effects in normal and nondiabetic hyperlipidemic subjects, but in diabetic subjects the beneficial effects on lipid metabolism are offset by the deleterious effects on glucose homeostasis, and hence fish oils should be used with caution. Exercise has beneficial effects on carbohydrate and lipid metabolism in both NIDDM and IDDM, but in IDDM blood glucose levels and insulin dose requirements should be closely monitored during strenuous and/or prolonged exercise. Recently, soybean and flaxseed containing isoflavones and lignans have been found to have beneficial effects in lowering lipids in diabetic subjects.

Though we have gained significant knowledge on the fatty acid metabolism in diabetes, several areas need to be further explored.

1. The effect of ω-3 fatty acids, especially those from fish oils, on insulin has been studied in detail, but the effects on other hormones have not been investigated in detail in normal or diabetic subjects.
2. Lipid and carbohydrate metabolism are quantitatively different between males and females. In addition to pancreatic hormones, female sex hormones also play a role in lipid metabolism (Bhathena et al., 1989b). The differences in lipid metabolism between male and female diabetic subjects need to be studied in detail.
3. Recently, opiates and neuropeptides have been shown to be involved in the control of glucose and lipid metabolism. Limited data exist regarding the effect of dietary lipids on opiates and neuropeptides in diabetes.
4. The role of dietary fatty acids on insulin receptors in diabetes have been studied in detail, but the effects on the receptors of the counterregulatory hormones—glucagon, cortisol, growth hormone, catecholamines—need to be explored.
5. Diabetes, more often than not, is accompanied by increased risk and incidence of micro- and macroangiopathy, atherosclerosis, hypertension, nephropathy, peripheral polyneuropathy, and retinopathy. Though not discussed in this chapter, several abnormalities in the lipid metabolism have been well documented in these complications. However, the effects of dietary lipids on hormonal balance and metabolic fate of fatty acids—de novo synthesis, oxidation, desaturation, formation of eicosanoids—need to be further explored in these conditions.
6. Alteration in membrane fluidity has been clearly demonstrated in diabetic subjects. The effect of fatty acids on membrane fluidity in normal subjects has been studied in detail, and several of these studies have suggested the possible role of dietary fatty acids in the alteration in membrane fluidity in diabetic subjects. However, this needs to be demonstrated experimentally.
7. The TFAs appear to have more deleterious effects in humans than saturated fatty acids. No significant data exist on the metabolism of TFA in diabetes. Also the role of hormones on the metabolism of TFAs and the effects of TFAs on hormone levels in diabetes are not known.
8. The decrease in Δ9 and Δ4 desaturases and their regulation by dietary fatty acids and other factors remain unexplored.
9. The control of ω oxidation of fatty acids in diabetes also needs to be explored.
10. The role of oral hypoglycemic and lipid-lowering agents on platelet function and eicosanoid formation in diabetes is briefly reported here, but it needs further study.
11. Recently, amylin, interleukins and other cytokines, calcitonin gene-related peptide, and TNFs have been implicated in the pathogenesis of diabetes. Except for TNF's role in LPL modulation, not much is known about the role of these factors in lipid and fatty acid metabolism in diabetes. This is a new and exciting area of research.
12. Modified insulin (lispro insulin) where lysine and proline are exchanged at position B29 and B30, as well as acetylated insulin derivative (lys B29-tetradecanoyl des-[B30]) have been introduced to treat diabetes. Their effect on fatty acid and lipid metabolism needs to be evaluated.
13. Some of the advantages of breast feeding are attributed to the fatty acid composition of human milk (Lanting and Boersma, 1996). It is thus important to study long-term effect of fatty acids in breast milk compared to formula milk on the incidence of NIDDM and other chronic diseases in children.
14. Though progress has been made in the area of relationship between fatty acids and insulin resistance, the possible beneficial effects of lowering or preventing insulin resistance through increasing AA, EPA, and DHA and lowering linoleic acid and TFA on the incidence of NIDDM need to be further studied.
15. The studies on fatty acid metabolism in gestational diabetes are lacking and need to be carried out.

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