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Obesity, Non Alcoholic Fatty Liver Disease (NAFLD) and Coronary Artery Disease (CAD)

Dhastagir sultan Sheriff[1]* and Manopriya T[2]

[1]Elashhari FA- Department of Biochemistry, Faculty of Medicine, Garyounis University, Benghazi, Libya
[2]Institute of Research for Science and Medicine, Salem, India

Abstract

NAFLD is recognized as risk factor per se for Coronary Artery Disease (CAD). Subjects with fatty liver have an increased risk to develop CAD, and are accompanied by an increase in inflammatory markers, C-reactive protein and also proatherogenic factors. Studies evaluating endothelial function showed that subjects with Non alcoholic fatty liver disease (NAFLD) had decreased endothelium-dependent vasodilatation correlated with the severity of liver disease In these subjects a strong association was seen with high triglycerides, suggesting that hypertriglyceridemia might be a crucial link between hepatic steatosis, insulin resistance, and endothelial dysfunction.

Keywords: Non alcoholic fatty liver disease (NAFLD); Coronary artery disease (CAD); Hypertriglyceridemia

Introduction

Obesity is pandemic and is associated with many disorders including Non alcoholic fatty liver disease (NAFLD) which is emerging as a risk factor for coronary artery disease (CAD).

The relationship between obesity and incidence of diabetes, CAD and cancer has been shown by many studies [1]. Fat accumulates mainly in subcutaneous adipocytes, and deposition of triglyceride has been found in ectopic sites such as visceral area, liver, muscle, heart and pancreas. Vague and colleagues [2] reported an association between body fat distribution and atherosclerosis and the importance of abdominal obesity was recognized only in the 1980's when Larsson et al. [3] demonstrated that the waist/hip ratio was the best predictor of CAD and death, independently of commonly used indices of obesity. It had become evident that ectopic fat is an important predictor of disease, in particular insulin resistance and CAD, carrying more risk than general fat accumulation.

Major sites of ectopic fat accumulation and metabolic implications

The major site of fat accumulation is subcutaneous adipose tissue which is considered the "good" fat [4]. Ectopic fat is instead defined by the deposition of triglycerides within cells of non-adipose tissue like visceral area, liver, heart and/or muscle and is usually present in different organs (Figure 1) [5-10].

Visceral fat

Visceral fat represents ~10–15% of total fat. It is a depot highly lipolytic, releases free fatty acid (FFA) directly into the portal vein and thus into the liver [11,12] (Figure 2) and a direct relationship between visceral fat size and FFA release to the liver has been shown[13]. Visceral fat contributes to liver steatosis and hepatic insulin resistance [5,12,13] through hepatic overload of FFA and increased hepatic gluconeogenesis, i.e., the main cause of prevailing fasting hyperglycemia [14].

FFAs released during lipolysis mainly from subcutaneous and visceral adipose tissue are the main sources for intracellular triglyceride in liver and heart, and are also associated to increased production of glucose, VLDL, reactive oxygen species (ROS) and advanced glycation end products (AGEs).

Cardiac fat

Another site of ectopic fat accumulation is the heart. Subjects with insulin resistance have increased fat deposition around the heart (epicardial and intrathoracic fat) and intra-myocardial cells [8,9,15,16]. Several studies indicate that fat accumulates mainly as extra-pericardial fat. Both epicardial and extra-pericardial fat correlate with increased visceral fat[8,17,18], insulin resistance [7,8], increased triglyceride and blood pressure [7,8]and in general with metabolic syndrome[7]. An association between fat accumulation in cardiomyocytes with intrathoracic and visceral fat, was observed [19].

Hepatic fat

Subjects with non-alcoholic fatty liver disease (NAFLD), tend to

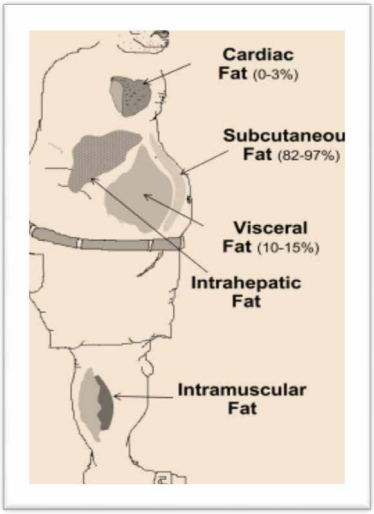

Figure 1: Distribution Pattern of Body Fat.

***Corresponding author:** Dhastagir sultan Sheriff, Elashhari FA- Department of Biochemistry, Faculty of Medicine, Garyounis University, Benghazi, Libya, E-mail: dhastagir@yahoo.ca

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have a preferential accumulation of visceral fat [20]. Visceral adiposity is more prevalent in male subjects and increases with the degree of obesity [5,20,21]. NAFLD is associated with increased insulin resistance at the level of liver, muscle and adipose tissue [5,20]. Subjects with NAFLD are shown to have deposition of fat in cardiac [9], and skeletal muscles [10] and, now NAFLD is considered the hepatic manifestation of metabolic syndrome (Figure 3).

Ectopic fat and cardiovascular disease

All ectopic fat depots are related to the conventional risk factors for CAD (i.e., hyperlipidemia, diabetes, hypertension, that is also linked to a sedentary lifestyle and ectopic fat accumulation, in particular abdominal fat [21-24].

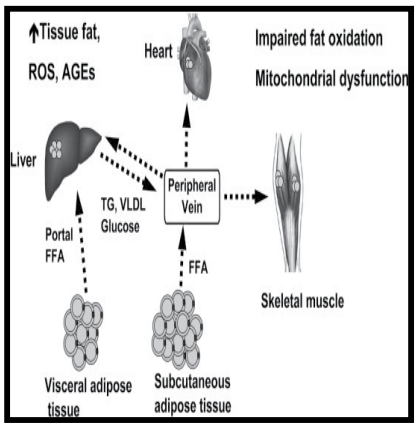

Figure 2: Free Fatty Acids(FFAs) released during lipolysis mainly from subcutaneous and visceral adipose tissue are the main sources for intracellular triglyceride in liver and heart, are also associated with increased production of glucose, VLDL, reactive oxygen species (ROS) and advanced glycation end products (AGEs).

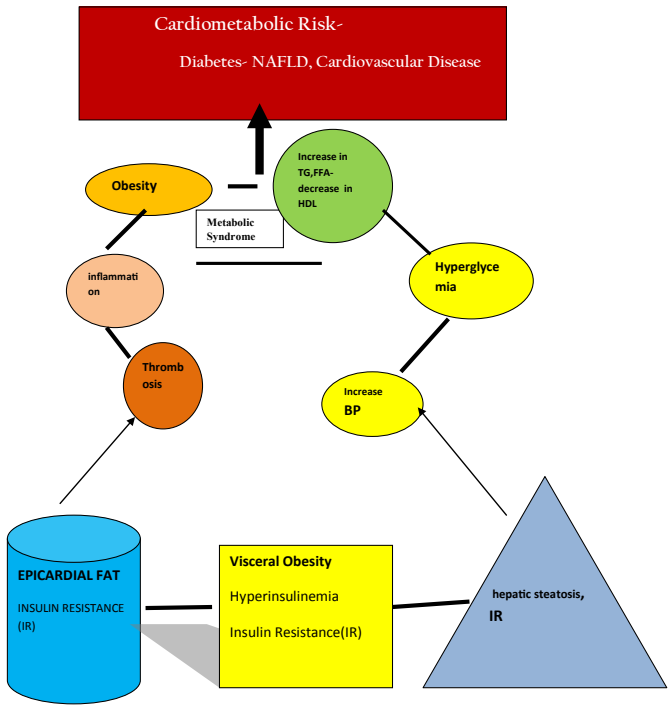

Figure 3: Hepato-adipo-cardiovascular Axis, insulin resistance and Coronary artery disease. (CAD).

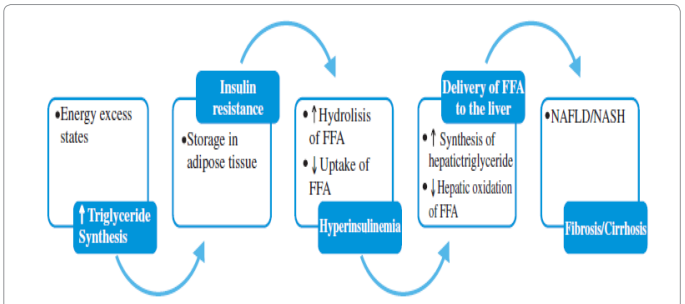

Figure 4: Triglyceride synthesis.

Abdominal fat and CAD

Visceral fat is associated with cardiometabolic risk factors as shown in the Figure 3 and there is a strong association between CAD and abdominal fat [24,25]. The Heart Outcomes Protection Evaluation (HOPE) study (6620 men and 2182 women followed for 4.5 years) showed that increased waist circumference (men >103 cm or women >98 cm) increased the risk of cardiovascular death by 29%, of myocardial infarction by 27%, and of death from any cause by 35% [26]. The INTERHEART study, showed that increased waist-to-hip ratio is a predictor of myocardial infarction independently of BMI, even in very lean subjects (BMI <20) [25]. Framingham cohort study showed that visceral fat was associated with increased CAD [16].

Hepatic fat and CAD

NAFLD is recognized as risk factor per se for CAD: [27-29] Subjects with fatty liver have an increased risk to develop CAD [30,31].and are accompanied by an increase in inflammatory markers, C-reactive protein and also proatherogenic factors [6,32]. A recent study showed that cardiac energy metabolism was impaired in subjects with NAFLD, which also had an increase in both epicardial and extra-pericardial fat deposition [9,27]. Studies evaluating endothelial function showed that subjects with NAFLD had decreased endothelium-dependent vasodilatation correlated with the severity of liver disease [30]. In these subjects a strong association was seen with high triglycerides, suggesting that hypertriglyceridemia might be a crucial link between hepatic steatosis, insulin resistance, and endothelial dysfunction (Figure 4).

Triglyceride synthesis increases in states of energy excess. Insulin resistance and hyperinsulinemia lead to increased lipolysis of triglyceride depots in adipose tissue, amplifying the delivery of FFA to the liver. Insulin further stimulates liver triglyceride synthesis while inhibiting fatty acid oxidation as well as inhibiting production of VLDL Overall, the current body of evidence strongly suggests that fatty liver may be not only a marker but also an early mediator of atherosclerosis [33]. Early carotid atherosclerosis is already present in subjects with simple steatosis [29] and worsens in subjects with NAFLD and non-alcoholic steatohepatitis (NASH) [34]. Carotid intima media thickness (IMT) increased with the severity of hepatic fat, in patients with NAFLD and highest in those with NASH [33]. The associations between liver disease and carotid atherosclerosis were independent of traditional risk factors, metabolic syndrome components and insulin resistance [33-36], indicating that other factors might be involved.

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