REVIEW

Influence of Dietary Treatment on Lipid Metabolism in Metabolic Syndrome

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Summary

The metabolic syndrome is a very common disease associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease. Disturbed lipoprotein metabolism characterized by elevated TAG, low HDL-cholesterol concentrations and insulin-resistance are the key features of the metabolic syndrome. Nutrition, especially the quality of dietary fat, plays an important role in the development and progression of the metabolic syndrome through influence on the expression of the gene encoding key regulatory enzymes of lipid and glucose metabolism. Dietary ω-6 and ω-3 PUFA reduce triglyceride accumulation in skeletal muscle, suppress hepatic lipogenesis, reduce hepatic triglyceride output and induce fatty acid oxidation in both liver and skeletal muscle, resulting in improvements of the metabolic syndrome. Genetic variation that predisposes to metabolic disturbances could interact with diet, modulating individual susceptibility to developing these conditions. Individuals with a "sensitive genotype" will be most susceptible to the impact of dietary therapy in order to reduce the risk of the metabolic syndrome.

Keywords: lipid metabolism, unsaturated fatty acid, metabolic syndrome, insulin sensitivity

Sažetak

Metabolički sindrom je vrlo rasprostranjena bolest, povezana sa povećanim rizikom za razvoj šećerne bolesti tipa 2 i kardiovaskularnih bolesti. Narušen metabolizam lipoproteina, karakteriziran povećanjem nivoa ukupnih triglicerida i niskom koncentracijom HDL-kolesterola, te rezistencija na inzulin su ključne značajke metaboličkog sindroma. Prehrana, pogotovo sastav masnih kiselina u hrani, ima veliki utjecaj na razvoj metaboličkog sindroma. ω-6 i ω-3 polinezasićene masne kiseline snižavaju koncentraciju triglicerida u mišićima i izlučivanje triglicerida iz jetre, a povećavaju brzinu oksidacije masnih kiselina u jetri i mišićnom tkivu, djelovanjem na ekspresiju gena koji kodiraju za enzime ključne u regulaciji metabolizma lipida i glukoze, što u konačnici rezultira poboljšanjem simptoma metaboličkog sindroma. Individualna sklonost razvoju metaboličkog sindroma ovisi i o genetičkoj predispoziciji za metaboličke poremećaje. Osobe koje imaju genetičku predispoziciju za razvoj metaboličkog sindroma intenzivnije reagiraju na dijetalnu terapiju usmjerenu na smanjenje rizika za razvoj metaboličkog sindroma.

Ključne riječi: metabolizam lipida, nezasićene masne kiseline, metabolički sindrom, osjetljivost na inzulin

Selected Abbreviations and Acronyms:

MS - metabolic syndrome
T2DM - type 2 diabetes mellitus (T2DM)
CVD - cardiovascular disease
WHO - World Health Organization
TAG - triacylglycerol
NEFA - nonesterified fatty acids
TNF-α - tumor necrosis factor α
LEPR - leptin receptors
LMW - low molecular weight
HMW - high molecular weight
HDL – high density lipoprotein
LDL – low density lipoprotein
VLDL – very low density lipoprotein
CETP - cholesteryl ester transfer protein
LPL - lipoprotein lipases
LDLR - LDL receptor
MUFA - monounsaturated fatty acid
PUFA - polyunsaturated fatty acid
SFA - saturated fatty acid
PPARα - peroxisome proliferator-activated receptor α .
CLA - conjugated linoleic acid

Introduction

The metabolic syndrome (MS) represents a multi-component disorder characterized by abdominal obesity, insulin resistance, dyslipidaemia and hypertension. It is associated with a high risk of development of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (Isomaa *et al*., 2001). The World Health Organization (WHO) have defined the metabolic syndrome as impaired insulin sensitivity, glucose intolerance or diabetes mellitus in combination with at least two other metabolic disorders including abdominal obesity, increased triacylglycerol (TAG) concentration, reduced HDL-cholesterol concentration and urinary microalbuminuria (Alberti and Zimmet, 1998). The WHO estimates that the global prevalence of diabetes will double from 171 million people in 2000. to 366 million in 2030. (Wild *et al.*, 2005). One billion people in the world overweight and 300 million are considered obese. Estimates for 2030. are that 2 billion people will be overweight and 1.12 billion obese around the world (Kelly *et al.*, 2008). Obesity is the principal etiological factor that predisposes to insulin resistance and the metabolic syndrome (Kahn and Flier, 2000). Prolonged excessive/imbalanced dietary fat intake and surplus adipose tissue initiate secretion of proinflammatory cytokines leading to disturbed fatty acid metabolism. Results are increased lipolysis, increased triacylglycerol (TAG) and nonesterified fatty acids (NEFA) concentration. Subsequently, this results in accumulation of TAG and activated lipids in the form of long-chain fatty acyl-CoA esters, which disrupt normal metabolic functions in adipocytes, muscle, and liver (Unger, 2002). These events finally lead to reduced insulin responsiveness, resulting in impaired insulin action, compensatory hyperinsulinemia, and glucose intolerance (Saltiel, 2000; Roche *et al.*, 2005; Guilherme *et al.*, 2008).

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Metabolic syndrome definition

The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the metabolic syndrome as a multiplex risk factor for CVD (Grundy *et al.*, 2004). ATP III identified 6 components of the metabolic syndrome that relate to CVD:

- Abdominal obesity
- Atherogenic dyslipidemia
- Raised blood pressure
- Insulin resistance - glucose intolerance
- Proinflammatory state
- Prothrombotic state

According to ATP III, *underlying* risk factors for CVD are obesity (especially abdominal obesity), physical inactivity, and atherogenic diet; the *major* risk factors are cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, family history of premature coronary heart disease (CHD), and aging; and the *emerging* risk factors include elevated triglycerides, small LDL particles, insulin resistance, glucose intolerance, proinflammatory state, and prothrombotic state. International Diabetes Federation (IDF) declares criteria fairly consistent with ATPIII (table 1.). Patients having at least 3 of 5 characteristics (abdominal obesity, elevated triglycerides, decreased HDL-cholesterol, increased blood pressure or increased fasting plasma glucose) can be diagnosed as having the metabolic syndrome.

Table 1. *Diagnostic criteria for metabolic syndrome according to ATPIII and IDF*

	ATP III	**IDF**
Risk factor	**Defining level**	**Defining level**
Abdominal obesity	men >102 cm women >88 cm	men ≥94 cm women ≥ 80 cm
Triglycerides	≥1,7 mmol/L	≥1,7 mmol/L
HDL-cholesterol	men ≥1,03 mmol/L women ≥1,29 mmol/L	men ≥1,03 mmol/L women ≥1,29 mmol/L
Blood pressure	≥130/≥85 mmHg	≥130/≥85 mmHg or previously diagnosed hypertension
Fasting glucose	≥6,1 mmol/L	≥5,6 mmol/L or previously diagnosed T2DM

Adipose tissue and insulin resistance

Insulin resistance (IR) is defined as decreased response to insulin, which leads to hyperinsulinemia. The main characteristics of IR are disinhibited gluconeogenesis, impaired uptake of glucose by muscle and disinhibited lipolysis in adipose tissue. The most important factor for IR development is obesity. Distribution of body fat mass is essential for eventual metabolic complications since visceral and subcutaneous adipose tissues differ in their endocrine activities. Specific receptors such as angiotensin II receptors type-1 (AT1), β1-, β2- and β3-adrenergic receptors, glucocorticoid and androgen receptors are represented to a larger degree in visceral adipose tissue where they promote lipolysis (Vohl *et al.*, 2004). On the other hand, antilipolytic insulin receptors, α-2A adrenergic receptors, and estrogen receptors are predominantly expressed in subcutaneous adipose tissue (Vohl *et al.*, 2004). Additionally, visceral adipose secretes its products to the portal circulation, which brings the released FFA directly to the liver where they promote gluconeogenesis, VLDL synthesis, decrease glucose uptake and cause overall IR, while subcutaneous adipose tissue secretes higher level of leptin and adiponectin (Kershaw and Flier, 2004).

Insulin resistance is the link for different metabolic abnormalities clustering in the metabolic syndrome. It can be induced by different factors, including dietary habits. High fat/high energy diet is often associated with overweight. Excessive adipose tissue results in increased fatty acid flux to other tissues and increased TAG storage in peripheral tissues, which promotes insulin resistance. Adipose tissue secretes several inflammatory factors, collectively known as adipocytokines. The most important adipocytokines, which have a direct effect on insulin sensitivity include tumor necrosis factor α (TNF-α), leptin, interleukin 6 (IL-6), and adiponectin (Dandona *et al.*, 2004).

TNF-α is the main factor triggering the secretion of FFA from adipose tissue into the circulation (Ruan and Lodish, 2000). Obesity leads to an increased production of TNF-α which inhibits normal function of the insulin receptor (IR) (Hotamisigil, 2003). It has been demonstrated that knocking out the TNF-α and TNF-α receptor genes improves insulin resistance in several animal models of obesity-associated insulin resistance (Peraldi and Spiegleman, 1998; Hotamisigil, 1999).

Leptin is a hormone secreted predominantly by adipose tissue and is a signal of energy sufficiency. Leptin has been shown to stimulate glucose uptake and fatty acid oxidation (Wauters *et al*., 2000). Furthermore, leptin modulates insulin secretion and action via leptin receptors (LEPR) that are present in pancreatic β cells, adipose tissue, and muscle (Seufert *et al*., 1999). Several studies have shown that LEPR polymorphisms are associated with insulin and glucose metabolism (Wauters *et al*., 2001), insulin resistance (Chiu *et al*., 2004), and T2DM (Han *et al*., 2008).

Higher IL-6 levels have been associated with obesity and visceral fat deposition, increased risk of impaired glucose tolerance, T2DM (Qi *et al*., 2007; Stephens *et al*., 2007) and high blood pressure (Fernandez-Real *et al*., 2001.). Visceral adipose tissue secretes about two to three times more IL-6 than subcutaneous tissue. IL-6 inhibits insulin transduction in hepatocytes (Senn *et al*., 2002), adipogenesis and secretion of adiponectin (Kershaw and Flier, 2004).

Whilst most adipocytokines are associated with insulin resistance, greater levels of adiponectin are associated with im-

proved insulin sensitivity by reversing insulin resistance associated with obesity and lipodystrophy (Yamauchi *et al*., 2001). Plasma adiponectin levels are inversely associated with several risk factors for the metabolic syndrome including adiposity, insulin resistance, increased blood pressure, TAG concentrations and TNF-α receptor concentrations (Fernandez-Real *et al*., 2003). In the liver, it induces fatty acid oxidation, decreases lipid synthesis and uptake of FFA, and represses gluconeogenesis by enzyme down-regulation (Meier and Gressner, 2004). In muscle, adiponectin favors glucose and FFA oxidation. Adiponectin concentrations are in negative correlations with triglycerides and LDL-cholesterol, and positive correlations with whole-body fat oxidation and HDL levels (Trujillo *et al*., 2005; Abbasi *et al*., 2004). Adiponectin exists in the form of low molecular weight (LMW) and high molecular weight (HMW) multimers. Pajvani *et al.* (2004) found that administration of HMW, but not LMW, adiponectin multimers lowered glucose in mice. In addition, the HMW: total adiponectin ratio but not total adiponectin, correlated with insulin sensitivity in humans and rodents (Pajvani *et al*., 2004). Insulin-resistant individuals and those with T2DM are found to have lower levels of the HMW multimer. The HMW: total adiponectin ratio is independently correlated with concentrations of LDL and HDL particle, as well as LDL and HDL particle size. Individuals with a higher proportion of HMW adiponectin have higher concentrations of less atherogenic LDL and higher concentrations of cardio protective HDL. Total adiponectin, and HMW and LMW adiponectin are all positively correlated with fat oxidation and negatively correlated with carbohydrate oxidation in resting humans (Lara-Castroa et al., 2007). Adiponectin inhibits conversion of macrophages to foam cells and inflammatory events in atherogenesis (Kershaw and Flier, 2004). Adiponectin also suppresses secretion of TNF-α (Aldhahi and Hamdy, 2003). Low adiponectin is associated with endothelial dysfunction in coronary vessels (Schachinger *et al*., 2000), and with the extent of coronary artery disease (von Eynatten *et al*., 2006).

Lipoprotein metabolism and metabolic syndrome

Dietary lipids are carried from the intestinal mucosa cells to other tissues by lipoproteins called chylomicrons. The principle apoproteins of nascent chylomicrons are apo B-48, apo A-I, apo A-II and apo-AIV. Apo B-48 is essential for chylomicron formation in the intestine. Apo B-48 is combined with lipid by the action of microsomal transfer protein. In circulation, the nascent chylomicrons acquire apo-C and apo-E from plasma HDL in exchange for phospholipids (Welty *et al*., 1999). Apo-CII activate membrane bound lipoprotein lipase, LPL located on adipose and muscle tissues and bind chylomicrons to it. The fatty acids transported to the adipose cell are bound again into triacylglycerols and stored, while in the muscle the fatty acids are oxidized to provide energy. As the tissues absorb the fatty acids, the chylomicrons are reduced to cholesterol enriched remnants. As the chylomicron shrinks it transfers part of its phospholipids and apoproteins A and C to HDL. The apo-C proteins are continuously recycled between chylomicrons and HDL. The remnants lacking apo A and C proteins do not bind to the LPLs in the capillaries and are rapidly taken up by the liver via receptors that bind apo E (Welty *et al*., 1999). The liver synthesizes fatty acids and cholesterol and packages them for transport in the blood plasma in VLDLs. Apo B-100 is the major protein of VLDL. Apo B-100 is combined with lipid in the liver by the action of microsomal transfer protein (Welty *et al*., 1999). The nascent VLDL acquires apo-C and E from HDL. VLDLs bind to the same membrane bound lipoprotein lipases (LPLs) located on adipose and muscle tissues as chylomicrons do. As the tissues absorb the fatty acids, the VLDLs progressively shrink to IDL and transfer a substantial portion of its phospholipids and apoprotein C to HDL. IDLs bind to receptors of liver cells where they are absorbed, or they can be further catabolized by LPLs, eventually loosing apo-E to form LDLs. Low-density lipoproteins (LDL) is the major cholesterol carrying lipoprotein that carries cholesterol from the liver to the rest of the body (Welty *et al*., 1999). The sole protein of LDL is Apo B-100. LDL is cleared from plasma in part through the action of the LDL receptor (LDLR) by both the liver and peripheral cells. The structural requirements for binding LDL and VLDL differ: LDL binds its receptor via apoB-100, VLDL via apoE. After binding LDL the LDL receptors migrate to areas of the plasma membrane coated with the clathrin on the cytoplasmic side of it. The clathrin proteins promote endocytosis. Once the vesicle is inside of the cell, the clathrin spontaneously dissociates from the endosomal vesicle, and lowered pH of the vesicle results in LDL dissociation from the receptor. The LDL receptors are recycled to the cell surface. The vesicle fuses with a lysosome which then degrades the lipoprotein to its primary components, fatty acids, glycerol, cholesterol and amino acids. The cholesterol is incorporated into the intracellular cholesterol pool which is used for membrane or steroid synthesis. The liver also absorbs LDLs by the same endocytosis mechanism. Approximately 75% of the LDLs are absorbed by the liver. High-density lipoproteins (HDL) scavenge cholesterol from the bloodstream, from LDL, and from artery walls and ferry it back to the liver for disposal, so HDL cholesterol is often referred to as good, or protective, cholesterol. HDLs are secreted by liver and intestinal cells. The primary function of HDLs is to remove excess cholesterol and carry it to the liver to be metabolized into bile salts. HDL contains enzymes that either esterifies cholesterol or transfer cholesteryl esters. Apo AI is essential for HDL formation because in its absence no HDL is present in plasma (Ordovas *et al*., 1989). The liver and intestine synthesize apolipoprotein A-I (apo A-I), which can interact with the adenosine triphosphate–binding cassette transporter A1 (ABCA1) located on the arterial macrophages, transporting free cholesterol to the extracellular HDL. Lipidation of the HDL particles generates nascent HDL (Curtiss *et al*., 2006). Subsequently, lechithincholesterol transferase (LCAT), enzyme that circulates with HDL, esterifies free cholesterol within nascent HDL with long chain fatty acids from phospholipids to produce mature HDL particles. These mature HDL particles can further take up free cholesterol. LCAT thus facilitating the storage and transport of excess cholesterol. Mature HDL has at least 2 metabolic fates. In the direct pathway, cholesteryl esters contained within HDL can undergo selective uptake by hepatocytes and steroid hormone–producing cells via the scavenger receptor type B1 and subsequent excretion into the bile (Lewis and Rader, 2005). In the indirect pathway, cholesteryl esters within HDL can be exchanged for triglycerides in apolipoprotein B–rich particles (LDL and VLDL) through the action of cholesteryl ester transfer protein (CETP), which is another peripheral protein that circulates with HDL. CETP promotes the net transfer of cholesterol esters from HDL to LDL, IDL and VLDL. This process transforms VLDLs and IDLs into LDLs. The triglyceride-rich HDL can then undergo hydrolysis by hepatic lipase and endothelial lipase to form small HDL for further participation in transport (Lewis and Rader, 2005). In addition to its major role in reverse cholesterol transport, HDL has other biological activities. These include antioxidant (counteracting LDL oxidation) effects, anti-inflammatory effects, antithrombotic/profibrinolytic (reducing

platelet aggregation and coagulation) effects, and vasoprotective (facilitating vascular relaxation and inhibiting leukocyte chemotaxis and adhesion) effects (Assmann and Gotto, 2004; Navab *et al*., 2004).

Recent studies have shown that increased liver fat content is associated with overproduction of triglyceride-rich large VLDL particles in humans (Adiels *et al.*, 2006). Major role in the catabolism of triglyceride-rich lipoproteins plays lipoprotein lipase (Nilsson-Ehle *et al*., 1980; Beisiegel *et al.*, 1991). Generation of small dense LDL occurs as a result of disturbances in lipid metabolism, which are characteristic of T2DM, obesity, insulin resistance, and CVD (Packard, 2003).

Increased plasma cholesteryl ester transfer protein activity enhances lipid exchange, which removes cholesteryl ester from the LDL particle core, and replaces it with triglycerides from VLDL and chylomicrons. LDL, enriched with triglycerides, becomes a good substrate for hepatic lipase. If hepatic lipase activity is sufficiently high, hepatic lipase-mediated hydrolysis of triglycerides on triglyceride-rich LDL will generate small dense LDL particles (Chung *et al.*, 1998). Some studies have demonstrated that hepatic lipase was the strongest contributor to small dense LDL levels, whereas lipoprotein lipase activity was associated with an increase in large buoyant LDL particles (Carr *et al*., 2002).

Plasma HDL levels are regulated by the hepatic and intestinal synthesis of apolipoprotein A-I, and by the rate of HDL maturation and catabolism (Zannis *et al.*, 2006). Hepatic lipase activity is also a major determinant of HDL-cholesterol levels (Collet *et al.*, 1999). In insulin resistance and T2DM, the abnormal HDL subclass distribution (Lara-Castro *et al.*, 2006; Okamoto *et al.*, 2002) accelerates atherosclerosis by reducing the efflux of cholesterol from macrophage foam cells.

Dietary fat and metabolic syndrome

Disturbed lipoprotein metabolism characterized by elevated TAG and low HDL-cholesterol concentrations, and insulin-resistance are the key features of the metabolic syndrome. Plasma low-density lipoprotein (LDL)-cholesterol concentrations are often normal, but there is a relative increase of small, dense, atherogenic particles. Dietary ω-6 and ω-3 PUFA reduce triglyceride accumulation in skeletal muscle (Baur *et al.*, 1998) that is associated with improvements of the metabolic syndrome (Clarke, 2000). Ingestion of fats rich in ω-6, and particularly ω-3 PUFA, suppress hepatic lipogenesis (Jump and Clarke, 1999), reduce hepatic triglyceride output (Nestel *et al*., 1984) and induce fatty acid oxidation in both liver and skeletal muscle (Thomassen *et al*. 1982; Power and Newsholme, 1997).

Insulin sensitivity is affected by the quality of dietary fat, independently of its effects on body weight. Saturated fat significantly worsens insulin-resistance, while monounsaturated and polyunsaturated fatty acids improve it. Fatty acids play a role in both the cellular and molecular mechanisms of insulin resistance, because they are a determinant of the membrane property that affects insulin sensitivity (Ginsberg *et al.*, 1982), and they act as a physiological signaling molecule that induces insulin resistance (Griffin *et al.*, 1999).

Vessby *et al.* (2001) has demonstrated that decreasing dietary SFA and increasing MUFA improves insulin sensitivity but has no effect on insulin secretion. Perez-Jimenez *et al.* (2001) have shown that isoenergetic substitution of SFA by MUFA markedly improves insulin sensitivity. In contrast, Lovejoy *et al.* (2002) have failed to show any marked effect of high-MUFA, high-SFA or trans-fatty acid-rich diets on insulin sensitivity. A number of positive health benefits relevant to the metabolic syndrome have been associated with increased long-chain (LC) ω-3 PUFA intake, particularly in relation to TAG metabolism (Roche and Gibney, 2000). Animal studies show that feeding LC ω-3 PUFA has positive effects on glucose metabolism and insulin resistance (Aguilera *et al*., 2004). The health impact of increased LC ω-3 PUFA consumption on insulin resistance in human subjects is not clear yet since some intervention studies have reported positive effects on insulin sensitivity in individuals with impaired glucose tolerance and diabetes (Fasching *et al*., 1991), while other studies have not (Vessby *et al*., 2001; Brady *et al*., 2004).

Table 2. *Survey of enzymes included in lipid metabolism coded by genes whose expression is down- or up- regulated by PUFA*

PUFA	
SUPPRESSION	**INDUCTION**
glucokinase	carnitine palmitoyltransferase
pyruvate kinase	acyl-CoA oxidase
glucose-6-phosphate dehydrogenase	uncoupling protein-3
citrate lyase	
acetyl-CoA carboxylase	
fatty acid synthase	
stearoyl-CoA desaturase	
Δ-6 and Δ-5 desaturases	

The search for the genetic basis of obesity and insulin resistance is fundamental to the understanding of the effects of dietary fatty acids and the metabolic syndrome. PUFA exert their beneficial effects by up-regulating the expression of genes encoding proteins involved in fatty acid oxidation (table 2.) by activating the transcription factor peroxisome proliferator-activated receptor α (PPARα). Simultaneously PUFA suppress expression of genes encoding proteins of lipid synthesis (table 2.) by reducing the nuclear abundance and DNA-binding affinity of factors responsible for imparting insulin and carbohydrate control to lipogenic and glycolytic genes (Clarke, 2001). The outcome is an improvement in the symptoms of the metabolic syndrome and a reduced risk of heart disease. One of the first PUFA-dependent repartitioning of lipid metabolism involves inhibition of the production of hepatic malonyl-CoA (Wilson *et al.*, 1990). Since malonyl-CoA acts as an inhibitor of carnitine palmitoyltransferase this effect leads to enhanced fatty acid oxidation by increasing fatty acid entry into the mitochondria and peroxisomes (Zammit, 1999). In parallel PUFA-dependent induction of genes encoding proteins involved in fatty acid oxidation and ketogenesis occurs (Clarke, 2000; Jump and Clarke, 1999; Clarke *et al.*, 1999).

The interaction of PPARα with its DNA recognition site is markedly enhanced by ligands such as the conjugated linoleic acid and PUFA (Zammit, 1999; Issemann and Green, 1990). In general, PPARα activation leads to the induction of several hepatic, cardiac and skeletal muscle genes encoding proteins involved in lipid transport, oxidation and thermogenesis, including carnitine palmitoyltransferase, peroxisomal acyl-CoA

oxidase and uncoupling protein-3 (Clarke, 2000; Aoyama *et al.*, 1998; Xu *et* al., 1999). PUFA metabolites such as eicosanoids or oxidized fatty acids are even far more potent transcriptional activators of PPARα-dependent genes (Krey *et al.*, 1997; Lee *at al*. 2011). Hyperglycemia was found to suppress PPARα expression and induce PPARγ expression, increase β-cell and cardiomyocyte lipids and accelerate cell death (Zhou *et al*., 2000). PPARγ plays a critical role in adipogenesis, insulin sensitivity and blood pressure (Barroso *et al.*, 1999; Lee *at al*. 2011).

Dietary PUFA inhibit hepatic lipogenesis by suppressing the expression of hepatic enzymes involved in fatty acid biosynthesis and glucose metabolism, including glucokinase, pyruvate kinase, glucose-6-phosphate dehydrogenase, citrate lyase, acetyl-CoA carboxylase, fatty acid synthase, stearoyl-CoA desaturase and the Δ-6 and Δ-5 desaturases (Duplus *et al.*, 2000; Cho *et al.*, 1999).

SREBP are a family of transcription factors that were first isolated as a result of their properties for binding to the sterol regulatory element (Osborne, 2000; Brown and Goldstein, 1999). PUFA rapidly reduce the nuclear content of hepatic SREBP-1a, acting as a regulator of genes encoding proteins involved in both lipogenesis and cholesterogenesis. SREBP-2 is a regulator of genes encoding proteins involved in cholesterol metabolism (Osborne, 2000; Brown and Goldstein, 1999). Diets rich in 18:2(ω-6) or 20:5 and 22:6(ω-3) were found to reduce the hepatic nuclear and precursor content of mature SREBP-1 by 65 and 90% and by 60 and 75%, respectively (Xu *et al.*, 1999). The decrease in SREBP-1 was accompanied by a comparable decrease in the transcription rate of hepatic fatty acid synthase (Xu *et al.*, 1999).

Group of fatty acids, known as conjugated linoleic acid (CLA), in particular the cis-9, trans-11-CLA isomer, may have the potential to improve lipid and insulin metabolism (Roche *et al.,* 2002; Moloney *et al.*, 2004). This effect has been ascribed to differential SREBP-1c gene expression, a regulatory transcription factor involved in lipogenesis and glucose metabolism (Foretz *et al*., 1999; Gosmain *et al*., 2004). Feeding a cis-9, trans-11-CLA isomer-rich diet has divergent tissue-specific effects on SREBP-1c expression, markedly reducing hepatic SREBP-1c and increasing adipose tissue SREBP-1c expression, both of which could contribute to improved lipid and glucose metabolism (Roche *et al*., 2002). This study has shown TNF-α-regulated SREBP-1c expression in human adipocytes, but not in hepatocytes (Roche *et al.*, 2002), supporting the hypothesis for cross-talk between molecular markers of insulin sensitivity and adipocytokines, which in turn can be modified by fatty acids.

Unlike PUFA, saturated and monounsaturated fatty acids had no effect on the concentration of SREBP-1 or on lipogenic gene expression (Xu *et al.*, 1999; Worgall *et al.*, 1998; Hannah *et al.*, 2001).

Dietary treatment of MS

The aim of dietary treatment of the metabolic syndrome is to improve insulin sensitivity, lipid metabolism and the associated cardiovascular abnormalities. It is not necessary to achieve the ideal BMI to improve the metabolic profile. Weinstock *et al*. (1998) showed that 5–10% weight reduction is sufficient to induce a clinically relevant effect. Many studies recorded the improvement of insulin sensitivity due to weight reduction was higher than that obtained with insulin-sensitizing drugs. The beneficial effects of weight reduction are usually preserved as long as weight is not regained. Fat intake is positively correlated with plasma insulin values and negatively with insulin sensitivity. However, high monounsaturated fat diet improves insulin sensitivity compared to a high-saturated-fat diet only if total fat intake does not exceed 38% of total energy (Vessby *et al*., 1999). Salt, alcohol and carbohydrates are other dietary components that influence insulin sensitivity, plasma triglyceride level and blood pressure. Since glucose and lipid metabolism are strongly related, any derangement of carbohydrate metabolism induced by a high-carbohydrate diet will also increase plasma triglycerides and decrease plasma HDL concentrations (Garg, 1998). Optimal diet for people with the metabolic syndrome has to reduce plasma cholesterol levels and LDL as much as possible. The diet should be limited in the intake of saturated fat, to avoid unfavorable effects on insulin sensitivity, blood pressure and plasma lipids. High fibre/low-GI foods should be used without specific limitations instead of carbohydrate-rich foods with a high GI. Moderate amounts of fat containing MUFA and PUFA could be permitted since they do not induce detrimental metabolic effects.

Unsaturated fats are predominantly found in vegetable oils, nuts, and seeds. MUFAs are found in high concentrations in canola, peanut and olive oils, avocados, almonds, hazelnuts, pumpkin and sesame seeds. About 50% of monounsaturated fatty acids are provided by animal products, primarily meat fat. The major monounsaturated fatty acid in the diet is oleic acid. The overall data indicate that monounsaturated fats do not lower LDL or HDL cholesterol relative to saturated fat as much as does polyunsaturated fat (Mensink and Katan, 1992; Valsta *et al*., 1992). The saturated fat and monounsaturated fat contents of most natural diets are similar, and when saturated fat is restricted, the monounsaturated fat content of the diet decreases.

PUFAs are found in high concentrations in sunflower, corn, soybean, and flaxseed oils, and also in foods such as walnuts, flax seeds, and fish. The major ω-6 fatty acid in the diet is α-linoleic acid, which serves as the precursor for arachidonic acid (20:4ω-6), which has important biological effects in the body. α-linoleic acid could not be synthesized by the human body and is therefore an essential fatty acid. The other major essential fatty acid in the diet is α-linolenic acid (18:3ω-3). This fatty acid can be rapidly converted in the body to eicosapentaenoic acid (20:5ω-3), which can be further elongated, desaturated, and oxidized to docosahexaenoic acid (22:6ω-3) (Siguel *et al*., 1987). Sources of ω-6 polyunsaturated fatty acids include nuts, seeds, certain vegetables, and vegetable oils such as soybean oil, sunflower oil, and corn oil. Certain oils, such as blackcurrant seed oil and evening primrose oil, are high in γ-linolenic acid (18:3ω-6). Arachidonic acid is formed from linoleic acid in animal cells, but not plant cells, and is present in the diet in small amounts in meat, poultry, and eggs. Most ω-6 polyunsaturated fatty acids are consumed in the form of linoleic acid. Other ω-6 polyunsaturated fatty acids, such as arachidonic acid and γ-linolenic acid, are present in small amounts in the diet.

ω-3 fats are an important type of polyunsaturated fat the human body can't make, so they must come from food. The major sources of ω-3 fatty acids include certain vegetable oils and fish (Kris-Etherton *et al*., 2000). Vegetable oils such as soybean and flaxseed oils contain high amounts of α-linolenic acid. Fish oils provide a mixture of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), so fatty fish are the major dietary sources of EPA and DHA. Smaller amounts are also present in meat and eggs. ω-3 Fatty acids found in fish oil, especially eicosapentaenoic acid, lower triacylglycerol concentrations significantly and reduce coronary heart disease risk as well, independently of their influence on lipoprotein concentrations (Harris, 1997).

The average concentration of conjugated linoleic acid (CLA) in dairy products and ruminant meats is approximately 5 mg of CLA/g of fat (Chin *et al*., 1992). Although numerous CLA isomers have been reported to be found in meat, milk, and dairy products (Ha *et al*., 1989), the cis-9,trans-11 isomer is the predominant form of CLA present in these foods (Ma *et al*., 1999). The conjugated linoleic acid content of milk can vary depending on a number of factors, such as animal feed diet, supplement use, and number of lactations (MacDonald, 2000). Ma *et al.* (1999) reported values of 1.8 mg of CLA/g of fat for skim milk, 3.4 mg/g for whole milk, 4.3 mg/g for 1% fat milk, 5.0 mg/g for 2% fat milk, and 5.5 mg/g for half-and-half cream. In addition, values ranged from 2.7 to 6.2 mg of CLA/g of fat for various cheeses and 1.2 to 3.2 mg of CLA/g of fat for different types of raw and cooked beef products.

Conclusion

The metabolic syndrome (MS) is a multi-component metabolic disorder associated with a high risk of development of T2DM and CVD. Insulin resistance is the link for different metabolic abnormalities clustering in the metabolic syndrome. It can be induced by different factors, including dietary habits. Obesity is concerned to be the principal aetiological factor that predisposes to insulin resistance and the metabolic syndrome. Adipose tissue secretes several inflammatory factors, collectively known as adipocytokines, which have a direct effect on insulin sensitivity. Many studies recorded that the improvement of insulin sensitivity due to weight reduction is higher than that obtained with insulin-sensitizing drugs. Insulin sensitivity is affected by the quality of dietary fat, independently of its effects on body weight. Saturated fat worsen insulin-resistance, while unsaturated fatty acids, especially PUFA, improve it on molecular level influencing the DNA-binding activity and abundance of transcription factors included in regulation of the expression of genes encoding key regulatory enzymes of lipid and glucose metabolism.

Furthermore, there is evidence that genetic variation that predisposes to metabolic disturbances could interact with diet, modulating individual susceptibility to developing these conditions. Individuals with a ″sensitive genotype″ will be most susceptible to the impact of dietary therapy in order to reduce the risk of the metabolic syndrome.

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