The metabolic syndrome and the liver

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Abstract

Together with the worldwide epidemic proportions of obesity the incidence of 'the metabolic syndrome' is rising across countries. The metabolic syndrome is described as a complex condition that is linked to (intra-abdominal) obesity and is characterized by insulin resistance, dyslipidaemia and hypertension. Several definitions for the metabolic syndrome have been suggested, all trying to identify individuals at high risk for both type 2 diabetes and cardiovascular disease. The primary hepatic complication of obesity and insulin resistance is nonalcoholic fatty liver disease (NAFLD). NAFLD is not included as a component of the metabolic syndrome as it is currently defined ; however, data suggest an association. Although the data are mainly epidemiological, the pathogenesis of NAFLD and the metabolic syndrome show common components, with the focus on insulin resistance as a key factor. Even so the treatment of patients with the metabolic syndrome and NAFLD shows a certain degree of similarity, and should focus on the management of associated conditions including obesity, glucose and lipid abnormalities. Lifestyle modifications comprising healthy eating habits and regular exercise are the primary interventions recommended to patients with the metabolic syndrome and those with NAFLD. A pharmacological approach like insulin-sensitizing agents, lipid lowering drugs, antihypertensive drugs and antiobesity agents can be successful in the treatment of certain risk factors that are currently clustering with both the metabolic syndrome and NAFLD. In some cases bariatric surgery may be necessary. (Acta gastroenterol. belg., **2008**, 71, **48-59**).

Abbreviations

ACE	angiotensin-converting enzyme
ADA	American Diabetes Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CB_1	cannabinoid 1
CB_2	cannabinoid 2
CHD	coronary heart disease
CRESCENDO	Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (trial)
CRP	C-reactive protein
DECODE	Diabetes Epidemiology : Collaborative analysis of Diagnostic criteria in Europe
DPP	Diabetes Prevention Program
DREAM	Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (study)
EASD	European Association for the Study of Diabetes
EGIR	European Group for the Study of Insulin Resistance
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
FDPS	Finish Diabetes Prevention Study
FFA	free fatty acids
GGT	gamma glutamyl transpeptidase
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HDL	high-density liplipoprotein
ICAM-1	intercellular adhesion molecule-1
IDF	International Diabetes Federation
IL	interleukin
IR	insulin resistance
LDL	low-density lipoprotein
LDL-ox	oxidized LDL
MCP-1	monocyte chemoattractant protein-1
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCEP-ATP III	Third Adult Treatment Panel of the National Cholesterol Education Program
NEFA	non-esterified fatty acid
ObelHyx	Obesity Linked with Hypercholesterolemia treated with Xenical (study)
PAI-1	plasminogen activator inhibitor-1
PPAR	peroxisome proliferator-activated receptor
RBP-4	retinol-binding protein 4
ROS	reactive oxygen species
SCOUT	Sibutramine Cardiovascular Outcomes (trial)
TNF-α	tumor necrosis factor-α
VLCD	very low calorie diet
VLDL1	very low-density lipoprotein 1
WHO	World Health Organization

Introduction

The prevalence of obesity is rising worldwide to epidemic proportions, not only in developed countries but also in the developing world (1,2). Obesity is an important risk factor for cardiometabolic diseases, including type 2 diabetes, hypertension, dyslipidaemia and coronary heart disease (CHD) (3-7). The incidence of 'the metabolic syndrome', a complex condition linked to (intra-abdominal) obesity and characterized by insulin resistance, dyslipidaemia and hypertension, is even so increasing (8,9). The risk of developing end stage liver disease and hepatocellular cancer as a consequence of nonalcoholic fatty liver disease (NAFLD), the primary hepatic complication of obesity and insulin resistance, has only more recently been recognized. Although NAFLD has not been included as a component of the metabolic syndrome as it is currently defined, available data indicate that the onset of NAFLD is an early event in the development of insulin resistance and might predict the presence or future development of the metabol-

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ic syndrome (10). The treatment goals of the metabolic syndrome and NAFLD share similar approaches such as lifestyle intervention and in some individual cases pharmacological treatment. The purpose of this article is to give a brief overview of the metabolic syndrome, its association with NAFLD, and the similarities in treatment between the two conditions.

Metabolic syndrome

Definitions

The metabolic syndrome was first described by Reaven in 1988 as syndrome X : a clustering of insulin resistance, hyperinsulinaemia, glucose intolerance, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol and hypertension (11). The importance of the metabolic syndrome may serve to identify individuals at high risk of both type 2 diabetes and cardiovascular disease. As it became more clear that abdominal obesity increases cardiovascular disease risk, and this independently of body mass index (BMI) (4), several expert groups have tried to produce diagnostic criteria. The first attempt to criteria was driven by a World Health Organization (WHO) diabetes group in 1999 (12). The European Group for the Study of Insulin Resistance (EGIR) then produced a modification of the WHO criteria (13). In 2001 the US Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP-ATP III) proposed a new clinical definition of the metabolic syndrome with a focus on cardiovascular disease. This definition was based on the WHO definition and required three abnormalities to be present, among abdominal obesity, hypertriglyceridaemia, low HDL-cholesterol, high blood pressure and high fasting glucose (14). Because of a strong need for a practical definition, the International Diabetes Federation (IDF) developed in 2005 a definition that would be useful in any country for the identification of people at high risk for cardiovascular disease and diabetes (15). Currently, the (adapted) NCEP-ATP III criteria are still widely used (Table 1).

According to the NCEP-ATP III criteria, 25% of adults in the US can be classified as having the metabolic syndrome (16). European data based on the DECODE (Diabetes Epidemiology : Collaborative analysis of Diagnostic criteria in Europe) study show an overall prevalence of the metabolic syndrome in non-diabetic adult Europeans of 15% according to the modified WHO criteria (8). An Italian cohort analysis using the initial NCEP-ATP III criteria suggests the presence of the metabolic syndrome in 18% of women and 15 % in men (9). Prevalences can vary depending on the criteria used.

There is a stepwise increase in the prevalence of the metabolic syndrome with age (16) as well as with worsening of glucose tolerance (17). Several studies show that the metabolic syndrome based on the NCEP-ATP III criteria is probably a much better predictor for the development of type 2 diabetes as it is for the development of cardiovascular disease, although it is also clearly shown that the metabolic syndrome is associated with a statistically increased risk for cardiovascular disease and overall mortality (18-20).

In obesity the regional fat distribution appears to be an important indicator for metabolic and cardiovascular alterations. Intra-abdominal fat deposition appears to be an independent and powerful predictor of adverse cardiovascular outcomes. This is probably due to the highly active endocrine activity of intra-abdominal adipocytes (21,22). Waist circumference is a simple measurement to evaluate this visceral adipose tissue (23). Therefore, as suggested by the International Diabetes Federation to adjust the definition of the metabolic syndrome in 2005, central obesity was included as an essential criterion (Table 1) (15).

Table 1. — **Criteria Metabolic syndrome according to IDF and NCEP-ATP III**

IDF (Adapted from Alberti, 2005) (15)	**NCEP-ATP III** (Adapted from Expert panel on detection, evaluation and treatment of high blood cholestorol in adults, 2001) (14)
Abdominal obesity (waist circumference)* ≥ 94 cm in men ≥ 80 cm in women plus any two of the following • Triglycerides ≥ 150 mg/dL or specific treatment for this lipid abnormality • HDL-cholesterol < 40 mg/dL in men < 50 mg/dL in women or specific treatment for this lipid abnormality • Blood pressure Systolic ≥ 130 mmHg or Diastolic ≥ 85 mmHg or treatment of previous diagnosed hypertension • Fasting glucose ≥ 100 mg/dL** or previously diagnosed type 2 diabetes	Patient with three or more of the below criteria 1. Abdominal obesity (waist circumference) > 102 cm in men > 88 cm in women 2. Triglycerides ≥ 150 mg/dL 3. HDL cholesterol < 40 mg/dL in men < 50 mg/dL in women 4. Blood pressure ≥ 130/85 mmHg 5. Fasting glucose ≥ 110 mg/dL Cave adjusted glucose 100 mg/dL

* If BMI is over 30 kg/m² then central obesity can be assumed, and waist circumference does not need to be measured. Ethnicity specific values, values are given European men and women.

** In clinical practice, impaired glucose tolerance is also acceptable, but all reports of the prevalence of the metabolic syndrome should use only the fasting plasma glucose and presence of previously diagnosed diabetes to assess this criterion. Prevalences also incorporating the 2 hour glucose results can be added as supplementary findings.

Limitations

A joint statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (24) discussed the clinical evidence for the definition of the 'syndrome' and the underlying pathogenesis. Their concerns are that the criteria are ambiguous or incomplete. The value of including diabetes in the definition is questionable and insulin resistance as the unifying aetiology is uncertain. Ford (25) showed in a meta-analysis that the metabolic syndrome is a much better predictor for the development of type 2 diabetes as it is for the development of cardiovascular disease or all-cause mortality. Although the presence of the metabolic syndrome leads to an approximately twofold increase in relative CVD risk, it should not replace the need to assess overall cardiovascular risk taking into account well-established CVD risk factors, such as age, gender, smoking, blood pressure, cholesterol (or LDL-cholesterol) and diabetes (26). Other risk factors associated with the metabolic syndrome should probably be included such as disturbances in the haemostatic and fibrinolytic system (27-29). Recently C-reactive protein (CRP) has also attracted considerable attention, as a marker of low-grade inflammation (30).

NAFLD

Definition

NAFLD is defined as an excess accumulation of fat, mainly triglycerides, in hepatocytes that exceeds 5% of the liver weight and this in the absence of significant alcohol consumption and with the exclusion of secondary causes of steatosis (Table 2) (31-33). NAFLD refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis. In some patients with excess liver fat, hepatocytes are injured and this sets off a cascade of necroinflammatory changes that include the accumulation of mixed inflammatory cells and hepatocyte ballooning. A subset of such patients then develops progressive fibrosis that can lead to cirrhosis. Only a fraction, possibly a third, of patients with NAFLD develops substantial necroinflammatory changes that meet current criteria for nonalcoholic steatohepatitis (NASH) (10).

Knowledge of the epidemiology of NAFLD is limited by the lack of an accurate, noninvasive measure for use in screening of the general population. Based on existing studies of relatively unselected populations, the prevalence of NAFLD and NASH is estimated to be approximately 20-30% and 2-4% respectively. Risk factors for NAFLD include obesity, type 2 diabetes, dyslipidaemia, hypertension, age, male gender and race. NAFLD appears to be more common in men than women and in hispanics compared to caucasians and African Americans, and increases with age (33-35). The prevalence of NAFLD increases up to 75 % in an obese population (33). Given the rise of childhood obesity, NAFLD is also recognized as the most common cause of liver disease in children (35-38). Type 2 diabetes is associated with a 2-5 fold increased risk of NAFLD (32).

Table 2. — **Causes of nonalcoholic fatty liver disease (Adapted from Adams 2005) (31)**

Cause	Associations
Primary	Features of the metabolic syndrome
Secondary	
Nutritional	Total parental nutrition, rapid weight loss, starvation, intestinal bypass surgery
Drugs	Glucocorticoids, estrogens, tamoxifen, methotrexate, zidovudine Amiodarone, ASA, intravenous tetracycline, didanosine, cocaine, perhexilene, hypervitaminosis A, diltiazem
Toxins	Toxic mushrooms (Amanita phalloides, Lepiota) Petrochemicals, phosphorus, Bacillus cereus toxin
Metabolic	Lipodystrophy, dysbetalipoproteinemia, Weber-Christian disease, Wolman's disease Acute fatty liver of pregnancy, Reye's syndrome
Other	Inflammatory bowel disease, HIV infection, small-bowel diverticulosis with bacterial overgrowth

NAFLD is considered as the hepatic manifestation of the metabolic syndrome. It is debated, however, whether the metabolic syndrome is a predictor of nonalcoholic fatty liver disease or if it is a consequence. Subjects with NAFLD have been reported to have high prevalence rates of the metabolic syndrome and associated disorders (39-43). Furthermore, liver markers have shown to be associated with features of the metabolic syndrome in large representative samples of the general population (31). Although NAFLD has not been included in the definition of the metabolic syndrome, several studies indicate that NAFLD may be an early event in the development of insulin resistance and might thus predict the presence or future development of the metabolic syndrome (10). Data in a Japanese population indicate that men and women who met the criteria for the metabolic syndrome at baseline were more likely to develop NAFLD during follow-up (44).

Potential mechanisms linking the metabolic syndrome and NAFLD (Fig. 1) (29)

The pathophysiology of NAFLD has to date not been completely clarified. In 1998 the 'two hit' model of the pathogenesis of NAFLD has been proposed. The 'first hit' is the excessive accumulation of fat in the liver. This is a consequence of an imbalance between the influx and synthesis of liver lipids on one hand and their β-oxidation and export on the other hand. The fatty liver becomes sensitive to presumed 'second hits' leading to hepatocyte injury, inflammation and fibrosis. These 'second hits' are oxidative stress (and subsequent lipid peroxidation), proinflammatory cytokines (tumor necrosis factor-α (TNF-α)), and adipocytokines (45,46).

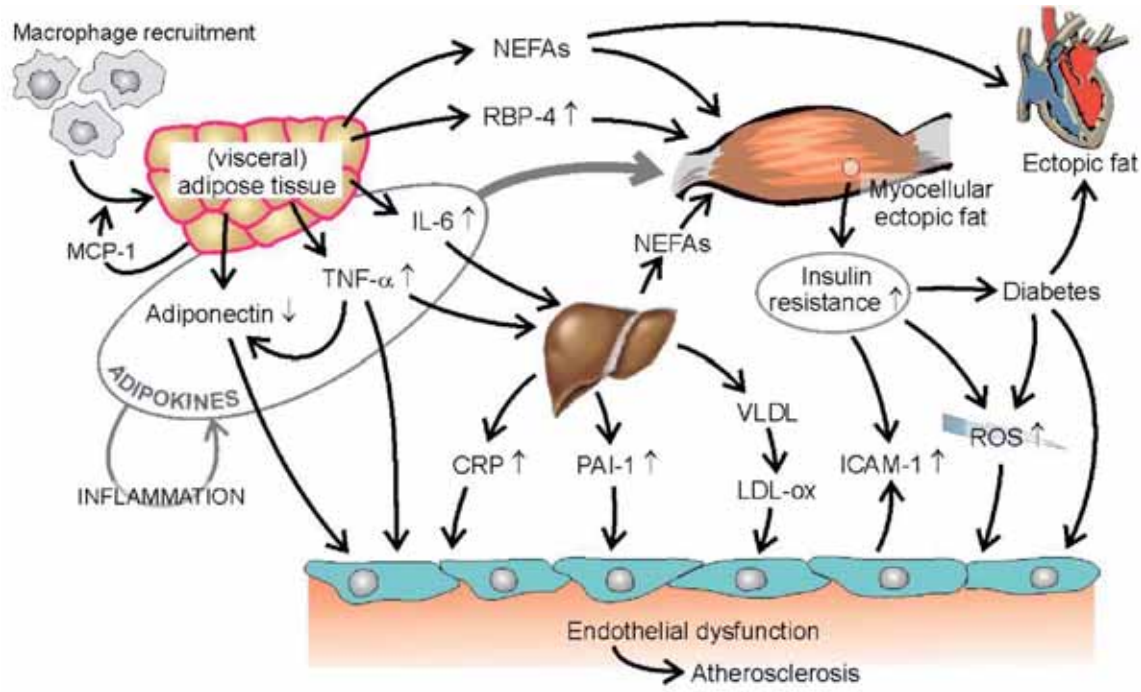

Fig. 1. — Contribution of liver and fat tissue to mechanisms linking obesity to cardiovascular disease. Both abdominal (visceral) fat and insulin resistance may contribute to cardiovascular disease in obesity. Visceral fat in particular contributes to endothelial dysfunction through the direct effect of adipokines, mainly adiponectin and TNF-α, which are secreted by fat tissue after macrophage recruitment [through monocyte chemoattractant protein-1 (MCP-1)]. Indirect effects of TNF-α and IL-6 might influence inflammation (CRP) and (subsequent) endothelial dysfunction. Insulin resistance induced by cytokines (IL-6, TNF-α and adiponectin), NEFA and retinol-binding protein 4 (RBP-4) may induce oxidative stress and subsequent endothelial dysfunction [PAI-1 and intercellular adhesion molecule-1 (ICAM-1)]. Fat accumulation, insulin resistance, liver-induced inflammation and dyslipidaemic features may all lead to the premature atherosclerotic process (Adapted from Van Gaal L. *et al.* Nature 2006) (29).

Insulin resistance

Insulin resistance (IR) is often mentioned as a key mechanism in NAFLD. Obesity, type 2 diabetes and hyperlipidaemia are associated with insulin resistance and are often present in patients with NAFLD. There are even insulin resistant patients with NAFLD who are not obese and show a normal glucose tolerance (41). This implicates that hyperinsulinaemia can correlate with NAFLD independently of BMI and fat distribution, indicating that other factors beside visceral obesity contribute to the association between NAFLD and IR (34). IR may play an important role in the accumulation of fat in the hepatocytes. Molecules like TNF-α, fatty acids and others appear to interfere with the insulin signalling pathway. The effects of insulin resistance in muscle and adipose tissue interact with the compensatory hyperinsulinaemia on tissues that remain insulin sensitive. This causes changes in the lipid metabolism, such as enhanced peripheral lipolysis, increased hepatic uptake of free fatty acids (FFA), and increased hepatic triglyceride synthesis. The influx and neosynthesis of FFA are more important than FFA oxidation and triglyceride secretion, resulting in an accumulation of fat in the liver. This hepatic fat subsequently contributes to an impaired glucose metabolism and insulin sensitivity within the liver (33,47,48).

Oxidative stress

Many studies show that oxidative stress is an important feature of NAFLD. Increased levels of fatty acids in the hepatocytes provide a source of oxidative stress. In obese patients reactive oxygen species (ROS) can result from production by the hepatocytes but also by the adipose tissue. Oxidative stress may be in part responsible for the progression from steatosis to steatohepatitis and cirrhosis. This could occur by three main mechanisms : lipid peroxidation, cytokine induction and Fas ligand induction. Lipid peroxidation (caused by ROS) of plasma or mitochondrial membranes can lead to cell necrosis or can induce apoptosis. ROS also increases Fas-ligand on hepatocytes causing apoptotic cell death ; it also increases the production of proinflammatory cytokines (TNF-α, interleukine(IL)-6, IL-8,…) (33,43).

Inflammatory cytokines

Data suggest also a role for inflammatory cytokines (TNF-α, IL-6, IL-8, …) in NAFLD. They may cause

systemic and hepatic insulin resistance. They also could be responsible for hepatocyte injury and apoptosis. Low-grade systemic inflammation occurring in the metabolic syndrome links insulin resistance, endothelial dysfunction and cardiovscular disease This systemic subclinical inflammation is also found in obese people and in subjects with NAFLD (49,50).

Adipokines

Studies have shown that the adipose tissue is not simply a reservoir of energy, but an 'endocrine organ' secreting different so-called adipokines or adipocytokines. Adipocytokines are bioactive substances (peptides) mainly produced by visceral adipose tissue. These adipokines include TNFα, adiponectin, leptin, plasminogen activator inhibitor-1 (PAI-1), IL-6, resistin and angiotensinogen (51). Adipokines may modulate insulin resistance (52-54). The metabolic effect of insulin resistance, partially mediated by decreased plasma adiponectin levels, includes fatty acid flux from adipose tissue to the liver and induces the accumulation of fat in the liver. Elevated plasma glucose can further increase hepatic fat content through multiple pathways, resulting in an overproduction of very low-density lipoprotein 1 (VLDL1) particles and leading to the characteristic dyslipidaemia associated with type 2 diabetes (55,56).

Importance of fat distribution

The distribution of body fat may be at least as important as total adipose tissue in the development of hepatic steatosis. Central adiposity has been shown to be associated with NAFLD in normal weight, obese, and diabetic individuals (34). Visceral adipose tissue has greater lipolytic potential than subcutaneous adipose tissue, and the release of FFA from visceral fat directly into the portal circulation creates a 'first-pass' effect. Increased FFA concentrations, in turn, are considered a major mediator of insulin resistance. In contrast, FFA flux and concentrations in individuals with predominatly lower body obesity tend to be normal, regardless of BMI. Therefore patients with central obesity are characteristically insulin resistant, and more commonly present with NAFLD than patients with lower-body obesity (35,57).

Hyperlipidaemia

In patients with the metabolic syndrome lipid profile frequently shows some unfavourable changes (low HDL-cholesterol, increased triglycerides and small dense low-density lipoprotein (LDL)) (54). Hypertriglyceridaemia rather than hypercholesterolaemia may increase the risk of NAFLD (33,34).

Environmental factors

Obese patients with NASH appear to have a higher intake of saturated fat and a lower intake of the antioxidant vitamins C and E compared to obese controls without evidence of liver disease. Polyunsaturated fatty acids reduce steatosis and improve insulin sensitivity (58).

Genetic factors

Polymorphisms of genes involved in insulin resistance, fat metabolism and inflammation might be responsible for insulin resistance and might therefore be involved in the pathogenesis of both the metabolic syndrome and NAFLD (43,58).

The management of the metabolic syndrome – from lifestyle intervention to pharmacotherapy (Table 3) (59)

In the management of the metabolic syndrome targeted risk factors can succesfully be treated pharmacologically, using cholesterol lowering drugs, antihypertensive drugs, antidiabetic drugs, antithrombotic and antiplatelet drugs. We are, however, less succesfull in the outcome of less conventional risk factors such as smoking, overweight and obesity, low HDL-cholesterol, insulin resistance, visceral and hepatic fat deposition.

Treatment of patients with NAFLD should focus on the management of associated conditions including obesity, glucose and lipid abnormalities (35,60,61). Lifestyle modification comprising healthy eating habits and regular exercise are the primary interventions recommended to patients with NAFLD (10). It is well established that moderate weight loss has a beneficial effect on cardiovascular risk factors. Weight reductions of 5 to 10% have been associated with improvements in fasting glycaemia and hemoglobin A1c (HbA1c), systolic and diastolic blood pressure and lipid parameters (62,63).

It is noteworthy that the liver seems to be able to mobilize its fat rapidly. It was found that lifestyle changes, mostly focused on weight loss, reduce liver transaminases and decrease liver fat content (64). The degree of fatty infiltration usually decreases with weight loss in most patients, although the degree of necroinflammation and fibrosis may worsen. The rate of weight loss is therefore important and may have a critical role in determining whether liver histology will improve or worsen. In patients with a high degree of fatty infiltration, rapid weight loss may promote necroinflammation, portal fibrosis, and bile stasis. Rapid weight loss is of concern in patients chosing a very low calorie diet (VLCD) or bariatric surgery (10). A weight loss of about 500 g per week in children and 1600 g per week in adults has been advocated as target. But the most effective rate and degree of weight loss still have to be established (33).

Lifestyle intervention with diet and increased physical activity

Dietary and lifestyle changes may be able to bring about regression of even severe coronary atherosclerosis

Table 3. — **Pathophysiologically based treatment of nonalcoholic fatty liver disease (Adapted from McCullough 2006) (59)**

Cause	Treatment
Nonhepatic	
Obesity	Moderatie weight loss and exercise* Bariatric surgery§ Orlistat§
Western diet	Increased amount of vitamins (A, C, and E), fiber, and polyunsaturated fatty acids§
Cytokine or adipokine abnormalities	Anticytokine therapy : inhibitors, blockers, or replacement‡
Increased visceral fat	Weight loss* Cannabinoid receptor antagonists
Bacterial overgrowth	Nonabsorbable antibiotics‡ Probiotics‡
Insulin resistance	Thiazolidinediones§ Metformin§ Exercise Incretin (glucogon-like receptor 1)
Hypertriglyceridemia	Hypolipidemic agents (clofibrate§, gemfibrozil§, probucol§)
Hepatic	
Oxidative stress	Antioxidant†
Lipid peroxidation	Peroxisome proliferators-activated receptor‡
Iron	Phlebotomy
Cytoprotection	Ursodeoxycholic acid*
Glutathione deficiency	Betaine§ and S-adenosyl-L-methionine‡
Apoptosis	Caspase inhibition α-Adrenergic agonists‡

* At least one controlled trial in humans has been performed.
§ An uncontrolled trial in humans has been performed.
‡ This agent has been used only in animal models thus far.
† This agent has not been shown to be effective. In the only controlled trials, patients who received increased amounts of vitamin E plus vitamin C or of ursodeoxycholic acid in their diet did not have improvement as compared with patients in the placebo group.

after only 1 year without the use of lipid lowering drugs as was concluded by the Lifestyle Heart Trial (65). The Finnish Diabetes Prevention Study (FDPS) stated that type 2 diabetes can be prevented by changes in lifestyle of high-risk subjects (66). In 2002 data of the Diabetes Prevention Program (DPP) concluded that lifestyle changes and treatment with metformin both reduced the incidence of diabetes in individuals at high risk. The lifestyle intervention was more effective than metformin (67). Early weight loss in obese diabetic patients was associated with a prolonged survival (68).

Diet

A Very Low Calorie Diet (VLCD) versus a more moderate hypocaloric diet

Paisey *et al.* published 5 year results of a programme comparing VLCD with a conventional weight loss programme in obese diabetic patients. VLCD was found safe and effective in this population. Subjects with a conventional diet, however, had a slower but more sustained weight loss (69). Some caution should be taken when inducing rapid weight loss by means of a VLCD in patients with NAFLD since this can worsen hepatic inflammation and fibrosis (10).

Low carbohydrate diets versus low fat diets

Low fat diets are traditionally the most recommended by medical professionals. These diets have shown to be safe, cardio-protective and effective in weight loss. Adherence, however, has been a problem. Low carbohydrate diets have therefore been popular the last decades. Carbohydrate restriction leads to ketosis resulting in weight loss, a decrease in blood glucose, insulin and triglyceride levels (70). In a randomised controlled trial by Foster et al, the low-carbohydrate, high-protein, high-fat diet was compared with a low-calorie, high carbohydrate, low fat diet (convential diet). The study concluded that the low-carbohydrate diet produced a greater weight loss than the conventional diet in the first six months, but the differences were not significant after one year. The low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease (71). Samaha *et al.* confirmed these results and noted a moderate improvement in insulin sensitivity and triglyceride levels in the carbohydrate restricted

diet, even after adjustment for the amount of weight loss (72). In general, low-carbohydrate diets show greater improvements in insulin sensitivity, triglyceride and high-density cholesterol levels. It is therefore possible that for patients with the metabolic syndrome, a low-carbohydrate diet may be more advantageous. This may also positively affect NAFLD (70). Future studies evaluating long-term cardiovascular outcomes are required to determine long-term safety and efficacy of these low-carbohydrate, high-protein, high-fat diets, specifically in NAFLD.

Dietary fat content

Westerbacka *et al.* suggest that the amount of dietary fat influences liver fat content and that the diet composition may influence liver fat content and fasting insulin concentrations in humans (73). The importance of fatty acid composition of diet remains to be studied.

Alcohol intake

The role of minimal or moderate alcohol intake in pathogenesis and potential progression of NAFLD has not been widely investigated. Therefore, specific recommendations regarding these factors cannot be made (48).

Exercise

Physical inactivity is, besides obesity, a modifiable risk factor for the metabolic syndrome. Cross-sectional and prospective studies have generally found that levels of physical activity and fitness are inversely releated to the prevalence of the metabolic syndome (74,75). A fit fat individual may even benefit of exercise even in the absence of weight loss (76,77), probably because physical activity preferentially reduces abdominal fat, improves (muscle) insulin sensitivity, and prevents further weight gain. Perseghin *et al.* demonstrated that a higher level of habitual physical activity is associated with a lower intrahepatic fat content and suggested that this relationship may be due to the effect of exercise per se (78).

Pharmacological approach

Pharmacological treatment should be initiated only when there is no change in the course of disease after adequate lifestyle changes have been undertaken (48).

Insulin-sensitizing agents

Because of the possible causal nature of insulin resistance, therapeutic interventions aiming at improving insulin sensitivity may be one approach to treat the metabolic syndrome and NAFLD. Insulin-sentizing agents, like metformin or thiazolidinediones may improve the reduced insulin sensitivity in respectively the liver and the periphery (61). Peroxisome proliferator-activated receptor(PPAR)-γ agonists (or thiazolidinediones) not only increase insulin responsiveness, but have numerous other, potentially beneficial effects such as lipid modifying actions, reduction in advanced glycosylation endproducts formation and pro-fibrinolytic and anti-thrombotic actions. Weight gain is, however, a known side effect of this class of drugs. The weight gained during the use of these drugs tends to be more peripheral fat rather than central fat and therefore it may not be associated with increased risks associated with the metabolic syndrome. This class of drugs also has an effect on NAFLD. Rosiglitazone may cause significant improvement in histological features, including necroinflammatory changes and fibrosis, with persistence of mild portal inflammation (79). Belfort *et al.* showed that pioglitazone in combination with a hypocaloric diet led to metabolic and histological improvements (80). In the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study rosiglitazone increased the likelihood of regression to normoglycaemia, but also led to a reduction in alanine aminotransferase (ALT) levels (81).

Lipid lowering drugs

The atherogenic dyslipidaemia characterizing the metabolic syndrome is an important target for cardiovascular disease risk reduction in patients with the metabolic syndrome. Statin therapy provides effective reduction of LDL-cholesterol, lowers apo B-containing lipoproteins and improves particle composition to a less atherogenic phenotype. The fibrates or PPARα agonists in turn are effective in normalizing lipid levels : they lower triglycerides and increase HDL-cholesterol (82). Statins, however, are frequently associated with usually mild elevations of aminotransferases. An expert panel concluded that statins are safe in patients with pre-existing liver disease except for those with decompensated cirrhosis or acute liver failure, patients in whom there are no data but extra caution is warranted (83).

Antihypertensive drugs

Hypertension is a major component of the metabolic syndrome and a major cardiovascular risk factor. An angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker is the most suitable therapy to be started in patients with the metabolic syndrome, alone or in combination (84).

Antiobesity drugs

Orlistat

Orlistat is a lipase inhibitor, which reduces the absorption of dietary fat by 30%. This agent reduces weight in obese adults and adolescents with or without comorbidities (including type 2 diabetes mellitus, hypercholesterolaemia, hypertension, metabolic syndrome). In obese patients, orlistat in combination with a hypocaloric diet improved metabolic risk factors and reduced the risk of developing type 2 diabetes (85). The ObelHyx (Obesity Linked with hypercholesterolemia treated with Xenical) study group concluded that orlistat promotes weight loss and reduces LDL-cholesterol

beyond the effect of weight loss in overweight or obese patients with hypercholesterolaemia (86). Sjöström *et al.* performed a randomised controlled trial and concluded that orlistat taken with an appropriate diet promotes significant weight loss and reduces weight regain in obese patients over a 2-year period (87). Orlistat (120 mg three times a day) also improved serum ALT levels and steatosis (diagnosed by ultrasound and confirmed by liver biopsy) more than lifestyle modification alone (88-90). Orlistat is generally well tolerated, with gastrointestinal adverse events (like fatty and oily stool, faecal urgency, and oily spotting) being most commonly reported effects (89, 91, 92). The drug has recently been approved in the US as an over-the-counter 60 mg formulation.

Sibutramine

Sibutramine, a monoamine-reuptake inhibitor, reduces food intake and attenuates the fall in metabolic rate associated with weight loss (93). Following a very-low-calorie diet sibutramine is effective in maintaining and improving weight loss for up to 1 year (94). Weight loss following sibutramine is also associated with several favourable metabolic effects, such as improved insulin sensitivity, an increase in HDL-cholesterol, a reduction in triglycerides, a lowering of uric acid concentrations, and a favourable influence on adipocytokines. There even may be an effect of sibutramine on HDL-cholesterol, independent of weight loss (95). Preliminary findings also suggest that weight loss following treatment with sibutramine is useful in patients with NAFLD (93). A study investigating the effects of sibutramine and orlistat in obese patients with NASH showed that both sibutramine-induced and orlistat-induced weight losses result in reduction of insulin resistance, and improvements in biochemical markers and ultrasound findings of NASH (96). Because sibutramine is associated with increases in blood pressure and pulse rate, the drug is not recommended in patients with uncontrolled hypertension, pre-existing cardiovascular disease, or tachycardia (92). Long-term data on the effect of sibutramine on major obesity-releated morbidity and mortality are lacking. However, the ongoing Sibutramine Cardiovascular Outcomes (SCOUT) trial is assessing the efficacy of sibutramine in reducing myocardial infarction, stroke, and cardiovascular mortality in 9000 obese and overweight patients (97).

Rimonabant

The endocannabinoid system contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects (98,99). This system consists of endogenous ligands and two types of G-protein-coupled cannabinoid receptors. Cannabinoid 1 (CB_1) receptor is located in numerous organs involved in the regulation of energy homeostatis, including brain, adipose tissue, liver, muscle, and the gastrointestinal tract (100). Cannabinoid 2 (CB_2) receptors are predominantly linked with the immune system (101). Rimonabant, a selective CB_1 blocker, produces clinically meaningful weight loss and additional improvements in waist circumference, lipid concentrations and insulin resistance (102). CB_1-blockade by rimonabant stimulates adiponectin production in adipocytes (100). Animal studies demonstrate that rimonabant may play a hepatoprotective role and suggests that this CB_1 receptor antagonist potentially has clinical applications in the treatment of obesity-associated liver diseases and related features of the metabolic syndrome (103). Selective CB_1 antagonists may even help to prevent the development of fatty liver in the presence of a high-fat diet (104). An increased incidence of gastrointestinal side effects (nausea, vomiting) and mood-related disorders has been reported (105). No data on cardiovascular morbidity and mortality have been reported, but several rimonabant studies examining clinical endpoints are underway. The largest is the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial. Rimonabant is currently under consideration for approval at the Food and Drug Administration (FDA) and has been approved by European Agency for the Evaluation of Medicinal Products (EMEA) (92). Psychiatric disorders, including depression and anxiety, were the most common reasons for subjects to withdraw from rimonabant studies.

Incretins and/or incretin mimetics

The presence of nutrients in the gastrointestinal tract rapidly stimulates the release of incretins : glucagon-like peptide-1 (GLP-1) from L cells located primarily in the distal gut (ileum and colon), and glucose-dependent insulinotropic peptide (GIP) from K cells in the proximal gut (duodenum). These incretins exert several beneficial actions, including stimulating the insulin response in pancreatic beta cells and reducing glucagon production from pancreatic alpha cells when glucose levels are elevated. Increased insulin levels improve glucose uptake by peripheral tissues ; the combination of increased insulin and decreased glucagon reduces hepatic glucose output (106-109). By decreasing β-cell workload and improving β-cell response, GLP-1 is an important regulator of glucose homeostasis (110,111). GLP-1 has also profound effects on the central nervous system, resulting in increased satiety and a reduction of food intake (112,113). It also slows gastric emptying by a local action. Exenatide is an example of an incretin mimetic. After subcutaneous administration to patients with type 2 diabetes, exenatide shares some of the glucoregulatory effects with endogenous GLP-1 (114-116). A case report of a 59-year old male with poorly controlled type 2 diabetes and treated with exenatide in addition to metformin monotherapy demonstrated a significant decrease in hepatic fat accumulation (quantified by proton magnetic resonance spectroscopy) accompanied by significant beneficial changes in several cardiovascular disease risk factors (117).

Surgery

Bariatric surgery is considered as an effective treatment option in some NAFLD patients with severe obesity or with concomitant obesity-associated disorders (118). There are several surgical approaches for morbidly obese patients : malabsorptive procedures (jejuno-ileal bypass and biIiopancreatic diversions), restrictive procedures (gastric banding) and combined restrictive and malabsorptive procedures (Roux-en-Y gastric bypass). Previous studies report postoperative complications, such as progression of liver disease and subacute liver failure (119). Although bariatric surgery produces significant weight loss, the additional effects of malabsorption and diversion of gut contents have confounded the effect of weight loss after these procedures (120).

Adjustable gastric banding

An inflatable silicone band around the upper stomach partitions the stomach into a 30 mL proximal pouch and a large, distal remnant, connected through a narrow nondistensible adjustable constriction (121). Gastric banding causes weight loss by limiting the capacity of the stomach to accumulate food and by slowing the flow of ingested foods, without malabsorption and without major alteration to the structure and function of the gastrointestinal tract. A study by Dixon *et al.* examined the effect of adjustable gastric banding on the histological features of NAFLD and plasma aminotransferase levels. There were improvements in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), lobular steatosis, inflammation and fibrosis between baseline and follow-up (122).

Roux-en-Y gastric bypass

Gastric bypass divides the stomach into a small proximal pouch measuring 30 mL and a separate, large, distal defunctionalized remnant. The upper pouch is joined to the jejunum through a narrow distensible gastrojejunal anastomosis. The proximal part of the divided jejunum is reattached to the jejunum 75-150 cm below the gastrojejunal anastomosis creating a Roux-en-Y limb (121). Several studies show a significant improvement in glycaemia, HbA1c and lipid profiles. Furthermore Roux-en-Y gastric bypass results in significant improvement in the histological features of NAFLD and NASH (123-126).

Biliopancreatic diversion

Biliopancreatic diversion, with or without a pylorus-sparing ‘duodenal switch’ causes malabsorption as pancreatic and biliary secretions are diverted to the distal small intestine approximately 50 cm from the ileocecal valve. Absorption is limited to the distal ileum. A sleeve gastrectomy is depicted (121,127). Cases have been reported of severe liver decompensation and even need for liver transplantation after this procedure.

Liposuction

There is an absence of an effect of liposuction on insulin action and risk factors for coronary heart disease : reduction of subcutaneous fat mass does not improve metabolic risk or inflammatory status (128). We found no data of the effect of liposuction on hepatic fat and/or function in humans.

Omentectomy

Surgical resection of the omentum (or part of it) results in a reduction of the amount of visceral fat. When combined with adjustable gastric banding significant positive and long-term effects are observed in the glucose and insulin metabolic profiles of obese subjects when compared to adjustable gastic banding alone (129). There are no data available of studies with the technique of omentectomy in subjects with NAFLD.

Summary

As the prevalence of obesity keeps rising worldwide, so will that of the metabolic syndrome and NAFLD. It is also recognized that the consequences of NAFLD are not always benign. Although the pathophysiology of NAFLD still has not been completely clarified, it shows great similarity with the pathogenesis of the metabolic syndrome. Insulin resistance, oxidative stress and inflammaton seem to be key factors. NAFLD is even considered to be the hepatic manifestation of the metabolic syndrome. It is important to develop new strategies to prevent and treat NAFLD. Weight loss through lifestyle intervention significantly improves markers of the metabolic syndrome and affects the liver favourably in NAFLD. Large placebo-controlled trials are necessary to evaluate the effect of a pharmacological or surgical approach on the metabolic syndrome and NAFLD.

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