Non-alcoholic steatohepatitis (NASH) – is it a part of the metabolic syndrome?

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Summary

Metabolic syndrome is one of the most frequent diseases of our age, and it is accompanied by numerous complications. Clinical studies have been published suggesting that, in addition to the already well-known consequences of the metabolic syndrome, hepatic involvement should also be taken into consideration in a significant part of cases. Fatty liver or in most cases the histological picture of non-alcoholic steatohepatitis can mainly be observed in metabolic syndrome. These conditions may develop into hepatic cirrhosis, hepatic failure, or even hepatocellular cancer. The more components of the metabolic syndrome are present, and the more severe they are, the higher the likelihood of this transition is to happen. All these facts underscore the importance of assessing the hepatological status in patients with the metabolic syndrome.

Key words: non-alcoholic steatohepatitis, metabolic syndrome, insulin resistance, obesity, and adipocytokines.

List of abbreviations

Acyl-CoA – acetyl coenzyme A
AGE – advanced glycation end products
ALP – alkaline phosphatase
ALT – alanine aminotransferase
ANA – antinuclear antibody
AST – aspartate aminotransferase
BMI – body mass index
CETP – cholesterol ester transfer protein
CRP – C-reactive protein
CT – computer tomography
DM – diabetes mellitus
FFA – free fatty acid
GGT – gamma-glutamyl transpeptidase
GLUT-4 – glucose transporter 4
HDL – high density lipoprotein
HFE – hemochromatosis gene
IDL – intermediary density lipoprotein
IL-6 – interleukin 6
IL-8 – interleukin 8
INF-α – interferon alpha
IR – insulin resistance

IRS – insulin receptor substrate
LDL – low density lipoprotein
MCV – mean corpuscular volume
MRC – mitochondrial respiratory chain
MRI – magnetic resonance imaging
NAFLD – non-alcoholic fatty liver disease
NASH – non-alcoholic steatohepatitis
NF-κβ – nuclear transcription factor kappa beta
NO – nitrogen monoxide
NRF-1 – nuclear respiratory factor 1
OGTT – oral glucose tolerance test
PAI-1 – plasminogen activator inhibitor 1
PCOS – polycystic ovary syndrome
PGC1 – PPAR-gamma co-activator (1 alpha and 1 beta)
PPAR – peroxysome-proliferator-activated receptor
Ser/Thr phosphorylation – serine-threonine phosphorylation
US – ultrasound examination
TG – triglyceride
TNF-α – tumour necrosis factor alpha
TGF-β – transforming growth factor beta
VLDL – very low density lipoprotein

Introduction

Hepatic lesions may be caused by several factors including environmental damages, infections, alcohol, medicines and chemicals, as well as metabolic and genetic injuries. Presently we examine the relationship between the hepatic lesion and metabolic disturbances, searching the literature published in the recent years for evidence supporting our hypothesis, namely: non-alcoholic steatohepatitis, as an inherent part, belongs to the metabolic syndrome.

The clinical significance of the hepatic lesion is usually underestimated in the case of patients with metabolic disorders. More and more clinical studies demonstrate that various stages of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) can be diagnosed by liver biopsy in a decisive majority of patients with the metabolic syndrome [1]. NASH can be considered as the hepatic manifestation of insulin resistance, i. e. metabolic syndrome, and some authors even regard it as the next component in the system of diagnostic criteria for the syndrome [2]. In case of NASH the patient has an increased risk that the process will develop into hepatic cirrhosis, terminal hepatic failure, or hepatocellular cancer.

In addition to the clinical studies, the following facts also suggest an existing relationship between the two entities: a) the components of the metabolic syndrome (obesity, insulin resistance, dyslipidaemia, and – in a certain aspect – hypertension) constitute the risk factors of primary NASH; b) common features seen in the presumed pathologic mechanism: insulin resistance, disorders of the lipid metabolism, obesity, and the role of the adipocytokines; c) the beneficial effect on NASH exerted by certain medicines used in the treatment of insulin resistance. Due to the dramatic increase in the prevalence of obesity, the number of patients with metabolic syndrome complicated by NASH is increasing continuously [3]. In the future more attention should be paid to the hepatological status of patients with the metabolic syndrome as well, in order to prevent the hepatic complications [1].

Non-alcoholic steatohepatitis

The term 'non-alcoholic fatty liver' was first used by *Ludwig et al.* in 1980 for patients whom they examined by liver biopsy and found a histological picture similar to that in alcoholic liver disease; alcohol consumption, however, could be excluded on the base of the history [4].

Non-alcoholic fatty liver disease (NAFLD) includes a wide spectrum of diseases. Based on retrospective studies, there are four different stages recognized in the course of NAFLD, in accordance with the histological picture: 1. steatosis, 2. steatohepatitis, 3. steatosis with the swelling of the hepatocytes, and 4. fibrosis with the presence of Mallory's bodies. NASH constitutes a group of NAFLD, where in addition to the accumulation of triglycerides (TG) also necrobiotic inflammatory reaction, fibrosis or even cirrhosis can be observed. The development of cryptogenic cirrhosis is probably due to NASH in most part [5].

The clinical significance of NAFLD lies in its high incidence (10 to 24% and 2 to 3% of the population is affected by NAFLD and NASH, respectively), and this rate is even increasing, and the disease leads to the development of hepatic cirrhosis and hepatic failure. In primary NASH there is underlying insulin resistance, obesity, type 2 diabetes mellitus, and hyperlipidaemia, and it has to be differentiated from the secondary steatoses having dissimilar pathologic mechanism and clinical course. In the latter the following factors may underlie: certain medicines and chemicals, hereditary disorders of metabolism, nutritional deficiencies, infections, chronic inflammatory bowel diseases, and surgical interventions causing portal endotoxinaemia.

NASH is clinically asymptomatic in 90%, rarely the patients experience weakness, malaise, fatigue, and sometimes pain under the right costal margin, abdominal discomfort, or bloating. Thus NASH is found by 'serendipity' in a significant part of cases, and it is detected by examinations aimed at other directions. At physical examination hepatomegaly and palpation of a soft, non-tender liver with a rounded edge may be characteristic. In case of hepatic cirrhosis the characteristic clinical signs and symptoms can be observed.

NASH is characterized by elevated transaminase levels [6], however in certain cases the condition may exist at normal AST and ALT values as well [7]. More specific laboratory parameter is the change in de Ritis's ratio that also helps in differentiating from the alcoholic liver diseases. Namely, the ratio of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values is less than 1.0 in NASH (its increase may show the progression of the disease, while AST levels increase in fibrosis). In addition, higher levels of gamma-glutamyl transpeptidase (GGT) and high mean corpuscular volume (MCV) characterize the laboratory values of patients with NASH. The alkaline phosphatase (ALP) value may be elevated in about one third of the patients, but the levels of bilirubin and albumin are normal.

Positive antinuclear antibody (ANA+) and higher levels of iron and ferritin in the serum can be measured in more than 25% and in 25 to 50% of the patients respectively, and there is marked transferrin saturation. Histological and genetic evidence of haemochromatosis is not characteristic of the disease, nevertheless the incidence of the HFE gene's Cys282Tyr mutation has been found to be significantly higher in some patients [8]. The significant iron deposition may accelerate the transition of the condition into fibrosis and cirrhosis, although the concerning studies are controversial. Laboratory features of insulin resistance, diabetes mellitus and dyslipidemia can also be detected in a high percentage of the cases.

Performance of a liver biopsy is recommended in case of the concurrent presence of abnormal necro-inflammatory enzymes and signs suggesting steatosis. However, the histological picture is of little or no help in differentiating from the alcoholic liver diseases [4]. The abdominal ultrasound examination shows an increased echogeneity of the fatty liver in comparison to the parenchymal part of the kidney. However, the picture of 'bright liver' seen by US is a feature of only the more severe cases, and the recognition of early forms requires great experience and up-to-date equipment. At computer tomography (CT) the lesion is described as of low density, mostly with a diffuse appearance, rarely however it may present itself in a focal form, mimicking metastases. In that case MRI may help in the differential diagnosis.

The currently valid diagnostic criteria of NASH are shown in Table I. As for its pathogenesis, the so-called 'two-hits theory' is the most accepted now. The first hit is the accumulation of TGs in the liver, and its risk factors are basically identical with the components of the metabolic syndrome: 1. Obesity: almost all patients (69 to 100%) are obese (BMI>30kg/m^2) 2. Insulin resistance and type 2 diabetes mellitus: 34 to 75% of patients have type 2 diabetes mellitus. 3. Dyslipidaemia: hyperlipidaemia can be demonstrated in 20 to 81% of the cases. 4. Hypertension is classified as independent predictive factor of NASH, together with insulin resistance and elevation of the ALT level. The second hit is the secondary pathologic release of free radicals

Table I. Diagnostic criteria of non-alcoholic steatohepatitis (NASH)

Clinical criteria
1. Chronic slight elevation of the aminotransferase levels.
2. Exclusion of significant alcohol consumption (40g/week), based on history obtained from the family and the family doctor of the patient.
3. Asymptomatic clinical course or non-specific clinical symptoms.
4. Exclusion of hepatic diseases of viral or other known aetiology.
Laboratory criteria
1. Elevation of the levels of aminotransferase enzymes up to 1 to 4 times the normal values, and elevation of the levels of γ-glutamyl-transpeptidase (GGT).
2. Results of all other liver tests are in the normal range.
3. Negative results of HBsAg and AMA antibodies.
4. ANA is present in a dilution <320.
5. Normal values of coeruloplasmin, α-1-antitrypsin and transferrin saturation, see Table
Imaging procedures
Ultrasound: bright liver
CT and MRI

Histology
Diffuse or centrolobular macrovesicular steatosis, balloon-like alterations and necroses of hepatocytes, mixed inflammatory infiltration with or without fibrosis, Mallory's hyaline bodies, lipogranulomes, and glycogen reserves.

Table II. Diagnostic criteria of the metabolic syndrome

• Abdominal-type obesity: waist circumference >102 cm (men), or >88 cm (women)
• Abnormal serum triglyceride: ≥1.69 mmol/L (≥150 mg/dL)
• Abnormal serum HDL-cholesterol: <1.04 mmol/L (<40 mg/dL) (men), or <1.29 mmol/L (<50 mg/dL) (women)
• Abnormal blood pressure level: ≥130/≥85 mmHg*
• Abnormal fasting serum glucose: ≥6.1 mmol/L (≥110 mg/dL)

**Without antihypertensive treatment. (In case of patients with known hypertension the criterion is documented hypertension in the history, independently of the actual blood pressure values).*
Non-SI units (used in the USA) are indicated for the sake of the accuracy of citation.

Table III. Criteria of the metabolic syndrome according to the Metabolic Workgroup of the Hungarian Diabetes Association, 2002

1. Glucose intolerance (IFG or IGT or DM) or insulin resistance (HOMA >4.4)
2. Hypertension (documented in the history or newly detected BP >140/90 mmHg)
3. Dyslipidaemia – serum triglyceride level ≥1.7 mmol/L, or – serum HDL-cholesterol level <1.0 mmol/L, or – serum total cholesterol level >5.2 mmol/L (LDL-cholesterol >3.4 mmol/L).
4. Obesity (overweight): BMI ≥27.0 kg/m^2 or waist circumference >80 cm (women), >94 cm (men)

and the induction of the microsomal monooxygenase system by the mitochondrial β- and peroxisomal ω-oxidation, producing an inflammatory reaction and fibrogenesis, thus leading to progression of steatosis into steatohepatitis.

NAFLD or NASH is a benign condition in most cases, and it may even be reversible in states without fibrosis, if the pathogenetic factor ceases to exist. However, if the presumptive etiologic factor cannot be eliminated, the process becomes progressive, and may lead to the above-mentioned hepatic cirrhosis with all its complications. Important risk factors are an age over 45 years; obesity; type 2 diabetes mellitus, and dyslipidaemia.

Metabolic syndrome

The existence of the syndrome – referred to by many as the 'plague of our age' – was already suggested decades ago, based on animal experiments or clinical observations. The concomitant occurrence of diabetes, hyperlipaemia and gout was first described by Camus in 1966 as 'trisyndrome metabolique'. It should be underscored that in 1975 *Haller and Hanefeld* regarded obesity, diabetes mellitus, hyperlipaemia, hypertension and gout – due to overfeeding, lack of exercise, sociocultural and genetic factors – as a clinical entity called 'das metabolische Syndrome' that can lead to atherosclerosis, cholelithiasis and hepatic steatosis [9]. However the metabolic syndrome has come into science's foreground only since 1988, owing to *Raeven*, who integrated the cardiovascular risk factors of metabolic origin, previously considered as independent, into a causal unity. Since then, however the syndrome, referred to by newer and newer names, has become one of the central issues of medical literature and reasoning. The syndrome characterized by obesity, diabetes, dyslipidaemia and hypertension has become known as 'Kaplan's fatal four', visceral fat syndrome, civilization syndrome, syndrome X, metabolic cardiovascular syndrome, insulin resistance syndrome, dysmetabolic syndrome X, etc. At present the name metabolic syndrome is the most accepted. Its diagnostic criteria are based on the statement published by the ATP III in 2001 [10] (Table II). In Hungary the system of criteria compiled by experts of the Metabolic Workgroup of the Hungarian Diabetes Society in 2002 [11] is valid (Table III).

According to ATP III the five basic elements of the diagnosis are: abdominal obesity, hypertension, abnormal HDL-cholesterol and triglyceride, as well as abnormal fasting blood glucose values. The diagnosis can be established if at least three of the above criteria are present at the same time [10]. According to the Hungarian recommendation the diagnosis can be established, if – in addition to the glucose intolerance – at least two other conditions of the following are present: hypertension, dyslipidaemia, and obesity [11]. Beyond these, several factors are considered characteristic of the syndrome, such as hyperuricaemia, postprandial hyperglycaemia, hyper-apo-β-lipoproteinaemia, accumulation of the free fatty

acids, increase of the atherogenic small dense LDL-cholesterol concentration, hypercoagulable state (hyperfibrinogenaemia, increased factor VII activity, elevation of the PAI-1 level, increased platelet activity), hyperhomocysteinaemia, microalbuminuria, hyperleptinaemia, sleep apnoea syndrome, polycystic ovary syndrome (PCOS), elevation of the levels of inflammatory markers (CRP, selectines, adhesion molecules, proinflammatory cytokines), increased risk of certain tumours and cardiovascular complications, as well as the hepatic lesion discussed in this paper, manifesting characteristically in the form of non-alcoholic steatohepatitis (NASH) [12].

The prevalence of the metabolic syndrome in Caucasian populations is an estimated 25 to 30% [13]. As for the pathogenesis, several theories have been suggested, and the following ones are the most important: 1. Insulin resistance; 2. Obesity; 3. Disorders of the lipid metabolism; 4. Elevated sympathetic activity; 5. Development of microangiopathy; 6. Abnormal function of the hypothalamus-pituitary-adrenocortical axis [14].

What demonstrates that non-alcoholic steatohepatitis is a part of the metabolic syndrome?

Already in 1975 the above mentioned studies of *Haller and Hanefeld* pointed out that fatty liver disease might be one of the potential consequences of the condition known today as the metabolic syndrome [9]. Since then, especially in the recent years, more and more studies have been published that are searching the relationship between NASH and the metabolic syndrome. By analyzing relations between NASH and obesity, as well as interconnections with insulin resistance, type 2 diabetes mellitus and disorders of lipid metabolism, several working groups have come to the conclusion, primarily on the basis of epidemiological studies, that NAFLD can be considered as the hepatic consequence of the metabolic syndrome [1, 2, 11, 13, 15–21]. Risk factors of primary NASH: obesity, insulin resistance or type 2 diabetes mellitus, dyslipidaemia, together with the hypertension, constitute the components of the metabolic syndrome (Figure 1).

Insulin resistance

Insulin resistance (IR) is of decisive importance in NASH [16, 22–29], (especially in the presence of a reduced mitochondrial oxidation), what comes to effect by the following way, according to the current stand of scientific knowledge: a) there is an increased lipolysis in the peripheral tissues; b) the fatty acid uptake by the hepatocytes increases; c) the β-oxidation of the fatty acids taken up by the hepatocytes is of a greater extent; d) at the same time the uptake of lipoprotein by the tissues is reduced because of the insufficiency of lipoprotein lipase [25]. IR is much more severe in patients with NASH than in those diagnosed with 'simple' fatty liver [30].

It has been demonstrated in patients with the metabolic syndrome that on the one hand IR inhibits the glucose uptake of the whole body, and on the other hand it reduces the process of glucose and lipid oxidation, and it increases the intracellular potassium level (arrhythmogenic effect). In addition, after a time the β-cells of the islets of Langerhans in the pancreas become exhausted through the compensatory hyperinsulinaemia, and the ensuing hypoinsulinaemia leads to hyperglycaemia and manifests type 2 diabetes mellitus. It is important to note that the rise of the blood glucose levels leads to the accumulation of advanced glycation end products (AGEs) and, after

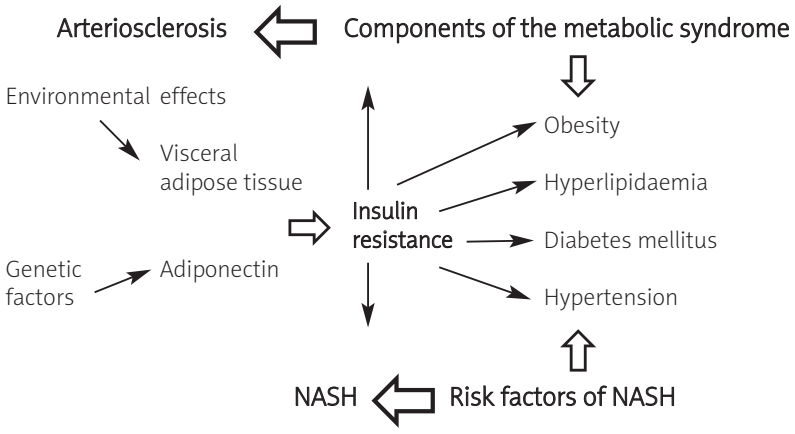

Figure 1. Connections between metabolic syndrome and non-alcoholic steatohepatitis

all, to oxidative stress. The superoxide anion activates NF-κ-β that leads to – among others – the apoptosis of the endothelial cells, and thus endothelial dysfunction. This process is even enhanced by the accumulation of free fatty acids, hyperglycaemia, hyperinsulinaemia, and TNF-α. At the same time the reabsorption of Na^+/H_2O in the kidney is increased due to the hyperinsulinaemia, which causes retention of Na^+ and water; the activity of Ca^{++}-ATP-ase is reduced, causing intracellular accumulation of Ca^{++} that leads to an increase of the vascular tonicity. The sympathethical tone increases, which – in addition to the increased vascular tonus – causes vasoconstriction, and also the stimulation of certain growth factors appears. Hypertension develops as the common result of all these events (Figure 1) [14].

Free fatty acids (FFA) have – among others – a decisive role in the development of insulin resistance by being transformed into acyl-CoA intracellularly [31] (Figure 2). In addition to the free fatty acids, TNF-α and hyperinsulinaemia also play a role in the activation of one of the mechanisms responsible for the negative control of signal transduction of insulin – namely the Ser/Thr-phosphorylation of insulin receptor and insulin-receptor-substrate (IRS) proteins – that blocks the signal transduction processes of the insulin [32]. By this way the muscle cells, hepatocytes, and adipocytes all become resistant to insulin. As a result of this, the glucose cannot enter the cells in spite of the presence of insulin, and cannot exert its effect on the metabolism, and so e. g. in the skeletal muscle the glycogen synthesis, stimulated by the insulin, is clearly reduced due to the stalling of GLUT-4 [31]. Underlying the process, possible genetic defects or disorders of the capillary density are being supposed in addition to the above-mentioned substances.

It is important to note the mitochondrial disorders observed in NASH: The mitochondria are swollen, and ribbed; they lose their cristae, and often contain paracristal inclusions [5]. The activity of MRC complexes is reduced in patients with NASH, showing a positive correlation with TNF-α levels, IR, and BMI values [33]. Inherited defects in the mitochondrial oxidative phosphorylation are supposed to exist in the offspring – diagnosed with IR – of patients with type 2 diabetes mellitus, leading to disorders in the intramyocellular fatty acid metabolism [34]. The nuclear respiratory factor-1 (NRF-1) -dependent genes coding enzymes that play crucial roles in the oxidative metabolism and mitochondrial function, are expressed to a lesser extent in DM and IR possibly due to the

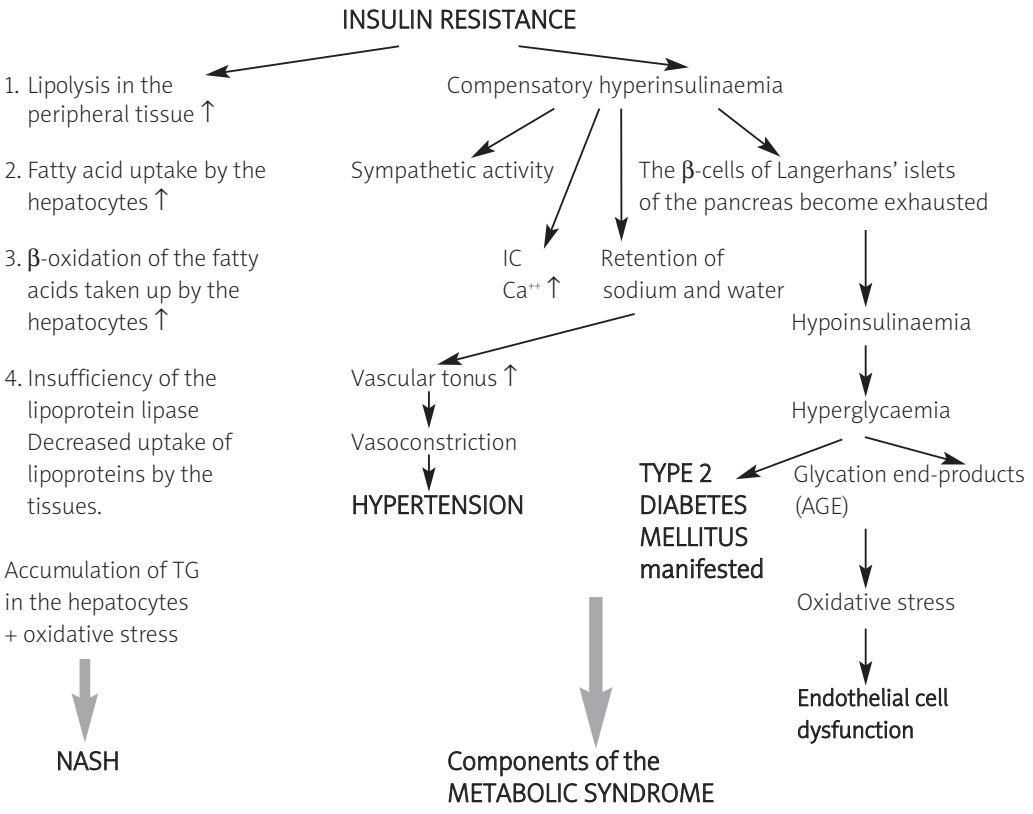

Figure 2. Role of the insulin resistance in the development of NASH and metabolic syndrome

reduction of PGC1-expression (PPAR-γ co-activator 1-β and 1-α) [29]. Based on all these, a connecting link between NASH and the metabolic syndrome is formed also by the – possibly hereditary – disorders of the mitochondrial function. It has also been demonstrated in NASH, that IR is the main risk factor for the transition into severe fibrosis [8]. Some authors recommend OGTT to be performed in the presence of non-alcoholic fatty liver, stating that by that means we can diagnose DM in its early stage [35, 36].

Obesity and disorders of lipid metabolism

The increased level of free fatty acids (FFA) is due mainly to the obesity and the changes in lipid metabolism. Obesity can lead to steatosis through at least four mechanisms: a) increased FFA supply of the liver; b) increased hepatic FFA synthesis; c) insufficient β-oxidation of FFA; and d) insufficient very low-density lipoprotein (VLDL) synthesis or secretion [2].

In the metabolic syndrome FFA is released from the abnormal mesenteric tissue to an extent depending on the ratio of the β-3-, and α-2 receptors in the given fat tissue, as β-3-adreno-receptors and α-2-receptors are responsible for the induction and the inhibition of the lipolytic process, respectively. Polymorphism of the β-3-receptor has been brought into connection with IR and visceral obesity for a long time, and recently with NAFL (Figure 3), too [12].

The lipid triad in IR (low HDL and elevated TG levels, as well as accumulation of LDL-cholesterol with increased density but of smaller size) is mostly due to the visceral obesity. Two significant enzymatic defects – reduced lipoprotein lipase and increased hepatic triglyceride-lipase activity – can be observed, which explains the development of dyslipidaemia. As insulin can inhibit neither the hormone-sensitive lipase, nor the increase of the hepatic VLDL production, there is an increased FFA release towards the liver in IR. The reduced function of lipoprotein lipase increases the FFA and VLDL levels in the vascular system, followed by development of IDL and LDL. The hepatic lipase hydrolyses TG from the LDL, and so the atherogenic 'small dense' LDL cholesterol is formed. The rise of the LDL level plays a decisive role in the development of the vascular injury and in the appearance of the intravascular atherogenic processes by going into an oxidized state due to the effect of various stimuli, and by coalescing into the 'foamy cell' that evolved from a macrophage.

The HDL molecule becomes richer in TG under the influence of the cholesterol ester transfer protein (CETP), and – as a consequence – it will be metabolized vigorously by the hepatic lipase, so that the HDL level decreases. That is very important, because HDL inhibits the appearance of adhesion molecules and the lipid peroxidation on the endothelial surface. The liver produces more VLDL that is rich in TG, because FFA, the precursor of VLDL, enters the liver with an increased flow. Hyperinsulinaemia increases the production of apolipoprotein B 100 and 48, the main apolipoproteins of the VLDL and IDL that are established CHD risk factors due to their atherogenic properties [37].

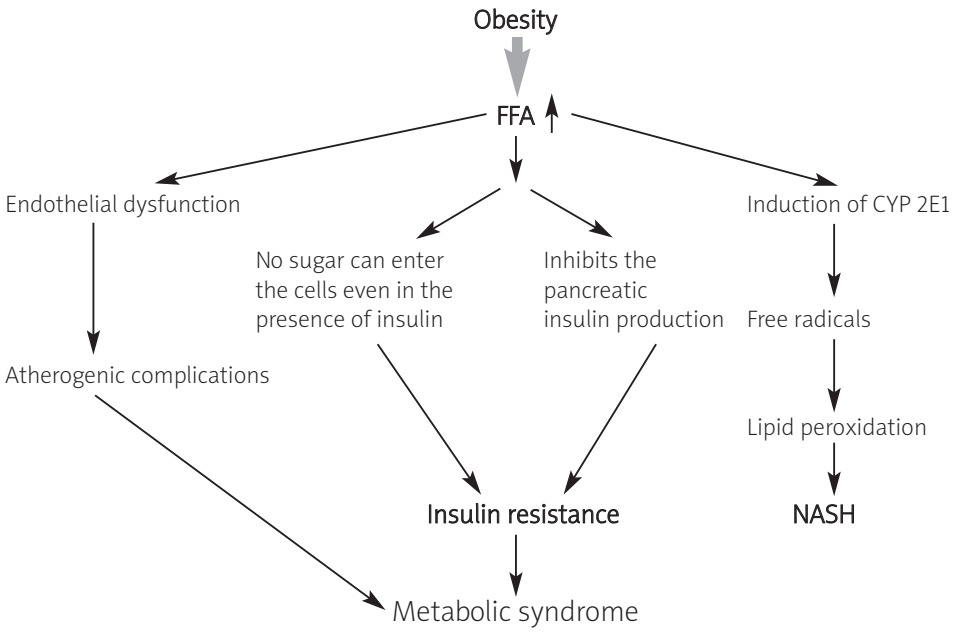

Figure 3. Role of the free fatty acids (FFA) in the development of NASH and the metabolic syndrome

Adipocytokines

Adipose tissue has recently turned out to function also as an endocrine organ that has an important role in metabolic regulation. So more and more emphasis is laid on the so-called adipocytokines produced by the adipose tissue (leptin, adiponectin, resistin, TNF-α IL-6, etc.) [38]. Especially the effect of leptin is known in the development of NASH. The elevated level of *leptin* increases the uptake of FFA in the liver, and at the same time it inhibits their β-oxidation. In addition, by increasing several mechanisms of the inflammatory reaction, leptin promotes the progression of fatty liver into steatohepatitis, and it has also been demonstrated that leptin increases the phagocytic ability of macrophages, as well [5].

In central obesity, characteristic to the metabolic syndrome, leptin is also released from the abnormal mesenteric adipocytes, and by coupling to its hypothalamic receptors it promotes expenditure of energy by increasing sympathetic activity and inducing thermogenesis. If there is also insulin resistance, the above mentioned mechanism is abolished due to the damage of certain receptor sites, and as a consequence, the compensation of the excess body mass will not happen.

Adiponectin is known to increase fatty acid oxidation, leading to the reduction of the TG content of cells in the liver and muscle tissue, and it also improves the insulin sensitivity of the cells. However, it inhibits the migration of monocytes and macrophages, as well as the development of foamy cells. In insulin resistance and type 2 diabetes mellitus the significantly reduced levels of adiponectin have already been demonstrated [39]. More and more attention is paid to glitazones that stimulate peroxysome-proliferator-activated receptor and increase adiponectin secretion in humans. The PPAR-δ effect can primarily be registered in the adipose tissue, and it regulates the differentiation of adipocytes and lipid storage. Their activation inhibits the flow of fatty acids into the liver and the skeletal muscle, and it actually initiates redistribution of fat. However in the metabolic syndrome and in type 2 diabetes, there is a disorder of gene expression; and this inhibitory process cannot come into force. PPAR-α expression is effective primarily in the liver, and it has a decisive influence on the increase of lipid oxidation, and it also probably reduces lipid accumulation in the skeletal muscle [14]. The hypothetical model of the secretion and effect of adiponectin are shown in Figure 4, based on data of the literature [36].

The pathogenic role of TNF-α, as adipocytokine or as inflammatory mediator is also in the focus of attention [40]. Namely, a role is attributed in the development of NASH to the inflammation reaction induced by bacterial endotoxins, associated with the release of TNF-α, as well as IL-6, IL-8 and other cytokines, resulting in hepatocellular necrosis. Based on the similar histological features in both non-alcoholic and alcoholic hepatic impairment, it is supposed that the above-mentioned mechanism leading to the alcohol-induced lesion applies to the NASH as well.

Furthermore, it should be underscored that unsaturated fatty acids accumulating in the hepatocytes cause changes in the mechanisms of the intracellular metabolism and the excretion of VLDL-cholesterol, inducing alterations in the processes of gluconeogenesis and oxidative phosphorylation. This, in turn, causes the release of various mediator substances – tumour necrosis factor-α (TNF-α), or nitrogen oxide (NO), interferon-α (INF-α), etc. – from the cells.

Elevated levels of TNF-α due to the increased expression of TNF-α in the adipose tissue have also

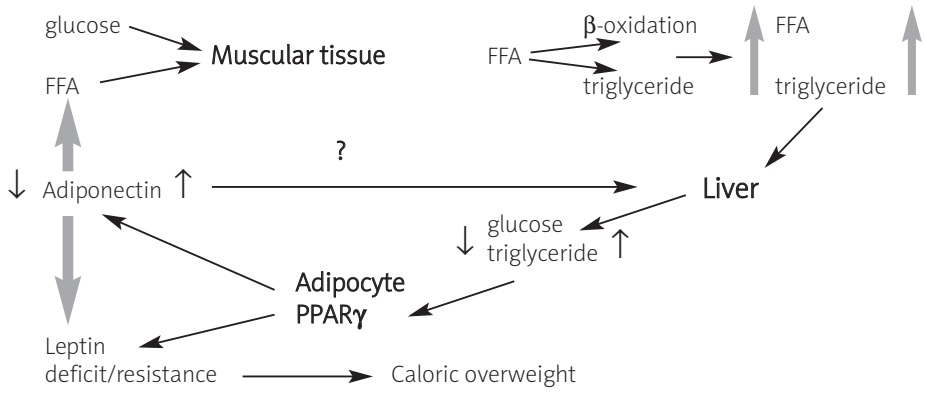

Figure 4. Hypothetical model of the secretion and effect of adiponectin

been demonstrated in obese and overweight patients with type 2 diabetes mellitus [2]. TNF-α is known to be an important mediator in the development of IR by exerting influence on the activity of the insulin receptor tyrosine kinase. TNF-α induces IR in the pancreatic β-cells and it stimulates the release of substances that are toxic for the β-cells. It has been demonstrated that TNF-α polymorphism (TNFA allele) is significantly higher in patients with NAFLD, which is associated with IR and the pancreatic β-cell function. TNF-α polymorphism may be one of the genetic factors that play a role in the development of IR and its consequences, so as NASH and the metabolic syndrome [30, 41].

It turned out that the elevation of PAI-1 levels (characteristic of the metabolic syndrome) shows a close correlation not primarily with the increase of adipose tissue, but with the hepatic steatosis [27]. In obesity complicated by insulin resistance the role of TNF-α in activating PAI-1 synthesis is presumed on the one hand. On the other hand, lipoproteins, accumulated due to the increased hepatic inflow of free fatty acids and deposition of TG, may induce production of PAI-1 in the endothelial cells and the hepatocytes [42].

In overfed rats the adipocytes show an increased local production of angiotensinogen leading to the elevation of angiotensin II levels in the perivascular adipose tissue, which plays a role in the development of the hypertension, and presumably also of the insulin resistance [43]. Angiotensin II is also known for inducing the production of TGF-β, one of the profibrogenetic factors in NASH [5].

It is an interesting observation that steatosis of non-alcoholic origin demonstrated in patients with hepatitis C virus infection shows a close correlation with the components of the metabolic syndrome, and at the same time it is also a risk factor of the advanced fibrosis [44]. In addition, these patients respond much worse to interferon-α (INF-α) treatment. According to some observations, important risk factors of the chronic cryptogenic hepatic involvement in patients with hepatocellular cancer are obesity and diabetes mellitus, by either directly promoting the development of the hepatic lesion, or leading to it through the previously developed NASH [45].

As a summary of our discussion, we can say that in the pathogenesis of both NASH and metabolic syndrome an outstandingly important role is attributed to insulin resistance. The accumulation of fat in the liver may be due to either a genetic defect responsible for the IR or the excessive intake of calories and the consequential obesity, or both – as in the metabolic syndrome. The process itself may be conducted, to all probability, by the adipocytokines. For the development of the inflammatory form of fatty liver, the responsibility may lie in the loss of equilibrium between pro- and anti-inflammatory cytokines leading to the release of reactive oxygen radicals and intrahepatic lipid peroxidation. The progression may be helped or accelerated by pro-oxidant xenobiotics and environmental factors [22]. In the development of the metabolic syndrome and its consequences, adipocytokines and inflammation, as well as oxidative stress play also an important role [46].

Therapy

The importance of the changes in lifestyle cannot be emphasised enough both in NASH and in the metabolic syndrome [37]. A gradual reduction of body weight (by 0.45 to 0.9 kg/week) combined with exercise therapy improves insulin resistance, leading to the mitigation the histological alterations of NASH, and diminishes the risks of complications of the metabolic syndrome as well. It should be emphasised, however, that an abrupt loss of weight should be avoided, because it carries the risk of the development of hepatic insufficiency [2]. In addition to a weight loss program designed by a professional, also medicines helping weight loss (sibutramine, orlistat) may be administered.

Improving control of carbohydrate metabolism is of crucial importance in the metabolic syndrome, and it seems to be the same in NASH, as well. Primarily, recommendations concerning lifestyle (low caloric dietary restriction, exercise therapy) should be followed. For the medicinal treatment of insulin resistance, two groups are recommended in NASH currently: biguanides including metformin [4, 47] and thiazolidinediones including rosiglitazone [48], and pioglitazone [49]. A recent study demonstrated also the beneficial effect of the alpha-glucosidase acarbose in rats [50].

Correction of lipid disorders should also be taken into consideration. In a study gemfibrozil resulted in the improvement of hepatic function. This also applies to probucol that has antioxidant properties as well. Clofibrate, however, has not influenced the laboratory and histological alterations of the condition significantly. There is no experience with enzyme inductors of 3-hydroxy-3-methylglutaryl-Coenzyme-A--reductase.

The principal role in the therapy of NASH is currently represented by the treatment of diabetes, hyperlipidaemia, and obesity, together with ursodeoxycholic acid (UDCA) as antioxidant, as well as metadoxine [4]. UDCA is a hydrophilic bile acid with hepatoprotective properties. As for UDCA, control studies have already been known, in connection with

the reversal of the progression of steatosis. The results of these studies showed that UDCA significantly reduced the levels of enzymes showing hepatocellular damage. Similar results are known with silymarin-type natural radical scavengers.

Metadoxine has been demonstrated to play an important role in the replacement of NADH, GSH and ATP in the central nervous system and liver of mice in case of oxidative stress. Clinical studies demonstrated that it normalizes ALT and AST levels, thus it takes part in the regeneration of the hepatocytes [4].

Anti-TNF-α antibodies can be pointed out as therapeutic possibility of the future [51]. For preventing the progression of NASH, and reducing transaminase levels, phlebotomy can be performed in order to remove the excess iron, as this procedure has been shown to have a beneficial effect in reducing excess iron observed also in IR (IRHIO) and in improving IR [23].

Conclusions

In a significant percentage of patients with the metabolic syndrome, hepatic lesion that may be indicated by elevated levels of transaminases should be taken into account [6, 52]. In the decisive majority of cases there is an underlying non-alcoholic fatty liver disease, or its more advanced form, non-alcoholic steatohepatitis. Insulin resistance and obesity, as well as certain adipocytokines play prominently important roles in the pathogenesis of the metabolic syndrome and NASH. Correction of these metabolic disturbances can be attained primarily by lifestyle changes and medicinal treatment of insulin resistance, beside other therapeutic possibilities. In the era of an increasing escalation of obesity, we should take into account not only the metabolic syndrome and all its complications known up to date, but also the effects on the liver and their consequences in more and more patients. Introduction of recommendations concerning appropriate lifestyle can be an important factor in the prevention of the metabolic syndrome and the hepatic damage.

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