Review Article

Association between non-alcoholic fatty liver disease and metabolic syndrome

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Abstract

Metabolic syndrome describes the co-occurrence of central adiposity, dysglycaemia, hypertension, lipid abnormalities and a number of other metabolic changes that increase risk of cardiovascular disease. This multi-system condition has adverse effects on many organs, the liver being one of them. Non-alcoholic fatty liver disease appears to be the hepatic manifestation of metabolic syndrome, and is increasingly recognised as a major contributor to the burden of chronic liver disease world-wide. Metabolic syndrome and non-alcoholic fatty liver disease appear to have a common pathogenesis, arising from insulin resistance, central adiposity and chronic low grade inflammation. Treatment of metabolic syndrome may have a significant impact on progression of non-alcoholic fatty liver disease, and therapeutic options treating the underlying cause of metabolic syndrome (weight loss and insulin sensitising drug therapy) appear to be valid options in treating liver disease to prevent progression to fibrosis and cirrhosis. Recent studies suggest a possible role for vitamin E. Prevention of obesity is extremely important to reduce the risk of this condition leading to a growing cause of liver morbidity in the future.

Keywords

Non-alcoholic steatohepatitis, non-alcoholic fatty liver disease, metabolic syndrome

Introduction

Metabolic syndrome (MetS) describes the co-occurrence of a constellation of metabolic disorders, which increase the risk of developing atherosclerotic vascular disease and Type 2 diabetes (T2D). The syndrome affects around one in five people worldwide, with the prevalence mirroring the rapid rise in obesity [1]. Non-alcoholic fatty liver disease (NAFLD) is common, and increasingly recognised as a major cause of hepatic morbidity in developed and developing countries. Epidemiological evidence suggests a close link between the prevalence of MetS and NALFD. This brief review discusses the evidence suggesting a potential link between MetS and NAFLD, and the potential pathogenic mechanisms behind this link.

Definition of metabolic syndrome

In 1947 Jean Vague, observed that upper body obesity predisposed to diabetes, atherosclerosis and gout [2]. Some thirty years later, Haller and colleagues used the term "metabolic syndrome" for the association of diabetes mellitus, obesity and hepatic steatosis when describing the additive effects of risk factors on atherosclerosis [3]. Gerald Reaven subsequently proposed that insulin resistance was an underlying factor linking the metabolic abnormalities associated with his "syndrome X" [4]. MetS has been variously named as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome and CHAOS (coronary artery disease, hypertension, adult onset diabetes, obesity, stroke).

There has been some debate over the clinical utility of the metabolic syndrome to delineate increased risk of cardiovascular disease, and whether the label of metabolic syndrome offers any benefit over and above the individual risk. A very recent position of the World Health Organization,

is that the MetS has limited practical utility as a diagnostic or management tool [5], and some authors suggest that the use of term metabolic syndrome may divert focus away from simpler and more precise risk models [6].

Nevertheless, a number of major international organisations have developed definitions for MetS, and in recent years, a single unified definition has been agreed, based on the presence of abdominal obesity and a number of other cardiovascular factors (Table 1) [7].

Epidemiology of metabolic syndrome

Prevalence of MetS in Europe varies from 12-26% depending on geographical area, urbanisation and ethnic mix [8]. Studies in Asia, suggest the prevalence is 5-20%, with an overall global prevalence of around 16% of the adult population [8,9]. Prevalence in India appears to be highest, at around 26% of the adult urban population [10,11], and prevalence appears to be increasing as obesity rates and urbanisation increase. Data from the USA National Health and Nutritional Examination Survey (NHANES) show an age adjusted prevalence increase by 23.5% in women and 22.2% in men between 1994 and 2000 [12].

Overweight and obesity appears to be increasing in children and adolescents, suggesting that the prevalence of metabolic syndrome is also increasing, and likely to go on increasing for the foreseeable future. A recent study comprising of 105 obese adolescent subjects undergoing laparoscopic obesity surgery, reported a 25% incidence of Non-alcoholic steato-hepatitis (NASH), and also confirms that the presence of metabolic syndrome in obese adolescents predicts impaired glucose tolerance and NAFLD [13].

Risk factors for the development of metabolic syndrome and NAFLD

Non-alcoholic fatty liver disease is common, and may contribute significantly to the burden of chronic liver disease. It is important to note, however, that selection bias may be a factor in the study of MetS in patients with NAFLD and NASH. Liver biopsy is generally only performed in selected patients, and the natural history of the disease may be completely different in subjects from the general population. A recent study of long term follow up of NAFLD patients suggests that overall prognosis of NAFLD is good, and only a minority of patients develop NASH and cirrhosis [14]. Neverthless, the number of people with NAFLD is large, and hence even a small number of them progressing to NASH is likely to lead to a significant burden of chronic liver disease (figure 1).

Risk factors for the development of MetS and NAFLD include:

- Increasing age - around 44% of the US population above the age of 50 years have MetS, possibly due to weight gain, reduced physical activity & hormonal effects [12].
- Obesity - increased waist circumference and central adiposity is strongly linked with MetS, with an increase of 1 cm in waist circumference increasing the risk of MetS by around 7.4% [15].
- Physical inactivity - is a potent predictor of cardiovascular mortality and morbidity, probably mediated via central adiposity, reduced high density lipoprotein (HDL) cholesterol levels and hypertension [16].
- Female sex - women are affected by MetS more commonly than men, particularly post menopause [17].
- Hormonal changes – low levels of testosterone and sex hormone binding globulin (SHBG) [18], growth hormone (GH) [19], and high levels of glucocorticoids [20] are all associated with increased risk of MetS.
- Stress - physiological, emotional or psychological stress can be an underlying cause of MetS, possibly due to imbalance of the hypothalamic-pituitary-adrenal (HPA) axis [21].
- Ethnicity - South Asians appear to be the highest risk for development of MetS [10,11,22].
- Polycystic Ovarian Syndrome (PCOS) - Peripheral insulin resistance with a compensatory hyperinsulinaemia is frequently seen in PCOS, and the insulin excess leads to ovarian and adrenal androgen production. PCOS is frequently, although not always, associated with obesity and glucose intolerance [23]. Treatment with metformin can improve insulin sensitivity and lead to ovulatory cycles.

Common pathogenesis of metabolic syndrome and NAFLD

A number of pathogenic mechanisms underlying MetS and NAFLD have been postulated, all of which are likely to be

interlinked:

- Insulin resistance - fasting hyperinsulinaemia at baseline is related to MetS and subsequent development of T2D. Elevated insulin levels as well as fasting proinsulin levels both are associated with a number of metabolic disorders related to insulin resistance syndrome [24]. Insulin resistance is characteristic in patients with NAFLD and NASH [25]
- Systemic Inflammation - markers of systemic inflammation such as C-reactive protein (CRP), fibrinogen, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), are all increased in MetS [26]. Raised levels of high sensitivity CRP is a potent predictor for development non-alcoholic steatohepatitis (NASH) [27], with degree of insulin resistance directly proportional to the degree of liver fibrosis.
- Visceral adiposity - adipocytes are highly metabolically active tissue, with autocrine, paracrine and endocrine functions. Visceral fat surrounds the internal organs and is composed of the mesenteric and omental depots, and higher levels of visceral adiposity are associated with increase in plasma TNF- α, as well as altered levels of adiponectin, resistin and PAI-1 [28]. TNF- α triggers production of inflammatory cytokines, leading to inflammation.
- Lipotoxicity – It has been proposed that obesity and hyperleptinemia protect lipid-intolerant nonadipose organs against lipotoxic lipid spillover during sustained caloric surplus [29]. It is suggested that metabolic syndrome may be due to lipotoxicity caused by age-related resistance to antilipotoxic protection by leptin.
- Liver-gut axis - recent evidence in animals suggests that changes in gut microbial flora may predispose to metabolic disorders, with a high-fat diet being associated with higher endotoxaemia and lower caecal Bifidobacterium in mice [30]. It has been hypothesized that this endotoxaemia may contribute to diabetes, obesity and NASH.

Despite NAFLD and NASH being commoner amongst obese subjects, some studies suggest that hepatic steatosis is prevalent amongst lean patients. In an unselected autopsy series of 351 nonalcoholic patients, steatosis was noted in 70% of obese and 35% of lean patients, and steatohepatitis was found in 18.5% of obese and 2.7% of lean patients. Advanced fibrosis was greater in obese (13.8%) than in lean (6.6%) patients, and the difference was associated with the concomitant increased prevalence of diabetes [31].

Association between hepatic steatosis and insulin resistance

There is firm epidemiological evidence that NASH is strongly associated with MetS. Most cases of NAFLD occur in patients with obesity (60-95%), T2D (28-55%) and hyperlipidaemia (27-92%) [32], and liver biopsy in patients with T2D shows hepatic steatosis at histological examination in around 50% of cases. Measures of insulin resistance are increased in patients with NAFLD compared to matched controls, and patients with NASH have more MetS compared to age, sex and severity of fibrosis matched patients with hepatitis [32]. Reduced insulin sensitivity is shown in many studies of patients with NAFLD or NASH, including studies with hyperinsulinaemic, euglycaemic clamps, and oral / intravenous glucose tolerance tests [25]. There appears to be a direct correlation with the degree of insulin resistance with severity of liver disease from mild NAFLD to severe NASH and cirrhosis.

Both peripheral and hepatic insulin resistance is present in patients with NAFLD, irrespective of the coexistence of impaired glucose tolerance or obesity. This observation, together with the frequent presence of hypertension, hypertriglyceridemia, central adiposity and family history of diabetes, has led to NAFLD disease being considered as the “hepatic manifestation of the metabolic syndrome”.

Insulin resistance and increased non-esterified fatty acid (NEFA) are associated with increased intra-hepatic production of free fatty acids (FFA) from glucose not taken up by peripheral adipocytes and myocytes [33]. Excess hepatic fatty acids are not oxidised and are converted to diacyl- and triacylglycerols, and are stored in the hepatocyte cytoplasm, leading to steatosis. There are a combination of genetic and acquired factors that are responsible for insulin resistance leading to the development of steatosis, through increased lipolysis and delivery of free fatty acids to the liver.

The development of progressive liver disease in people with NAFLD may be mediated via oxidative stress [34]. Examination of liver biopsies shows increase lipid peroxidation (a marker of oxidative stress) in patients with NASH compared to control subjects, suggesting that the hepatocytes in NASH are been subject to increased oxidative

stress. In animal models of NASH, increased reactive oxygen species (ROS) formation from the mitochondria, leading to increased hepatic supply of free fatty acids (FFA) has been demonstrated, arising from insulin resistance and visceral obesity. Humans with NASH exhibit ultrastructural mitochondrial lesions and have decreased activity of respiratory chain complexes. Other potential sources of oxidative stress that have been suggested to play a role in NASH include the cytochrome P450 enzymes, CYP2E1 and CYP3A4, and an increased in liver iron observed in some patients.

A report of NASH and cryptogenic cirrhosis occurring within kindreds suggested that genetic factors may be important [35]. Genes involved in the development of insulin resistance and free fatty acid formation may play a pertinent role. Similarly, genetic factors that play a role in determining body mass and distribution may be important in the development of NASH, as illustrated by a study demonstrating an association between the gene encoding a microsomal triglyceride transfer factor and raised transaminases in patients with T2D [36], which has been replicated in a Brazilian study of patients with NASH [37]. Other genetic loci that have been associated with NASH are the angiotensin II type 1 receptor [38], apolipoprotein E [39], methylenetetrahydrofolate [40], and the CD14 genes [41].

Treatment of NAFLD in patients with metabolic syndrome (Table 2)

Currently there is no established therapy for NAFLD or NASH to prevent progression to fibrosis, cirrhosis and liver failure. Lifestyle change and weight loss remain the mainstay of therapy, and are effective in improving liver function tests and histology [42]. In view of the association between insulin resistance and NAFLD/NASH, therapeutic agents improving insulin resistance have been considered for use in patients with such hepatic problems. Supplementation with vitamin E has been examined in patients with NASH in small studies, with some positive results.

Weight loss

The Diabetes Prevention Programme (DPP) studied 3234 study pre-diabetic obese individuals from 27 clinical centres around US, who were randomised to lifestyle intervention, metformin 850 mg twice a day, and placebo [43]. In the lifestyle intervention group, a mean 5.6 kg weight loss led to a 58% reduction in progression to diabetes. Metformin therapy led to a 31% reduction in progression to diabetes. Similar results have been found from studies in China and Finland, suggesting that improved lifestyle leading to a modest weight loss improves metabolic indices.

Small randomized trials suggest that weight loss programmes with a hypocaloric diet and exercise can improve fibrosis scores in adults and children with NAFLD [44, 45]. Several studies also suggest an emerging role for bariatric surgery, resulting in both chemical improvement and histologic improvement of NASH [46]. Roux-en-Y gastric bypass has shown improvement in NASH in 100% of patients [47].

Pharmacological therapy in the treatment of NAFLD/NASH

Drugs used in treatment of T2D may be useful in treatment of NAFLD or NASH.

- Metformin - in open label studies, metformin is effective in improving liver biochemistry, but did not result in improvement of fibrosis in a small study of patients with NASH [48]. A large scale RCT is needed to establish whether metformin has any protective role in patients with NAFLD or NASH.

- Glitazones - Glitazones improve insulin sensitivity by acting as selective agonists of the nuclear peroxisome proliferator-activated receptor (PPAR γ). Small clinical trials involving glitazones in the management of NASH have shown a beneficial effect on liver biochemistry and histology [49-51]. A more recent study of larger numbers of patients has suggested that pioglitazone does not have a significant modulatory effect on liver fibrosis in patients with NASH, but did lead to reduction in steatosis and inflammation [52].

- Orlistat - Orlistat inhibits pancreatic lipase, thus reducing fat absorption. The drug is effective in reducing weight to a modest degree (5-10% weight loss), and also improves lipid profiles. Use of orlistat in patients with obesity and IGT leads to a reduction in the incidence of newly detected diabetes by 37% compared with placebo. Weight loss is associated with a reduction in hepatic steatosis. Small case series studies of liver biopsies in patients with NASH who lose weight has shown histo-pathological improvements following treatment for 6-12 months with orlistat [53].

- Vitamin E - Recently published data suggests an

important role for vitamin E in reducing progression of NASH [52]. Vitamin E is a potent anti-oxidant, and in a placebo controlled randomised trial of 247 subjects with NASH, 43% of patients on vitamin E 800 IU daily had a significant improvement in liver histology, with few adverse effects. Importantly, however, fibrosis scores did not change, and vitamin E.

- Lipid lowering agents – statins have been used in small clinical trials to determine efficacy in NASH. A small Japanese study of 31 patients treated with atorvastatin showed an improvement in liver steatosis and nonalcoholic fatty liver disease activity score [54]. A prospective open labeled study of atorvastatin versus fenofibrate or both in 186 patients with NAFLD showed significant regression of NAFLD in patients treated with the statin [55].

Conclusion

The link between MetS and NAFLD is well established, but there are many questions unanswered. Whilst patho-physiological mechanisms are beginning to be unravelled, underlying genetic factors need to be established. Why are some people more susceptible to the adverse effects of fat in the liver compared to others? The role of inflammatory substances in the development and progression of fatty liver is clearly important. Further elucidation of this area may enable effective treatments to prevent development or progression of the condition, and may also be useful in identifying at risk subjects.

Much greater study is required into the use of drug therapy in the treatment of established NAFLD and NASH. Large RCTs are urgently needed to address whether older and newer drugs may prevent the progression to end stage liver disease.

Rapid development, urbanisation and consequent change in diet and physical activity levels has led to a rapid growth in obesity and prevalence of MetS. The commensurate rise in NAFLD worldwide is consequent on these changes. Whilst fatty liver disease is less of a burden of total liver disease worldwide, compared to viral hepatitis and alcohol, it is likely to grow in prevalence, especially in the developing world, unless major improvements in the prevention and management of MetS are developed.

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Table 1. Definition of metabolic syndrome

Glucose	5.6mmol/L (>100mg/dL) or previously diagnosed Type 2 diabetes
Blood Pressure	>130/85 mmHg
Triglycerides	>1.7mmol/l (150mg/dL) or specific treatment for this
High Density Lipoprotein (HDL) Cholesterol	Men: 1.03mmol/L (<40mg/dL) Women: 1.29mmol/L (<50mg/dL)
Obesity	BMI>30kg/m^2 or Abdominal Waist Circumference – population specific: Europid men: >102cm (40") Europid women >88cm (34.5") South Asian men: >90cm (35") South Asian women: >80cm (31.5")

Table 2. Tests used in diagnosis of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Test	Abnormality
Liver Function Test	Elevated aspartate aminotransferase [AST] and alanine aminotransferase [ALT]. AST: ALT ratio > 1 may indicate more severe disease
NAFLD Fibrosis Score	Age, hyperglycemia, BMI, platelet count, albumin and AST/ALT ratio has been suggested as predictive of degree of fibrosis [56]
Ultrasound	Liver may be hyperechogenic or bright. Steatosis is detected only when substantial (30% or more) fatty change is present
Ultrasound Elastography	Non invasive scan, as yet not fully validated for routine diagnostic and follow up use.
Liver biopsy	Gold standard. Histologic findings of NASH include: · Steatosis - usually macrovesicular · Inflammatory infiltrates · Ballooning degeneration · Fibrosis. · First 3 findings are used to calculate the NAFLD activity score (0-8).

Figure 1. Progression of non-alcoholic fatty liver disease