

Fatty Acids: Friends or Foe? Relation Between Dietary Fat and Insulin Sensitivity

E.E. Blaak*

Department of Human Biology, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, P.O.Box 616, 6200 MD Maastricht, The Netherlands

Abstract: A high dietary fat intake is associated with an increased risk for the development of obesity. Obesity, in a particular abdominal obesity, is one of the major risk factors for the development of insulin resistance and type 2 diabetes mellitus. There are indications for a direct relation between dietary fat and insulin sensitivity, independent of body weight, which may be mainly mediated by dietary fat quality. Cross sectional studies in humans show a clear relationship between dietary fat quality and markers of insulin sensitivity. Also, the composition of fatty acids in serum lipids and tissues (muscle, adipose tissue), partly reflecting dietary fatty acid intake, show that insulin resistance is related to a specific pattern of fatty acids with a high content of SFAs (mainly palmitic acid) and a low concentration of PUFAs (mainly n-3 and n-6 PUFAs). There is increased evidence that lipid overflow to non-adipose tissues (lipotoxicity) may interfere with insulin-mediated glucose uptake through an accumulation of intramyocellular lipids. PUFAs may regulate fuel partitioning within the muscle cell through effects on membrane phospholipid composition and intramuscular fat storage mediated by changes in membrane fluidity, intracellular signaling molecules and gene expression. The relationship between dietary fat and insulin sensitivity needs additional confirmation in well-controlled human dietary intervention trials.

Key Words: Insulin sensitivity, dietary fat intake, dietary fat quality, obesity, reduced oxidative capacity, membrane fluidity, gene expression, intramyocellular fat storage.

INTRODUCTION

The prevalence of obesity, insulin resistance and type 2 diabetes mellitus (metabolic syndrome) is rising in all regions of the world. By 2010, some 31m people in Europe will require treatment of diabetes and related complications [1,2]. Further, by 2025, prevalence of diabetes has been estimated to be 300 million worldwide [1] with major consequences for community health and medical care. Insulin resistance is the pathogenetic link underlying the different metabolic abnormalities (abdominal obesity, dyslipidemia, hypertension) clustering in the metabolic syndrome. The rapid change in prevalence of these metabolic abnormalities indicates that environmental factors in addition to genetic predisposition are of major importance for the development. The most important lifestyle factors associated with the development of insulin resistance and diabetes are probably dietary habits (a high fat diet) and a reduced physical activity. A notable development is recent evidence from controlled trials showing that lifestyle intervention, directed at diet and physical activity is very effective in preventing the development of diabetes in high risk individuals with a risk reduction of 58% after 3y of intervention [3-5]. This review will focus on the relationship between dietary fat intake, and in particular dietary fat quality, and insulin sensitivity.

TYPES OF DIETARY FATTY ACIDS

During the three decades from 1968 to 1998, a remarkable increase in dietary fat intake was registered world wide.

In most countries the level of fat intake is above the recommended 30-35 % of total energy content [6].

About one-third to one-half of the fatty acids in the Western diet are saturated (saturated fatty acids, SFAs), while the amount of poly-unsaturated fatty acids (PUFAs) varies inversely with the saturated from one third to one tenth of the dietary fat.

The common saturated fatty acids (SFAs) in the diet are palmitic (16:0) and stearic acids (18:0), which are mainly present in lard, mutton and beef, and lauric (12:0) and myristic acids (14:0) which are present in coconut and palm oils. Mono-unsaturated (MUFAs) and PUFAs are obtained entirely from the diet. The major source of MUFAs is olive oil, which mainly contains oleic acid (18:1 n-9). The major PUFA in the diet is linoleic acid (18:2, n-6), derived primarily from plant oil such as corn, safflower, soybean and sunflower oil, with lower amounts of fatty acids of the n-3 series, alpha linolenic acid (18:3 n-3), derived from plants, and the PUFAs eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), obtained primarily from fish oils.

DIETARY FAT, BODY WEIGHT AND INSULIN SENSITIVITY

Obesity, in particular abdominal obesity, appears to be the key pathological factor in the etiology of the insulin resistance and type 2 diabetes mellitus [1,7]. There are indications from cross sectional studies and human dietary intervention trials that a high dietary fat intake is an independent risk factor for the development of obesity [8]. Moreover, there are indications that subjects prone to the development of obesity may have a diminished ability to use fat as a fuel

*Address correspondence to this author at the Department of Human Biology, Nutrition and Toxicology Research Institute Maastricht, Maastricht University, P.O.Box 616, 6200 MD Maastricht, The Netherlands; Tel: 3143-3881639; Fax: 3143 3670976; E-mail E.Blaak @HB. Unimaas.nl

which would make them even more susceptible to a positive fat and energy balance and weight gain on a high fat diet. Indeed, post-obese women [9] or women predisposed to the development of obesity [10] have a lower postprandial and 24h fat oxidation as compared with never-obese women. Also, longitudinal studies in Pima Indians in Arizona [11] have shown that low fat oxidizers show a greater risk of gaining body weight over time as compared to high fat oxidizers. Conversely, weight stable obese subjects show high rates of fasting fat oxidation and a positive correlation between fat mass and fat oxidation [12,13], independent of fat free mass). Based on these findings it has been postulated that obesity can be seen as an adaptation to a relatively high fat diet where the increase in fat mass may then increase fat oxidation (by promoting availability of free fatty acids) until a new equilibrium is achieved where fat oxidation again equals fat intake [12].

The importance of overweight in the etiology of insulin resistance and type 2 diabetes mellitus is illustrated in intervention studies showing that weight reduction increases insulin sensitivity in peripheral tissues, mainly *via* a stimulation of non-oxidative glucose disposal [14]. Furthermore, weight loss may improve all abnormalities clustering in the metabolic syndrome and weight loss and increased physical activity are effective in the prevention of type 2 diabetes [3,4].

DIETARY FAT AND INSULIN SENSITIVITY

Epidemiological evidence suggests that insulin resistance in association with hyperinsulinemia is linked to the ingestion of dietary fat [15-17]. Additionally, there are studies showing that a high dietary fat intake is associated with an increased risk for the development of diabetes, also independent of obesity [18-20]. This risk may be modulated by dietary fat quality, since in most studies change in total fat intake per se in the range of 20 to 40% of total energy intake has no major effect on insulin sensitivity [21-25].

In relation to the effects on dietary fat composition on insulin sensitivity, there is considerable evidence from experimental animal studies that saturated fat impairs whereas n-3 fatty acids improve insulin action, and that monounsaturated and n-6 polyunsaturated fatty acids have less negative effects on insulin sensitivity than saturated fat [26]. Also, cross-sectional studies in humans clearly shows a relationship between dietary fat quality and markers of insulin sensitivity (plasma insulin values, [21,27,28]). However, the methods used for measuring dietary intake in these studies (food frequency questionnaire, dietary history of 24 h diet recall) are far from perfect. From literature, we know that energy and fat intake are underreported and that this underestimation is more pronounced in obese subjects as compared to lean subjects [29]. Secondly, in these cross-sectional studies often surrogate markers of insulin sensitivity are used (plasma insulin values, oral glucose tolerance test).

The composition in fatty acids in serum lipid esters and in tissues may partly reflect dietary fatty acid composition and may thus represent a more reliable marker of dietary fat intake. A change in the proportion of fatty acids in the diet is reflected in serum triglyceride concentration during the first hours, whilst the fatty acid composition of the serum cholesterol esters and phospholipids is related to the average

fatty acids composition during the last 3 to 6 weeks [30]. Also, it has been shown in a human dietary intervention trial using diets with varying dietary fat quality for 3 months that fatty acid composition of the diet is reflected in the fatty acid composition of skeletal muscle phospholipids and triglycerides [31]. Also, fatty acids in the adipose tissue triglycerides reflect dietary intake during many months or years.

Studies relating body lipids with insulin sensitivity, using more accurate techniques for measuring insulin sensitivity like the clamp technique, have shown consistently that a higher proportion of unsaturated fatty acids in plasma or muscle is linked with an improved insulin sensitivity [32-36]. Several studies indicate that insulin resistance is characterized by specific pattern of fatty acids within serum lipids or skeletal muscle membranes or storage lipids. (for reviews [18,30]). Impaired insulin action in patients with disorders related to insulin resistance (diabetes, obesity, coronary heart disease) is associated with high proportions of palmitic and palmitoleic acid, low levels of linoleic acid and a high proportion of digammalinoleic acid (DHLA, 20:3 n-6) in the serum [30,33,35,37-39], (Table 1).

Table 1. Overview on Findings on Fatty acid Profile in Serum and Skeletal Muscle Cell Membrane in Relation to Insulin Resistance

High saturated fat
Low unsaturated fat
High 16:0
Low 18:2 n-6
High 16:1/16:0 (9 desaturase)
High 18:3 n-6/18:2 n-6 (6 desaturase)
Low 20:4 n-6/20:3 n-6 (5 desaturase)
Low n-3, n-6 C20-22 PUFAs (skeletal muscle)

Adapted from reference [18].

Borkman *et al.* [33] were the first who found that the fatty acid composition of the membrane phospholipids of skeletal muscle in Australian men was related to whole body insulin sensitivity and that insulin sensitivity was directly related to the sum of proportions of n-6 and n-3 PUFAs with 20-22 carbon atoms in the membrane phospholipids fraction of muscle tissue. In a study in Pima Indians similar findings were obtained [40]. In a Swedish study in 70-year old men, a significant and independent relationship between palmitic acid (16:0) in serum and muscle and insulin sensitivity was observed, whilst no significant relations were observed between the PUFAs with 20-22 carbons or n-3 fatty acids and insulin sensitivity [34].

In addition, insulin resistance may be associated with altered desaturase activities (table). Mice lacking stearoyl-CoA desaturase-1 (SCD-1), a mouse isoform of the delta 9 desaturase enzyme (converting amongst others 16:0 into 16:1 n-7), are more insulin sensitive than their wild type littermates [41]. An increased delta 6 desaturase (18:3 n-6/18:2 n-6) and a reduced delta 5 desaturase (20:4 n-6/20:3 n-6) have also been associated with insulin resistance and type 2 diabetes mellitus [30]. Partly, similar relationships were seen

between fatty acid composition of adipose tissue triglycerides and insulin sensitivity [30].

The differences in fatty acid pattern among, healthy, insulin resistant or diabetic subjects may be related to an altered dietary fat quality, compared to healthy people. However, the fatty acid profile in serum can also be influenced by physical activity. In healthy young men, an increased physical activity was associated to less palmitic acid in phospholipids of skeletal muscle and an improved delta 5 desaturase activity, despite an identical fatty acid composition of the diet [42]. Another possibility is that the fatty acid pattern may be secondary to the metabolic derangement of insulin resistance or to the diabetic state. However, several prospective studies in healthy subjects showed that the serum fatty acid profile of a high saturated fat or low unsaturated fat preceded the development of diabetes and cardiovascular disease [38,43], contradicting the idea that the different fatty acid patterns were consequences of the insulin resistant conditions per se.

Thus, insulin resistance and insulin resistant related disorders (diabetes, cardiovascular disease) are related to specific changes in fatty acid pattern. This deviant fatty acid

pattern may at least partly related to dietary fatty acid intake, supporting the relationship between dietary fat quality and insulin sensitivity.

DISTURBED FATTY ACID METABOLISM AND INSULIN SENSITIVITY

Evidence is accumulating that insulin resistance is related to lipid overflow from adipose to non-adipose tissue, which may cause an excessive storage of fatty acids in liver and skeletal muscle, leading to lipotoxicity and an impairment of cellular metabolism. Furthermore, in skeletal muscle, accumulation of intramyocellular triacylglycerols (IMTG) may lead to insulin resistance through interference with insulin signal transduction. There is evidence that this is not a direct causal relationship but that rather an increased content of lipid intermediates like long chain fatty acyl-CoA, diacylglycerol or ceramides stimulate signal transduction pathways that interfere with insulin signaling [44,45], (Fig. 1). Different mechanisms may be responsible for the lipid accumulation in skeletal muscle. As indicated above, lipid overflow to muscle may be a determining factor for increased storage of TG and lipid intermediates, since the blood-tissue concentration

Mechanism of fatty acid-induced insulin resistance in skeletal muscle

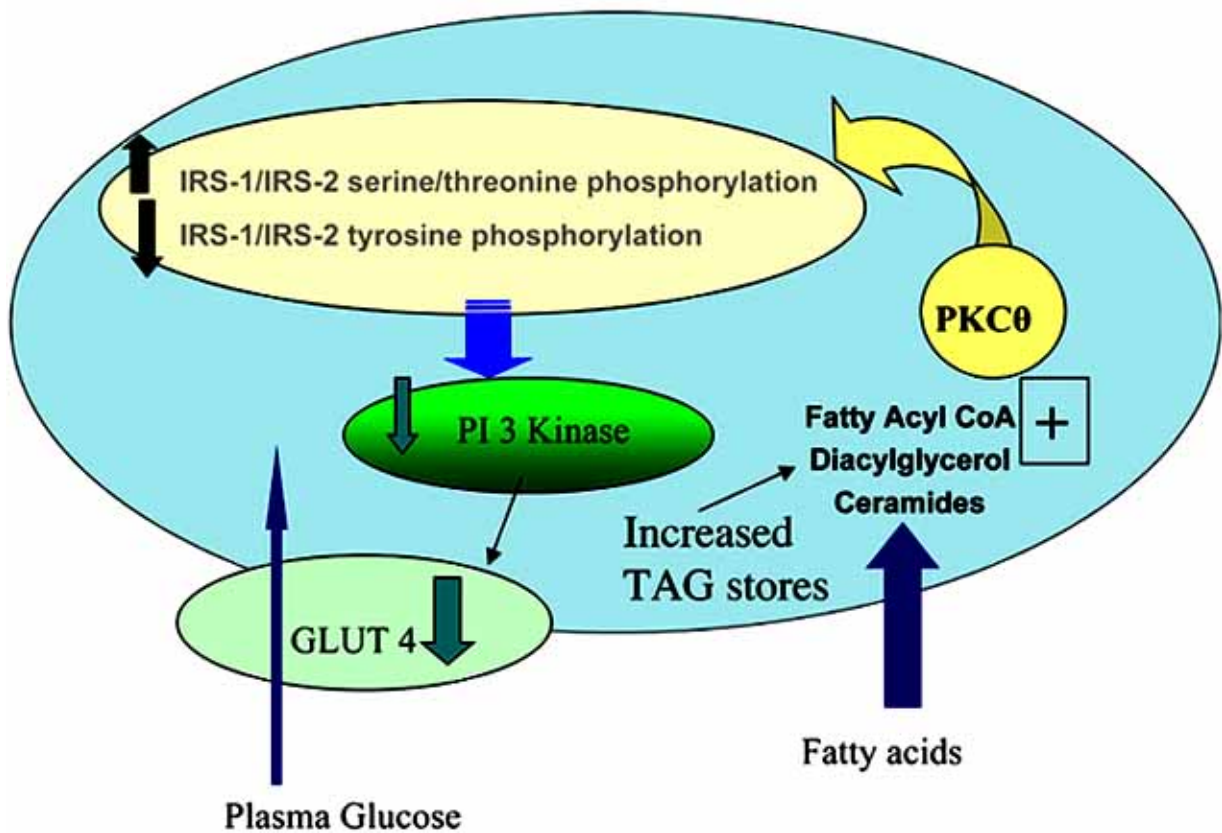


Fig. (1). Mechanism for the link between lipid metabolism and skeletal muscle insulin resistance. A high supply of fatty acids (FFA) to muscle, a reduced intracellular oxidation of fatty acids and/or increased triglyceride stores (TAG) lead to an increased content of lipid metabolites like diacylglycerol, fatty acylCoA and ceramides. These metabolites stimulate a serine/threonine cascade (possibly initiated *via* PKC θ) leading to phosphorylation of the serine/threonine sites on the insulin receptor substrates (IRS 1 and 2), and a subsequent reduced ability to stimulate PI-3 kinase. The result is a reduced activity of the glucose transporter GLUT4, Adapted from reference [57].

gradient may be one of the determining factor of muscle fatty acid uptake [46]. In the postprandial period, dietary fatty acids are transported in the form of TG in the chylomicrons and are taken up in adipose tissue, skeletal muscle and liver. The insulin-mediated uptake of dietary fatty acids may be reduced in adipose tissue of insulin resistant subjects [47], leading to an increased flux of lipids to non-adipose tissues. Recent ^{13}C magnetic resonance studies have shown that the postprandial increase in muscle and liver TG is increased in type 2 diabetic subjects as compared to a control group [48]. Beside lipid supply, recent 'in vitro' studies of the group of Bonen and coworkers have shown that the fatty acid transport capacity may be fourfold increased in type 2 diabetic subjects together with an increased content of the fatty acid transporter CD36/FAT in the sarcolemma of muscle [49]. From these results, it was concluded that an increased fatty acid transport activity may play a role in skeletal muscle TG accumulation. During fasting, a reduced skeletal muscle fatty acid (FFA) uptake was shown in 'in vivo conditions' in recently diagnosed type 2 diabetic subjects [50] and in subjects with impaired glucose tolerance (prediabetic state [51]). This raises doubts whether the disturbed CD36/FAT activity or content is an important determinant of the 'in vivo' fatty acid uptake.

Excessive lipid accumulation in skeletal muscle of obese and type 2 diabetic subjects may also be related to a reduced fatty acid oxidation. The fraction of skeletal muscle fatty acid uptake that is directly oxidized is reduced in skeletal muscle of obese type 2 diabetic subjects as compared to healthy controls during β -adrenergic stimulation (Fig. 2, [52]) and during exercise [53]. Obese and diabetic subjects manifest high lipid oxidation during insulin-stimulated conditions, despite a reduced lipid oxidation during fasting conditions, during exercise and during β -adrenergic stimulation (metabolic inflexibility in the regulation of substrate oxidation, [54,55] Fig. 2). The latter may be a key mechanism responsible for the accumulation of lipid in skeletal muscle, since it does not improve after weight reduction in type 2 diabetic or obese subjects and it is already present in the prediabetic state of impaired glucose tolerance [53].

The biochemical mechanism for the reduced fat oxidation in obesity and type 2 diabetes mellitus may be a reduction of the entry of acyl-CoA into the mitochondria due to a reduced carnitine palmitoyl transferase activity, possibly as consequence of increased concentrations of malonylCoA [56], Fig. (3). Beside that, evidence is accumulating for a role of a reduced mitochondrial content and/or function in the reduced fat oxidative capacity in obesity and diabetes [57].

Thus, a dysbalance between fatty acid uptake and oxidation may lead to increased TG storage in skeletal muscle. Recently, a great deal of attention has focused on the content, localization and composition of fat within skeletal muscle as determinants of skeletal muscle insulin resistance. There is evidence from human studies using muscle biopsies [40,58] or computed tomography scanning [59] that muscle triglycerides are negatively correlated with skeletal muscle insulin sensitivity. Proton magnetic resonance spectroscopy validated methods for the measurement of lipid depots in muscle have shown a negative correlation between intramyocellular lipids and insulin sensitivity in healthy subjects [48] and first degree relatives of type 2 diabetic subjects

[60]. Furthermore, lipid droplet size or localization within the myocyte may be related to degree of insulin sensitivity [61].

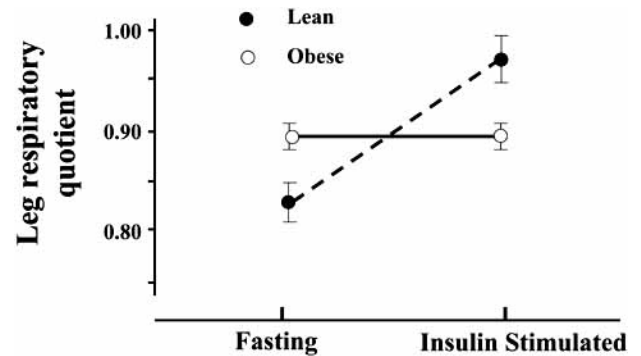


Fig. (2). Concept of metabolic inflexibility of substrate utilization. The local respiratory quotient across the leg (leg RQ) measured during fasting conditions (overnight fast) and during a hyperinsulinemic euglycemic clamp (insulin stimulated). Insulin resistant obese subjects (and type 2 diabetic subjects) have a high leg RQ during fasting, indicating a reduced leg fat oxidation. During insulin-stimulated conditions, the capacity to suppress fat oxidation is impaired in insulin resistant obese subjects. Based on reference [55].

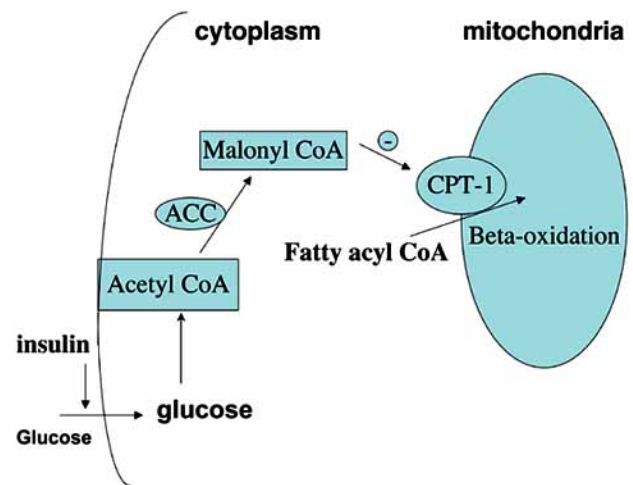


Fig. (3). Simplified scheme of mitochondrial fatty acid transport. Fatty acids are, after activation to fatty acyl CoA, transported across the mitochondrial membrane via the enzyme carnitine palmitoyl transferase -1(CPT1), CPT1 is regulated by Malonyl CoA; Malonyl CoA is formed from Acetyl CoA by the enzyme acetyl CoA carboxylase (ACC). A condition of hyperglycemia and hyperinsulinemia leads to an increase in malonyl CoA.

DIETARY FATTY ACIDS, FATTY ACID METABOLISM AND INSULIN SENSITIVITY: UNDERLYING MECHANISMS

Membrane Lipid Composition

Fatty acids are an important energy source in the body but they are also metabolized by desaturation or elongation

to obtain longer and more unsaturated fatty acids [30]. Some major reason for this is that there is a need to control the degree of saturation of cell membranes within the body. Both rodent and human studies have demonstrated that both diet and exercise may affect skeletal muscle membrane composition, whereas effects of diet have been reported to be greater in rat studies [62]. Fatty acid composition of muscle membrane phospholipids in man, in particular the proportion of n-6 and n-3 FA with 20-22 carbon are positively related to insulin sensitivity, whereas the amount of SFAs (palmitic acid) were negatively related to insulin sensitivity [33-35]. A high proportion of SFAs in the muscle membrane may impair insulin receptor binding and affinity, by a reduced ion permeability, by an altered ability to translocate glucose transporters [63] or by interaction with second messengers such as eicosanoids and diacylglycerol within the muscle cell [64,65].

Muscle Lipid Accumulation

As indicated under 'Disturbed fatty acid metabolism and insulin sensitivity', there is a strong support for a role of intramyocellular accumulation of lipid and lipid intermediates in the development of insulin resistance through interference with insulin signaling [44,45]. There is only limited information on the nutritional regulation of intramyocellular lipid concentrations [66]. The original observation on a relation between dietary fat quality and skeletal muscle triglyceride concentration and insulin resistance was gained in rats fed isocalorically on high fat diets differing only in fatty acid profile of the fat component. The effect of diet on insulin resistance were particularly pronounced in skeletal muscle and were related to a relative reduction of n-3 fatty acids in the muscle membrane and to a reduction in the diameter and number of fat droplets [26]. Also, muscle insulin resistance in rats induced by high SFAs fat feeding is readily influenced by three short term manipulations intended to lower lipid availability, supporting the relation between dietary fat intake and local lipid availability [67].

Additionally, another main function of the system of desaturases and elongases is to regulate the proportion of long chain fatty acids within the body, which may play a crucial role in expression of genes involved in lipogenesis and lipid oxidation [68]. There are now clear intracellular pathways that are differently tuned by fatty acids subtypes. PUFAs, in particular n-3 PUFAs can modulate the fuel partitioning inside the muscle cell, upregulating the genes involved in lipid oxidation (thermogenic pathways of peroxisomal fatty acid oxidation and mitochondrial uncoupling) and downregulating the expression of those genes coding for lipogenetic enzymes [68,69]. By inducing their own oxidation, PUFAs are used to a lesser extent for fat storage within the muscle cell than SFAs. They are able to regulate gene transcription within a few minutes, acting as agonists of PPARs and sterol regulatory element-binding (SREB) proteins. For instance, it has been clearly shown that PUFAs, particularly n-3 PUFAs potently down regulate SREBP expression, whereas SFAs and MUFAs have little effect [70]. Direct evidence of a role of fatty acid profile on SREBP, PPARs expression and lipogenesis in muscle is lacking.

However, there are indications from human muscle cell lines that dietary fatty acids may differently affect accumu-

lation of lipids. It has been found that saturated fatty acids (palmitate, stearate) accumulate preferentially as diacylglycerol, activating thereby protein kinase C, which may induce insulin resistance, whilst unsaturated fatty acids were readily converted to TG [65]. Further, oleic acid accumulates to a lesser extent as DAG or TG than palmitic acid. Also, type 2 diabetic myotubes expressed a reduced palmitate oxidation whereas oleic acid oxidation was not different between groups [71]. From these data it can be speculated that the reduced oxidative capacity in obese and type 2 diabetic subjects (see under paragraph 'disturbed fatty acid metabolism and insulin sensitivity') may be (partly) overcome by manipulating dietary fat quality towards more unsaturated fatty acids, leading to less lipid accumulation and an improved insulin sensitivity.

HUMAN DIETARY INTERVENTION STUDIES

On basis of the available indications for a relationship between dietary fatty acid pattern and insulin sensitivity, one would expect that changing the fatty acid composition of the diet would affect insulin sensitivity. Several studies have been conducted to demonstrate this relationship. Data from intervention studies are, however, controversial and remain uncertain [18,21,72]. In healthy subjects, intervention studies with high dietary SFA's or PUFA's in general have failed to demonstrate any change in insulin sensitivity. However, if certain criteria have to be fulfilled (isoenergetic diet, adequate methodology for measuring insulin sensitivity) then only a few studies fulfill the criteria. Further, it is important to underline that most studies were performed in very small groups of subjects and, generally, for a short period of time. Two well controlled studies, one performed in healthy subjects [73] and the other one in type 2 diabetic patients, obese and healthy subjects [74] show that moderate substitution of saturated fat with unsaturated fat (MUFA in healthy subjects and n-6 PUFA's in the one with diabetic subjects) is able to improve insulin sensitivity.

In the KANWU study by Vessby *et al.* [73] 162 subjects in 5 different countries were studied and were randomly assigned to either a diet rich in SFAs and the other with the same amount of calories from MUFAs. A random subsample in each group was also given a supplement of n-3 fatty acids (3.6 g/day). Insulin sensitivity, as assessed by an intravenous glucose tolerance test, was significantly impaired on the high SFAs diet, whilst no change in insulin sensitivity was observed on the high MUFA diet. The addition of n-3 fatty acids did not result in any change in insulin sensitivity.

The KANWU study did not attempt to change the total amount of fat. However, when subjects were divided in low and high fat consumers according their habitual fat intake (above and below median of 37 % of total energy intake, en%), the effect of dietary fat quality was clearly different in low and high fat consumers. In the high fat consumers (fat intake above 37 en%) the difference between the high SFA and high MUFA diet on insulin sensitivity disappeared almost entirely. In contrast, the difference between both diets became even more striking in the group consuming less than 37 en% of fat (21.3 %, see Fig. 4). These data suggest that dietary fat quality is only of importance for insulin sensitivity with a total fat intake equal of lower than 35-40 % of total energy intake. The total amount of dietary fat can influ-

ence insulin sensitivity and the risk for type 2 diabetes mellitus when exceeding this threshold of 35-40 en%. This is in line with several clinical studies that alterations in a change in total fat intake within the range 20-40 % of energy intake are unlikely to have an impact on insulin sensitivity [21-25].

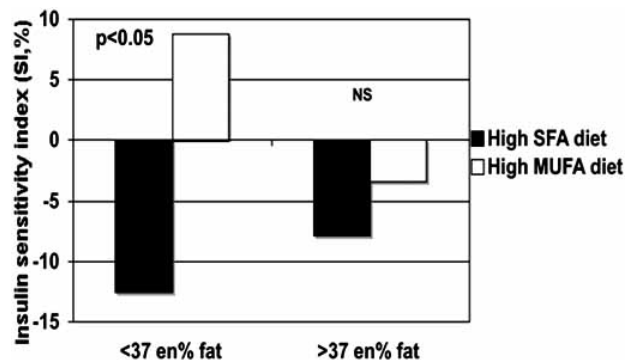


Fig. (4). The KANWU study: Effects of a change in dietary fat quality on insulin sensitivity when related to total dietary fat intake; SI (%) insulin sensitivity index; black bar: high SFAs diet, open bars: High MUFA diet; adapted from reference [72].

With respect to the effect of n-3 fatty acids on insulin sensitivity most well controlled intervention studies were performed in type 2 diabetic subjects.

Although animal studies have suggested positive effects of n-3 fatty acids on insulin sensitivity, no positive effects on insulin sensitivity could be demonstrated in controlled human dietary intervention trials [21,73,75-77].

DIETARY FAT AND THE METABOLIC SYNDROME

Insulin resistance is the pathogenic link underlying different metabolic abnormalities referred to as the metabolic syndrome. Although there is not yet a universally accepted set of criteria, most expert groups agree that the syndrome is characterized by impaired insulin sensitivity and hyperglycemia, dyslipidemia (elevated blood TG and reduced HDL-cholesterol), abdominal obesity and hypertension. High SFAs diet are associated with the development of insulin resistance and dyslipidemia, so there is strong public health justification of reducing the SFA content of the diet. The key question that remains is then whether these SFAs should be replaced by carbohydrates or by unsaturated fatty acids (MUFAs and PUFAs). Randomized controlled trials show that high MUFA diets result in lower TG and modestly higher HDL cholesterol levels as compared to low fat, high carbohydrate diets [78]. These data suggest that for the prevention of the lipid abnormalities in the metabolic syndrome a diet where SFAs are replaced by unsaturated fat is the preferred diet. However, as indicated above (see paragraph 'dietary fat, obesity and insulin sensitivity'), a high dietary fat intake is an important risk factor for the development of obesity. For this reason, others argue that a low fat, high carbohydrate diets should be preferred since these offer in the long term the best means of maintaining body weight. The issue of the most optimal diet in the metabolic syndrome is currently addressed within the dietary intervention part of the EU project LIPGENE (www.lipgene.tcd.ie, [79]), a sixth

framework EU project involving researchers from 14 EU countries.

IN CONCLUSION

A high dietary fat intake appears to be an important risk factor for the development of obesity and type 2 diabetes mellitus. This effect may be, in particularly pronounced, in subjects with a (possibly genetically determined) reduced fat oxidative capacity like has been shown in groups of obese and type 2 diabetic subjects. The total amount of dietary fat appears to be related to the prevalence of obesity, whilst the direct relationship between dietary fat and insulin sensitivity appears to be strongly influenced by dietary fat quality. An increased lipid supply may impair insulin action via an accumulation of intramuscular lipids which may interfere with insulin mediated glucose uptake. Dietary fat quality may regulate fuel partitioning within the muscle cell and may affect insulin resistance by affecting membrane phospholipid composition and thereby membrane fluidity; PUFAs may increase the expression of those genes involved in lipid oxidation and reducing the lipogenic genes. While there seems strong support for the relation between dietary fat and insulin resistance, further well-controlled human intervention trials are required to confirm these findings in humans.

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