

Review article

# Relationship of dietary fat to glucose metabolism

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## Abstract

The relationship between dietary fat and glucose metabolism has been recognized for at least 60 years. In experimental animals, high fat diets result in impaired glucose tolerance. This impairment is associated with decreased basal and insulin-stimulated glucose metabolism. Impaired insulin binding and/or glucose transporters has been related to changes in the fatty acid composition of the membrane induced by dietary fat modification. In humans, high-fat diets, independent of fatty acid profile, have been reported to result in decreased insulin sensitivity. Saturated fat, relative to monounsaturated and polyunsaturated fat, appears to be more deleterious with respect to fat-induced insulin insensitivity. Some of the adverse effects induced by fat feeding can be ameliorated with omega-3 fatty acid. Epidemiological data in humans suggest that subjects with higher intakes of fat are more prone to develop disturbances in glucose metabolism, type 2 diabetes or impaired glucose tolerance, than subjects with lower intakes of fat. Inconsistencies in the data may be attributable to clustering of high intakes of dietary fat (especially animal fat) with obesity and inactivity. Metabolic studies suggest that higher-fat diets containing a higher proportion of unsaturated fat result in better measures of glucose metabolism than high-carbohydrate diet. Clearly, the area of dietary fat and glucose metabolism has yet to be fully elucidated. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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## 1. Introduction

The amount and type of specific dietary fatty acids has a significant effect on various metabolic processes. The field studied most intensively is that of lipid metabolism, however, there is strong evidence that glucose metabolism might be affected as well. The pioneering studies about the possible effect of dietary fat on glucose metabolism in animals and humans were published by Himsworth in the 1930's [1,2]. On the basis of results garnered from a single subject fed diets containing 20 or 80% of energy as fat he concluded that "it is now securely established that the glucose tolerance of a

healthy individual is determined by the composition of the diet which he is receiving" [3]. Current dietary recommendations for diabetic patients by the American Diabetes Association [4] parallel those of the National Cholesterol Education Program (NCEP) for hyperlipidemic subjects [5]. The primary emphasis is on reducing total and saturated fat, and cholesterol intakes. In this review, both animal and human studies will be discussed according to the following scheme:

2. Animal data
  - 2.1. Level of fat
  - 2.2. Type of fat (degree of saturation)
3. Human studies
  - 3.1. Metabolic studies/in vivo feeding trials
  - 3.2. Metabolic studies/in vitro studies
  - 3.3. Epidemiological studies

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## 2. Animal data

### 2.1. Level of fat

In an initial report on the effect of high-fat diets inducing glucose intolerance, Himsworth [6] reported that rabbits fed 50 g fresh cabbage and 120 g soybean oil per day exhibited a decreased sugar tolerance compared with rabbits fed 250 g fresh cabbage and 150 g oat bran per day. He suggested that fat feeding “retards and diminishes the action of insulin on blood sugar; prevents or delays the progressive improvement of sugar tolerance which occurs on injection of consecutive doses of glucose; and impairs the ability of insulin to diminish the hyperglycemia following intravenous injection of glucose”. These differences were attributed to the availability of circulating insulin at the time of food ingestion or glucose infusion. At the time, the ability to monitor plasma insulin levels was yet to be developed. Himsworth did not report body weight in this study. It is very likely that the cabbage and oil fed rabbits were heavier at the end of the study, since they got more than twice the amount of energy compared to the cabbage and bran fed rabbits. Weight gain predisposes to disturbances in glucose metabolism. For this reason, interpretation of results of diet studies in which body weight has changed is difficult.

Little attention was paid to this observation until the late 1960's, during which a number of papers were published which confirmed Himsworth's original observation — that fat feeding in experimental animals (rats) resulted in hyperglycemia and was accompanied by impaired glucose tolerance. These observations in ‘fat-adapted’ rats were attributed to impaired disposal of glucose by peripheral tissues due to decreased sensitivity to endogenous insulin [7–16]. Focusing on adipose tissue, Zaragoza-Hermans and Felber [12] suggested that fat feeding induced a reduction in glucose uptake and oxidation, or conversion to fatty acids, that was secondary to decreased insulin sensitivity. However, the major site for insulin stimulated glucose utilization is muscle instead of adipose tissue. Interestingly, with the exception of Himsworth [6], the source of fat in the diets used to induce impairment of glucose metabolism (‘fat-adapted’) was lard (35–67% of energy). At this point no reference was made to the fatty acid composition of the diet and the consequent glucose intolerance, just to the level of fat.

Subsequent work up until 1986 continued to pursue the abnormalities in glucose metabolism induced by fat feeding, however, this work was for the most part still independent of the fatty acid composition of the diet (for the exceptions Section 2.2, 17–21). The major focus of the studies regarding the level of fat in the diet was to characterize further the type of glucose intolerance induced by fat feeding and determine the mecha-

nism(s) for the abnormalities observed. In most of these studies the major focus was on adipose tissue.

Ip et al. [22] compared adipocytes (fat cells) isolated from Sprague-Dawley albino rats fed a high-glucose or high-fat (lard, 67% of energy) diet with respect to insulin binding. They reported that adipocytes isolated from the rats fed the high-fat diet bound less insulin and showed a decreased response to insulin (glucose oxidation) compared with rats fed the high-glucose diet. These results were consistent, regardless of whether high or low affinity binding sites were assessed. The authors concluded that fat feeding modifies the fat cell so that decreased numbers of binding sites for insulin are available. No significant changes in affinity for the hormone were demonstrable. At this point, no mention was made that a change in the fatty acid composition of the membrane, hence membrane fluidity, may have altered receptor activity.

Soon thereafter, Olefsky and Saekow [23] reported the results of a similar study. Sprague-Dawley rats were fed either a high-fat (lard, 67% of energy) or high-glucose diet. Adipocytes isolated from rats fed the high-fat diet exhibited a decrease in number of insulin receptors as well as a decrease in activity of the glucose transport system and intracellular glucose metabolism. All aspects of glucose metabolism assessed, insulin binding (a measure of receptor number), glucose transport, and intracellular capacity to oxidize glucose, were depressed. In contrast, the high-glucose fed rats exhibited decreased insulin binding but enhanced activity of both the glucose transport system and intracellular pathways of glucose metabolism compared to the high-fat fed rats. The authors stated that “It has been shown that major changes in plasma membrane phospholipid composition occur on such a diet (high-saturated fat), and these alterations in membrane structure and composition could be responsible for the changes in plasma membrane function which we have observed.” This was the first time that the issue of the fatty acid composition of the high-fat diet and its subsequent effects on membrane composition and function was noted.

Lavau et al. [24] further addressed issues related to the mechanism by which high-fat diets resulted in insulin resistance in adipocytes. Wistar rats were fed a high-fat (lard, 70% of energy) or high-carbohydrate (wheat starch, 70% of energy) diet. They reported that rats consuming the high-fat diet exhibited a blunted response of glucose metabolism to insulin administration and suggested that this could be attributed to decreased intracellular capacity to utilize glucose for lipogenesis (fatty acid synthesis). Their conclusion was based on biochemical evidence indicating a decrease in the activities of intracellular enzymes associated with fatty acid synthesis.

Baxter and Schofield [25] reported that a high-fat diet (30% w/w, corn oil) fed to Wistar rats made diabetic

with streptozotocin caused a significant decrease in the extent of polydipsia (increased water intake), polyphagia (increased food intake), polyuria (increased urination), and glycosuria (glucose in the urine) relative to a high-carbohydrate diet. Thus, the authors shifted the focus of the work at this point from the effect of a high-fat diet on the induction of glucose intolerance to the effect of a high-fat diet on the control of experimentally induced diabetes. The authors stated that, "Thus, in general, the effect of the fat in the diet in the diabetic animals is to partly reverse some of the diabetes-induced enzyme changes." They attributed the beneficial effects of the high-fat diet to a decrease in the carbohydrate intake of the rats. No mention was made of why they departed from using lard (saturated fat) as the primary source of fat in the high-fat diet as had been done by previous workers in the field. It should also be noted that this is the only report suggesting a beneficial effect of fat feeding in diabetic animals. The use of an unsaturated source of dietary fat is an unlikely explanation for the discrepancy, since subsequent work, more consistent with the deleterious effects of dietary fat, also used an unsaturated source of fat [26,27]. Additionally, potentially partial preservation of  $\beta$  cell function after streptozotocin treatment may have contributed to the inconsistent findings of this study compared to previous work.

Salans et al. [28] focused on the effect of high-fat (50% of energy; vegetable oil) and low-fat (9% of energy) diets on glucose metabolism in adipocytes isolated from CD strain of rats. There was no effect of fat feeding on insulin binding or the cell sensitivity to insulin. However, fat feeding resulted in a significant decrease in the transport of glucose across the plasma membrane and in the maximal capacity of the cell for glucose utilization.

Hissin et al. [29] investigated the effect of fat feeding on glucose transport activity in adipocytes isolated from Sprague-Dawley rats fed a high-fat (50% of energy; vegetable oil) or low-fat diet. They reported that basal glucose transport activity was not significantly influenced by feeding the high-fat diet; however, maximally insulin-stimulated glucose transport activity decreased and was accompanied by a decrease in the glucose transport systems. Therefore, it appeared that the insulin resistance induced by consumption of the high-fat diet was attributable to a decrease in the intracellular pool of glucose transport systems. The authors suggested that this decrease may be a reflection of a general systematic impairment of insulin action. The changes observed due to fat feeding were unrelated to adipose tissue mass per se.

Shifting the tissue of interest to muscle, which is the major site of insulin action, Grundleger and Thenen [30] assessed the effect of feeding a high-fat (67% of energy, hydrogenated fat) or high-carbohydrate (67% of

energy, corn starch) diet to lean Zucker rats (a strain of rat whose litter mates become spontaneously obese) on insulin binding and glucose metabolism in soleus muscle. They reported that both in vivo and in vitro measures of insulin resistance were enhanced by fat feeding. These included decreased insulin receptor number independent of a change in receptor affinity, decreased insulin-stimulated glucose transport, and pathway-specific alterations in basal and insulin-stimulated glucose metabolism.

Storlien et al. [31] assessed the effect of fat feeding on in vivo insulin resistance and energy expenditure in rats. Wistar rats were pair fed high-fat (59% of energy, safflower oil) or high-carbohydrate (one-third sucrose, two-thirds starch) diets. The investigators concluded that the high-fat diet resulted in whole-body insulin resistance resulting from resistance both at the level of individual peripheral tissues (decreased glucose utilization in skeletal muscle and brown adipose tissue) and liver. They suggested that a reduction in postprandial thermogenesis could predispose the rats to the development of obesity. Fat feeding had no effect on basal metabolic rate. In this same year the first report on type of fat and fat induced glucose intolerance was recorded (see Section 2.2).

Kraegen et al. [32] investigated peripheral insulin action in Wistar rats fed high-fat (59% of energy, safflower oil) or high-carbohydrate (one-third sucrose, two-thirds starch) diets. Fat feeding did not result in hyperinsulinemia but mildly reduced basal glucose metabolism in skeletal muscle (diaphragm) and substantially reduced glucose metabolism in other tissues, such as adipose tissue and heart, despite hyperinsulinemia. When the rats were made hyperinsulinemic, insulin resistance was exacerbated (decreased mean whole body net glucose utilization in both skeletal muscle and adipose tissue). The authors concluded that fat feeding resulted in insulin resistance primarily due to decreases in the oxidative capacity of skeletal muscle.

Chisholm and O'Dea [26] designed a study to determine the effects of a high-fat diet on glucose sensitivity in rats with experimentally induced diabetes. Sprague-Dawley rats were fed either a high-fat (66% of energy; corn oil and lard) or a low-fat (12% of energy; whole-meal flour) diet. Both diets had a polyunsaturated-to-saturated fatty acid (*P/S*) ratio of 1:3. Mild insulin deficiency was induced with streptozotocin in half the rats in each group. Fasting glucose concentrations, but not insulin concentrations, were higher in the rats fed the high-fat diet, independent of streptozotocin treatment. This is in contrast with the report by Baxter and Schofield [25]. The rate of removal of an intravenous glucose load was impaired in both groups of rats fed the high-fat diet, independent of streptozotocin treatment, and could not be attributed to a defect in basal or insulin-stimulated glucose utilization in peripheral

tissues. Response to exogenous insulin was similar in all groups of rats. It was concluded that the high-fat diet, in either control or diabetic rats, did not result in alterations in glucose metabolism or insulin sensitivity in muscle.

Watarai et al. [33] further investigated the mechanism responsible for the insulin resistance observed after high-fat feeding in rats. Sprague-Dawley rats were fed either a high-fat (60% of energy, lard) or high-carbohydrate (61% of energy, wheat flour) diet. Consumption of the high-fat diet resulted in insulin resistance manifested by hyperinsulinemia and decreased response of adipocytes to insulin. Decreased insulin-stimulated glucose uptake was attributed to a decrease in the insulin-stimulated phosphorylation of the  $\beta$ -subunit of the insulin receptor. For the most part, this study was consistent with the results of previous work [22–24,28,29]. The different measures of insulin sensitivity of adipose tissue used in the different studies to date reflected a refinement of the technology available to evaluate the insulin/glucose relationship.

Nagy et al. [34] investigated the effect of a high-fat diet on tissue specific insulin sensitivity. Weanling Sprague-Dawley rats were fed either laboratory chow or a high-fat (31% lard) diet. Fat fed rats gained significantly more body weight and had higher glucose, insulin, and triglyceride levels. The activity of the insulin receptor's  $\beta$ -subunit (insulin-sensitive autophosphorylation, tyrosine kinase activity toward a synthetic substrate, and content of 'activated' phosphotyrosyl-containing insulin receptors) was assessed. These measures were increased in the partially purified receptors from kidney basolateral membranes and decreased in those from the liver and skeletal muscle of the rats fed the high-fat diet. The authors concluded that 'tissue-specific alterations in transmembrane signaling induced by high-fat feeding in target tissues for insulin... might contribute to the observed insulin resistance'.

To further investigate the mechanism by which fat feeding decreases insulin sensitivity, Pedersen et al. [35] investigated the activity of two glucose transporters (GLUT1 and GLUT4) in adipocytes as a function of dietary modification. Four groups of Sprague-Dawley rats were each fed diets that differed in fat and calorie contents. This review will focus on two groups, high-fat (lard) and high-carbohydrate (mainly sucrose and glucose) fed rats. Rats fed the high-fat diet exhibited lower plasma glucose and insulin concentrations than the rats fed the high-carbohydrate diet. Basal rates of glucose transport were similar between the two groups of animals, however, maximal insulin-stimulated rates of glucose transport were lower in the high-fat group. High-fat feeding resulted in a decrease in the levels of GLUT4 protein and mRNA. Additionally, GLUT4 protein concentrations per adipocyte decreased relatively more than the glucose transport rate, suggesting

up-regulation of functionally active GLUT4 transporters in the plasma membrane or enhanced glucose transporter intrinsic activity. The authors suggested that the mechanism responsible for the alterations in GLUT4 expression as a result of the high-fat diet might be related to the hypoinsulinemia, since similar responses of GLUT4 have been observed in both diabetic and fasted rats. Unexplained was the observation of lower plasma glucose concentrations in the high-fat fed rats compared to the high-carbohydrate fed rats relative to other work addressing the effect of fat feeding and insulin resistance.

Pascoe et al. [27] investigated dietary fat-induced insulin resistance by assessing the effect of fat feeding in control and mildly diabetic (very low-dose neonatal streptozotocin induced non-insulin dependent diabetes mellitus or type 2 diabetes) rats. Wistar rats consumed either a high-fat (safflower oil, 59% of energy) or high-carbohydrate (starch) diet. The fat fed rats exhibited reductions in basal glucose clearance and basal hepatic glucose output. Furthermore, whole-body and tissue-specific insulin sensitivity were significantly depressed in fat-fed rats compared to starch-fed rats.

Hedeskov et al. [36] assessed the effect of long-term fat feeding in NMRI mice. As previously observed, initially in rabbits, and subsequently in different strains of rats, fat feeding results in impaired glucose tolerance and plasma insulin concentrations increase. These observations are consistent with the development of insulin resistance and with reduced peripheral and hepatic uptake of glucose. Post-receptor metabolic disorders of the liver, muscle, and adipose tissue were identified by assessing the activities of a number of intracellular enzymes involved with glucose and fatty acid metabolism. The authors concluded that the fat-induced insulin resistance observed was similar to that demonstrated in human type 2 diabetes.

Traianedes et al. [37] assessed the effect of a high-fat diet on the metabolic control in Sprague-Dawley rats made mildly diabetic with streptozotocin. Rats were fed a low-fat (wholemeal flour) or high-fat diet (butter or lard). Fat feeding alone induced hyperglycemia, and this was exacerbated in the diabetic rats. This hyperglycemia was due predominantly to an increase in hepatic glucose production, both in the basal and hyperinsulinemic states. The authors concluded that a high-fat diet induces hepatic insulin resistance leading further to an overproduction of glucose by the liver.

Barnett et al. [38] studied the effect of the inhibition of fatty acid oxidation with etomoxir (inhibitor of carnitine palmitoyltransferase) on fat feeding in rats made diabetic with streptozotocin. In this study Sprague-Dawley rats (both diabetic and control) consumed a high-fat diet (50% of energy, butter): diabetic rats exhibited significantly higher fasting glucose and plasma triglyceride levels than normal rats. The inhibi-

tion of fatty acid oxidation reduced fasting glucose concentrations independent of alterations in fasting insulin levels. These data are consistent with improved insulin sensitivity, perhaps induced by a shift in available substrate for energy utilization; from fat to glucose.

Storlien et al. [21] assessed the effect of high-fat diets (59% of energy, safflower oil) on glucose sensitivity in Wistar rats. They suggested that the mechanism for the fat induced insulin resistance is attributable to either an increased accumulation of triglyceride in skeletal muscle, thereby providing an alternate fuel to glucose, or to a change in the fatty acid composition of the membrane, altering fluidity and perhaps receptor activity. (See Section 2.2 for additional results on type of fat).

Capito et al. [39] assessed the effect of fat induced diabetes on mouse pancreatic islet insulin secretion, insulin biosynthesis and glucose metabolism. Glucose stimulated insulin secretion was decreased in islet cells from fat fed mice and was accompanied by a significant decrease in islet glucose oxidation. Insulin secretion stimulated in islet cells by non-carbohydrate compounds was moderately, but not significantly, increased. Fat feeding resulted in decreased pancreatic insulin content and pro-insulin mRNA. These findings are similar to those found in humans diagnosed with type 2 diabetes.

Iwanishi and Kobayashi [40] used fat fed rats (Sprague-Dawley, 60% of energy saturated fat, lard) as a model of type 2 diabetes to evaluate the effect of an oral hypoglycemic agent, 5-[4-[2-(5-ethyl-12-para-ethoxy)]-benzyl]-2,4-thiazolidinedione (pioglitazone), as a form of therapy. Two weeks of treatment with pioglitazone resulted in a decrease in hyperlipidemia and hyperinsulinemia. These data suggested that insulin sensitivity was increased in the drug treated high-fat fed rats. The authors further reported that attenuation of the hyperinsulinemia was attributable to increased insulin-stimulated autophosphorylation of insulin receptors. Pioglitazone had no effect on insulin binding to the hindlimb skeletal muscle. The benefits of pioglitazone treatment of fat-induced glucose intolerance was due to an increased sensitivity to insulin that resulted from activation of the tyrosine kinase activity of the insulin receptors.

Storlien et al. [21,31] had initially reported that the insulin resistance observed in rats as a result of fat feeding was primarily due to increased triglyceride storage in the muscle and/or changes in membrane fatty acid composition. To pursue this work further Storlien et al. [41] assessed the effect of altering intracellular skeletal muscle triglyceride levels with benfluorex on insulin resistance. Using their standard model for diet-induced diabetes (59% of energy fat as safflower oil; Storlien et al. [31]) fat feeding had no significant effect on plasma triglyceride levels, but increased skeletal

muscle triglyceride content. Treatment with benfluorex normalized stored triglyceride levels in muscle and prevented the development of skeletal muscle insulin resistance. The authors concluded that their work “supported the hypothesis that the development of muscle insulin resistance...” is linked to local or systemic oversupply of lipid”. A possible mechanism for the effect on glucose utilization of the increased lipid availability in muscle tissue might be the glucose/fatty acid cycle [42,43]: with increasing availability of triglycerides in the muscle tissue more triglycerides are being utilized to produce energy for muscle tissue and less glucose is utilized as a source of energy, leading to decreased glucose utilization. However, in a recent study insulin stimulated glucose transport was reduced in muscles of fat-fed rats under anoxic conditions under which fatty acid oxidation should not have occurred [44].

Kusunoki et al. [45] assessed the effect of glucocorticoid blockade (antiglucocorticoid RU486) on fat feeding (59% of energy; safflower oil) induced insulin resistance in skeletal muscles of Wistar rats. Treating the rats with RU486 resulted in a significant improvement in the skeletal muscle insulin resistance produced by fat feeding. The authors stated that “The results suggest that glucocorticoids play, in a tissue-specific manner, a role in the maintenance and/or production of insulin resistance produced by high-fat feeding”.

From a review of the literature to this point on fat feeding in experimental animals and insulin resistance it can be concluded that high-fat diets result in insulin resistance, as evidenced in rabbits, rats (multiple strains), and mice. Striking has been the rather arbitrary selection of the type of fat (saturated and/or polyunsaturated) used to induce the insulin resistance. Multiple mechanisms for fat-induced glucose intolerance have been invoked and the syndrome is likely to be multifactorial. In rats, high fat feeding has been found to decrease basal and insulin-stimulated glucose utilization [30,31]. A decrease in the binding of insulin to its receptor resulting in an impairment in the action of some enzymes, e.g. pyruvate dehydrogenase and tyrosine kinase [33,34,46] has also been reported as well as the decrease in the active form of glycogen synthase leading to a defect in glucose storage as glycogen [36]. A decrease in the amount of GLUT4 has been reported in some [47,48], but not all studies [44]. In addition, high fat diets fed to mice have been reported to diminish GLUT4 translocation to the plasma membrane [49]. It has also been suggested that fatty acids cause  $\beta$ -cell insensitivity to glucose by down regulating acetyl-CoA carboxylase, the enzyme that catalyzes the formation of a key regulator of fatty acid oxidation, malonyl-CoA [50]. In a  $\beta$ -cell line, a prolonged exposure to palmitate, oleate, and linoleate resulted in high basal insulin release and suppression of glucose-induced insulin secre-

tion. No significant difference among individual fatty acids was reported [50].

## 2.2. Type of fat (degree of saturation)

To this point, insulin resistance had been reported to result from high-fat diets; however, the major fat source in the diet was either high in saturated fat [22–24,33–35,37,38,40], hydrogenated fat ([30] (otherwise undefined)), or polyunsaturated fat [6,21,25,27–29,31,32,41,45]. Work related to the impact of type of fatty acids, rather than total amount of fat, on glucose homeostasis is far more limited.

Directly addressing the issue of dietary fat type on insulin resistance, van Amelsvoort et al. [17] isolated adipocytes from Wistar rats born to dams fed high-fat diets enriched in either palm (saturated) or sunflower (polyunsaturated) oil while pregnant and then raised on a similarly enriched diet. They observed that feeding palm oil resulted in a lower rate of insulin stimulated glucose uptake and insulin binding to cells (lower number of low-affinity binding sites) than feeding sunflower oil. Assessing the fatty acid composition of the adipocyte phospholipid fraction (primarily membrane lipid), they reported that the profile reflected that of the fat fed to the dams and later to the offspring. They concluded that “diet-induced differences in fatty acid composition of the phospholipid... caused a difference in the physicochemical properties of the fat cell membranes, which could be responsible for the observed differences in insulin response.” The absence of a chow-fed group precluded assessing whether feeding a high-fat sunflower oil diet itself induced insulin resistance; however, from previous work [6,21,25,27–29,31,32,41,45], it can be assumed that it did.

Also focusing on the type of fat, Storlien et al. [18] investigated the effect of replacing  $\approx 6\%$  of linoleic acid in a high-fat diet containing 59% of energy from safflower oil with long-chain omega-3 fatty acids derived from fish oil (tuna) for 24 days. They reported that this modest substitution prevented the development of insulin resistance at the whole-body level in Wistar rats. The major sites of action were the liver and skeletal muscle. No effect was seen in heart and lung. The authors postulated that potential mechanisms responsible for the effects seen included alterations in the production of various prostaglandins, thromboxanes, and prostacyclins (unique to long-chain omega-3 fatty acids; eicosapentaenoic and docosahexaenoic acids), changes in membrane fluidity, or inhibition of very low density lipoprotein synthesis by the liver, hence, a switch in the fuel available for energy metabolism. It is important to note that the authors state that although “...the relation of fat intake to insulin resistance in humans has been established largely on the basis of epidemiological studies... there is little evidence con-

cerning alterations in insulin sensitivity in humans after the kind of changes in dietary fat described here”.

Field et al. [19,20] fed control and diabetic (streptozotocin-induced) rats high-fat diets with either a low-P/S ratio (0.2) or high-P/S ratio (2.1) for 42 days. Consumption of the low-P/S ratio diet resulted in an decrease in the polyunsaturated fatty acid content of membrane phospholipids of adipose tissue from both the control and diabetic rats. This was accompanied by a decrease in insulin binding in the control rats but not in the diabetic rats. Feeding the diet with a low-P/S ratio, hence higher saturated fat intake, decreased the rates of insulin stimulated glucose transport, oxidation and lipogenesis.

Further pursuing the relationship between fat type and insulin resistance, Storlien et al. [21] assessed the effect of high-fat diets (59% of energy) enriched in saturated fat (136 g edible tallow and 203 g safflower oil), monounsaturated fat (olive oil), polyunsaturated fat (safflower oil), polyunsaturated fat + long-chain omega-3 fatty acids (237 g safflower oil + 102 g fish oil), polyunsaturated fat + short-chain omega-3 fatty acids (268 g safflower oil + 71 g linseed oil, *n*-3 linolenic acid, 11% of energy), and saturated fat + short-chain omega-3 fatty acids (268 g edible tallow + 71 g linseed oil) on insulin resistance. The authors reported that regardless of the fatty acid profile, high-fat diets resulted in increased insulin resistance relative to chow-fed animals. Insulin resistance was greatest in the group of rats consuming the saturated fat-enriched diet relative to the other two diets. As previously reported by these authors [18], the addition of long-chain omega-3 fatty acids, eicosapentaenoic and docosahexaenoic acids (20:5*n*-3 and 22:6*n*-3, respectively), resulted in the amelioration of insulin resistance. In contrast, addition of similar amounts of a short-chain omega-3 fatty acid,  $\alpha$ -linolenic acid (18:3*n*-3), had no effect on insulin resistance. The addition of  $\alpha$ -linolenic acid to the saturated fat-enriched diet resulted in levels of insulin resistance similar to those of the chow-fed animals. There was a strong relationship between insulin-stimulated glucose metabolism and the percent of long-chain omega-3 fatty acids in the phospholipid fraction of red quadriceps (skeletal muscle).

The work cited in this section is particularly important because it established that relatively short-term (30 days) feeding of high-fat diets, independent of fatty acid profile, resulted in an impairment of insulin sensitivity, that saturated fat, relative to monounsaturated and polyunsaturated fats, was more deleterious with respect to fat-induced insulin insensitivity, and that some of the effects induced by feeding a high-fat diet could be ameliorated by adding omega-3 fatty acids to the diet as reported in multiple recent studies [51,52]. Differential effects of the omega-3 fatty acids according to chain length and number of double bonds on high-fat diets

containing different fatty acid profiles were noted. Differential effects of individual fatty acids (varying in chain length) have yet to be addressed. However, this is an important area given the recent report that long chain polyunsaturated fatty acid decrease glucose-6-phosphate dehydrogenase pre-mRNA accumulation whereas monounsaturated fatty acids do not [53]. Additionally, differences among (for example) saturated fatty acids may be important since there is evidence that under  $\text{Ca}^{2+}$  free conditions, palmitate and myristate augment insulin secretion by pancreatic  $\beta$ -cells to same extent as glucose, whereas other saturated fatty acids do not [54].

Regarding the quantitative effects of fatty acid subgroups on glucose homeostasis, the fatty acid modifications in the above mentioned studies have been extreme, and in general, the modification of either the amount of fat or the fatty acid composition has been much more substantial than likely to occur in human diets. For this reason the extrapolation of the quantitative effect of fatty acid groups to a human diet is difficult at this time.

### 3. Human studies

#### 3.1. *Metabolic studies/in vivo feeding trials*

Studies addressing both the level and type of fat will be reported together in this section because in many cases both were varied simultaneously. Dividing the studies into two categories would be arbitrary, and any benefits of forcing such an order are outweighed by the confusion it would create.

In 1927, Sweeney noted that the response to a dextrose tolerance test, used diagnostically for diabetes mellitus, was affected by the composition of the diet consumed a few days prior to the test [55]. Subjects (male medical students) were asked to consume diets high in protein, carbohydrate, or fat (olive oil, butter, mayonnaise made with egg yolk, and 20% cream). Glucose tolerance curves were highest after the subjects consumed the high-fat diet, intermediate after the high-protein diet, and lowest after the high-carbohydrate diet. These differences were attributed to differences in "... the activation of the insulin stimulating hormone...". That is, subjects habituated to the high-carbohydrate diet were the most primed, so to speak, for the rapid glucose influx, whereas subjects habituated to the high-fat diet were the least primed. Similar results were reported by Himsworth [1] and Conn [56].

The first study directly addressing the effect of the quality of fat on glucose metabolism was reported by Kinsell et al. [57] about 40 years ago. There was one subject in this study: a man with type 1 diabetes. He consumed a safflower oil enriched diet and a diet

enriched in synthetic palmitic acid-oleic acid triglyceride. The substitution of safflower oil for the palmitic acid-oleic acid triglyceride resulted in a decrease in the need of exogenous insulin.

Early work suggesting that glucose metabolism was improved by low-fat diets was limited to normal subjects or relatively small numbers of patients with type 2 diabetes [1,58–62]. However, in general, when the effect of a low-fat diet was assessed while controlling for body weight changes, no significant effect in either diabetic control (plasma glucose levels) or insulin requirements was observed [60,63].

In 1971, Brunzell et al. [64] assessed the effect of high-fat (40% of energy, unidentified source) and fat-free formula diets on fasting and postprandial (after an oral glucose load) plasma glucose and insulin levels in normoglycemic and mildly hyperglycemic subjects. The authors reported that fasting plasma glucose and insulin levels decreased in both groups of subjects after consumption of the low-fat diet. In response to an oral glucose tolerance test, total integrated glucose area under the curve was lower after consumption of the low-fat diet. No significant change in the incremental insulin area or percent insulin area was reported as a result of altering the diet. The authors suggested that the "...improvement in glucose tolerance (in response to the low-fat diet) may have been due in part to the decreased fasting glucose levels..." and that "...one possible effect of the carbohydrate-enriched diets is to increase the sensitivity to insulin of tissue sites of insulin action". Plasma triglyceride levels increased in response to the relatively short period (10 days) of time the subjects consumed the low-fat diet. These results have been confirmed in more recent studies [65–71]. The observation of increased plasma triglyceride levels is notable in light of a report by Albrink and Davidson [72] suggesting that increased triglyceride levels caused insulin resistance. However, although plasma triglyceride levels are typically increased in subjects with insulin resistance and type 2 diabetes, there is no evidence in humans that an increase in plasma triglyceride levels itself causes insulin resistance. Although not assessed at the time, increased plasma triglyceride levels were likely accompanied by a decrease in high density lipoprotein levels. Work by Stone and Connor [63] suggested that increased plasma triglyceride levels induced by high carbohydrate diets, and presumably decreased high density lipoprotein levels, was transient.

Obesity is associated with elevated basal plasma insulin levels. Grey and Kipnis [73] assessed the effect of high- or low-fat diets fed at levels to maintain body weight or allow weight loss in obese females on basal insulin concentrations. High-fat (53% of energy, fat type unreported) or low-fat (18% of energy) diets composed of natural foods were fed to subjects for 3-week periods. Basal insulin levels were lower on the high-fat

diet. Obese subjects then consumed high-fat (74% of energy) and low-fat (1% of energy) liquid formula diets in amounts that resulted in weight loss. Basal insulin levels were lower after consuming the high-fat diet compared to the low-fat diet. Re-feeding the low-fat diet, despite weight loss, resulted in an increase in basal insulin levels. After an oral glucose load, insulin secretory response was lower after the subjects consumed the high-fat diet compared to the low-fat diet. The authors concluded that "...the hyperinsulinemia characteristic of obesity may be a result, in part, of dietary factors rather than exclusively a consequence of the insulin antagonism associated with obesity". The extreme nature of the diets limits the generalizability of the data.

Beck-Nielsen et al. [74] supplemented the diets of normal volunteers with either 1000 kcal of sucrose or cream. They reported that there was no effect on fasting plasma insulin or glucose concentrations, or insulin sensitivity, but, there was a significant decrease in specific cell-bound insulin in the fat-supplemented group.

Vessby et al. [75] assessed the effect of substituting polyunsaturated for saturated fat in the diets of hyperlipidemic subjects. The total fat content of the diet was 44% of energy, the diet high in polyunsaturated fatty acids had a *P/S* ratio of 2, whereas the diet high in saturated fatty acids had a *P/S* ratio of 0.2. The diets were isocaloric. The diet high in saturated fatty acids resulted in less favorable glucose tolerance, especially in subjects with type 4 hyperlipidemia (elevated triglyceride levels).

Collier and coworkers conducted a number of studies on the effect of acute fat feeding on blood glucose and insulin levels. They reported that fat + carbohydrate feeding lowered blood glucose and increased insulin levels compared with carbohydrate feeding alone [76,77]. In a follow-up study [78], they assessed the effect of acute high-fat (37.5 g fat as butter + 75 g carbohydrate as lentils) and very low-fat (lentils) feeding on glucose-dependent insulinotropic polypeptide (GIP). GIP potentiates glucose-induced insulin secretion. Ingesting the high-fat relative to the very low-fat diet resulted in increased plasma insulin and C-peptide levels in response to an iv. glucose administration. The increased insulin levels were attributed to increased insulin secretion (as evidenced from increased C-peptide levels). It could not be determined whether increased insulin secretion was attributable to GIP or some other factor. Gatti et al. [79] have examined the acute effect of feeding different types of fats on plasma glucose and insulin responses in ten healthy subjects. Olive and corn oils decreased the postprandial area under the glucose curve, whereas butter delayed the plasma glucose rise without changing the area under the curve. No effect on plasma insulin concentrations was reported.

Coulston et al. [65] compared two isocaloric diets, one with 40% of energy as carbohydrate, 41% of energy as fat and the other with 60% of energy as carbohydrate, 21% of energy as fat, in healthy volunteers. No difference in fasting plasma glucose or insulin concentrations were found, whereas the concentration of plasma triglycerides, and insulin and triglyceride response to a test meal was significantly higher after consumption of the high-carbohydrate diet. In a follow-up study [66], a high-fat diet (40% of energy as both fat and carbohydrate) and a high-carbohydrate diet (60% of energy as carbohydrate, 20% of energy as fat) were consumed for 15 days each by patients with type 2 diabetes. The incremental glucose and insulin responses to a normal meal cycle (08:00–16:00 h), and fasting and postprandial triglyceride levels were higher after the high-carbohydrate compared to the high-fat diet. Subsequent work demonstrated that plasma glucose and insulin concentrations were higher throughout the day when the subjects consumed the high-carbohydrate diet compared to the high-fat diet [67]. The fasting plasma triglyceride levels were increased during the high-carbohydrate diet period.

Garg et al. [68] compared a high-carbohydrate diet (60% of energy as carbohydrate, 25% of energy as fat (9% of energy as monounsaturated fat)) to a high-fat diet enriched in monounsaturated fat (50% of energy as fat (33% of energy as monounsaturated fat), 35% of energy as carbohydrate) in patients with type 2 diabetes. The high-fat diet resulted in lower mean plasma glucose concentrations and reduced insulin requirement as well as decreased plasma triglyceride concentration compared to a high-carbohydrate diet. The authors reported in a follow-up study that in type 2 diabetics similar dietary perturbations had little effect on plasma glucose and insulin responses to a standard breakfast and an euglycemic hyperinsulinemic glucose clamp despite differences in plasma triglyceride levels [69]. In a third study by this group [70], a high-carbohydrate diet (55% of energy as carbohydrate, 30% of energy as fat (10% of energy as monounsaturated fat)) was found to increase fasting plasma triglyceride concentrations and day long glucose, insulin and triglyceride concentrations compared to a high-fat diet enriched in monounsaturated fat (45% of energy as fat (25% of energy as monounsaturated fat), 40% of energy as carbohydrate).

O'Dea et al. [80] assessed the effect of a high-fat (55% of energy, *P/S* = 0.26) and low-fat (12% of energy, *P/S* = 0.71) diet in the treatment of patients with type 2 diabetes. Basal plasma glucose and insulin levels were higher after the subjects consumed the high-fat diet. Levels of glucose and insulin were also higher in the postprandial state after a glucose load. Whether the effects observed were due to level of fat, independent of a concomitant increase in the saturated fat content of the diet, was not assessed.

Abbott et al. [81] assessed the effect of replacing fat (43% of energy to 33% of energy), primarily saturated fat, with carbohydrate, in the diet of Pima Indians diagnosed as having type 2 diabetes. The diets were isocaloric. The outcomes suggested that replacing dietary saturated fat with complex carbohydrate, independent of cholesterol intake, had no adverse effect on either fasting glucose or glucose concentrations 2 h after the oral glucose load. Even in the absence of weight loss, significant improvements in the lipoprotein profile of the subjects were noted.

Heine et al. [82] varied the *P/S* ratio (0.3 and 1.0) of diets fed to patients with type 2 diabetes. Serum total and LDL cholesterol concentrations declined after of the diet within the high *P/S* ratio. In addition, modest increases in insulin-mediated glucose disposal and no differences in glycemic control or blood glucose, plasma insulin, or C peptide responses were reported. The authors concluded that patients with type 2 diabetes may benefit from a reduction in the saturated fat intake with respect to plasma lipid concentrations without an apparent effect in glycemic control or carbohydrate tolerance.

Traianedes [83] assessed the effect of dietary fats on plasma glucose and insulin levels by altering the fatty acid composition of the diet ingested 12 h prior to a standard breakfast. The supplemental fat represented 53% of total energy intake and was provided as safflower oil (polyunsaturated), olive oil (monounsaturated), butter (saturated), or medium-chain triglycerides. No effect of a single dose of any of the fats tested on plasma glucose and insulin levels added to a standard meal was reported. Similar results by this group had been reported in relation to the effect of a fat-containing breakfast on carbohydrate tolerance after lunch [84]. Fat-impaired glucose tolerance was similar, whether the ingested fat was butter (saturated) or peanut butter (unsaturated). Fukagawa et al. [85] investigated the effect of replacing fat with carbohydrate in the diet of normal subjects. There was a decline in the total saturated, monounsaturated, and polyunsaturated fat content of the diet. The results of the study suggested that reducing the fat content of the diet improved “carbohydrate economy by enhanced peripheral sensitivity to insulin”.

Swinburn et al. [86] varied the fat content of the diet of normal Caucasians and Pima Indians (genetically predisposed to type 2 diabetes). The diets contained either 15% fat or 50% fat (*P/S* ratio from 2.7 and 0.5, respectively), the major change being a decrease in saturated fat content of the diets. Glucose-mediated glucose disposal,  $\beta$ -cell function, and glucose tolerance deteriorated after subjects consumed the high-fat diet. Caucasians and Pima Indians responded similarly, although the adverse effects of the high fat diet on plasma lipid levels were more pronounced in the Pima Indians.

Howard et al. [87] addressed the issue of substituting complex carbohydrate for saturated fat in the diet of Caucasians and Pima Indians in a series of two studies, one in which the total fat content of the diet was reduced from 42 to 21% of energy (saturated fat from 21 to 6%) and another in which the fat content of the diet was reduced from 50 to 15% of energy (saturated fat from 22 to 3%). There was no effect of diet on glucose tolerance after subjects were switched from the 42 to 21% fat diet; however, there was an improvement in glucose-mediated glucose disposal and insulin secretion when they were switched from the 50 to 15% fat diet. The reduction in saturated fat intake had a positive effect on the plasma lipid profile (total and LDL cholesterol) of the subjects in both studies. No effect on plasma triglyceride levels was reported. The authors suggested that “In individuals having a wide range of obesity and glucose tolerance, substitution of complex carbohydrates for saturated fat has beneficial effects on lowering low density lipoprotein cholesterol levels and possibly improving glucose tolerance and insulin secretion but without having any adverse effects on lipoprotein metabolism or energy expenditure”.

Borkman et al. [88] compared the effect of high-fat (50% of energy, 24% saturated fat) and low-fat (20% of energy, 9% saturated fat) diets on glucose tolerance. Mean whole-body glucose uptake during glucose infusion, and fasting blood glucose and serum insulin concentrations were similar, regardless of the dietary fat intake. Plasma lipid profiles were more favorable after subjects consumed the low-fat diet. With respect to plasma lipid profiles, similar findings were reported by Chen et al. [89].

Bonanome et al. [90] compared a high-fat diet (40% of energy fat (25% of energy monounsaturated fat), 45% of energy carbohydrate) to a high-carbohydrate diet (60% of energy carbohydrate, 25% of energy fat (10% of energy monounsaturated fat)) in 19 patients with type 2 diabetes consumed in isocaloric amounts. No difference in glycosylated hemoglobin or fasting plasma glucose, insulin, C-peptide or triglyceride concentrations were found between the diets.

Patients with type 2 diabetes consumed both a high-fat diet (40% of energy as both fat and carbohydrate, 29% of energy as monounsaturated fat) and a high-carbohydrate diet (60% of energy as carbohydrate, 20% of energy as fat (13% of energy as monounsaturated fat)) for 15 days [71]. The high-fat diet decreased both postprandial plasma glucose and insulin concentrations, as well as fasting plasma triglyceride concentration. Insulin mediated glucose disposal measured by the euglycemic hyperinsulinemic clamp was higher in the high-fat diet compared to the high-carbohydrate diet.

In patients with type 2 diabetes, Rasmussen et al. [91] examined the effect of isocaloric diets either high in fat (50% of energy as fat (30% of energy as monounsaturated

rated fat), 30% of energy as carbohydrate) or high in carbohydrate (50% of energy as carbohydrate, 30% of energy as fat (10% of energy as monounsaturated fat)) for a period of 3 weeks each. The high-fat diet resulted in lower fasting blood glucose, lower average blood glucose and lower peak blood glucose levels during a normal meal cycle compared to a high-carbohydrate diet. Again, in male type 2 diabetic subjects, Campbell et al. [92], reported that diets high in fat and enriched in monounsaturated fat (37% of energy as fat (22% of energy as monounsaturated fat), 40% of energy as carbohydrate) relative to high-carbohydrate (55% of energy as carbohydrate, 22% of energy as fat (8% of energy as monounsaturated fat)) resulted in a lower mean glucose profile, 24-h urinary glucose excretion, and fasting plasma triglyceride concentrations.

Uusitupa et al. [93] compared the effect of 9 or 20% saturated fat diets (total dietary fat 40% of energy) on glucose metabolism in normal female subjects. After consumption of the high saturated fat diet, in response to a standard glucose tolerance test, the area under the curve was greater and glucose disappearance rate was slower than after the subjects consumed the low saturated fat diet. In a follow-up study Schwab et al. [94] also had subjects consume high-fat diets, of which either 21 or 10% was saturated fat. In contrast to the previous study, the low saturated fat diet was high in polyunsaturated rather than monounsaturated fatty acids. Under these conditions, no difference in glucose metabolism was observed.

Sarkkinen et al. [95] compared the effects of two diets in subjects with impaired glucose tolerance, one diet contained 46% of energy carbohydrates and 34% of energy fat and the other diet contained 42% of energy carbohydrates and 40% of energy fat. The amount of saturated fat was equal in both diets (11% of energy). Fasting blood glucose concentration and glucose effectiveness (an index derived from the results of intravenous glucose tolerance test) was significantly lower in the group that consumed the diet higher in fat.

Christiansen et al. [96] examined the effects of diets enriched either in saturated fat, *cis*-monounsaturated fat or *trans*-monounsaturated fat (20% of energy) on glucose metabolism in obese type 2 diabetic patients. Postprandial serum insulin and C-peptide responses were greater after consumption of the saturated and *trans*-monounsaturated fat enriched diets compared to the *cis*-monounsaturated fat enriched diet. Somewhat surprising, difference among the diets were found in fasting levels of serum lipids and lipoproteins.

In a recently published study, Lovejoy et al. [97] compared the effect of a high-fat diet containing 50% of energy as fat and 35% of energy as carbohydrate, and the low-fat diet containing 20% of energy as fat and 55% of energy as carbohydrate to a habitual diet on insulin sensitivity both in African–American and Cau-

casian women. Independent of race, the high-fat diet induced a significant reduction compared to a habitual diet in insulin sensitivity index ( $S_I$ ) calculated by the minimal model method [98] from the results of frequently sampled intravenous glucose tolerance test. In contrast, the low-fat diet induced an increase in  $S_I$ , albeit not significant, in African–American women and a significant ( $P < 0.04$ ) 20% increase in Caucasian women compared to a habitual diet.

Focusing on the effects of individual saturated fatty acids, Eckel and coworkers [99] compared the short term (5 days) effects of diets enriched in medium chain triglycerides (MCT) (40% fat of energy of which 77.5% MCT) or long chain triglycerides on type 2 diabetic patients and control subjects in a cross-over study. The MCT enriched diet was reported to have a favorable effect on insulin mediated glucose metabolism. Storm et al. [100] compared the effects of a high-fat diet (45% total fat (16% palmitic and 13% stearic acid diet), 40% carbohydrate) and a high-carbohydrate diet (51% carbohydrate, 29% fat) in type 2 diabetic patients. No difference in fasting blood glucose was observed.

Schwab et al. [101] have compared the effects of a 12% palmitic acid and 7% stearic acid (total fat 37%) on glucose homeostasis in healthy females. No difference in glucose metabolism measured by an intravenous glucose tolerance test between the diet periods was observed. The same workers [102] compared the effect of an 11% palmitic and 5% lauric acid diet in a similar setting again in healthy females. As for the earlier work [101], no difference in the results of the intravenous glucose tolerance test was observed between the diet periods.

Pan et al. [103] examined the effect of diet and/or exercise intervention in the prevention of the onset of type 2 diabetes in 577 subjects with impaired glucose tolerance. Over a 6-year period, normal weight participants in the diet or diet + exercise intervention group were prescribed a diet with 55–65% of energy as carbohydrate and 25–30% of energy as fat. There was no special attention to the quality of fat. Obese subjects were encouraged to loose weight. The diet intervention was associated with 31% reduction in risk of developing type 2 diabetes, whereas the diet + exercise intervention was associated with a reduction of 42%.

In summary of the *in vivo* metabolic studies, high fat diets with favorable fatty acid composition (high *P/S* ratios) appear to result in more favorable glycemic control compared to high carbohydrate diets in type 2 diabetic patients [68,70]. In studies where only the dietary fat level, not the fatty acid profile, was modified, the results have been less consistent. In some studies, a high carbohydrate diet negatively affected glycemic control [66,67] whereas in other studies no effect was observed [69,81]. In subjects with normal glucose metabolism, no difference between the high fat

diet and the high carbohydrate diet has been demonstrated [65,88]. However, high carbohydrate diets relative to high fat diets have been reported to cause unfavorable changes in lipid profile (increased triglycerides, decreased HDL cholesterol levels) [64–71,92].

Regarding the quality of fat there are fewer studies published, and for the most part were short term. This has hampered elucidation of mechanisms with regard to insulin sensitivity and fatty acid type. In summary, it can be concluded that substitution of unsaturated fat for saturated fat may have positive effect on glucose metabolism. In the very limited data regarding individual saturated fatty acids no difference among saturated fatty acids has been demonstrated.

### 3.2. *Metabolic studies/in vitro*

Ginsberg et al. [104] assessed the effects of media enriched in either a monounsaturated fatty acid, oleic acid (18:1), or a polyunsaturated fatty acid, linoleic acid (18:2), on binding and number of insulin receptors in erythroleukemia cells cultured for five generations. Cells cultured in both medias exhibited an increased number of low affinity insulin receptors and decreased receptor affinity relative to the control cells. The authors concluded that an increase in the saturated fatty acid content of the membrane led to a decrease in membrane fluidity, and number of low affinity insulin receptors and an increase in affinity of the low affinity receptors.

Borkman et al. [105] assessed the relationship of insulin sensitivity and fatty acid composition in skeletal muscle phospholipids. They reported that in patients with coronary artery disease, fasting serum insulin concentration was negatively correlated with the percent of long-chain polyunsaturated fatty acids (arachidonic acid) in the phospholipids fraction, independent of age, sex, adiposity, and type of therapy. Similar results were found in normal subjects between fasting insulin concentrations and the fatty acid phospholipid profile of muscle. An additional measure, insulin sensitivity, was positively correlated with phospholipid polyunsaturated fatty acids. It was concluded that the data are consistent with the hypothesis that the fatty acid composition of skeletal muscle phospholipid influences the sensitivity of the tissue to insulin. No significant relationship of either measure with the saturated fatty acid content of skeletal muscle was reported.

Vessby et al. [106] further assessed the effect of skeletal muscle phospholipid fatty acid profile on insulin sensitivity. Seventy-year-old men served as study subjects. Peripheral insulin sensitivity was significantly and negatively correlated with the proportion of palmitic, palmitoleic, and di-homo- $\gamma$ -linolenic acids and consistent with that reported by Borkman et al. [105], and positively correlated with linoleic acid.

Baur et al. [107] examined the relationship of the fatty acid composition of skeletal muscle membrane phospholipid with the type of feeding of children younger than 2 years. The breast-fed infants had higher percentage of long-chain polyunsaturated fatty acids in muscle phospholipids and lower plasma glucose concentrations compared to the formula-fed group. A significant inverse correlation between fasting plasma glucose concentration and the percentage of long-chain polyunsaturated fatty acids in skeletal muscle membrane phospholipids was also reported.

In summary, *in vitro* data suggest that the fatty acid composition of the membranes of peripheral tissues affects insulin sensitivity. The possible mechanisms include the fluidity of cell membrane, the number and affinity of insulin receptors, and, as discussed in the Section 2 (animal data), changes in the activities of enzymes associated with glucose metabolism.

### 3.3. *Epidemiological studies (population based)*

Early work [57,108–112] suggested a population-wide relationship between diet, obesity, diabetes mellitus, and other degenerative disease associated with increased affluence. West et al. [113] reported that total fat, animal fat (a marker of saturated fat), and protein were positively related to the risk of developing diabetes and that there was an inverse association with carbohydrate intake.

Kawate et al. [114] compared Japanese people living in Hawaii or Japan and found that those living in Hawaii consumed twice the animal fat and simple carbohydrate, and had a significantly higher prevalence of diabetes than those living in Japan. Confounding factors include body mass index and level of physical activity. In a similar type of study focusing on Seventh-day Adventists, Snowdon [115] reported a positive association between the incidence of type 2 diabetes and animal product consumption.

Feskens and Kromhout [116] demonstrated that in normal subjects saturated fatty acid intake was positively correlated with fasting glucose concentrations, whereas fiber intake was inversely correlated with glucose area under the curve after an oral glucose tolerance test. No data on insulin levels were presented. In a more recent publication of the same cohort this group reported that insulin concentrations during the oral glucose tolerance test were inversely associated with the dietary intake of polyunsaturated fat and positively associated with the intake of saturated fat [117]. This group has also investigated the role of diet as a predictor of the onset of type 2 diabetes [118]. The intake of total, saturated and monounsaturated fat 20 years before the diagnosis was higher in men with newly diagnosed diabetes compared to men with normal or impaired glucose tolerance. The past intake of total fat

was also reported to be associated positively with the 2 h post-load glucose level. The intake of total fat and monounsaturated fat were correlated in the Western diet and may explain the positive association of monounsaturated fat and the onset of type 2 diabetes reported in this study.

Trevisan et al. [119] reported a cross-sectional association between the intake of various dietary fats and risk factors for coronary heart disease in a cohort of Italian men and women. Consumption of butter was positively associated with blood glucose concentrations both in men and women, whereas consumption of olive oil and other vegetable oils was inversely associated with blood glucose concentrations in both genders.

Salomaa et al. [120] assessed the relationship between dietary fatty acid intake and glucose tolerance in normal and diabetic subjects. There was a positive correlation between the proportion of palmitic and palmitoleic acids in plasma cholesteryl esters and glucose tolerance. Diabetic individuals had a higher intake of saturated fatty acids than control subjects. The authors postulated that alterations in the fatty acid composition of membrane lipids may be associated with insulin resistance and blood glucose regulation.

Tsunehara et al. [121] explored the relationship between diet and the high rates (four-fold increased) of glucose intolerance in second-generation Japanese-American men. They reported that those men with glucose intolerance had higher intakes of animal protein and fat, yet no difference in caloric intake. A similar relationship was reported by Dahlquist et al. [122], between children with and without insulin-dependent diabetes. Although a relationship between protein and diabetes was reported the authors stated that "Most nutrients classified as rich in protein are also rich in fat".

Marshall et al. [123] investigated the relationship of diet and risk for type 2 diabetes using data from two counties in southern Colorado. Increased risk of type 2 diabetes and impaired glucose tolerance was related to increased intake of fat. No data on the fatty acid profile of the diet was presented.

Maron et al. [124] addressed the potential association between diet and plasma insulin concentrations in non-diabetic men with cardiovascular disease. They reported that after adjusting for age, the intake of saturated fat and cholesterol were positively correlated with fasting insulin concentrations, body mass index, and waist-to-hip ratio. Multivariate analysis indicated that intake of saturated fat was significantly related to fasting insulin concentrations, independent of body mass index. These data support similar work in animals.

Lovejoy and DiGirolamo [125] investigated the potential association between habitual dietary intake and insulin sensitivity in lean and obese subjects. Percent of energy intake as fat was positively correlated with body

mass index and diminished insulin sensitivity (the opposite was true for fiber intake). There was no association of *P/S* ratio with body mass index or insulin sensitivity.

Colditz et al. [126] related the risk of developing clinical type 2 diabetes and diet in a large cohort of women participating in the Nurses' Health Study. Using a food frequency questionnaire, after controlling for body mass index, they reported that vegetable fat or linoleic acid intake was inversely related to the risk of developing type 2 diabetes. Animal fat intake was weakly, but not statistically, related to risk of developing type 2 diabetes. However, there was a strong inverse relationship between *P/S* ratio of the diet and risk of developing type 2 diabetes.

Parker et al. [127] assessed the relationship between diet, and fasting and postprandial insulin concentrations among individuals aged 43–85 years as part of the Normative Aging Study. Log-transformed fasting insulin concentrations were positively associated with saturated fatty acid intake, in addition to body mass index, abdomen–hip ratio, and total fat intake. Multivariate models indicated that saturated fatty acid intake, body mass index and abdomen–hip ratio were independent predictors of both fasting and postprandial insulin concentrations after adjusting for age, cigarette smoking, and physical activity. It was estimated that if saturated fatty acid intake (% of calories) were decreased from 14 to 8%, there would be an 18% decrease in fasting insulin and a 25% decrease in postprandial insulin concentrations. Drawing from the data generated from animal models, the authors proposed the insulin resistance observed was related to increases in the saturated fatty acid content of plasma membranes. With respect to methodology, it was felt that any error in assessing food intake using food frequency questionnaires would be biased against fat, thereby underestimating the effect.

Shimakawa et al. [128] related dietary fat intake to hemoglobin A<sub>1c</sub> levels, used as a measure of glycemic control, in individuals with type 2 diabetes. In males, but not females, % of energy consumed as fat was significantly correlated with hemoglobin A<sub>1c</sub> levels. No data on the fatty acid profile of the diet was available.

Mayer et al. [129] assessed the relationship between dietary fat intake, and fasting and postprandial insulin levels. They concluded that an increase in the intake of dietary fat was associated with an increase in fasting insulin concentrations. Saturated fat intake was significantly associated with the 2 h postglucose load insulin concentration before, but not after, adjustment for body weight. Similarly, within identical twin pairs, total dietary fat was positively related to fasting insulin before, but not after, adjustment for body weight. It was unclear whether there was an independent relationship of dietary fat intake and hyperinsulinemia, or whether it was related to obesity.

South Asian men settling in Europe exhibit high rates of type 2 diabetes and coronary disease. Sevak et al. [130] investigated this trend by focusing on diet, and fasting and postprandial insulin concentrations, in South Asian men and compared these parameters to European men. As a % of total energy, South Asians had lower total and saturated fat, and higher monounsaturated fat, polyunsaturated fat, carbohydrate, and alcohol intakes than European men. Total or saturated fatty acid intake were not related to fasting or 2 h post-glucose load insulin concentrations. Insulin concentrations were positively related to carbohydrate intake and inversely related to alcohol intake. The standard dietary risk factors for the development of hyperinsulinemia could not account for the differences observed between the two populations studied.

Marshall et al. [131] examined the effect of dietary fat intake on the development of type 2 diabetes in subjects with impaired glucose tolerance. The subjects were followed for 11–40 months (on average 22.6 months). The mean percentage of energy from fat was significantly higher in those subjects who developed type 2 diabetes (43.4%) compared to those who continued to have impaired glucose tolerance (40.6%) or those whose glucose tolerance reverted to normal (38.9%). After adjustment for energy intake, age, sex, ethnicity, and obesity, an increase in fat intake of 40 g/day was associated with a 3.4-fold increase in risk of type 2 diabetes. The results of the Insulin Resistance Atherosclerosis Study (IRAS) also suggested that a high intake of dietary fat may worsen glucose metabolism [132]. The subjects in this study were obese subjects who are already at increased risk for type 2 diabetes.

Vessby et al. [133] investigated whether the risk to develop type 2 diabetes among 50-year-old men was related to the fatty acid composition of serum cholesteryl esters. The follow-up period was 10 years. Those who developed type 2 diabetes had higher proportions of saturated fatty acids, palmitoleic acid, and  $\gamma$ -linolenic and dihomo- $\gamma$ -linolenic acids, and lower proportion of linoleic acid in serum cholesteryl esters compared to those who did not develop type 2 diabetes. The authors suggested that the reason for the higher proportion of  $\gamma$ -linolenic and dihomo- $\gamma$ -linolenic acids in those who developed type 2 diabetes may have been a result of changed activities of enzymes in fatty acid metabolism, e.g.  $\Delta$ -5 and  $\Delta$ -6 desaturases.

Bell et al. [134] assessed dietary intake and glycemic control (glycosylated hemoglobin  $A_{1c}$ ,  $GHbA_{1c}$ ) in a racially mixed population of adults with type 2 diabetes. Total energy intake predicted  $GHbA_{1c}$  levels in all subjects. Dietary fat had a positive association with glycemic control among black subjects. No association was seen for individual fatty acids or fatty acid subclasses.

The epidemiological data suggest that diets associated with affluence or Western countries are associated with a higher incidence of type 2 diabetes. That is, there appears to be a pattern suggesting a clustering of high intakes of dietary fat (especially animal fat), obesity and glucose intolerance. Clearly, there are many issues that impact on these observations, both dietary (e.g. type of carbohydrate — simple or complex, glycemic index) and environmental (e.g. level of physical activity). It is virtually impossible to separate them out in a meaningful way. However, regarding these issues, type of fat itself becomes somewhat moot. Saturated fat (with the notable exception of stearic acid) results in increased plasma lipid and lipoprotein levels. Since diabetes is an independent risk factor for the development of coronary heart disease, one would recommend to individuals with diabetes weight loss and adopt a Step 1 diet ( $\leq 30\%$  fat,  $< 10\%$  saturated fat,  $< 300$  mg cholesterol). If inadequate response occurs, a Step 2 diet ( $\leq 30\%$  fat,  $< 7\%$  saturated fat,  $< 200$  mg cholesterol) [135].

In conclusion, the evidence from animal studies suggests that a diet high in fat affects glucose metabolism negatively. In humans (mostly type 2 diabetic patients) the results have been inconsistent and are likely confounded by differences in body weight. In studies in which the fatty acid composition of a high-fat diet has been modified to contain a higher proportion of unsaturated fat the high-fat diet has improved glucose metabolism compared to a high-carbohydrate diet. Epidemiological data suggest that subjects with higher intakes of fat are more prone to develop disturbances in glucose metabolism, type 2 diabetes or impaired glucose tolerance, than subjects with lower intake of fat. These data are confounded by differences in body weight.

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