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Hepatic steatosis and vascular disease

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Abstract. – Nonalcoholic fatty liver disease (NAFLD) refers to a wide picture of liver damage, ranging from steatosis to steatohepatitis, fibrosis and cirrhosis. The epidemiological studies demonstrated an association of NAFLD with obesity, type 2 diabetes and hyperlipidemia. Under this light the metabolic syndrome (MS), including NAFLD, obesity, central fat distribution, diabetes, dyslipidemia, hypertension and atherosclerotic cardiovascular disease (CVD) can be considered the link to explain the presence of vascular diseases in patients with NAFLD. In NHANES III, the authors demonstrated that the presence of MS was associated with increased risk of myocardial infarction, stroke or both. In a prospective study on 1209 Finnish middle-aged men without CVD or diabetes at baseline, Lakka showed that MS *per se* is associated with an increased risk of CVD and all-cause mortality. Finally the Atherosclerosis Risk in Communities (ARIC) confirmed that subjects with MS were 2 times more likely to have prevalent coronary heart disease. From a pathophysiological point of view, growing evidences implicate the oxidative stress as the unifying mechanism for many CVD risk factors. Under this light there is emerging evidence suggesting that there is a significant increase in vascular oxidative stress in patients with MS, with the presence of endothelial dysfunction in the early stage of the syndrome. Indeed, the inflammation process evidentiated in these patients is initiated at the endothelial level, stressing the key role of this active and dynamic tissue in the pathophysiological pathways. Under this light the endothelium can be considered as the last effector of a multi-syndrome and the main target of all the future studies focused on the underlying mechamisms of this complex network. Because of the potential serious public health impact, the comprehension of these patophysiological pathways will be crucial to design new preventive measures and therapeutic strategies.

Key Words:

Metabolic syndrome, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Atherosclerosis, Inflammation, Cardiovascular disease, Endothelium.

Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to a wide picture of liver damage, ranging from steatosis to steatohepatitis, fibrosis and cirrhosis[1]. The epidemiological studies demonstrated an association of NAFLD with obesity, type 2 diabetes and hyperlipidemia, that are traditionally considered as risk factors for the "primary NAFLD"[2]. However few cases without evidence of these factors have been identified, suggesting the possibility of an inherited metabolic disorder that can be worsen by risky lifestyle behaviours[3]. On the basis of these observations the pathogenesis of NAFLD is still not clear, even if the insulin resistance appears to be the most reproducible factor in the natural history of this syndrome[4]. In particular, a decreased sensitivity to endogenous and exogenous insulin have been observed in patients with NAFLD, with a remarkable reduction of insulin effects on both lipid and glucose metabolism[3]. This defect can be observed in patients with NAFLD presenting both with normal weight and glucose tolerance and in patients with overweight and abnormal glucose regulation, suggesting a key role of insulin resistance[4]. Moreover, a large body of

evidence indicate a clinical association with features of the *metabolic syndrome (MS)*, particularly in the most aggressive stages of the disease[5]. Recentely, Bugianesi et al confirm that insulin resistance appears to be an intrinsic defect in NAFLD, with the metabolic pattern observed indicating that adipose tissue is an important site[6].

Metabolic Syndrome and Vascular Disease

Epidemiologic Studies

Under this light the metabolic syndrome, including NAFLD, obesity, central fat distribution, diabetes, dyslipidemia, hypertension and atherosclerotic cardiovascular disease (CVD) can be considered the link to explain the presence of vascular diseases in patients with NAFLD. In one of the most recent studies, the Third National Health and Nutrition Examination Survey (NHANES III) on the basis of self-reported histories the authors demonstrated that the presence of MS was associated with increased risk of myocardial infarction, stroke or both[7]. In a previous prospective study examining the association of the MS with cardiovascular and overall mortality on 1209 Finnish middle-aged men without CVD o diabetes at baseline, Lakka et al[8] showed that MS *per se* is associated with an increased risk of CVD and all-cause mortality. Another population-based survey recently confirmed the previous exposed results in 888 subjects with MS. In particular, changes in the atherosclerosis score, as well as the percent of subjects who developed new plaques or arterial stenosis > 40% were higher in patients with MS than in the control group[9]. Interestingly, by considering patients with manifest metabolic syndrome the presence of the MS is associated with advanced vascular damage (increased mean intima media thickness, increased prevalence of albuminuria and a trend, albeit non significant, toward a decreased ankle brachial pressure index)[10]. Finally, a study performed on 14,052 patients (Atherosclerosis Risk in Communities – ARIC) confirmed that subjects with MS were 2 times more likely to have prevalent coronary heart disease[11].

Pathophysiological Implications

The Metabolic Syndrome as Proinflammatory Condition

Growing evidences from animal studies and correlative data from human investigations implicate the oxidative stress as the unifying mechanism for many CVD risk factors, which additionally supports its central role in CVD. Under this light there is emerging evidence suggesting that there is a significant increase in vascular oxidative stress in patients with MS, with the presence of endothelial dysfunction in the early stage of the syndrome[12-13]. Moreover, the adipose tissue produce and or influence the action of many, such as leptin, adiponectin, TNF-α and IL-6)[14]. Indeed, the increased truncal obesity can be responsable for IR by lipotoxicity due to the release of free fatty acids in the portal circulation. It is important to underline that IL-6 is the chief stimulator of the production of C-reactive protein (CRP) in the liver. The last evidence can explain all the recent studies focalized on the indipendent prognostic importance of this parameter in patients with MS, as evaluated in 14719 apparently healthy women followed up for 8-year period, 24% of which were diagnosed with MS[15]**.** Moreover, by examining the relationship between abnormal liver function tests and CRP levels in middle-aged patients with characteristics of the MS, the association between elevated liver enzymes and CRP was independent of the presence of MS. This relationship raises the possibility that inflammatory process that accompany NAFLD contributes to the systemic inflammation observed in patients with obesity and other[16].

Endothelium: the Ultimate Frontier of a Complex Network

MS is a cluster of metabolic and cardiovascular abnormalities whose common denominator is thought to be insulin resistance. The inflammation process evidentiated in these patients is initiated at the endothelial level, stressing the key role of this active and dynamic tissue in the pathophysiological pathways of these patients. In particular, it is interesting that modest hyperinsulinemia of the same degree seen in insulin-resistant patients after overnight fast can cause severe endothelial dysfunction in large conduit arteries, an

effect that can be prevented by vitamin C. These data may provide a new epidemiological link between insulin-resistance and atherosclerosis, and, consequently, between NAFLD and atherosclerosis[17].

In conclusion, a remarkable decrease in insulin effects on both lipid and glucose metabolism can be observed in patients with NAFLD presenting both with normal weight and glucose tolerance and in patients with overweight and abnormal glucose regulation, suggesting a strong relationship among NAFLD, insulin resistance and MS. It is reasonable to emphasize that MS can be ultimately considered a proinflammatory state, since many associated abnormalities are themselves associated to vascular oxidative stress. Under this light the endothelium can be considered as the last effector of a multisyndrome and should be considered as the main target of all the future studies focused on the underlying mechamisms of this complex network. Because of the potential serious public health impact, the comprehension of these patophysiological pathways will be crucial to design new preventive measures and therapeutic strategies.

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Vascular damage and impairment play a crucial role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Nutraceutical supplements might have a role in reducing vascular damage, provided that their efficacy is proven by controlled studies and is supported by a mechanistic rationale. Therefore, the use of nutraceutical supplements can have some effects also in the prevention of NFLD.Â It has been observed that hepatic steatosis is related to an increased risk of cardiovascular disease (CVD). Alanine aminotransferase (ALT), an indicator of the severity of hepatic steatosis is also associated with CVD. This study focused on the relationship between hepatic steatosis and ALT with coronary calcification. Nonalcoholic fatty liver disease (NAFLD) refers to a wide picture of liver damage, ranging from steatosis to steatohepatitis, fibrosis and cirrhosis. The epidemiological studies demonstrated an association of NAFLD with obesity, type 2 diabetes and hyperlipidemia. Under this light the metabolic synd â€¦Â Hepatic steatosis and vascular disease. Eur Rev Med Pharmacol Sci. Sep-Oct 2005;9(5):269-71. Advanced liver disease and portosystemic shunting (PSS), far from being an isolated disorder of the liver, have well-known consequences on the body and, notably, on brain functioning. The alterations of brain functioning, which can produce behavioral, cognitive, and motor effects, were termed portosystemic encephalopathy (PSE) [3] and later included in the term HE [4]. Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence [5,6]. Even in its mildest form, HE reduces health-related quality of life and is a risk factor for b... n The third stage of hepatic steatosis is irreversible and is considered as a precirrhotic one. n The outcome of fatty hepatosis is cirrhosis of the liver. Fatty hepatosis.Â (lymphocytes, macrophages). n Has a cytopathic effect and causes immune disorders. n The disease is often found in alcoholics and injecting drug. users. n Rapidly progressing with the development of chronic forms of. hepatitis.