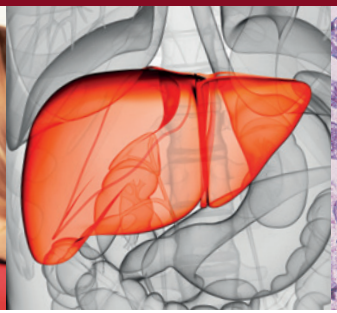
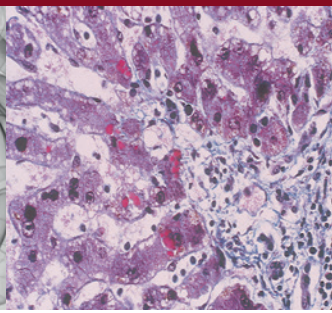
The role of the liver in metabolic syndrome

Obesity – insulin resistance – NAFLD

Pathophysiology, clinical symptoms and treatment options

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Preface

Metabolic syndrome, which affects approx. 25% of our population, is a combination of different risk factors and causes, including obesity, arterial hypertension, elevated blood glucose and lipid levels and a state of permanent inflammation. This condition is associated with an increased risk of myocardial infarction, stroke, type 2 diabetes and, in women, polycystic ovary syndrome. Excessive food intake, particularly of junk food, and a sedentary lifestyle are the main causes of metabolic syndrome. As a vital organ for metabolism, the liver is also affected by and plays an important role in metabolic syndrome. High-calorie diets have been shown to cause insulin resistance and increase the likelihood of developing non-alcoholic fatty liver disease (NAFLD). High-calorie diets and resulting obesity are the main causes of NAFLD. It is therefore hardly surprising that NAFLD is now the most common liver disease in industrialized nations (due to the spread of the "Western" lifestyle). NAFLD clinically manifests itself as fatty degeneration of the liver, while the progressive, chronic form (non-alcoholic steatohepatitis) is characterized by fatty degeneration, inflammation and ballooning of the liver cells, with or without fibrosis. Despite intensive research, the pathophysiological mechanisms by which the disease progresses are still unknown. It is certain, however, that a rise in the frequency of metabolic syndrome will result in an increased prevalence of NAFLD-related cirrhosis and, ultimately, hepatocellular carcinoma.

This brochure aims to show the complexity of metabolic syndrome and the central role of the liver in this context by looking at clinical aspects and pathophysiological mechanisms and showing possible preventive and therapeutic measures.

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Metabolic syndrome

Introduction

The International Diabetes Federation (IDF) estimates that between 20% and 25% of the world's adults are currently suffering from metabolic syndrome. According to the IDF definition in 2005 [1], the following criteria must be fulfilled before an individual can be diagnosed with metabolic syndrome:

Metabolic syndrome criteria

- Abdominal obesity with a waist circumference of ≥ 94 cm in European men and ≥ 80 cm in European women (different values apply to other ethnic groups); if body mass index (BMI) is > 30 kg/m^2, abdominal obesity is presumed to be present and waist circumference no longer needs to be measured [2].

Obesity plus two of the following factors:
– Hyperlipidemia
– Arterial hypertension
– Elevated fasting glucose levels

Plus two of the following factors:

- Elevated triglyceride levels ≥ 150 mg/dL / 1.7 mmol/L
  or specific medical treatment for this condition
- Reduced HDL cholesterol levels < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women
  or specific medical treatment for this condition
- Increased arterial blood pressure with systolic RR ≥ 130 mmHg
  or diastolic RR ≥ 85 mmHg
  or specific medical treatment for previously diagnosed arterial hypertension
- Elevated fasting plasma glucose levels ≥ 100 mg/dL (5.6 mmol/L)
  or type 2 diabetes

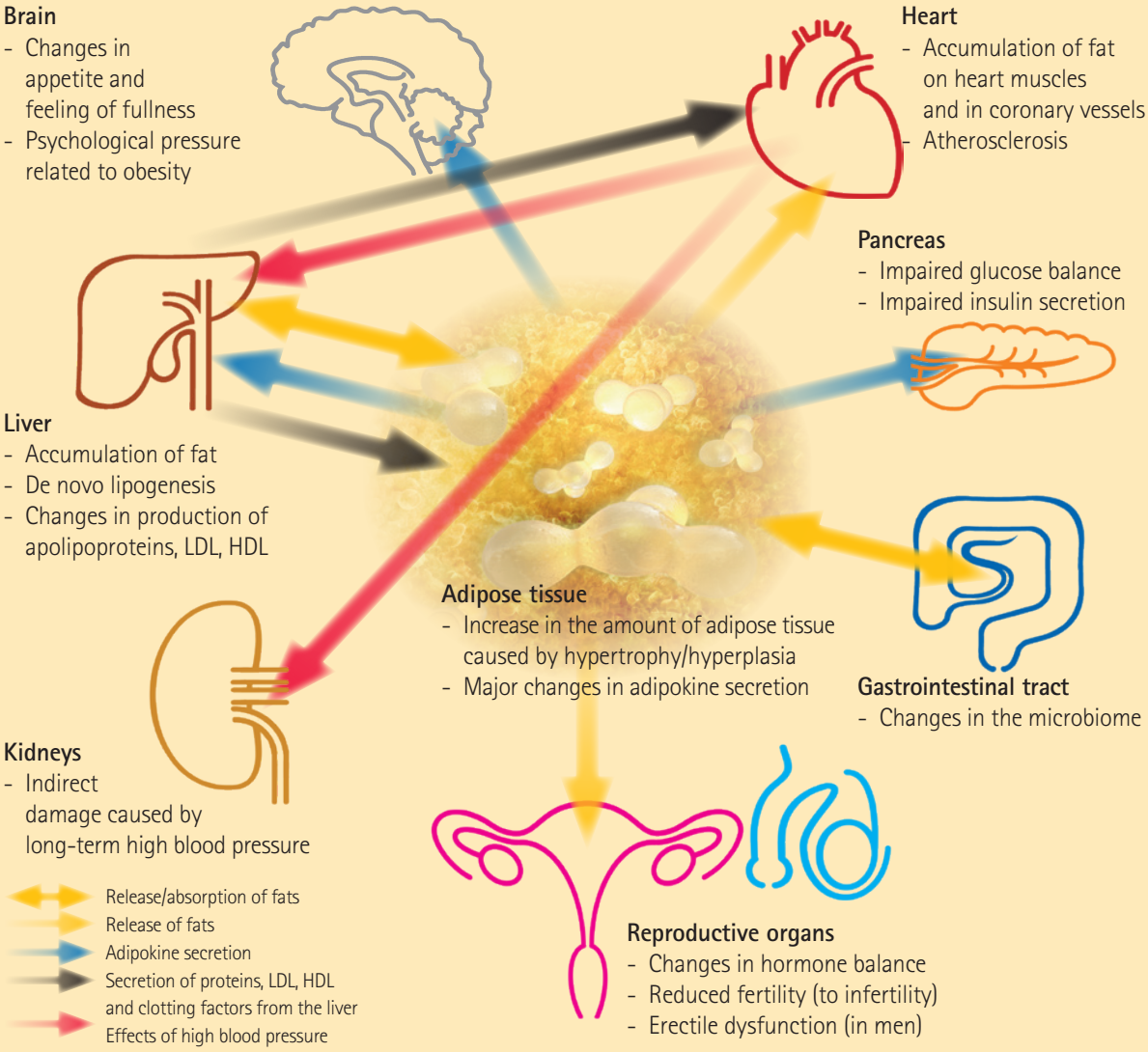
Around 25–30% of the German population have metabolic syndrome.

Metabolic syndrome itself is a significant risk factor for concomitant and secondary diseases, such as cardiovascular diseases, renal diseases, hormonal disorders and an increased risk of tumors *(figure 1).* According to the German National Health Interview and Examination Survey 1998, the prevalence of metabolic syndrome in Germany was 23.8%, or around 12 million people [3]. In a cohort study carried out in north Germany between 1997 and 2001, 28% of the subjects had metabolic syndrome [4]. 27.5% of the 2143 participants who did not suffer from metabolic syndrome at the beginning of the study developed the disease within five years. Although they only show a slight increase in incidence, these figures demonstrate that a substantial proportion of the population is affected by metabolic syndrome.

Figure 1

Metabolic syndrome as a significant risk factor for numerous concomitant and secondary diseases of the entire organism

Metabolic syndrome is caused by morbid obesity and excessive consumption of high-calorie and high-fat food. This has a negative impact on different organ systems: digestive organs (non-alcoholic fatty liver disease [NAFLD], diabetes), adipose tissue (obesity, dyslipidemia), cardiovascular system (high blood pressure) as well as the reproductive organs (e.g. polycystic ovary syndrome [PCOS]).



Currently unpublished data from the Heinz Nixdorf Recall study (of almost 5000 people in the Ruhr area of Germany) suggest that around 30% of the German population suffers from metabolic syndrome [5].

Main cause of metabolic syndrome: the "Western lifestyle"

The main cause of metabolic syndrome is excessive consumption of often high-sugar and high-fat foods combined with little exercise and physical activity, leading to overnutrition. "Western" diets mainly consist of highly processed, ready-made food with high sugar and fat contents, as it is inexpensive and can be prepared quickly and easily. At the same time, physical activity on a daily basis is reduced to a minimum as most journeys are made by car or using elevators and escalators. Furthermore, the majority of modern jobs involve sitting – usually in front of a computer – or standing [6]. If individuals are also not active outside of work and spend all of their free time in front of the television, computer or video consoles, they will very quickly start to consume many more calories than they burn.

Genetic predisposition presumed to have a small impact (except PNPLA3).

Genetic factors play a considerably smaller role in the afore mentioned development. Different gene variants that are responsible for metabolism and/or storing nutrients and predispose individuals to becoming overweight or developing diabetes and other components of metabolic syndrome are presumed to exist [7,8]. However, studies have shown that physical activity can counterbalance the negative effects of 12 gene variants [9]. A "hereditary" component of being overweight could be the result of epigenetic mechanisms or acquired behavioral patterns [8]. Exceptions may include PNPLA3, a gene that codes for the adiponutrin protein [10]. PNPLA3 polymorphism has been shown to be highly associated with overweight and obesity.

Epigenetic effects may account for a hereditary component of being overweight.

Animal experiments have also provided striking evidence for epigenetic effects [11]; such studies have yet to be carried out on humans, however. Despite this, expectant mothers should still continue to pay attention to their diets as nutrition during pregnancy and breastfeeding has not been ruled out from influencing the epigenetics of the embryo. Furthermore, increased consumption of fats during pregnancy is known to cause larger fat deposits in newborns that remain there until infancy [12].

Influence of the microbiome is probable but still uncertain.

The influence of the microbiome in the development of metabolic syndrome has also been under discussion for a relatively short time. The number and ratio of different bacterial species in the intestine seem to play an important role in healthy digestion as well as to influence available nutrient composition [13]. It has already been shown that fecal microbiota transplantation from subjects with healthy digestive systems does indeed ease the symptoms of intestinal inflammation, caused by Clostridium difficile, for example [14]. In a pilot study with a small number of subjects, fecal microbiota transplantation also reduced insulin resistance, albeit only temporarily [15], and possible side effects are not without controversy [16,17]. Obese patients have a smaller diversity of intestinal flora than those of an average weight. In particular, species of the Firmicutes phylum are less represented, causing species of the Proteobacteria group to occur in larger numbers.

Inverse correlation of Helicobacter pylori prevalence with obesity

Studies have demonstrated that successful weight loss leads to an increase in different species and, above all, in species of the Firmicutes phylum [13,15]. They have also shown an inverse correlation of Helicobacter pylori prevalence with obesity [18]. It is still unclear, however, whether intestinal flora changes are a product of unhealthy eating and therefore just a symptom of being overweight or having metabolic syndrome, or whether certain microbiome compositions increase the risk of becoming overweight and developing metabolic syndrome. As a result, current discussions are also centering on whether antibiotic treatments during childhood cause changes in the microbiome which increase the likelihood of obesity in later life [19].

Obesity

Overweight and obesity are not only important components of metabolic syndrome, but also cause a high risk of developing metabolic syndrome. The prevalence of obesity has increased in Germany over the last few years and may have reached a plateau. However, already overweight individuals seem to be getting heavier [20], as the number of people with morbid obesity (BMI > 40 kg/m²) is continuing to rise [21]. In 2008, the German Federal Ministry for Food, Agriculture and Consumer Protection published the National Nutrition Survey. Data about nutrition, lifestyle and consumer behavior were collected from 20,000 subjects [22]. 45% of the men and 30% of the women surveyed were classified as overweight (BMI > 25 kg/m² and < 30 kg/m²). 21% of the men and women respectively were obese, i.e. had a BMI > 30 kg/m².

Obesity = BMI > 30 kg/m²

Increase in obesity among children

The number of overweight/obese individuals increased with age. BMI decreased with higher levels of education, higher net income per capita and higher social class. A total of 12% of those surveyed were following a diet, 7% of which due to an illness and 5% of which to lose weight. Current data from the Robert Koch Institute (RKI) substantiate the trend towards an increase in overweight children. According to the KiGGS study (German Health Interview and Examination Survey for Children and Adolescents) conducted by the RKI, 15% of children and adolescents (3–17 years old) were overweight in 2006, a third of which were even classified as obese [23]. Since then, the number of overweight children and adolescents is likely to have increased further. This means that diseases associated with overweight develop as early as in adolescence and middle age.

Current figures indicate that 33.6% of adults in the USA are overweight and 34.9% obese [24]. These figures are 31.8% and 16.9% in children and adolescents respectively. For children and adolescents in particular, these figures have increased dramatically over the last ten years (in 2004, 17% of individuals aged between 2 and 19 were estimated to be overweight or obese) [25,26]. This trend has shown no sign of stopping.

This development is not limited to "Western" countries, however, but affects all societies experiencing industrialization and a "westernization" of lifestyle habits. These include the world's most populated countries, China and India [27,28].

These data point towards a global obesity epidemic associated with a range of comorbidities. Taking into account the considerable follow-up costs for the healthcare sector, particularly due to the large number of people affected, action needs to be taken to educate the public and recognize the problem on a social as well as personal level. As the options for therapeutic intervention are extremely limited, prevention is an essential part of tackling this health problem.

China and India are also experiencing an increase in obesity prevalence.

Adipose tissue as an endocrine organ

Adipose tissue is not a pure storage organ but interacts with the entire organism.

Overweight and obesity are ultimately the hypertrophy of adipose tissue [29]. The volume of adipose tissue can be increased by two processes: hyperplasia and hypertrophy of fat cells [30]. The extent to which each of these processes occurs appears to depend on individual, but as of yet unknown, factors. Hyperplasia and hypertrophy of the fat cells may occur to different extents in the subcutaneous and visceral adipose tissue of the same patient [30,31]. It is now known, however, that an increase in the size of fat cells, i.e. a morphological change, causes more extensive metabolic alterations [32,33]. The size of adipocytes in the omentum is strongly associated with metabolic state, which is not the case for subcutaneous adipocytes [34,35]. In principle, abundance of visceral fat (in the abdominal cavity) seems to be more linked to metabolic changes and cardiovascular risk factors than subcutaneous fat (in the hypodermis) [36]. This may be attributed to different adipokine patterns of these fat deposits [37]. Furthermore, current studies indicate that insulin resistance is most strongly associated with intrahepatic fat accumulation [38]. In this case, however, fat is not stored by fat cells, but by hepatocytes (liver cells).

Adipocytes produce signaling molecules (adipokines).

Adipocytes produce a range of different signaling molecules (adipokines), which have various functions *(figure 2 and table 1)*. In individuals of an average weight, adiponectin is produced by adipocytes in sufficient quantities. Adiponectin promotes insulin sensitivity in the liver and muscles [39,40], probably via adiponectin receptors AdipoR1 and AdipoR2 [41,42]. It also seems to stimulate insulin secretion in pancreatic β cells [43]. Adipokine secretion is reduced in obese patients [44], probably due to hypertrophied fat cells. Leptin is a transmitter substance that signals satiety, both from a postprandial high fat content in the blood and from full fat reserves, i.e. large adipocytes [40]. In obese patients, the concentration of leptin in the blood is directly proportional to the extent of obesity [45]. Leptin resistance will develop if leptin is continuously secreted from hypertrophied adipocytes – similar to insulin resistance as described below [46]. Leptin resistance reduces the feeling of satiety and also seems to influence the reproductive organs as well as the secretion of thyroid hormones via the hunger and satiety signals processed in the hypothalamus. Furthermore, leptin inhibits the secretion

Leptin resistance

Figure 2

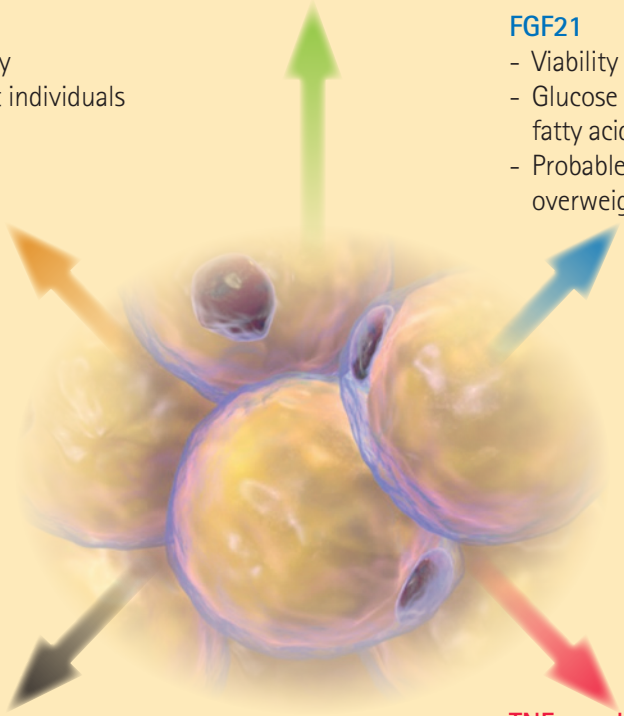
Effect of adipokines (adipose tissue hormones) on the organism

Contrary to earlier presumptions, adipose tissue is not an inert storage compartment for fat. Fat cells (adipocytes) produce different signaling molecules, known as adipokines, which influence metabolism and insulin action in various organs. FGF21 = fibroblast growth factor 21; TNFα = tumor necrosis factor α; MCP1 = monocyte chemotactic protein 1; β cells: insulin-producing cells in the pancreas.

Adiponektin
- Reduced levels in overweight individuals!
- Promotes insulin sensitivity in the liver and muscles
- Stimulates insulin secretion

Leptin
- Provides feeling of satiety
- Resistance in overweight individuals
- Inhibits insulin release

FGF21
- Viability of β cells
- Glucose uptake + fatty acid oxidation in hepatocytes
- Probable resistance in overweight individuals



Resistin
- Promotes insulin resistance
- Promotes glucose intolerance

TNFα and MCP1
- Proinflammatory cytokines
- Wide range of effects
- Induce inflammatory milieu in the entire organism

Source:
Blausen.com staff. "Blausen gallery 2014".
Wikiversity Journal of Medicine.
DOI:10.15347/wjm/2014.010. ISSN 20018762

Table 1

Known effects of adipokines (adipose tissue hormones) and hepatokines (transmitter substances from the liver)

Adipokine/hepatokine	Effect on metabolism in individuals of normal weight
Adiponektin	- Promotes insulin sensitivity in the liver and muscle - Promotes insulin secretion
Leptin	- Signals feeling of satiety to the hypothalamus - Indicates full fat reserves - Inhibits insulin secretion
Ghrelin	- Signals hunger - High levels before eating, lower levels after eating - Weight homeostasis/energy regulation - Antidepressant effects
Visfatin	- Increased production in visceral adipose tissue - Autocrine/paracrine effect (increases fat accumulation) - Also produced by β cells and induces insulin secretion
Resistin	Promotes blood flow to the pancreas
FGF21 (fibroblast growth factor)	Promotes - uptake of glucose in the liver - fatty acid oxidation and gluconeogenesis in the liver - adiponectin release in adipose tissue - viability of pancreatic β cells
TNFα (tumor necrosis factor α)	- Recruits immune cells - Stimulates cell proliferation or cell death (depending on the cell environment and status) - Pleiotropic effects
MCP1 (monocyte chemotactic protein 1 or CCL2)	- Chemokine that recruits monocytes to sites of inflammation - Controls differentiation of cells (e.g. bone-degrading osteoclasts) - Also produced by adipocytes
Apelin	- Inhibits insulin secretion - Promotes utilization of glucose by muscle
Chemerin	- Reduces uptake of insulin and glucose - Stimulates chemotaxis - Expressed in the liver, (white) adipose tissue, intestine, kidneys and thrombocytes
Betatrophin (ANGPTL8)	- Role in regulating serum lipid levels

Status in overweight/obese individuals	Outlook
Reduced production, making it less effective	Has yet to be determined as a matter of routine. Lower levels could indicate early metabolic changes and possibly even NAFLD progression
Excess production of leptin, causing resistance to develop	Treatments against leptin resistance are in the early stages of development
Low basic production and low levels of fluctuation before and after mealtimes	Possible use in monitoring after bariatric surgery (here: strong reductions in ghrelin levels), but no foreseeable use against metabolic syndrome
Increased, probably causing high quantities of fat to accumulate in visceral adipose tissue	Contradictory results in different models, pleiotropic effects need to be investigated by better studies
Increased production promotes insulin resistance and glucose intolerance	Current state of knowledge too poor for prognosis
Increased in overweight individuals Probable resistance	Current state of knowledge too poor for prognosis
Elevated due to continuous excess production of immune cells in the adipose tissue, causing an underlying, permanent state of inflammation in the body	Pleiotropic spectrum of regulation and activity, probably too unspecific for treatment, possible diagnostic significance
Increased production by adipocytes in obese individuals, reduces insulin sensitivity and glucose uptake by muscle cells, thus promoting insulin resistance	Pleiotropic effects probably too strong; only suitable for specific treatment approaches
Increased, possible resistance	Current state of knowledge too poor for prognosis
Stimulates insulin resistance (e.g. vascular), proinflammatory effect	Different isoforms are expressed depending on the tissue. Mechanisms still in the early stages of being clarified, prognosis not possible
Unknown	Only discovered recently and initially identified as a proliferation signal for β cells, but this has yet to be confirmed for humans

Resistin

Apelin

FGF21

TNFα
Ghrelin

of insulin from pancreatic β cells, thus lowering the risk of atherosclerosis [40,47]. Resistin is also produced by fat cells – higher levels are found in those with obesity. It promotes insulin resistance and glucose intolerance [48], but also helps to increase blood flow to the pancreas [49]. Apelin is an adipokine produced both by adipocytes as well as β cells, and may therefore be an autocrine and paracrine regulator [40]. Higher levels of apelin are also found in the serum of obese individuals. Apelin inhibits insulin secretion and promotes utilization of glucose by muscle [50,51]. Severely overweight individuals may also have a resistance to apelin, the mechanisms of which are still largely unclear. FGF21 is another protective adipokine, which is also produced by hepatocytes [52]. In addition to increasing glucose uptake in hepatocytes [53] and stimulating fatty acid oxidation and gluconeogenesis in the liver [54], FGF21 also increases the release of adiponectin from adipose tissue [55] and is presumed to improve the viability of β cells [40]. Serum FGF21 levels are elevated in overweight individuals, suggesting that they have developed a resistance [40]. However, additional studies must be conducted to shed light on any mechanisms of action and links between the adipokines described. Other adipokines that are secreted from adipocytes in larger quantities in obese compared with healthy individuals are TNFα, a proinflammatory, pleiotropic factor that may induce cell death or proliferation depending on the cell environment [56,57], and ghrelin, the "hunger hormone", which also has an antidepressant effect and is secreted to a larger extent following lack of sleep [58]. *Table 1* provides an overview of the effects of the adipokines listed here as well as a few newly discovered molecules classified as adipokines or hepatokines (transmitter substances produced in the liver). However, many of the signaling molecules that have only been discovered recently are still too under-researched to be used as diagnostic markers, let alone therapeutic targets.

In addition to adipose tissue hormones, hypertrophied adipocytes also release fatty acids into the blood due to increased lipolysis, despite already high concentrations of lipid components [29]. This hyperlipidemia is one of the components of metabolic syndrome and is directly associated with the risk for cardiovascular diseases and, specifically, with atherosclerosis.

Insulin resistance and diabetes

In terms of function, insulin resistance is considered to be an important component of metabolic syndrome. Insulin resistance occurs when the pancreas continuously releases excess insulin. Insulin ensures that glucose and fats can be absorbed by cells – particularly in the liver and muscles – in the absorption phase after food intake. However, dramatic increases in insulin levels, either permanently or for a short period, cause overexpression of the insulin receptors, preventing the cells from reacting to physiological insulin releases [59,60]. Liver cells in particular then break down their glycogen stores to release glucose into the organism [61]. If this continues for a longer period, the resulting insulin resistance will lead to the development of type 2 diabetes. This is presumed to be due to the permanent strain on β cells, which results in increased cell death and ultimately underproduction of insulin [62,63]. Insulin resistance also promotes the development of NAFLD, alters adipocyte signaling, causing them to release proinflammatory adipokines, resulting in increased uptake of fatty acids by adipocytes. This causes already excess fat mass to increase further. Insulin resistance also has an impact on muscle cells, including the heart, thus increasing cardiovascular problems. It is not yet clear which factor ultimately leads to insulin resistance or if several mechanisms are involved. Another possibility is that, depending on individual development, insulin resistance is caused as a result of changes to the nutrients provided by a liver affected by fatty degeneration [64,65]. Secretion of adipokine from adipose tissue could also cause the pancreas to release insulin in an uncontrolled manner, however.

Insulin resistance stimulates release of proinflammatory cytokines from adipocytes.

Intriguingly, approx. 25% of obese patients are "metabolically healthy" [66], i.e. do not have diabetes or insulin resistance and seem to be at lower risk of developing cardiovascular problems. The underlying mechanisms of this are still largely unclear [67]. However, some studies have identified better fitness levels as the main reason for "metabolically healthy" obese individuals [68–70]. At the very least, exercise could protect overweight or obese individuals from the worst consequences, even if this does not lead to weight loss.

"Metabolically healthy" obesity

Cardiovascular components

Dyslipidemia promotes atherosclerosis.

Cardiovascular diseases are probably the most well-known sequelae of being overweight and/or metabolic syndrome. They play an important role in increased mortality and morbidity in overweight individuals and are ultimately based on two factors. The first factor is dyslipidemia, prolonged levels of which significantly increase the risk of atherosclerosis [71]. Secondly, changes in the production of coagulation factors caused by the liver increases the risk of plaque formation [72]. All in all, after correction for other known risk factors, being severely overweight increases the risk of myocardial infarction by 37.6% and stroke by 29% [73].

Other affected organs

Adipose tissue, the liver and the cardiovascular system are the organs most involved in and affected by metabolic syndrome. However, evidence indicates that metabolic syndrome influences the entire organism. In fact, several studies suggest that insulin resistance and/or being overweight are associated with fertility problems in both men and women. In women, polycystic ovary syndrome (PCOS) is strongly associated with overweight and insulin resistance [74]. Insulin and changes in adipokine levels are presumed to negatively influence hormone balance and therefore fertility [75]. In men, BMI is negatively correlated with sperm motility, which is also affected by hormonal disorders from the hypothalamic-pituitary-gonadal axis, which reduces testosterone levels [76]. Furthermore, the sperm of obese men contains elevated concentrations of leptin and insulin [77], which may have a further negative impact on fertility. In addition, being severely overweight is also associated with erectile dysfunction. However, this could be the indirect result of increased blood pressure in those with metabolic syndrome.

Impaired fertility

Polycystic ovary syndrome

Low sperm motility

Due to the increased risk of atherosclerosis, metabolic syndrome also indirectly represents a risk factor for pulmonary vascular diseases and pulmonary high blood pressure [78]. The extent to which insulin resistance – irrespective of the known vascular problems – negatively impacts on lung function is unclear, however.

Pulmonary hypertension

Metabolic syndrome of the liver – NAFLD

Metabolic function of hepatocytes

The liver is a highly active, metabolic organ.

Although metabolic syndrome was identified as "syndrome X" back in 1988 and NAFLD has been known since 1981, NAFLD was first confirmed to be the manifestation of metabolic syndrome in the liver in 2008 [79]. The liver itself is a highly active, metabolic organ with an extremely large spectrum of functions and produced components. It would go beyond the scope of this brochure to cover all of the cell types and functions of the liver. *Table 2* therefore provides just a brief overview of the metabolic functions of the hepatocytes (liver parenchyma cells).

High regenerative capacity of the liver

Due to their biotransformation functions in particular, liver cells are continuously exposed to toxins, causing many cells to die. Presumably to compensate for this, liver cells have extremely high proliferation rates, allowing adult, fully differentiated hepatocytes to replace perished neighboring cells. The regenerative capacity is of such an extent that approx. 70% of the liver can be removed in healthy individuals. Compensatory hypertrophy allows the remaining tissue to replace losses to liver volume and simultaneously perform all of the afore mentioned functions.

Fatty acid oxidation as a significant contributor to the damage process

Chronic damage may continuously reduce the number of hepatocytes, however, prompting hepatic stellate cells to change into an activated state and produce a collagen matrix to stabilize the tissue [80,81]. If collagen replaces larger areas of the parenchyma as a result of long-term damage, this will initially lead to fibrosis and, ultimately, liver cirrhosis. This effect may also occur if fatty degeneration of the liver lasts for many years [82]. Changes in the basic metabolic conditions in the liver are presumed to be considerably more problematic, however, when large amounts of fat and/or fatty acids are (or have to be) stored in the liver cells. For example, this causes a shift from fatty acids metabolized by mitochondrial β oxidation towards ω oxidation, the latter of which occurs in the cytoplasm and causes massive oxidative stress for the cells [83–85]. Fatty acids also influence the gene expression of proteins involved in lipid and glucose metabolism via transcription factors (e.g. PPAR-γ, SREBP-c) [86–88].

Table 2

Metabolic function of hepatocytes (liver parenchyma cells)

Glucose metabolism

In the absorption phase, the liver absorbs glucose from the blood, polymerizes it to glycogen and stores this in the form of granules. The liver can release glucose during periods of high energy demand: If carbohydrate reserves are empty and energy demand is extremely high, the liver can synthesize glucose from proteins by means of gluconeogenesis (e.g. cachexia/sarcopenia in liver cirrhosis).

Lipid metabolism

During the absorption phase, the liver synthesizes triglycerides (as energy reserves) and sphingolipids (membrane components) from carbohydrates and lipids. During the post-absorption phase, the liver obtains the majority of its energy from the oxidation of fatty acids. The ketone bodies left over from this process are absorbed into the bloodstream to be used as an energy source by other organs. The liver also produces very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL), which transport cholesterol, triglycerides and fatty acids via the bloodstream to other organs. An important function of hepatocytes is the de novo synthesis of cholesterol, which fulfills diverse functions both as a membrane component and precursor for steroid hormones, D vitamins and bile acids.

Protein metabolism

In addition to synthesizing non-essential amino acids, the liver produces a range of proteins that play a central role in the entire organism, including blood plasma enzymes, almost all proteins involved in coagulation, and serum albumin. The latter serves as a transport and binding molecule for a variety of difficult-to-dissolve substances and signaling molecules in the blood. Furthermore, the liver activates signaling substances by converting prohormones to hormones, but also inactivates/degrades hormones, proteins and other signaling molecules. The liver is the only organ in the body that can detoxify ammonia produced during protein metabolism by converting it to urea. This enables the acid-base balance to be regulated, as large amounts of HCO_3^- can be bound.

Biotransformation

Biotransformation refers to the detoxification of endogenous and exogenous substances. Lipophilic substances that cannot be broken down are converted to hydrophilic substances and then excreted through urine or bile.

Bile formation

Bile transports cholesterol, bile acids (essential for lipid absorption in the small intestine), bilirubin (iron-free metabolite of hemoglobin) and other substances to the intestine. A large proportion of these substances is then transported back to the liver through enterohepatic circulation, which means that only a small quantity has to be synthesized de novo in the liver.

NAFLD epidemic

In addition to the obesity epidemic, we are also facing an NAFLD epidemic.

With the increasing incidence of overweight, obesity and metabolic syndrome, it is hardly surprising that NAFLD is now the most common liver disease in the USA and probably in large parts of Europe (United Kingdom, France, Germany, Hungary). NAFLD clinically manifests itself as fatty degeneration of the liver, while the progressive, chronic form (non-alcoholic steatohepatitis [NASH]) is characterized by fatty degeneration, inflammation and ballooning (abnormally enlarged cells) of the liver cells, with or without fibrosis [89,90] *(figure 3)*.

Cytokeratin 18 as a surrogate marker of liver cell damage

Currently, the only completely reliable way of distinguishing between simple steatosis (NAFL) and NASH is to perform a liver biopsy and histological examination of the tissue. However, typical serum biomarkers of liver damage (transaminase levels, γ-glutamyl transferase) are often used to predict the severity of NAFLD. There are also other surrogate markers of liver damage – specific apoptosis marker M30 (caspase-cleaved cytokeratin 18 fragment) has been delivering encouraging results for a few years [91–93], but does not seem to be exclusively specific to NAFLD [94,95]. As a gold standard, histological assessment is already defective and poses a problem when developing non-invasive biomarkers for distinguishing between simple steatosis and NASH [96,97].

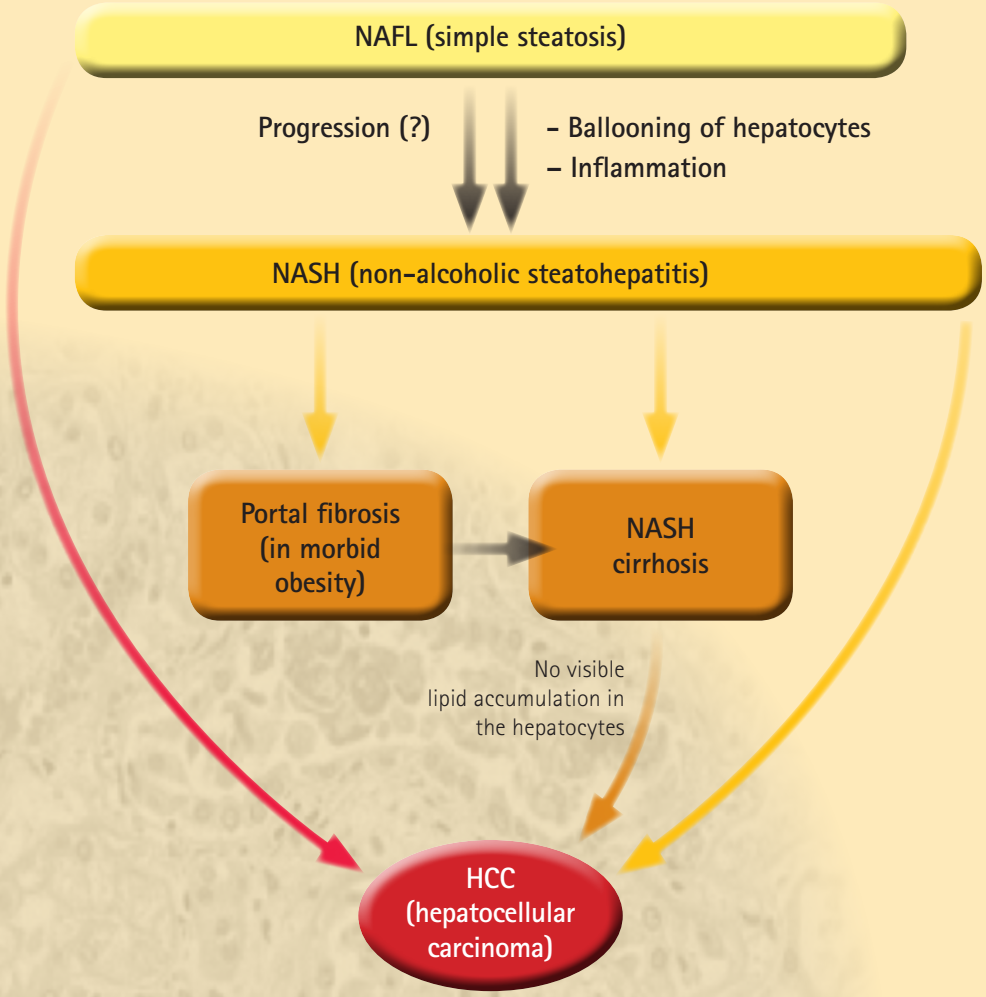
Threshold values for transaminase levels under discussion

Furthermore, it is still unclear whether NAFL and NASH are a continuum of transitional stages and temporal transition, or whether they may be separate entities [98] where fatty degeneration can take a harmless or severe course depending on genetic, external or internal factors. How and whether the severity of NAFLD should be determined without performing a liver biopsy is therefore still disputed [90,99]. The fact that the levels of typical liver biomarkers (ALT, AST) are often not elevated above current normal values makes it even more difficult to diagnose NAFLD using non-invasive methods. The typical limits for assessing NAFLD may be set too high [100,101]. New molecular markers, including cell death marker M30 as mentioned above, and possibly adipokines could provide a solution to this problem.

Figure 3

Non-alcoholic fatty liver disease (NAFLD) in different manifestations

NAFLD is an umbrella term for simple steatosis or fatty liver disease (NAFL) as well as non-alcoholic steatohepatitis (NASH). The latter is an advanced stage of liver disease and may progress to cirrhosis or the development of tumors.

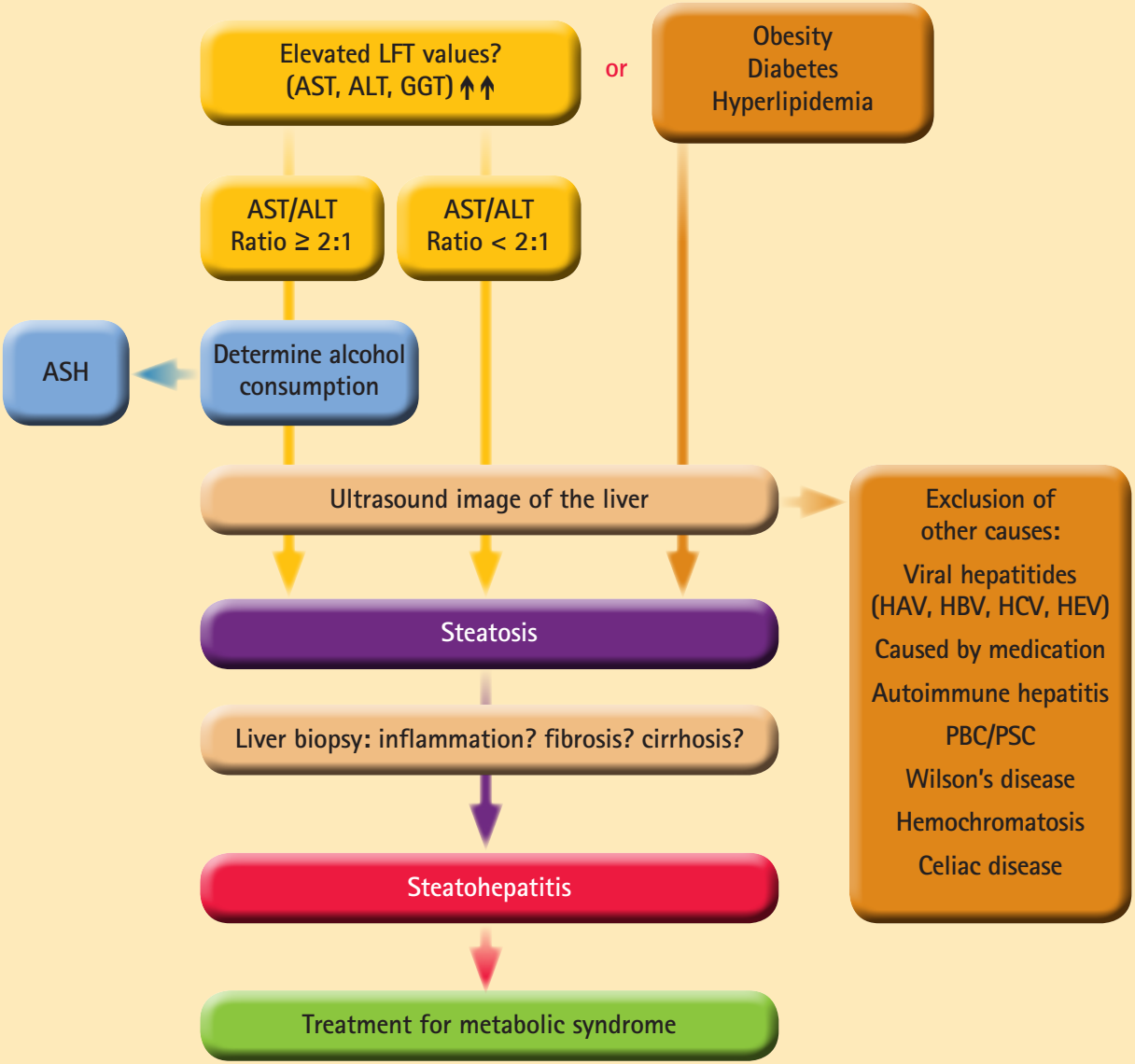


A combination of different markers is probably the most successful way of creating a reliable "score" for determining the severity of NAFLD [102].

Although this would increase the time and costs required to determine biomarkers, it would considerably improve the accuracy of the prognosis. In principle, non-invasive biomarkers can also be used to distinguish between primary alcoholic steatohepatitis (ASH) and NAFL in patients with a similar BMI [103]. As the metabolic profiles of alcoholic and non-alcoholic fatty liver diseases overlap, this distinction has a very high clinical significance *(figure 4)*.

Figure 4

Non-alcoholic fatty liver disease (NAFLD) – diagnostic algorithm



Possible ways of liver damage

The far-reaching consequences of metabolic syndrome affect the liver in different ways.

Hepatic de novo lipogenesis

Fatty-acid binding proteins

Obesity is characterized, for example, by an increase in lipolysis from adipocytes [104,105], which promotes the development of insulin resistance and increases the number of lipid components in the plasma. Circulating free fatty acids (FFA) produced from peripheral lipolysis are found in greater quantities in obese patients, but only represent part of the intrahepatic fatty acid pool in NAFLD [38,106]. A considerable amount of fatty acids exists as the result of increased production in the liver (hepatic de novo lipogenesis). This lipogenesis, which occurs despite an existing surplus of fatty acids, indicates serious changes in the metabolic regulation of hepatocytes caused by steatosis. To a large extent, fatty acids are actively absorbed by fatty-acid binding proteins (FABPs), the upregulation of which has been described for NAFLD patients and shown to correlate with both the serum levels of FFAs and the progression of the disease [107]. Scavenger receptor CD36/FAT (fatty acid translocase) transports long-chain fatty acids to hepatocytes, for example [108]. CD36 could play a functional role in altered hepatocyte metabolism [38] and may promote the development of tumors in those with NAFLD via mechanisms mediated by NF-κB and PTEN [109,110].

All in all, fat accumulation in the liver occurs when there is an imbalance of four processes [111]:

1. Uptake of triglycerides from circulation
2. De novo lipogenesis
3. Fatty acid oxidation
4. Triglyceride secretion

An increase in 1 or 2 or a reduction in 3 or 4 alone may lead to significant changes in lipid homeostasis in the liver. If two or more of these processes change, which appears to be the case in obesity, fat will inevitably accumulate in the liver and bring with it all of the metabolic consequences.

Two-hit theory

To date, a number of different hypotheses have been put forward to explain the development and progression of damage. The two-hit theory is the hypothesis that the steatotic liver has already been damaged by insulin resistance and fatty degeneration (first "hit"), causing a second "hit" to increase the likelihood of NASH developing [112]. Here, it must be noted that the mere accumulation of physiologically inert triglycerides (classic "fats") within hepatocytes, i.e. pure steatosis, will not cause liver damage [113]. On the other hand, an accumulation of FFAs and other toxic metabolites due to insulin resistance will induce a syndrome known as lipotoxicity [106,114–116]. It has actually been proven that the accumulation of triglycerides in fat droplets may even have a hepatic-protective effect [117,118]. NAFLD patients, particularly those in the advanced stages of the disease, commonly present with both aspects, however: an increase in triglyceride accumulation in inert fat droplets and a build-up of toxic free fatty acids. The second "hit" may be caused by oxidative stress [85], (sterile) inflammatory processes [119] and other damage mechanisms. The inflammatory components are probably caused by processes mediated by NF-κB and triggered by a reduced expression of NF-κB inhibitor IKKα or IKKβ [120,121]. A more recent variant of this theory is the multiple parallel hits hypothesis, which has a wider interpretation, variable sequence in which damage occurs as well as interindividual variance (e.g. genetic factors) [122]. Current data and the very complex pathogeneses of NAFLD and NASH indicate that this theory does indeed offer a very probable explanation.

Multiple parallel hits theory

Lipotoxicity is triggered by FFAs, acyl-CoAs and acetyl-CoAs. FFAs induce programmed cell death (apoptosis) by activating Toll-like and death receptors. Direct and indirect influence on diverse nuclear receptor signaling pathways also induces insulin resistance and causes free radicals to form. Furthermore, the excess β oxidation of long-chain fatty acids in peroxisomes, and ω oxidation in the endoplasmic reticulum in patients with NAFLD, cause lipotoxicity as a result of metabolites peroxides and oxygen radicals.

Inflammation and programmed cell death of hepatocytes

The direct, mechanical compression and release of catecholamines cause intrahepatic fat accumulation to reduce hepatic blood flow and thus inhibit mitochondrial function. This causes free radicals to form and Kupffer's cells to be activated, as well as inflammation and, ultimately, apoptosis of hepatocytes. Elevated blood glucose levels may induce apoptosis of hepatoma cells in vitro. Raised values from the HOMA model (homeostasis model assessment; derived from levels of insulin and glucose in the blood), as a measure for insulin resistance, are associated with hepatic cell death.

Free fatty acids (FFAs) as systemic, harmful mediators

As described in detail above, the mechanisms by which adipose tissue influences metabolic syndrome are now known. Adipokines influence glucose and insulin homeostasis and modulate metabolism as well as insulin resistance or sensitivity in the liver [40]. Furthermore, FFAs released from adipose tissue interact with peripheral organs and induce cellular alterations there, which increases insulin resistance or leads to increased expression of death receptors in fatty hepatocytes, for example [123,124]. Although FFAs are now accepted to play an important role in fat deposits in tissue other than adipose tissue, the reasons as to why FFAs are released from adipose tissue are still unclear. Current findings suggest an interaction between adipose tissue and the liver [57,124,125]. Exchanged signals include lipokine C16:1n7-palmitoleate recently identified as a lipid hormone, which is used by adipose tissue to interact with systemic metabolism and improves insulin sensitivity and glucose metabolism, for example [126]. Conversely, the liver affects lipolysis in adipocytes via lipoproteins; for example, apoB100-LDL inhibits lipolysis [127]. Normally, the production of hepatic apoB100-containing lipoproteins and the release of FFAs from adipose tissue occur in equilibrium. However, elevated levels of FFAs in the serum activate hepatic apoB100 synthesis, which increases the concentration of apoB100-containing lipoproteins (apoB100-LDL). By binding to LDLRs in adipocytes, apoB100-LDL can then induce gene expression(s) – the exact mechanism by which lipolysis is inhibited is still unknown, however.

Lipokines (fat components as signaling molecules)

The liver and microbiome

There is further an interaction between the liver and microbiome. Obese patients have a different spectrum of intestinal flora compared with patients of an average weight. In particular, they have fewer Firmicutes species and more species from the Proteobacteria phylum [13,15]. This affects the metabolism of various food components in the intestine and thus the available nutrients that can be absorbed by the intestinal epithelium. This may also cause more fragments of bacterial cell walls (e.g. LPS) to be released into the circulation. These substances are transported through the portal vein to the liver, where they can bind to Toll-like receptors to activate the innate immune system as PAMPs (pathogen-associated molecular patterns) [119]. This results in a sterile inflammatory reaction. It remains to be seen whether studies on humans will show that this effect is responsible for the development of NASH as opposed to pure steatosis.

Progression to NASH unclear

Despite this range of known mechanisms in steatotic liver cells, the exact pathogenesis of NAFLD and progression to NASH is still unknown. One reason may be that the drastic effects that metabolic syndrome has on different organ systems are at least partially due to the afore mentioned changes in the adipose tissue. It therefore seems likely that adipose tissue may influence the progression of NAFLD both metabolically and by releasing adipokines. The correlation of adipocyte size with the severity of NAFLD, which has been described several times, is one indication of this.

Although NAFLD has been known to be a chronic liver disease for a long time, its role (symptom or possible contributory cause) in metabolic syndrome is unclear [38,65,128] and, due to the extremely complex organ interactions, particularly in obesity, its development is not understood.

Specific risks of NAFLD

Liver steatosis increases sensitivity to toxins and hepatitis viruses.

Contrary to the long-standing view that – unlike NASH – pure liver steatosis (NAFL) is benign, several investigations have shown that NAFLD generally worsens most conditions that damage the liver, such as increasing liver sensitivity to hepatitis viruses and toxins (alcohol, medication) [129]. Liver-damaging drugs (e.g. paracetamol and certain antibiotics), when administered in doses that are harmless for healthy individuals, may cause serious liver damage to patients with NAFLD.

More than 50% of those that drink 40–60 g of alcohol per day have alcohol-induced fatty liver, known as ASH (alcoholic steatohepatitis). If obese patients also drink alcohol, they increase their risk of developing liver cirrhosis considerably [130]. In fact, an average of just one glass of red wine per day (2–3 units) may lead to liver cirrhosis in obese individuals, even though there is no alcohol abuse. The result is NASH/ASH cirrhosis, which is predominantly caused by metabolic components and is usually not the result of alcohol abuse.

NAFLD leads to hepatocellular carcinoma, even if cirrhosis is not present.

Most chronic liver diseases are characterized by a gradual progression from fibrosis and cirrhosis to the development of tumors. Over the last few years, however, there has been an increasing number of reports of liver tumors in NAFLD patients with no evidence of liver cirrhosis. In actual fact, less than 50% of patients with NAFLD-induced hepatocellular carcinoma are cirrhotic, compared to between 70% and 99% of those suffering from other chronic liver diseases [131]. As a result, the underlying mechanisms that lead to NAFLD-associated tumors cannot be directly attributed to fibrotic processes in the hepatic tissue and are therefore presumed to differ from those for other chronic liver diseases [132]. The mechanisms and factors involved in this process are still largely unknown.

Some tumor suppressor genes also play an important role in lipid and glucose metabolism, causing excess fats and glucose in overweight patients to change the expression of these genes and/or regulate transcription factors [133].

Today's third most common indication for liver transplantation, NAFLD-related liver cirrhosis, is set to overtake virus-related liver cirrhosis in the next few years – by 2020 at the latest according to USA estimations [82].

Moreover, NAFLD livers are the second choice for donor organs and rejected by many transplantation centers [134]. There are conflicting results on this subject, however. Animal models have shown that, in the absence of inflammatory components, moderate fatty degeneration of the liver does not impair liver regeneration following a partial resection, and may even promote proliferation of hepatocytes [118].

Non-alcoholic fatty liver disease represents a serious health risk that extends beyond existing liver injuries.

Patients with diabetes and NAFLD have an increased risk of developing atherosclerosis [135] and coronary artery disease (CAD). However, some data suggest that patients with NAFLD, but no diabetes, also have an increased risk of developing CAD. A long-term study carried out over 21 years showed cardiovascular events or malignancy to be the main causes of death in patients with NAFLD [136]. Histological severity of NAFLD, as well as simple fatty liver disease (NAFL) without inflammation, was associated with an increased risk of cardiovascular events and an atherogenic lipid profile [136]. These data were used to determine whether typical serum biomarkers for liver damage could be used to predict cardiovascular events. γ-glutamyl transferase (GGT) is a promising marker for hepatobiliary dysfunction and, traditionally, for increased alcohol consumption. GGT promotes the oxidation of LDLs and is located in foam cells in human atherosclerotic plaque, suggesting that it may play a role in atherogenesis [137].

GGT and ALT as predictive markers for cardiovascular events

In fact, serum GGT levels are significantly associated with established cardiovascular risk factors, such as triglycerides, BMI and cholesterol. Furthermore, elevated levels of GGT in the serum are linked to a range of cardiovascular risk factors and the incidence of metabolic syndrome. In patients with acute coronary syndrome, GGT levels can be used to predict cardiovascular events and mortality. ALT, another specific marker for liver damage, particularly in those with NAFLD, is also being considered as a biomarker for cardiovascular and metabolic diseases. An epidemiological assessment (Hoorn Study) concluded that there was a significant association between

raised ALT levels and CAD, even in the absence of metabolic syndrome and the risk of atherosclerotic lesions [138]. Normal as well as raised ALT levels are therefore associated with the risk of developing metabolic syndrome.

NAFLD as a risk factor for chronic kidney damage

Metabolic syndrome also affects the kidneys, which are indirectly damaged via the liver. Patients with NAFLD and diabetes have a higher prevalence of chronic kidney damage than patients with diabetes but no NAFLD. This increased incidence was independent of gender, age, BMI, waist circumference, blood pressure, smoking, diabetes, microalbuminuria, glomerular filtration rate and medication. NAFLD was also shown to represent an independent risk factor for chronic kidney disease in a Korean study [139].

Treatment options for metabolic syndrome, obesity and NAFLD

The extent to which the already far-reaching effects of obesity and metabolic syndrome will impact on health and society in the future is becoming increasingly clear, which means that therapeutic measures are essential. These are limited and beset with significant problems or disadvantages, however. Lifestyle changes are not a quick fix and require active cooperation from patients, the effectiveness of active pharmaceutical ingredients is mostly limited to parts of metabolic syndrome (usually insulin resistance/diabetes) and may cause side effects, and surgical options are extremely effective, but subject patients to a major invasive procedure and all of the risks associated with major abdominal surgery. Available treatment options, their advantages and disadvantages and their effectiveness in the treatment of different aspects of metabolic syndrome are shown in detail below.

Lifestyle changes

Losing excess weight is the first and, according to current evidence, most important therapeutic measure for treating all aspects of metabolic syndrome. Although this fact may seem straightforward, achieving results can be complicated and difficult. Many studies have shown that diets, in the traditional sense of the term, will not lead to weight loss in the long term. This is based on the well-known yo-yo effect, which can be explained by simple biological processes [140]. Organisms that are not receiving enough calories will reduce basal metabolic rate (BMR) and thus the number of calories burned as far as possible. In obese patients, it was shown that even moderate calorie restriction over a six-week period (calorie intake greater than 70% of BMR) reduces BMR by up to 250 kcal per day, potentially rising to 500 kcal after 30 weeks [141]. In contrast to this quick reaction to calorie restriction, BMR will not return to its original rate for a period of six months after normal calorie intake is resumed. This almost always creates a surplus of calories in organisms after a diet, which is then free to refill energy stores (especially adipose tissue) [142]. This effect is also caused by a persistent feeling of hunger after weight loss, probably caused by impaired adipokine secretion. Positive results can therefore only be

Yo-yo effect of dieting caused by decreased basal metabolic rate

achieved by making long-term changes to eating habits. Current data are too insufficient to determine the ideal macronutrient composition for losing weight or one all-encompassing general recommendation for treating insulin resistance and hyperlipidemia associated with metabolic syndrome [143–145]. Larger studies comprising a range of diets and meta-analyses tend to indicate that protein-rich foods with moderate carbohydrate and fat consumption may aid weight loss [146–148].

Protein-rich foods for effective weight loss

Although weight loss achieved through different diets does not differ significantly, high-protein diets often lead to a greater reduction in fat mass and less loss of fat-free mass [147,149,150]. This would, at least theoretically, limit the decrease in basal metabolic rate, as mentioned above. High-protein diets also usually improve lipid components in the serum as well as insulin resistance to a greater extent than conventional low-fat, high-carbohydrate diets. Furthermore, based on the authors' personal experience and discussions with nutritionists and fitness trainers, high-protein diets seem to help many people to lose weight more effectively. It remains unclear whether greater feelings of satiety leading indirectly and unintentionally to lower calorie intake or actual macronutrient composition are behind this.

Long-term lifestyle changes are the ideal treatment for metabolic syndrome and NAFLD.

Weight loss of 5–10% of the original body weight may significantly improve steatosis and fibrosis in the liver [151,152]. Drastic lifestyle changes very successfully improve insulin resistance and cardiovascular risk factors in the short term [153,154]. This applies to overweight or obese adolescents in particular [155–157]. A large long-term study recently concluded, however, that drastic lifestyle changes only reduce the risk of myocardial infarction or cardiovascular mortality to the same extent as diabetes education and medication [158]. However, it must be noted that, in both groups, roughly the same proportion of subjects was already suffering from pre-existing cardiovascular diseases at the beginning of the study (14%, which is virtually equal to the percentage of subjects affected by cardiovascular events during the study).

Furthermore, the group that underwent intensive lifestyle intervention achieved a greater weight loss than the control group over the same period, although the average BMI was classified as obese at all times. Patients in the intervention group also put a considerable amount of weight back on after the first year, which may suggest a lack of compliance and therefore insufficient support measures, or a lack of physical activity. Medication to treat insulin resistance, diabetes or cardiovascular risk factors, such as hyperlipidemia or high blood pressure, was taken by the control group throughout the study, while subjects from the intervention group often stopped taking medication due to improvements in these comorbidities. Finally, the frequency of cardiovascular events and mortality was nominally lower in the intervention group, although not to a significant extent. In our view, the conclusion that drastic lifestyle changes are no more effective than diabetes education and medication is flawed. Instead, this study clarifies that even insufficient changes that are made too late are just as effective against cardiovascular risks and insulin resistance as long-term medication for these conditions! The message is clear: Drastic lifestyle changes should be made early on – and sustained – in order to considerably reduce health risk factors.

Lifestyle changes reduce risk factors.

Increasing the number of calories burned is an important part of weight loss. Upping levels of physical activity is the only way to counteract reductions in basal metabolic rate caused by reduced calorie intake [142,159]. Physical activity also has further positive effects on components of metabolic syndrome. Regular exercise of sufficient intensity reduces cardiovascular risk factors and improves insulin resistance [160–162]. Furthermore, exercise reduces the severity of NAFLD, even if it does not lead to weight loss [163,164], decreases fat content in the liver [165] and improves insulin signaling there [166]. Evidence suggests that exercise regimes comprising cardio and strength training will achieve better results than cardio or strength training alone [162]. However, current findings are not significant enough to make a clear recommendation. In any case, physical activity must be of a sufficient intensity in order to be effective. Merely taking part in exercise programs or completing low intensity activity will only have a negligible effect on sustaining weight loss [167–169].

For advice for patients who have been overweight or obese for many years and/or have diabetes, see pages 46/47.

Last but not least, it would be naive to assume that a small increase in physical activity could reverse the effects of a disease caused by years, or even decades, of overnutrition and (much) too little exercise. As the chronic condition of overweight can only be counteracted gradually, even with intensive efforts, a high degree of self-discipline and endurance is required. Staying motivated is therefore the biggest barrier to preventing relapses to old habits and thus new weight gain [170,171]. Support from an individual's social environment and psychological assistance may be helpful in this respect [172,173]. Once again, further studies are required to determine effective strategies for retaining motivation and avoiding relapses.

Pharmacotherapy

Most individual components of metabolic syndrome can already be treated pharmacologically. Insulin resistance, for example, can be treated with thiazolidinediones (glitazones) [174,175]. However, it is important to note that the side effects of glitazones include weight gain and edemas. Further weight gain is of course counterproductive in already obese patients in particular, even if insulin resistance can be controlled in this way. Glitazones are therefore only used in exceptional cases and most of these medications have already been taken off the market.

Anti-diabetic drugs:
- Metformin
- (GLP-1) mimetics
- (DPP-4) inhibitors

Metformin is another active pharmaceutical ingredient used to improve insulin sensitivity. Metformin, a drug in the biguanide class, suppresses de novo glucose production in the liver and thus lowers blood glucose levels [176]. Other mechanisms could also be involved, but this has not been proven with certainty. One advantage of metformin is that it promotes weight loss. Its side effects include gastrointestinal complaints and vitamin B_{12} deficiency in the long term. Medications that either function as glucagon-like peptide-1 (GLP-1) mimetics or dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) have only recently become available on the market. Incretin GLP-1 increases insulin secretion and decreases glucagon secretion, which has the overall effect of reducing blood glucose after eating [177]. DPP-4 is an enzyme (peptidase) that breaks down GLP-1, which means that inhibiting it prolongs the half-life of GLP-1 and thus increases (GLP-1) concentrations in the blood [178,179]. Both variants seem to be a safe and efficient form of treatment [180,181]. It is still unknown whether this form of treatment could reduce NAFLD. Long-term studies are probably required to show such an effect.

Orlistat

Orlistat can be prescribed for weight loss, irrespective of whether the patient is resistant to insulin [182]. Furthermore, this drug has been shown to reduce AST and ALT levels as well as improve histological findings in the liver. However, this effect may not be due to the active pharmaceutical ingredient itself, but may be solely attributed to the weight loss. Further studies are required to confirm this. As orlistat is a lipase inhibitor which acts by reducing the absorption of fat, its effects on low-fat foods are very limited [183]. It also commonly leads to digestive problems, which

may have a negative impact on compliance. The cause of individual cases of liver failure that occurred in patients taking the drug could not be attributed to orlistat [183,184]. Two further pharmacological treatments have also recently been approved in the USA. Lorcaserin in combination with behavior modification (diet and exercise) was found to achieve weight loss in a greater number of patients (over 5%) than behavior modification alone [185,186]. The average weight loss did not differ significantly, however. The side effects of this appetite suppressant include headaches and nausea. A combined preparation of phentermine and topiramate was shown to bring about a higher percentage of weight loss than placebo. The side effects of this medication include constipation, insomnia and sensory disturbances [187,188].

Vitamin D
Ursodeoxycholic acid
E. coli Nissle®

Other substances that were tested for their ability to counteract insulin resistance, overweight and NAFLD contain vitamin D, ursodeoxycholic acid (UDCA) and prebiotic E. coli Nissle®. However, none of these active ingredients has yet been shown to have a significant effect on the biomarkers of metabolic syndrome [174].

Statins

Different pharmacological therapeutics for other components of metabolic syndrome are also available. Statins (known as "fat reducers") are generally used to reduce LDL cholesterol and therefore cardiovascular risk. This is also a desirable effect for patients with NAFLD, which, as described above, is associated with a high cardiovascular risk. Administration of statins to NAFLD patients, even those with raised LFT values, seems to be safe [189]. Statins have not yet been confirmed to have a direct effect on NAFLD, and most studies and/or case series have been too small or conducted over too insufficient observation periods to draw a clear conclusion on this matter [190–192]. High blood pressure treatment is also usually recommended for patients with NAFLD and/or metabolic syndrome [193]. In fact, small studies have even shown that medication for reducing blood pressure also lowers typical liver serum biomarkers [194,195].

For treating the NAFLD component of metabolic syndrome there are currently no active ingredients on the market that have been histologically proved to reduce steatosis [90]. In one meta-analysis, thiazolidinedione (glitazone) did reduce steatosis and inflammation in the liver, but, as described above, was linked with weight gain (here: 2–5 kg) in up to 75% of patients and edemas in up to 10% [196].

There are studies, however, that do not recommend the use of glitazones in patients with NAFLD but no diabetes. Although fibrates, statins and omega 3 fatty acids reduced AST levels in the serum slightly, and combined treatment with pioglitazone and vitamin E lowered AST and ALT levels in the serum [197–199], none of the effects were found to extend beyond those achieved by weight loss or physical activity. The side effects of vitamin E, such as an increased tendency to bleed and increased incidence of carcinoma of the prostate, must also be noted. Vitamin D is only likely to be successful as an antifibrotic treatment in NAFLD patients without vitamin D receptor polymorphisms [200]; however, current findings do not provide clear conclusions on this matter. The use of prebiotic and probiotic active ingredients in the treatment of NAFLD is also promising in principle, but once again there is a lack of robust data for an evidence-based recommendation [201].

Pharmacological treatment of overweight may support lifestyle changes but does not significantly improve NAFLD.

Vitamin E

Surgical treatment options for metabolic syndrome

Bariatric surgery is the most effective weight loss technique for morbidly obese individuals, but is associated with significant complications.

Bariatric surgical procedures are now an established way to lose weight [202]. Surgical procedures to treat morbid obesity and secondary diseases associated with obesity are generally based on two procedures that can be carried out separately or together: restricting food intake by reducing the size of the stomach (restriction) and reducing nutrient and thus calorie intake (malabsorption) by resecting part of the small intestine. There is no all-encompassing procedure that can be recommended for all patients. Contraindications, BMI, age, gender, comorbidities, profession and the patient's preference should be taken into account when selecting a suitable treatment. Established operative procedures currently include gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass and biliopancreatic diversion with or without duodenal switch *(figure 5)*. Gastric electrical stimulation, duodenal-jejunal bypass and intestinal transposition are becoming increasingly significant for the treatment of metabolic complications, even in low weight categories.

Forms of bariatric surgery:
- **Adjustable gastric band**
- **Sleeve gastrectomy**
- **Gastric bypass**
- **Biliopancreatic diversion**

Bariatric surgery reduces prevalence of diabetes by 70%.

Current data show surgical treatment options to be an effective method of treating type 2 diabetes [202, 203]. In addition to weight loss, changes in gastrointestinal hormones and therefore insulin resistance, inflammation and free fatty acids play a key role. Surgical procedures may put type 2 diabetes into remission or significantly reduce medication requirements in over 70% of patients. Reduced insulin demand and normalizing fasting glucose levels were observed shortly after all types of surgery combining restrictive and malabsorptive elements, regardless of the initial weight loss [203]. This is probably attributed to a rapid improvement in gastrointestinal and neuroendocrine hormone secretion as well as adipokine production from adipose tissue. Other improvements include a reduction in surrogate parameters of NAFLD, such as classic transaminase levels and M30 as cell death markers for hepatocytes [204,205]. In a group of obese patients, we were able to show that certain long-chain fatty acids and apolipoproteins were also associated with the severity of liver injury (NAS) prior to bariatric surgery [206]. Concentrations of these fatty acids and apolipoproteins in the serum had considerably reduced six weeks after bariatric surgery. This could be a further indication of the positive effect of bariatric surgery on NAFLD.

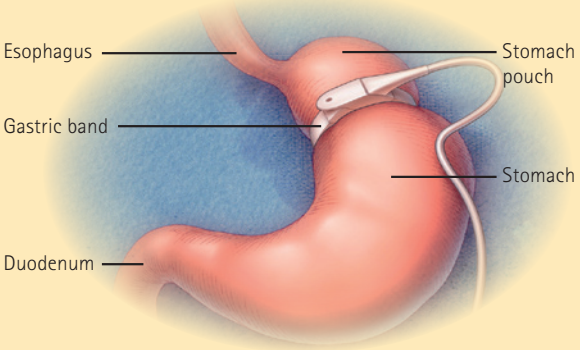
Figure 5

Schematic representation of different surgical methods for treating overweight individuals

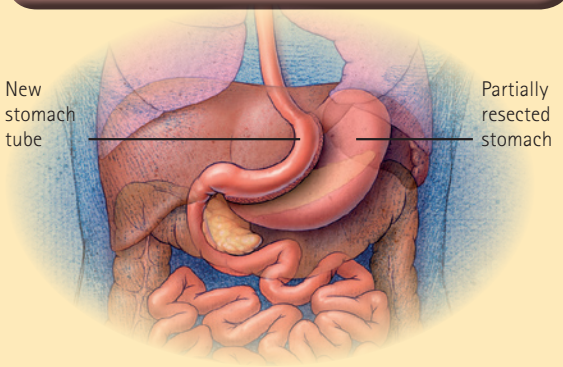
Bariatric surgical procedures achieve weight loss by influencing the digestive system. Restrictive procedures reduce the size of the stomach, resulting in a feeling of satiety after considerably smaller portions of food. Combined restrictive and malabsorptive procedures not only reduce the volume of the stomach, but also shorten the distance in which food comes into contact with stomach and/or bowel mucosa. This not only reduces calorie intake from food, but also decreases the absorption of valuable vitamins and trace elements.

Purely restrictive procedures

Adjustable gastric band

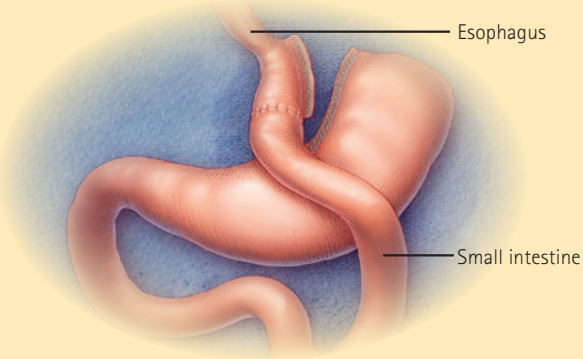


Sleeve gastrectomy

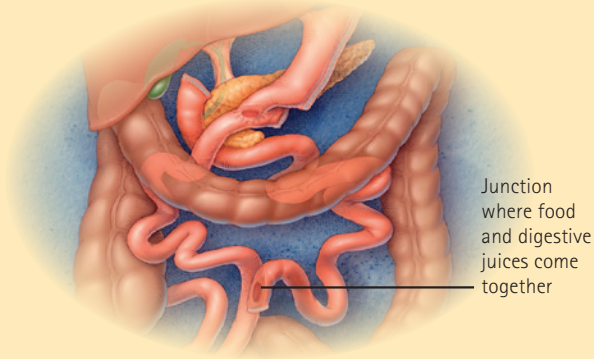


Combined restrictive and malabsorptive procedure

Roux-en-Y gastric bypass



Biliopancreatic diversion



Source: Covidien Deutschland GmbH

Reduction of fatty acids and apolipoproteins in the blood

As performing liver biopsies on obese patients is often prohibited by technical reasons – even after six months of weight loss following bariatric surgery – there is still no histological confirmation that bariatric surgery actually reduces steatosis or inflammation in the liver (except individual reports for follow-on operations). Bariatric surgical procedures are therefore not recommended by a practice guideline for treating NAFLD in the absence of diabetes [207].

All in all, obesity surgery can be seen as a safe and effective way to lose weight and reduce metabolic comorbidities. However, these procedures are also associated with a certain residual risk. All-cause mortality rates and intraoperative and postoperative complication rates themselves are low (< 1% mortality rate and postoperative complications in 1.5–17% of patients, depending on the method used) [208–210]. One of the most common complications is anastomotic leakage, which requires a further operation to correct. Following malabsorptive or combined procedures in particular, nutritional habits must be monitored for the rest of the patients' lives. Deficiencies in vitamins and trace elements are common nonetheless [209,211]. Gastrointestinal side effects that commonly occur following bariatric surgery are reduced if surgery is accompanied by lifestyle changes or pharmacological treatment. The long-term prognosis, e.g. if weight loss can be sustained in the long term, for all bariatric surgeries is still unclear and it is possible that patients may experience postoperative depression [212].

Deficiencies in vitamins and trace elements

Postoperative depression

Endoscopic treatment options

Gastric balloon

EndoBarrier

Two endoscopic, and therefore non-invasive, procedures have been recently developed analogously to bariatric surgical methods. One of these new techniques is the gastric balloon, which can be inserted using an endoscope and then filled with saline solution [213]. It works by reducing the size of the stomach. Combined with calorie restriction and exercise, this procedure can result in greater weight loss than dieting and exercise alone, as well as improve liver steatosis [214,215]. The second technique is an EndoBarrier, which can be inserted using an endoscope [216]. EndoBarrier is an inert plastic sleeve that lines part of the small intestine and causes malabsorption by mechanically separating food from the intestinal wall. There are still no data pertaining to the effects of the techniques on NAFLD. However, these methods have already been shown to effectively reduce overweight and type 2 diabetes and also seem to improve cardiovascular risk factors [217,218], which, in principle, would also suggest possible improvements in NAFLD.

Conclusion and clinical summary

The authors are of the opinion that treatment and research must focus more on the components that may cause the development of metabolic syndrome as well as their interaction with each other. Most importantly, these components include considerable changes in adipose tissue and adipocyte biology as a result of fat accumulation in cells. There is growing evidence to suggest that insulin resistance, which is currently considered to cause metabolic syndrome, arises from the secretion of adipokines from hypertrophied fat cells. As a key metabolic organ, the liver's role in the syndrome also needs to be clarified. NAFLD is currently seen as a consequence rather than a cause of metabolic syndrome. It has yet to be clarified whether this is truly the case or whether the liver contributes to the development of insulin resistance. There is increasing evidence to suggest that the liver does have a causal link, however. Furthermore, given the wide interindividual variation in humans, metabolic syndrome is presumed not to develop identically in all cases. For example, the syndrome may develop primarily from the adipose tissue, be caused by changes in the liver or be triggered by the microbiome through different processes. Despite the very complex nature of the syndrome and the many unanswered questions we are confronted with, however, there is a clear course of action.

As all aspects of this condition are intertwined, the aim is to reduce all of the components: weight loss by reducing fat mass and adipocyte size, treatment of insulin resistance and diabetes as well as, future treatments permitting, treatment of NAFLD. Available treatment options leave us confronted with another problem. It is almost impossible to manage all components pharmacologically due to the side effects alone, and there is still no sign of pharmacological management for NAFLD. While surgical measures are effective and, compared with other operative procedures, do not carry extreme risks for patients, they subject patients to intensive follow-up monitoring and residual risks. Above all, however, there is no viable way of offering bariatric surgical measures to the estimated 12 million obese patients. This is neither feasible nor economical for the healthcare sector.

The remaining option is to help patients to make changes to their lifestyle. This requires a long-term, multi-discipline approach, as patients must sustain strenuous efforts to lose weight (fat mass) for the rest of their lives in order to see results. Pediatricians, internists, surgeons, nutritionists, physiotherapists, sports medicine specialists and, last but not least, psychologists must work together to provide support and advice to patients experiencing problems with weight loss. Such support should be preventive, and not suggested for the first time when patients walk into doctors' offices presenting with BMIs of 35 and the first comorbidities.

The population must be made more aware of the dangers of our comfortable lifestyle and current eating habits. This awareness should be raised at a very early stage to counteract further increases in the number of obese children and adolescents. Conceivable options include broaching the issue of unhealthy eating habits and showing alternatives to children and adolescents while they are still at school. It is understandable that overweight patients are looking for an easy solution. Unfortunately, though, this does not exist – and nor does a "miracle cure" for weight loss.

Appendix

What is your risk of developing metabolic liver disease?

This patient questionnaire can be printed out and downloaded to give to patients from www.ursofalk.com/handouts

Patient questionnaire

	Points
1. What is your body mass index? (BMI = weight in kg/height in m^2)	
a. 19–25	0
b. 25–30	2
c. 31–40	4
d. Over 40	6
2. How would you describe your diet?	
a. I am conscious of what I eat and consume a lot of vegetables and lean, protein-rich foods	0
b. I generally try to eat a balanced diet, but this is not always the case	2
c. I am not especially conscious of what I eat and consume a lot of convenience products and junk food	6
3. Which of the following best describes your profession?	
a. My job involves a lot of physical activity	0
b. My job involves standing/walking	2
c. I mainly sit down for my job	4
4. How often do you exercise?	
a. Several times a week	0
b. Once a week	1
c. Less than once a week	3
d. I do not exercise	5
5. How active are you in your free time – besides exercise?	
a. I am physically active in my free time and am actually always moving around	0
b. I am sometimes active in my free time, e.g. I go walking or cycling	1
c. My free time mostly involves sedentary activities	4

	Points
6. How much alcohol do you consume?	
a. I drink no alcohol or only drink very seldom (low quantities once or twice a month)	0
b. I drink alcohol occasionally (approx. once a week)	1
c. I drink alcohol more than once a week	2
d. I drink alcohol every day or relatively large quantities at weekends only (more than three glasses of beer or wine in one sitting)	4
7. Do you have elevated blood glucose levels or diabetes?	
a. No	0
b. I don't know	2
c. Elevated blood glucose	4
d. Diabetes	8
8. Do you have elevated LFT values (AST, ALT, GGT)?	
a. No	0
b. I don't know	1
c. Yes	4
9. Do you have elevated blood lipid levels?	
a. No	0
b. I don't know	2
c. Yes	6
Total	

Assessment: see evaluation

Evaluation

0–10 points:
You are at low risk of developing metabolic liver disease. Stay active and eat healthily to keep your liver efficient and strong.

11–18 points:
You have a moderate risk of developing metabolic liver disease. Try to exercise more to protect yourself more effectively.

19–27 points:
You have a relatively high risk of developing metabolic liver disease. Avoid alcohol consumption. Have a doctor check your LFT values. If you are overweight, you should consider making changes to your lifestyle. Make better food choices and do more exercise!

Over 27 points:
You have a very high risk of developing metabolic liver disease. If you are not already undergoing medical treatment, you should consult a doctor immediately. Have your LFT values and blood glucose (diabetes!) checked. You are urgently advised to make extensive changes to your lifestyle.

Appendix

Patient advice for making lifestyle changes to prevent overweight, diabetes and metabolic liver diseases

- Liver biomarkers (ALT, AST, GGT) in the blood should be tested in patients that have been overweight or obese for many years and/or have diabetes. Elevated levels should be treated immediately. Please consider that current values may be too high.

- Making strict, long-term changes to your lifestyle is the best way to protect your health. This requires a lot of willpower and staying power. Look to include measures that will actively support your plans (e.g. clubs, self-help groups, free-time activities, active holidays and gyms).

Permanent lifestyle changes

- Important lifestyle changes:

  - Eat plenty of vegetables, fruit in moderation (contains fructose!)
  - Avoid sugary drinks (coke, lemonade and fruit juices). Low-calorie drinks (diet versions) are a possible alternative and considered to be harmless according to current findings.
    However, it is always better to drink mineral water, coffee and tea wherever possible.
  - Do plenty of exercise (at least three hours per week) but have your doctor check your cardiovascular risk beforehand. Find a form of exercise that you enjoy and can imagine doing for the rest of your life (!).
  - In addition to exercise, try to incorporate physical activity into your day-to-day life and free time (e.g. ride a bicycle to work, take the stairs instead of the elevator, cover short distances by foot, use a pedometer or apps to monitor your level of activity and increase this continuously).
  - Do not follow a diet, but make permanent changes to your eating habits. Try to eat healthily and be aware of calories (if necessary, seek nutrition advice).
  - Monitor your progress and document
    a) your weight (weigh yourself once to twice a week)
    b) what you eat and how often
    c) how physically active you are

This patient advice can be printed out and downloaded to give to patients from www.ursofalk.com/handouts

- For obese individuals:

  Be cautious with alcohol consumption. Even relatively small quantities of alcohol can increase metabolic damage to the liver! Ideally, no alcohol should be consumed at all.

Be cautious with alcohol consumption

- You should get vaccinated against hepatitis A and B to reduce your general risk of developing liver diseases.

Vaccination against hepatitis A and B

- If you have been overweight for a long time and have already tried to lose weight (without success), you may want to consider seeking the help of a psychologist. The development and persistence of overweight and especially obesity are chronic processes that can only be stopped by long-term, sustained efforts. This requires a lot of self-discipline and willpower, and you may find that psychological counseling helps.

Psychological consultation

- If you are at high risk (see the questionnaire on page 44) of metabolic liver diseases, you are strongly advised to seek medical care. Even if you have a moderate risk, you should seek medical advice if you are not seeing any improvements on your own.

Regular medical care

- For women of childbearing age: If you are overweight/obese and pregnant, you are particularly advised to watch what you eat. Reduce your consumption of fatty foods to a minimum and eat plenty of vegetables. If you are trying to become pregnant, you should first aim to lose around 5% of your current body weight. This is in the interest of your child, to ensure that he/she is not born with a significant predisposition to obesity.

Pregnancy

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