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Review

Metabolic syndrome and nonalcoholic fatty liver disease: Is insulin resistance the link?

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ABSTRACT

Metabolic syndrome (MetS) is a disease composed of different risk factors such as obesity, type 2 diabetes or dyslipidemia. The prevalence of this syndrome is increasing worldwide in parallel with the rise in obesity. Nonalcoholic fatty liver disease (NAFLD) is now the most frequent chronic liver disease in western countries, affecting more than 30% of the general population. NAFLD encompasses a spectrum of liver manifestations ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis, which may ultimately progress to hepatocellular carcinoma. There is accumulating evidence supporting an association between NAFLD and MetS. Indeed, NAFLD is recognized as the liver manifestation of MetS. Insulin resistance is increasingly recognized as a key factor linking MetS and NAFLD. Insulin resistance is associated with excessive fat accumulation in ectopic tissues, such as the liver, and increased circulating free fatty acids, which can further promote inflammation and endoplasmic reticulum stress. This in turn aggravates and maintains the insulin resistant state, constituting a vicious cycle. Importantly, evidence shows that most of the patients developing NAFLD present at least one of the MetS traits. This review will define MetS and NAFLD, provide an overview of the common pathophysiological mechanisms linking MetS and NAFLD, and give a perspective regarding treatment of these ever growing metabolic diseases.

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1. Introduction

Obesity is now a worldwide pandemic and is expected to affect 10% of the global population by 2030 if the current trend is maintained (Webber et al., 2014). In the United States, national surveys

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have observed a marked increase in the prevalence of obesity over time. For instance, ~20% of men and ~25% of women in the adult population and more than one-sixth of children are obese (Ogden et al., 2012). However, this increased prevalence of obesity is not confined to western countries. Notably, obesity is recognized as a major health problem in the United Arab Emirates (Hodge et al., 1995; Musaiger, 1996; Popkin, 1994). Moreover, obesity increases at an alarming rate in all Arabic-speaking countries with a prevalence of 2% to 55% in adult females and 1% to 30% in adult males (Badran and Laher, 2011). Other populations are also affected by this disorder, such as Indians, with a recent study reporting a prevalence of overweight and obesity in children up to 23% and 36%, respectively (Hoque et al., 2014). Obesity results from an imbalance between caloric intake and energy expenditure, leading to an excess of energy, which is stored as fat mainly in white adipose tissue (Chugh and Sharma, 2012; McKenney and Short, 2011). Importantly, obesity increases or exacerbates several health problems including cardiovascular diseases and type 2 diabetes (Kopelman, 2000). Metabolic alterations associated with obesity have been recognized and grouped to define the metabolic syndrome (MetS). MetS is a leading cause of mortality and morbidity in industrialized countries (Simons et al., 2011). It is characterized by the combination of multiple disorders including obesity, dyslipidemia, increased blood pressure, insulin resistance and a proinflammatory state (Reaven, 2002). The prevalence of MetS correlates with the global epidemic of obesity and is growing at an alarming rate, affecting more than 20% of the global adult population (Onat, 2011).

The rising epidemic of MetS and its related complications, such as cardiovascular diseases, has been accompanied by an increase in liver alterations including nonalcoholic fatty liver disease (NAFLD) (Angulo, 2002; Marchesini et al., 2003). In particular, it has been proposed that NAFLD may be the hepatic manifestation of MetS (Marchesini et al., 2003). NAFLD encompasses a wide spectrum of manifestations ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis (Tarantino et al., 2012). One of the major hallmarks of this disease is the consistent association with one of the characteristics of MetS, for instance type 2 diabetes mellitus, dyslipidemia or obesity (Vanni et al., 2010). Moreover, NAFLD is clearly associated with insulin resistance, which is a key risk factor for the development of type 2 diabetes (Jornayvaz and Shulman, 2012). Therefore, the aims of this review are 1) to discuss how MetS and NAFLD impact each other; 2) to describe the common mechanisms between these disorders; and 3) to provide an overview of the current diagnosis and treatment of both MetS and NAFLD.

2. Diagnosis and pathogenesis of MetS and NAFLD

MetS has received several definitions during the last decade. Therefore, it was important to find a consensus between different medical associations such as the World Health Organization (WHO), the European Group for the study of Insulin Resistance (EGIR), the National Cholesterol Education Program (NCEP), and finally the Third Adult Treatment Panel (ATPIII) (Alberti et al., 2006). The main aim of this consensus was to identify common criteria in order to use them in the clinical diagnosis of MetS worldwide. Using the ATPIII definition as a basis, the committee came with a new definition. Although insulin resistance is a critical feature of MetS, it remains difficult to measure in day-to-day clinical practice and thus was not included in the new definition. Central obesity, which is much easier to measure, was considered. Therefore, the new definition classified patients with MetS as subjects having central obesity and one of the following factors: raised triglycerides $\geq$1.7 mmol/l; reduced HDL-cholesterol $<$1.03 mmol/l in males and $<$1.29 mmol/l in females; raised systolic blood pressure $\geq$130 mmHg or diastolic blood pressure $\geq$85 mmHg; raised fasting plasma glucose, with fasting plasma glucose $\geq$5.6 mmol/l or previously diagnosed type 2 diabetes (Alberti et al., 2006). The major characteristic of this definition is that central obesity is required to diagnose MetS. As insulin resistance is frequently associated with obesity, the consensus considered obesity as a surrogate marker of insulin resistance in the definition of MetS. However, this definition of MetS is still a matter of debate (Jornayvaz et al., 2010b).

NAFLD is a pathological entity encompassing a whole histological spectrum ranging from simple steatosis to steatohepatitis, with inflammation and fibrosis, to cirrhosis (Contos et al., 2004). Cirrhosis, which is irreversible, can further progress to hepatocellular carcinoma (Farazi and DePinho, 2006). The development of NAFLD is notably based on the concept of the “two hits” hypothesis (Day and James, 1998). The first hit is the accumulation of triglycerides, leading to hepatic steatosis, while the second hit is the production of free radicals and inflammatory mediators giving rise to NASH. However, more recently, it has been argued that multiple hits derive simultaneously from adipose tissue and gut to promote liver inflammation, suggesting that cellular inflammation and insulin resistance are acting at the same time (Tilg and Moschen, 2010). Others have proposed that hepatic insulin resistance may be at the origin of the development of NAFLD. Indeed, mice specifically lacking the insulin receptor in the liver (LIRKO mice) develop hepatic insulin resistance associated with hyperglycemia, suggesting that hepatic function is critical to control peripheral insulin responsiveness (Michael et al., 2000). Additionally, this insulin resistance leads to altered liver function. Thus, one could propose that hepatic insulin resistance is the first step in the development of peripheral insulin resistance and NAFLD. In accordance with this hypothesis, deletion of the insulin receptor in skeletal muscle (MIRKO mice) does not impair peripheral glucose levels (Bruning et al., 1998). In addition to insulin resistance, other aspects of MetS such as obesity have been related to NAFLD. For instance, 85% of the patients developing NAFLD present at least one of the MetS characteristics (Gariani et al., 2013).

Clinically, NAFLD does not manifest with specific symptoms and is commonly silent. Currently, the diagnosis of NAFLD is based on exclusion criteria. For instance, causes such as alcohol consumption (more than 20 g/day for women and 30 g/day for men), autoimmune liver disease, viral hepatitis infection, hemochromatosis, Wilson’s disease, or drug consumption, must be excluded before considering NAFLD. Liver biopsy remains the gold standard to diagnose NAFLD, but this approach is associated with potential risks, such as bleeding. Therefore, patients need to be well selected before undergoing liver biopsy, although data are currently lacking regarding specific criteria. Alternative methods to assess NAFLD, such as non invasive imagery, are beyond the scope of this review and have been discussed elsewhere (Musso et al., 2011).

3. NAFLD: the liver manifestation of MetS

NAFLD is frequently associated with central obesity, insulin resistance and dyslipidemia, all of which are features of MetS. Therefore, NAFLD has been identified as the liver manifestation of MetS, with obesity as the main common component. Nevertheless, it should be noted that NAFLD also develops in non-obese patients, even though it is less common. For instance, several studies have shown that NAFLD could be detected in non-obese subjects with metabolic alterations (Kim et al., 2004; Musso et al., 2008; Sinn et al., 2012). Furthermore, these studies reported that NAFLD could be considered as an independent predictor of insulin resistance in non-obese patients (Kim et al., 2004; Musso et al., 2008;