Non-Alcoholic Fatty Liver Disease and Metabolic Syndrome

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Metabolic syndrome (MetS) is characterized by an association of cardiovascular and diabetes mellitus type 2 risk factors. Although the definition of MetS slightly differs depending on the society that described it, its central diagnostic criteria include impaired fasting glucose, low HDL-cholesterol, elevated triglycerides levels and high blood pressure. Insulin resistance (IR) is believed to be the main cause of MetS and is connected to the level of visceral or intra-abdominal adipose tissue, which could be assessed either by calculating body mass index or by measuring waist circumference. Studies revealed that IR may also be present in non-obese patients, and considered visceral adiposity to be the main effector of MetS' pathology. Visceral adiposity is strongly linked with hepatic fatty infiltration also known as non-alcoholic fatty liver disease (NAFLD), therefore, the level of fatty acids in the hepatic parenchyma is indirectly linked with MetS, being both a cause and a consequence of this syndrome.

metabolic syndrome insulin resistance NAFLD early diagnosis hepatocellular carcinoma

1. Introduction

Metabolic syndrome (MetS), also known as insulin resistance (IR) syndrome or Syndrome X (terminology not commonly used as another syndrome X has been documented in cardiology), represents an association of risk factors for cardiovascular (CV) disease (CVD) and type 2 diabetes mellitus (T2DM) that co-occur more frequently than by chance. These risk factors are represented by high blood pressure (HBP), impaired fasting glucose (IFG), increased level of triglycerides (TG), low high-density lipoprotein (HDL) cholesterol levels, and obesity (mostly abdominal type). It is becoming increasingly clear that this constellation of metabolic disorders is connected to IR and is more frequently found in people with abdominal obesity, particularly in those with an excess of intra-abdominal or visceral adipose tissue [1]. IR creates an atherogenic, inflammatory and prothrombotic state and it is not only a factor which increases the risk of T2DM but also a prevalent cause of CVD [2]. Non-alcoholic fatty liver disease (NAFLD) is strongly related with IR, and it can be a cause, but also a consequence of MetS [3]. It is estimated that 32.4% of the population worldwide has NAFLD. The incidence and prevalence have rapidly increased over time, from 25.5% before 2005 to 37.8% in 2016 [4], synchronising with the global obesity pandemic [5] and becoming one of the leading causes of cirrhosis in some countries [6]. Moreover, it is predicted that, in terms of indication for liver transplantation, NAFLD will exceed the viral ethology [7]. The overall prevalence of NAFLD was significantly higher in male than in female. Liver biopsy is the gold standard for diagnosis NAFLD, but due to

its inconvenience, other non-invasive ways of diagnosis were developed (serum biomarkers and imaging-based biomarkers).

2. Definition of MetS

The challenge represented by MetS is that various organizations offered slightly different clinical screening parameters and cut-off values for identifying individuals with MetS which are somewhat ambiguous compared to the conceptual description of the MetS. The first formalized definition of MetS was offered in 1998 from a consultation group towards the World Health Organisation (WHO). The WHO diagnosis has mandatory markers of IR (glucose ˃ 6.1 mmol/L or > 110 mg/dL, 2 h glucose ˃ 7.8 mmol/L or > 140 mg/dL) and a minimum of two additional risk factors: low HDL-cholesterol level (HDL-cholesterol ˂ 0.9 mmol/L or < 35 mg/dL in males and ˂ 1.0 mmol/L or < 40 mg/dL in females), high TG levels (˃1.7 mmol/L or >150 mg/dL), obesity (waist/hip ratio ˃ 0.9 in male or ˃ 0.85 in female or body mass index (BMI) ˃ 30 kg/m^2), HBP with systolic (˃140/90 mmHg). In 2001, the National Cholesterol Education Program Adult Treatment Panel III (ATP) [8] developed a new definition for MetS that did not require the expression of IR or a single factor for diagnosis, but rather the presence of 3 out of the 5 factors listed below which include abdominal obesity (waist ˃ 102 cm in males or ˃ 88 cm in females) (which is strongly associated with IR), elevated TG (˃1.7 mmol/L or >150 mg/dL), reduced HDL cholesterol (˂1.0 mmol/L or <40 mg/dL in males, ˂1.3 mmol/L or <50 mg/dL in females or drug treatment for low HDL cholesterol), elevated blood pressure (BP) (˃130/85 mmHg or drug treatment for HBP), and IFG (glucose > 5.6 mmol/L or > 100 mg/dL or drug treatment for elevated blood glucose) (IFG or T2DM). To integrate these two different definitions, the International Diabetes Federation (IDF) [9] and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [10] promulgated in 2005 a new definition for MetS, but there were variations based on waist size. IDF, in comparison with WHO's definition, assert abdominal obesity as mandatory (waist ˃ 94 cm in males or ˃ 80 cm in females) along with the presence of two or more of the following: blood glucose > 5.6 mmol/L (100 mg/dL) or diagnosed DM, HDL cholesterol ˂ 1.0 mmol/L (<40 mg/dL) in males, ˂1.3 mmol/L (<50 mg/dL) in females or drug treatment for low HDL cholesterol, blood TG ˂ 1.7 mmol/L (<150 mg/dL) or drug treatment for elevated TG, BP ˃ 135/85 mmHg or drug treatment for HBP. AHA/NHLBI did not consider abdominal obesity as mandatory, and the waist parameters are 102 instead of 94 in males and 88 instead of 80 in females. The parameters of the waist circumference (WC) from AHA/NHLBI are indicators for a BMI of approximately 30 kg/m^2, and those from IDF are more suggestive of a BMI of 25 kg/m^2. Although they are not as widely used, somewhat slightly different definitions were utilized by other organizations such the European Group for the Study of IR (EGIR) and the American Association of Clinical Endocrinologists (AACE) in 2003. Because of its heterogenous definition and cut-off criteria, the data existing on the epidemiology of MetS differs. It is observed that the prevalence of MetS is higher using AHA and IDF (more sensitive criteria) compared to the ATP III definition, with a ranging prevalence from 12.5% to 31.4% worldwide [11].

3. MetS and Liver Involvement

Initially, Reaven did not include obesity in his description of syndrome X since he could identify non-obese people with IR and people with obesity who were insulin sensitive. Obesity assessed by BMI alone, is not a predictor of MetS if not correlated with WC, age, gender, and ethnicity, because IR has a strong connection with visceral adipose tissue. It is important to identify people with adipose tissue that is distributed in deep compartments because adipocytes from deep compartments are more metabolically active compared with superficial adipocytes and are correlated with IR [12]. In this context, studies evaluating adiposity using computed tomography (CT) revealed that an excessive build-up of visceral adipose tissue was a key correlate of the characteristics of IR; however, CT is unlikely to be employed widely due to the radiation exposure and cost of use [13]. More recently, anomalies that are clustered together, as with those seen in visceral obesity, were found to be nearly identical in people with extra liver fat. Liver fat accumulation may be evaluated non-invasively and with high precision thanks to the development of magnetic resonance spectroscopy. The data provided by this method corresponds with the findings of liver biopsies, making it the best non-invasive way to determine the hepatic triglyceride content (HTGC) and to identify hepatic steatosis [14]. Liver fat is tightly associated with fasting insulin concentrations and direct measurements of hepatic insulin sensitivity, while the amount of subcutaneous adipose tissue is not [15]. A fatty liver overproduces glucose and lipids, especially very low-density lipoproteins (VLDL), the main players of MetS, but also the majority of the well-known CV risk factors, including fibrinogen, C-reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1) and coagulation factors [15][16].

4. NAFLD in the Pathogenesis of Metabolic Syndrome

NAFLD refers to the presence of fat in the liver (˃5–10% of hepatocytes are fatty) which is not associated with other known causes of steatosis such as: alcohol (defined as >20 g of alcohol daily for females and >30 g for males in European and American recommendations [17]), viruses, drugs, toxins, autoimmune disease or iron overload and is accompanied most frequently, if not always, by IR [18]. NAFLD ranges from simple fatty infiltration, without evidence of inflammation (non-alcoholic fatty liver (NAFL)), to fat and inflammation (non-alcoholic steatohepatitis (NASH)) and cirrhosis, which can progress to end-stage liver disease (ESLD) or directly to HCC. It is not a rule that all subjects with MetS develop NAFLD, nor do all subjects with NAFLD develop NASH [19]. NAFLD and MetS may be linked in a vicious cycle, with NAFLD becoming both a symptom and a cause of MetS [20]. From the histological point of view, alcoholic steatohepatitis is indistinguishable from NASH and is characterized by small and large macrovesicular steatosis droplets, but may also be composed of a mixture of large and small vacuoles, ballooning necrosis, mild inflammation, fibrosis, and it can be diagnosed by identifying these features on biopsy liver samples as a gold standard method [21]. In the USA, NASH is the third most common reason for liver transplantation [22] and the most common cause of cryptogenic cirrhosis. According to reviews, 3–6% of people globally are thought to have NASH. It can proceed to cirrhosis and ESLD, even though CVD is the primary cause of mortality in persons with this condition [23]. In addition, the percentage of individuals in the United States who have NASH as the primary cause of their HCC has increased 7.7-fold (from 2.1 to 16.2%) [24]. NAFL is typically asymptomatic, and most patients have normal transaminases levels, even though the disorder is the most common reason for unexpectedly elevated transaminase. At this time, it is not recommended to screen asymptomatic people or people with MetS or simple steatosis [18]. According to a recent assessment, NAFLD may be responsible

for 80% of cases of increased transaminase levels in the American population [25] and similar data have been obtained in the Italian [26] and Japanese [27] population. Due to the increase in Western industrialized food, and the sedentary lifestyle, there is an obesity epidemic beginning in childhood with the increase of DM and, respectively, an increase in NAFLD which is now recognized as the most prevalent chronic liver disease, with a worldwide prevalence of 25% [28], with a high prevalence rate reaching 60–70% in patients with DM [29]. T2DM is the most important risk factor for NAFLD and seems to be correlated with the progression of the disease, with the presence of advanced fibrosis (AF), and is associated with liver-related mortality, but it is usually overlooked in clinical practice [30].

5. New Therapeutic Perspectives in the Association between NAFLD and MetS

Montemayor et al. reported [31] in a study on 128 patients aged 40–60 years with BMI between 27 and 40 kg/m^2, with diagnosis of NAFLD and MetS, that conventional diet (CD) 43 patients, Mediterranean Diet (MD)—high meal frequency, 43 patients, and MD—physical activity (PA), 42 patients, decreased the intrahepatic fat content and liver stiffness alongside with BMI, insulin, HbA1c, diastolic BP, HDL-C and ALT after 12 months as seen in **Table 1**.

Table 1. Novel therapeutic approaches in NAFLD and MetS.

Author	Study Groups	Intervention	Outcome
Montemayor et al. [31]	128 patients	Conventional Diet, Mediterranean diet (MD)–high meal frequency MD–physical activity groups.	↓ intrahepatic fat contents ↓ liver stiffness ameliorated BMI, insulin, Hb1Ac, diastolic blood pressure, HDL-cholesterol, and ALT
Konieczna et al. [32]	5867 patients	Energy-restricted MD, physical activity promotion and behavioral support	↓ of BMI, waist circumference ↓ HbA1c ↓ TG
Van Kleef et al. [33]	667 patients	Different intensities of physical activity	↓ NAFLD ↓ waist circumference

Author	Study Groups	Intervention	Outcome
Lassailly et al. [34]	180 patients	Bariatric surgery	↓ fibrosis reversed NASH
Pedersen et al. [35]	40 patients	Roux-en-Y gastric bypass sleeve, gastrectomy	↓ NAFLD reversed NASH
Newsome et al. [36]	320 patients	semaglutide	↓ fibrosis resolution of NASH
Mirarchi et al. [37]	Review with 511 patients from 13 studies	SGLT-2i	↓ liver fat content ↓ AST/ALT ↓ liver stiffness.
Vilar-Gomez et al. [38]	180 patients	Vitamin E	↓ overall mortality and transplant rates ↓ rates of hepatic decompensation ↓ risk of death ↓ need for transplant Benefits both in patients with or without T2DM

oprotein-cholesterol; ALT—alanine aminotransferase; TG—triglycerides; NAFLD—nonalcoholic fatty liver disease; NASH- non alcohol steatohepatitis; SGLT-2i—sodium-glucose loop transporter 2; AST—aspartate amino transferase; T2DM—type 2 diabetes mellitus.

Konieczna et al. [32] reported in a study on 5867 patients with NAFLD risk factors who used to consume ultra-processed foods, that administration of energy-restricted MD, PA and behavioural support decreases the BMI, WC, HbA1c, TG after one year. The dietary intake and PA were assessed at 0, 6 and 12 months using a semi-quantitative food frequency questionnaire and validated Minnesota-REGICOR short PA questionnaire as seen in **Table 1**.

Van Kleef et al. [33] reported in a study of 667 patients, 229 of which had NAFLD (assessed by ultrasound (US) after excluding secondary causes of liver steatosis such as excessive alcohol consumption, steatogenic drug use, and hepatitis B or C), a mean age of 63.3 years and were females 53%. Of these, 229 (34.3%) had NAFLD and associated a higher prevalence of overweight, DM, HBP, and lipid abnormalities. The intervention consisted in PA —61.9% light intensity, 29.8% moderate intensity, and 8.2% vigorous intensity; and resulted in amelioration of NAFLD incidence and in WC as seen in **Table 1**.

Recently, Lassailly et al. [34] reported long-term outcomes in a group of 180 patients with severe obesity and biopsy-confirmed NASH who underwent metabolic and bariatric surgery (MBS). At the 5-year post-surgical follow-up, NASH was resolved without deteriorating fibrosis in 84% of patients, fibrosis was reduced compared to baseline in 70.2%, and it was totally resolved in 56%. MBS is now restricted to adults with a BMI of at least 35 kg/m^2, a clinical indication that excludes many NAFLD patients as seen in **Table 1**.

In a study of 40 patients with obesity who underwent bariatric surgery, Pedersen et al. [35] concluded that bariatric surgery reduces NAFLD and can reverse NASH. The study divides the patients in two subgroups that were treated with two different surgical methods: 16 patients underwent Roux-en-Y gastric bypass (RYGB), and 24 patients underwent sleeve gastrectomy (SG). RYGB appeared to minimize hepatic steatosis and enhance the plasma lipoprotein profile better than SG. Even though there are presently no NAFLD guidelines evaluating the efficacy of bariatric surgery in treating NAFLD, SG looks to be an equally good alternative to RYGB in bariatric patients with NAFLD as seen in **Table 1**.

Newsome et al. [36] studied the efficacy of three different dosages of semaglutide once daily (0.1, 0.2, and 0.4 mg) vs. placebo in a large cohort of 320 patients with NASH, aged 18–75 years, 61% female, and 62% with T2DM. NASH resolution was observed in 59% of volunteers treated with the highest dose of semaglutide, compared to 17% in the placebo group. The combined endpoint of NASH resolution and fibrosis improvement was reported in 37% vs. 15% of semaglutide vs. placebo-treated patients as seen in **Table 1**.

Regarding the other novel antidiabetic non-insulinic drug [39], Mirarchi et al. [37] reported in a review of 13 studies the benefits of sodium-glucose cotransporter-2 inhibitors in patients with NAFLD decrease liver fat content, AST/ALT levels and liver stiffness as seen in **Table 1**.

About Vitamin E use in liver involvement, Vilar-Gomez et al. [38] reported in a study on 180 with biopsy-proven NASH and bridging fibrosis or cirrhosis—90 that received treatment with vitamin E and 90 matched patients without vitamin E treatment; that vitamin E treatment increase transplant-free survival rates and and lower rates of hepatic decompensation, risk of death or need for liver transplant. The benefits were present both in patients with or without T2DM as seen in **Table 1**.

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