The Role of Non-Alcoholic Fatty Liver Disease in Cardiovascular Disease

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Abstract

Background/Aims: Fatty liver is the hepatic component of the metabolic syndrome. Insulin resistance, the pathogenic driver of the metabolic syndrome, refers to a constellation of features such as overweight/obesity, glucose intolerance, dyslipidemia and hypertension, all of which are important risk factors for cardiovascular disease (CVD). The aim of this article is to summarize the available data linking non-alcoholic fatty liver disease (NAFLD) with CVD. Methods: Two approaches were used to address this issue. First, data in support of the presence of the typical in vivo pathogenic features of atherosclerosis in individuals with NAFLD were described to confirm whether or not the association between NAFLD and CVD is plausible. Second, epidemiological data linking NAFLD with CVD outcome was reviewed. Results: Individuals with NAFLD are characterized by abnormal endothelial function. Data about the carotid intima-media thickness, which as a surrogate marker of atherosclerosis, are controversial, as is higher CAD even if altered myocardial perfusion has been described. Data in support of altered cardiac intermediary metabolism and energy metabolism are more robust. Low-grade inflammation is typically linked to NAFLD and animal studies, suggested that NAFLD may represent a potential mediator of the systemic inflammation. Epidemiologic studies support a causal link between fatty liver and type 2 diabetes but the causal association between NAFLD and CVD is rather weak. Conclusion: NAFLD is characterized by the early onset of the typical metabolic and vascular pathogenic alterations of atherosclerosis. In spite of this background, the evidence for the association between NAFLD and CVD is weak.
el of the adipose tissue [1–7]. It is therefore not surprising that NAFLD may be associated with the typical risk factors for cardiovascular disease (CVD) as highlighted by the analysis of data generated in a large European population [8]. Since the prevalence of NAFLD in the adult population [9], but also in overweight/obese children and adolescents [10], is rather high, there is general concern about the possibility that NAFLD may have a deleterious prognostic impact in these subjects due to the cardiovascular risk rather than to the hepatic outcome.

**Fatty Liver and Endothelial Dysfunction**

The arterial endothelium is a target for the atherosclerotic process. Atherosclerosis is associated with endothelial dysfunction in the very early stages of the disease process. Changes in the caliber of large arteries may be experimentally modulated and easily and noninvasively quantified. The response is mediated by nitric oxide released by endothelial epithelium in response to the shear stress generated by artery occlusion, and is considered a measure of endothelial function. Villanova et al. [11] took advantage of this, and evaluated the flow-mediated vasodilation of the brachial artery in patients with NAFLD. They found that flow-mediated vasodilation was lower in NAFLD versus controls. Since diagnosis of NAFLD was biopsy-based, they also established that the defect was more pronounced in those with steatohepatitis than in those with pure fatty liver. Very elegantly, the authors also showed that the defect had to reside at the endothelium level because no differences were observed in flow-independent vasodilation (which is the response to sublingual nitroglycerin, modulating its effect at the level of the arterial smooth muscle).

**Coronary Alterations in Patients with Type 2 Diabetes Mellitus and NAFLD: A Cross-Sectional Study**

The availability of data regarding the morphology of coronary vessels is limited in patients with NAFLD. Lautamaki et al. [12] reported a study performed in 55 patients with type 2 diabetes and coronary artery disease. These patients were divided into two groups with low and high liver fat content. These subjects also underwent classical coronary angiography to establish the extension of the atherosclerotic coronary disease. The median of the degree of the main stenotic lesion was 60% with a quite wide range (9–100%), but no significant differences could be detected between the groups, also in terms of the main stenotic vessel. The authors also measured myocardial perfusion with $[^{15}\text{O}]\text{H}_{2}\text{O}$ during hyperinsulinemic eu-glycemia using positron emission tomography. When coronary flow reserve was used as an indicator of endothelial function, it was found to be 28% lower in patients with fatty liver, indicating more severe coronary dysfunction in these patients in spite of similar angiograms.

**Cardiac Metabolism in Patients with NAFLD**

In the same study, Lautamaki et al. [12] also assessed myocardial glucose uptake with 2-deoxy-2-[^18F]fluoro-D-glucose and found that the high liver fat group had a lower insulin-stimulated myocardial glucose uptake and glucose extraction rate compared with the low liver fat group. In the multiple regression analysis, liver fat content was the most significant explanatory variable for myocardial insulin resistance.

Magnetic resonance spectroscopy (MRS) techniques have been applied to study in vivo metabolic pathways in different organs and tissues [13], including the heart [14]. In particular, the assessment of cardiac energy metabolism may be performed noninvasively by means of 31P-MRS [14]. We have applied this technique to young men with newly diagnosed fatty liver in which cardiac metabolic remodeling appeared to be an early independent event, as the surrogate marker of cardiac energy metabolism (PCr/ATP ratio) in these subjects was significantly lower than in the control group [15]. Although the cross-sectional nature of our study did not allow conclusions regarding the future risks of cardiovascular events, it suggested that in patients with NAFLD, abnormalities in cardiac metabolism may precede the development of functional and structural remodeling of the heart. In our previous study, homeostatic model assessment HOMA2-S was the most relevant predictive factor of the PCr/ATP ratio in obese men [16], but we did not detect this association in patients with fatty liver which was also characterized by higher amounts of fat in the epicardial area and (particularly) the extrapericardial area [15].

**Systemic Inflammation in Patients with NAFLD**

The metabolic syndrome is well known to be associated with systemic low-grade inflammation, a feature which has been linked to the macrophage infiltration of...
the adipose tissue that in obesity participates in the activation of inflammatory pathways [17]. This is not an exclusive feature of the adipose tissue; by promoting the release of cytokines, liver inflammation can also lead to insulin resistance [18]. In support of this view, Westerbacka et al. [19] obtained liver biopsies from 24 subjects who had varying amounts of histologically determined fat in the liver ranging from normal to steatosis due to NAFLD, and found that the mRNA expression of inflammatory genes, such as the monocyte-attracting chemokine CCL2 [monocyte chemoattractant protein (MCP)-1], were overexpressed proportionally to the amount of the hepatic fat content. An attractive hypothesis to account for the pro-inflammatory effects of NAFLD is that increased concentrations of intracellular fatty acid metabolites activate IKK-β and nuclear factor-κB [20]. Chronic inflammation of the liver secondary to triglyceride infiltration could, thereby, increase the production of factors that cause systemic insulin resistance.

Animal Models of Hepatic Insulin Resistance and the Development of CVD

Results in animal models would also support this hypothesis. Transgenic activation of the inflammatory mediators IKK-β and nuclear factor-κB in the liver induced systemic insulin resistance, increased circulating levels of interleukin (IL)-6 and upregulated IL-6 target genes in peripheral tissues, including muscle [21]. Conversely, administration of antibodies to neutralize circulating IL-6 normalized IL-6 target gene expression and corrected the insulin resistance. Finally, it has been demonstrated that 100% of mice with selective liver knockout of the insulin receptor gene (LIRKO) – pure hepatic insulin resistance – develop the metabolic syndrome with severe dyslipidemia and atherosclerosis within 12 weeks after being placed on an atherogenic diet. None of the control mice developed the metabolic syndrome or atherosclerosis [22].

Association of Surrogate Markers of NAFLD with the Onset of Type 2 Diabetes Mellitus

Even though it should be kept in mind that liver enzymes as ‘surrogate measures’ of liver fat are far from perfect, an increasing amount of epidemiological reports suggest that NAFLD is associated with incident type 2 diabetes. In particular, sustained and nontransient ALT elevations were found to be associated with incident type 2 diabetes mellitus [23].

Association of NAFLD with CVD: Epidemiological Evidence

There was a nested case-control study with a 5- to 12-year follow-up performed in 137 CVD deaths and 249 controls (frequency-matched on age, sex and examination year; age range 26–85 years). The results suggested that serum GGT (γ-glutamyltransferase) within its normal range can predict CVD mortality in those aged less than 70 years, but may have limited usefulness for risk assessment in older adults [24]. The question could be: ‘Does GGT enhance CVD event prediction beyond classical risk factors?’ The answer was recently produced by a study generated by the British Regional Heart Study, which is a prospective study of 6,997 men aged 40–59 with no history of CVD (coronary heart disease or stroke) or diabetes drawn from general practices in 24 British towns and followed up for 24 years. Elevated GGT was associated with a significantly increased risk of stroke, fatal CHD events and CVD mortality independent of established CVD risk factors (Framingham score), and the authors suggested that it may be useful as an additional marker for long-term CVD risk [25].

‘What about direct measures of liver fat content and CVD?’ In this case we have no studies linked to incident events, only surrogate markers. In the Diabetes Heart Study, 623 randomly selected participants were evaluated for hepatic steatosis, defined as a liver:spleen attenuation ratio of <1.0 by computed tomography. The study quantified visceral fat; subcutaneous fat; coronary, aortic and carotid artery calcium by computed tomography, and carotid atherosclerosis by ultrasound. They found no significant associations between the liver:spleen attenuation ratio and coronary, aortic or carotid calcium, or carotid intimal thickness [26]. In the Dijon Study, 101 patients with type 2 diabetes mellitus were studied measuring liver fat using 1H-MRS and carotid intima-media thickness using ultrasound, and found no significant difference between those with and those without hepatic steatosis for intima-media thickness values [27]. This result was in contrast with a previous report by Targher et al. [28] in a very similar population in which NAFLD was established based on the liver biopsy.
Conclusions

In spite of the fact that NAFLD is characterized by the early onset of the typical metabolic and vascular pathogenic alterations of atherosclerosis, the evidence for the association between NAFLD and CVD is, at this stage, weak.

References


Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the content of the article.