Early up-regulation of hepatic matrix metalloproteinases in a rat model of cardiometabolic syndrome

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The cardiometabolic syndrome (CMS), with its increased risk for cardiovascular disease (CVD), nonalcoholic fatty liver disease (NAFLD), and chronic kidney disease has become a growing worldwide health problem. Insulin resistance is a key factor for the development of the CMS and is strongly related to obesity, hyperlipidemia, hypertension, type 2 diabetes mellitus (T2DM), and NAFLD.

NAFLD includes a spectrum of histopathological findings, including simple fatty liver, non-alcoholic steatohepatitis (NASH), the more aggressive form of fatty liver disease, fibrosis and ultimately cirrhosis, which may progress to hepatocellular carcinoma. Despite this evidence, the mechanism behind the pathogenesis and the progression of this pathology is still not fully understood. Our study was aimed to evaluate the effect of impaired glucose and lipid metabolism in the onset and development of CMS.

Sprague-Dawley rats were fed with a normocaloric diet (NPD group) or with a high fat diet (HFD group), respectively. One month later, streptozocin (STZ, 35 mg/Kg, i.p.) was administered in a subgroup of both NPD and HFD rats to induce diabetes and the sacrifice was carried out after sixty days.

At the end of the study, we observed an impaired cardiac function in hyperlipidemic (HFD), hyperglycaemic (NPD+STZ) and hyperglycaemic/hyperlipidemic (HFD+STZ) rats as compared to NPD group. Heart dysfunction was also associated to an enhancement of plasmatic lipid levels as well as to an accumulation of oxidized lipid products in liver. In particular, our results showed an increase of blood cholesterol levels in HFD+STZ animals as compared to NPD, NPD+STZ or HFD rats. In addition, HFD animals also showed enhanced triglycerides levels as compared to NPD and NPD+STZ groups, which were also associated to lipid accumulation in liver. The progression of hepatic degeneration caused by oxidized lipids, was also observed in HFD+STZ group, although the triglycerides levels were lower as compared with HFD rats. In the progression from steatosis to steatohepatitis (NASH), lipid accumulation sensitizes hepatocytes to inflammatory cytokines with a consequent free radicals overproduction. In turn, this event causes chronic inflammation and extracellular matrix (ECM) remodeling by matrix metalloproteinases (MMPs) finally leading to fibrosis. For liver fibrogenesis, the infiltration of blood-derived macrophages, in addition to the activation of liver-resident Kupffer cells appears essential. In HFD+STZ rats, the progression in hepatic degeneration was associated with MMP-2/MMP-9 activation as compared to NPD rats. This activation was also observed in liver of hyperlipidemic rats, but not in hyperglycaemic rats. It has been demonstrated that hyperglycemia alone is not sufficient to stimulate macrophage proliferation in lesions of atherosclerosis or in isolated macrophages. In contrast, hyperlipidaemia

in concert with hyperglycaemia induces accumulation of proliferating lesion macrophages. Moreover, glucose-oxidized LDL significantly stimulates macrophage proliferation, suggesting that a combination of hyperglycaemia and hyperlipidaemia may contribute to enhance macrophage proliferation in diabetes. Our results suggest that, in liver, hyperglycaemia associated with hyperlipidaemia first enhances macrophage activation and proliferation and subsequently oxidative damage. In this process MMP-2/MMP-9 activation is an early event, probably triggered by cholesterol-induced mitochondrial dysfunction, as demonstrated by liver response to a hyperlipidemic diet. In addition, together with the blood markers of both hyperlipidemia and liver dysfunction, we hypothesize the use of MMP-2/MMP-9 as an early biomarker of NAFLD and predictive of cardiometabolic syndrome.

The cardiometabolic syndrome is emerging as a global public health issue. Insulin resistance and NAFLD represent key events in the pathogenesis of this syndrome. The prevention of cardiovascular risk factors remains a valid approach to counteract oxidative damage induced-cardiac and liver dysfunction. Here, we propose MMPs as an early biomarker for the identification of cardiometabolic syndrome.