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Review Article

Nonalcoholic fatty liver disease: A precursor of the metabolic syndrome

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ABSTRACT

The conventional paradigm of nonalcoholic fatty liver disease representing the "hepatic manifestation of the metabolic syndrome" is outdated. We identified and summarized longitudinal studies that, supporting the association of nonalcoholic fatty liver disease with either type 2 diabetes mellitus or metabolic syndrome, suggest that nonalcoholic fatty liver disease precedes the development of both conditions.

Online Medical databases were searched, relevant articles were identified, their references were further assessed and tabulated data were checked.

Although several cross-sectional studies linked nonalcoholic fatty liver disease to either diabetes and other components of the metabolic syndrome, we focused on 28 longitudinal studies which provided evidence for nonalcoholic fatty liver disease as a risk factor for the future development of diabetes. Moreover, additional 19 longitudinal reported that nonalcoholic fatty liver disease precedes and is a risk factor for the future development of the metabolic syndrome.

Finally, molecular and genetic studies are discussed supporting the view that aetiology of steatosis and lipid intra-hepatocytic compartmentation are a major determinant of whether fatty liver is/is not associated with insulin resistance and metabolic syndrome.

Data support the novel paradigm of nonalcoholic fatty liver disease as a strong determinant for the development of the metabolic syndrome, which has potentially relevant clinical implications for diagnosing, preventing and treating metabolic syndrome.

1. Introduction

Steatosis and steatohepatitis, in the absence of competing aetiologies such as high alcohol intake, hepatitis C virus (HCV) infection, drugs and other endocrine disorders, are both part of the nonalcoholic fatty liver disease (NAFLD) spectrum [1–3]. NAFLD may either occur in the absence of fatty changes – and is often alluded to either as "cryptogenic" or nonalcoholic steatohepatitis (NASH)-cirrhosis [4,5] – or encompass hepatic and extra-hepatic complications, from hepatocellular carcinoma to atherosclerosis [6]. NAFLD is presently recognized as one the most common causes of altered liver tests, of end-stage liver disease requiring liver transplantation, and is frequently associated with the constellation of clinico-laboratory features that comprise the metabolic syndrome [7–9].

The metabolic syndrome is a cluster of cardio-metabolic conditions, generally triggered by an expansion of the adipose visceral tissue [10], which include insulin resistance – with or without impaired glucose metabolism and type 2 diabetes (T2D) – atherogenic dyslipidemia [low high density lipoprotein (HDL)-cholesterol and high triglycerides], and high blood pressure [11]. The present definition of metabolic syndrome, at variance with one of its earliest proposals [12], does not include hepatic steatosis despite evidence supporting this association [13]. The existence and the utility of metabolic syndrome as a separate entity has been challenged by some experts [14]. Moreover, it remains controversial whether the presence of the full-blown syndrome really adds to the cardiovascular risk dictated by its individual components, particularly T2D [15,16]. Nevertheless, the single traits of the metabolic syndrome tend to aggregate in the same individuals and, more importantly, the presence of each of them often anticipates the appearance of

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Table 1
Nonalcoholic fatty liver disease and metabolic syndrome – the original spectrum of similarities.

	Steatosis	Metabolic syndrome
Epidemiology		
Prevalence in the general population	Up to 25% of adults	Epidemic in the elderly
Prevalence grows with age	Yes	Strongly age-dependent
Males more affected	Yes (adults, children)	Yes
Anthropometry		
Association with central obesity	Abdominal adiposity is an independent predictor	Visceral fat is correlated with Insulin response and dyslipidemia
Metabolism – Association with		
Hyperinsulinemia	Documented	Pathogenic mainstay
Hypertension	In drinkers and non-drinkers	Yes
Obesity	Yes	Yes
Hypertriglyceridemia	Yes	Yes
Low HDL Cholesterol	Circumstantial Evidence	Yes
Clinical features		
Systemic disease	Yes	Yes
Accelerated atherogenesis	Circumstantial Evidence	Yes
Response to diet and/or exercise	In the obese	Yes
Experimental pathology		
Animal Models (rat)	Atherogenic diet induces steatosis	Hypertensive animals have hyperinsulinemia and hypertriglyceridemia

Adapted from Lonardo [20].

additional components over time [17]. This, together with the possible progression to organ failure and of the development of some cancer types, including primary liver cancer [9,11,18,19], makes metabolic syndrome a relevant condition in clinical practice and a major public health concern worldwide.

In 1999, European researchers [20–22] provided biological, clinical and epidemiological evidence for the theory that NAFLD should be regarded as the hepatic manifestation of the metabolic syndrome (Table 1) [20]. Since then, a "chicken and egg" scientific debate has arisen, concerning the primacy of metabolic syndrome (and insulin resistance) over NAFLD or, conversely, of NAFLD over the metabolic syndrome [23]. Moreover, while most studies acknowledge NAFLD to be a risk factor for T2D [24], the notion that NAFLD anticipates the future development of components of the metabolic syndrome other than T2D is far less accepted, although it has been suggested by few authors [23,25,26] mainly based on their expert opinion.

In our systematic review of the literature, we discuss all available data supporting the view that NAFLD, rather than being a mere "manifestation of the metabolic syndrome" is indeed a necessary precursor of the future development of metabolic syndrome in humans. To this end, further to identifying all relevant cross-sectional studies, we specifically address the evidence from prospective studies showing that NAFLD is an independent risk factor for the future development of both T2D and other components of the metabolic syndrome. Methodological limitations of such data are briefly analysed. Finally, we discuss how some examples of dissociation of NAFLD from metabolic syndrome – seemingly contradicting our thesis – eventually confirm the general paradigm of NAFLD being a precursor of the metabolic syndrome.

2. Research strategy

The PubMed data base was manually searched for the following terms: "Metabolic syndrome"; "Type 2 Diabetes"; "Obesity"; "Dyslipidemia" "Hyperlipidemia"; "Insulin resistance"; "Predictor"; "Fatty liver"; "Follow-up"; "Association" and "Dissociation". The research was updated at the 28th of April 2014. Further bibliographic updates were performed whenever needed during the revision process.

All of the identified articles and their references were further checked in duplicate in order to identify appropriate articles. Pertinent studies were identified as a result of the agreement two investigators, who also tabulated the methods and chief findings of the selected material.

The accuracy of the tabulated data was independently performed by all authors.

3. Association of NAFLD with other conditions

3.1. Type 2 diabetes

Many cross-sectional studies demonstrate that NAFLD is associated with insulin resistance/pre-diabetes/T2D [27–39]. Despite a variable follow-up range, data appear consistent in disclosing that the "NAFLD pathway" to T2D follows a route characterized by insulin resistance developing at various anatomic sites, notably including hepatic insulin resistance. Interestingly, the NAFLD-T2D association occurs irrespective of potential confounders and particularly obesity and moderate alcohol drinking, suggesting that NAFLD may closely mirror the development of fatty pancreas disease [40] and thus reflect tissue lipotoxicity. Moreover, a quantitative relationship links fasting plasma glucose with NAFLD prevalence: the higher the former, the higher the latter [29]. However, widely acknowledged predictors of T2D in non-NAFLD populations (such as high fasting glucose and low HDL-cholesterol and adiponectin, mirroring insulin resistance) and low physical activity also predict T2D in NAFLD suggesting that NAFLD probably amplifies the physiological determinants of T2D. Finally, most findings appear to be confirmed irrespective of ethnicity (e.g. T2D-prone Asians vs. Caucasians) and of the diagnostic technique followed to capture NAFLD, spanning from the most invasive or accurate tests (liver histology, magnetic resonance imaging) to the most insensitive (liver tests), via the most widely performed ultrasonography scanning.

However, the above studies [27–39] are cross-sectional. Accordingly, they do not rule out the possibility that primarily impaired gluco-regulation may eventually result in the development of NAFLD. In order to clarify this issue, in Supplementary Table S-1 the studies showing NAFLD as a risk factor for the future development of T2D were summarized. Eleven out of 12 studies were conducted in Far East, most of them from Korea. With such a limitation, they confirm that NAFLD is an independent risk factor for the development of T2D, although confirmation from Western countries appears necessary. Moreover, the diagnostic technique used to detect NAFLD may lead to different results. For instance,