Correlation between Plasma Osteopontin Level and Severity of Hepatic Fibrosis in Non Alcoholic Fatty Liver Disease

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LIST OF ABBREVIATIONS

ALD..... Alcoholic liver disease

ALP ..... Alkaline phosphatase

ALT ..... Alanine transaminase

ASH ..... Alcoholic steatohepatitis

AST ..... Aspartate transaminase

BMI ..... Body mass index

BSP-1..... Bone sialoprotein I

CT ..... Computed Tomography

DM ..... Diabetes Mellatus

ETA-1 ..... T-lymphocyte activation

FBS ..... Fasting blood sugar

FFAs ..... Free fatty acids

FLD ..... Fatty liver disease

HBV ..... Chronic viral hepatitis B

HCC ..... Hepatocellular carcinoma

HCV ..... Chronic viral hepatitis C

HDL ..... High-density lipoprotein

Hh pathway ... Hedgehog pathway

HIV..... Chronic autoimmune hepatitis

HSCs ..... Hepatic satellite cells

IRS ..... Insulin receptor substrate

LDL ..... low-density lipoprotein

LPS ..... Lipopolysaccharide

MF-HSCs ..... Myofibroblastic HSCs

MRIs ..... Magnetic resonance images

NAFLD ..... Non Alcoholic Fatty liver disease

NASH ..... Non Alcoholi Steoto-Hepatitis

NF ..... Nuclear factor

NK ..... Natural killer

OPN..... Osteopontin

PP ..... Post prandial

PPAR-α ..... Peroxisome-proliferator–activated receptor-α

TGF ..... Transforming growth factor

TNF ..... Tumor necrosis factor

Th .....T-helper

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INTRODUCTION

NAFLD is considered to cover a spectrum of disease activity. This spectrum begins as fatty accumulation in the liver (hepatic steatosis). A liver can remain fatty without disturbing liver function, but by varying mechanisms and possible insults to the liver may also progress to evident inflammation of the liver. When inflammation occurs in this setting, the condition is then called NASH. Over time, up to 20 percent of patients with NASH may develop cirrhosis **(Adams and Anglo, 2009)**.

The exact cause of NAFLD is still unknown. However, both obesity and insulin resistance probably play a strong role in the disease process. The exact reasons and mechanisms by which the disease progresses from one stage to the next are not known **(Clark and Diehl, 2003).**

Most patients with NAFLD have few or no symptoms. Patients may complain of fatigue, malaise, and dull right-upper-quadrant abdominal discomfort. Mild jaundice may be noticed although this is rare. More commonly NASH is diagnosed following abnormal liver function tests during routine blood tests. By definition, alcohol consumption of over 20 g/day (about 25 ml/day) excludes the condition **(Nseir et al., 2010).**

NAFLD is associated with insulin resistance and metabolic syndrome (obesity, hyperlipidemia, type II diabetes mellitus and high blood pressure) **(Pagano et al., 2002).**

Common findings are elevated liver enzymes and a liver ultrasound showing steatosis. An ultrasound may also be used to exclude gallstone problems (cholelithiasis). A liver biopsy is the only test widely accepted as definitively distinguishing NASH from other forms of liver disease and can be used to assess the severity of the inflammation and resultant fibrosis If any **(Chalasani et al., 2012).**

However, liver biopsy has several disadvantages, including poor patient compliance as it is painful and of high costs, sampling errors, limited usefulness for dynamic follow up, and a risk of complications typical of invasive procedures such as pneumothorax, bleeding, or puncture of the biliary tree. In rare cases, patients die of bleeding **(Mirella and Cristina, 2007).**

it is worth mentioning that the histological tested fragment is however a small part of the liver, and the scar lesions, which are secondary to chronic inflammatory processes are unevenly distributed in the liver mass. Thus, liver biopsy is a method neither ideal nor sufficient to diagnose and determine the stage of liver fibrosis. In this context, a noninvasive method

to assess liver fibrosis is more than welcome **(Wieckowska et al., 2007).**

Non-invasive diagnostic tests have been developed, such as FibroTest, that estimates liver fibrosis,**(Haflon et al., 2008)**. And SteatoTest, that estimates steatosis **(Ratziu et al., 2006).**

Osteopontin is a secreted phosphorylated glycoprotein that is expressed by a variety of cell types and that mediates numerous and diverse biological functions, it was expressed mainly by kupffer cells, hepatic macrophages and Hepatic satellite cells (HSCs). It stimulates T cell proliferation and induces T cell and macrophages to express other T helper type 1 cytokines during inflammation **(Ramaiah and Rittling, 2007).**

AIM OF THE WORK

The aim of the present study is to evaluate the level of plasma Osteopontin as a non-invasive biomarker in patients with NAFLD and correlate its level with the severity of hepatic fibrosis as seen by histopathological examination of liver biopsy.

FATTY LIVER

Introduction:

Fatty liver, also known as FLD, is a reversible condition where large vacuoles of triglyceride fat accumulate in liver cells via the process of steatosis (i.e. abnormal retention of lipids within a cell). Despite having multiple causes, fatty liver can be considered a single disease that occurs worldwide in those with excessive alcohol intake and those who are obese (with or without effects of insulin resistance). The condition is also associated with other diseases that influence fat metabolism. Morphologically, it is difficult to distinguish alcoholic FLD from nonalcoholic FLD, and both show microvesicular and macrovesicular fatty changes at different stages **(Reddy and Rao 2006).**

Accumulation of fat may also be accompanied by a progressive inflammation of the liver (hepatitis), called steatohepatitis. By considering the contribution by alcohol, fatty liver may be termed alcoholic steatosis or NAFLD, and the more severe forms as alcoholic steatohepatitis (part of alcoholic liver disease) and NASH **(Manton et al., 2000).**

Epidemiology:

The prevalence of FLD in the general population ranges from 10% to 24% in various countries **(Angulo, 2002).**

However, the condition is observed in up to 75% of obese people, 35% of whom will progress to NAFLD **(Hamaguchi, 2005).**

Despite no evidence of excessive alcohol consumption. FLD is the most common cause of abnormal liver function tests **(Angulo, 2002).**

Fatty livers occur in 33% of European-Americans, 45% of Hispanic-Americans, and 24% of African-Americans **(Daniel and DeNoon, 2008).**

Pathology:

Fatty change represents the intracytoplasmic accumulation of triglycerides (neutral fats). At the beginning, the hepatocytes present small fat vacuoles (liposomes) around the nucleus (microvesicular fatty change). In this stage, liver cells are filled with multiple fat droplets that do not displace the centrally located nucleus. In the late stages, the size of the vacuoles increases, pushing the nucleus to the periphery of the cell, giving characteristic signet ring appearance (macrovesicular fatty change). These vesicles are well