Review

Obesity, Nonalcoholic Fatty Liver Disease and Adipocytokines Network in Promotion of Cancer

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Abstract

Western populations are becoming increasingly sedentary and the incidence of nonalcoholic fatty liver disease (NAFLD) is increasing and becoming one of the most common causes of liver disease worldwide. Also, NAFLD is considered one the new emerging risk factors for development of tumors of the gastro-intestinal tract, particularly hepatocellular carcinoma (HCC). Visceral obesity is an important risk factor for the onset of NAFLD. An accumulation of ectopic fat, including visceral obesity and fatty liver leads to a dysfunction of the adipose tissue with impaired production of adipocytokines which, in turn, favor an increase in pro-inflammatory cytokines. In this review, we discuss how the obesity-related chronic state of low-grade inflammation and the presence of NAFLD lead to the emergence of a microenvironment favorable to the development of cancer.

Key words: NAFLD, adipocytokines, inflammation, obesity, cancer

Introduction

Fatty liver (triglyceride content > 5% of organ weight) is the most common liver disease found in the obese. It is classified as non-alcoholic fatty liver disease (NAFLD) if independent from the alcohol consumption. In addition, NAFLD is strongly associated with features of the metabolic syndrome, including obesity, insulin resistance, type 2 diabetes (DM2) and dyslipidemia [1,2]. NAFLD represents a new emerging risk factors for the onset of extra-hepatic tumors, particularly in the development of tumors of the gastro-intestinal tract [3,4]. Risk factors associated with the development of NAFLD include bad eating habits associated with a sedentary lifestyle. Therefore, patients with NAFLD are strongly recommended to follow a *regimen* including dietary restrictions associated with physical activity. Bad eating habits and sedentary lifestyle are increasing in Western Countries and NAFLD is accordingly becoming one of the most common causes of liver disease worldwide [5,6]. The prevalence of NAFLD is 15-30% of the general population and it is close to 50-90% in obese subjects. This prevalence correlates with the obesity rate. In fact, hepatic steatosis is found in 65% of subjects with grade I-II obesity (BMI = 30-39.9 kg/m2) and in 85% of patients with grade III obesity (BMI = 40-59 kg/m2). The prevalence of NAFLD and its inflammatory progression into non-alcoholic steatohepatitis (NASH) varies according to age, gender and degree of obesity [7]. Since NAFLD represents a spectrum of disease and histological patterns, a staging encompassing both the histological findings and the prognostic aspects has been proposed (**Table 1**). In the stages of NAFLD progression, classes I and II are considered substantially benign and reversible if the patients are adequately treated. Despite considered a benign condition in most cases, NAFLD can progress towards cirrhosis and liver failure (class III and IV) in a discrete percentage of subjects over a period of about two decades [8]. It is worth mentioning that a significant proportion of patients develop NAFLD despite having a normal body mass index (BMI) and

few metabolic syndrome features. Patients with NAFLD are generally asymptomatic and NAFLD is often diagnosed during an occasional ultrasound evaluation of the abdomen. Indeed, several cases of NAFLD are associated with other metabolic disorders, including hypertriglyceridaemia, hypercholesterolemia, and hypertension, thus configuring the clinical pattern of the so-called "*metabolic syndrome*" [9]. Visceral obesity is an important risk factor for the onset of NAFLD. An accumulation of ectopic fat, including visceral obesity and fatty liver leads to dysfunction of adipose tissue with impaired production of adipocytokines. This in turn will favor an increase in pro-inflammatory cytokines such as TNF-α (*Tumor Necrosis Factor-alfa*) and a decrease in anti-inflammatory adipokines such as adiponectin [10]. Thus, the prevalence of NAFLD increases with the increase of the body mass index (BMI). NAFLD is currently considered the liver manifestation of the metabolic syndrome (MS) which represents, as shown by numerous studies, a condition that increases the risk of cancer, particularly for the gastrointestinal tract [11,12]. It is becoming clear that insulin resistance associated with the metabolic syndrome and the consequent activation of the inflammatory cascade jointly with the development of NAFLD may act as promoting factors for cancer development [13,14]. Thus, insulin resistance and metabolic syndrome represent common risk factors for both NAFLD and cancer (Figure 1).

Table 1. Histological classification of NAFLD

Class	Histological framework
Class I	Simple fatty liver disease
Class II	Fatty liver with lobular inflammation
Class III	Fatty liver with lobular inflammation and balloniform hepatocytes
Class IV	Fatty liver with lobular inflammation, balloniform hepatocytes, Mallory bodies and fibrosis (stage 1-4)

Natural history of NAFLD

Hepatic steatosis develops when the amount of fatty acids that accumulate in liver cells exceeds the consumption. This imbalance between inputs and outputs, with an intrahepatic deposit of triglycerides, can occur as a result of four mechanisms: i) increased inflow of fatty acids (FA) from the peripheral circulation; ii) increased hepatic synthesis of FA (*de novo* lipogenesis); iii) reduced intrahepatic and peripheral FA oxidation; IV) reduced triglycerides release in the circulation through the VLDL. All these
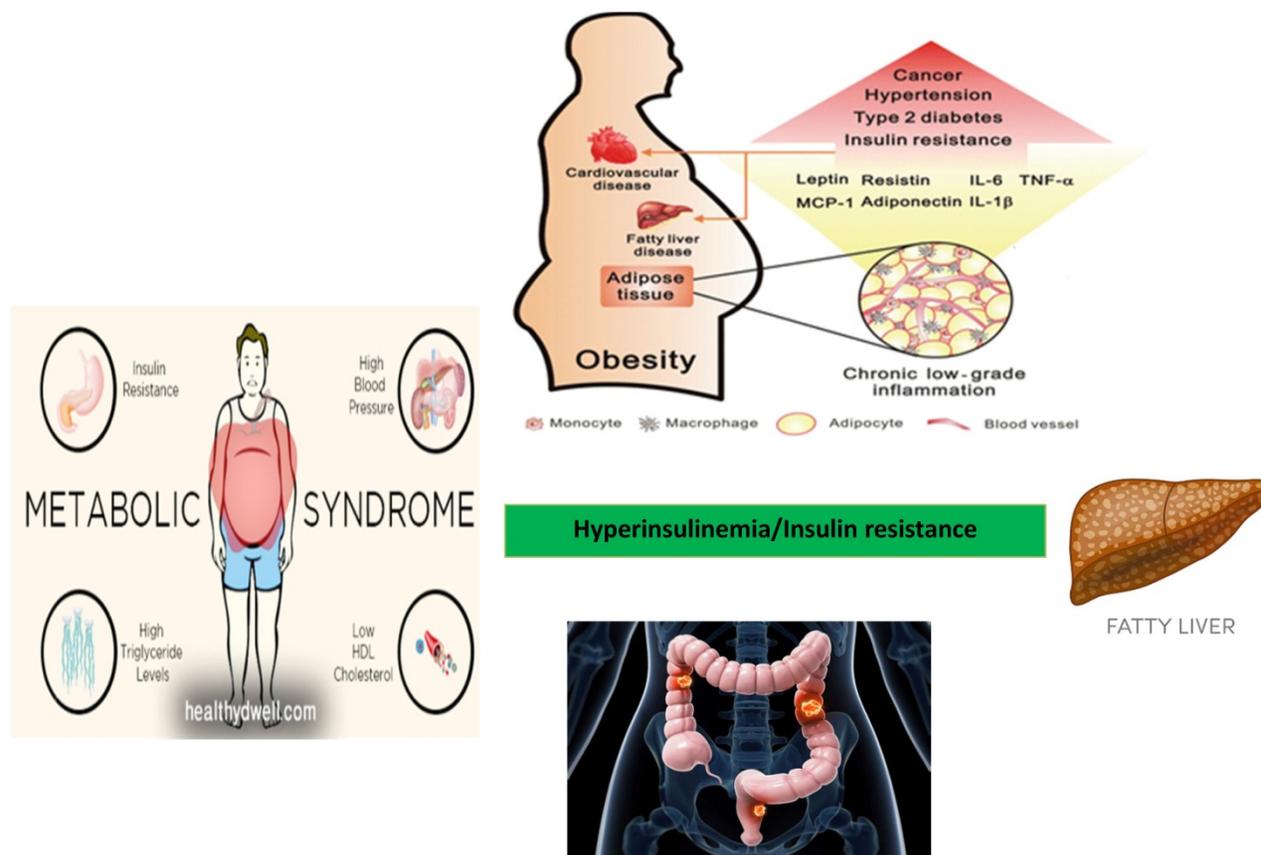

Figure 1. Relationship between metabolic syndrome, NAFLD, and development of colorectal adenoma and carcinoma.

mechanisms contribute to the pathogenesis of hepatic steatosis supported by metabolic alterations [15,16]. The actors involved in this process are numerous, but the primary role is played by the adipose tissue expansion and particularly by hypertrophic adipocyte and insulin resistance generated at hepatic and muscular level [17]. Elevated serum levels of free fatty acids (FFAs) and cholesterol, insulin resistance, and adipocyte proliferation are generally present in obesity associated with bad dietary habits and bad lifestyle. Insulin resistance worsens adipocyte function and induces hepatic *de novo* lipogenesis. In addition, insulin resistance promotes the release of proinflammatory adipokines including interleukin (IL)-6, IL-1β and tumor necrosis factor (TNF)-α. These adipokines can in turn worsen the state of insulin resistance [18,19]. This condition results in an increased of hepatic flux of FFAs and leads to accumulation of triglycerides (TGs), mitochondrial dysfunction, reactive oxygen species (ROS) production, and eventually hepatic inflammation and fibrogenesis [20]. Recent findings support the evidence that increased FFA levels leads to an accumulation of certain types of lipid derivatives including ceramides, which inhibit the action of insulin [21]. Ceramides can be considered mediators of insulin resistance and lipotoxicity. Elevated plasma levels of ceramide are detectable in obese subjects and

may contribute, for example, to insulin resistance through activation of TNF-α and other inflammatory mediators [22]. This corroborates the role of ceramide in the pathogenesis of NAFLD with a direct pro-inflammatory effects. In addition, the development of liver dysfunction, hepatic insulin resistance and steatosis in rodents are associated with increased levels of ceramide in both liver and peripheral blood [23]. Additionally, adiponectin lowers the hepatic content of ceramide by improving the blood glucose homeostasis through its receptor-associated ceramidase activity [24]. Ectopic fat deposition is "lipotoxic" and has been linked to the severity of insulin resistance. Holland and colleagues demonstrated that ceramide metabolism influences the insulin-sensitizing effects of adiponectin on the liver which is its primary target tissue [25]. Adiponectin displays anti-lipotoxic effects that are thought to protect tissues (i.e. the liver and muscle) from the accumulation of triglycerides. Decreased adiponectin levels may impair ceramide clearance by facilitating ceramide accumulation within the tissue [26]. An increase in hepatic ceramides is associated to elevated levels of plasma ceramides in obese patients and may promote insulin resistance at level of skeletal muscle. Taken together, these data indicate that insulin resistance represents one of the key factors in the pathogenesis of NAFLD (Figure 2).
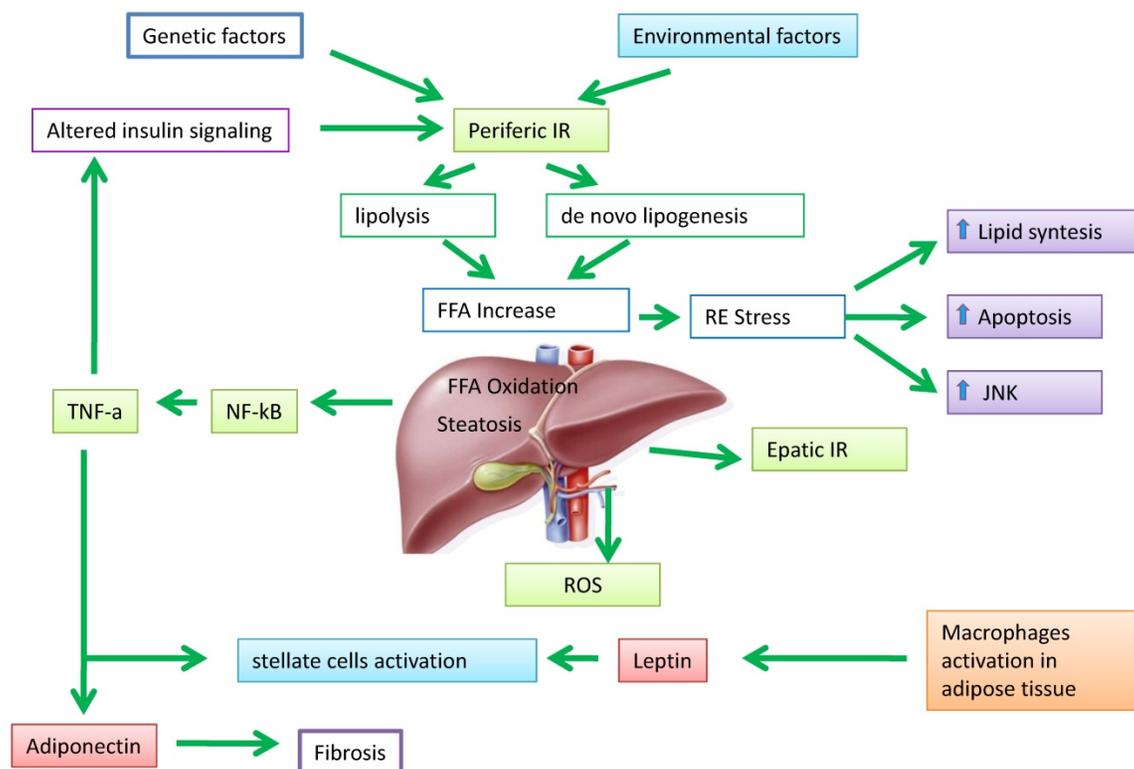

Figure 2. The pathogenesis of NAFLD. Peripheral insulin resistance (IR) promotes increased production of free fatty acids (FFA) direct in the liver, resulting in an imbalance between oxidation/divestiture and uptake/synthesis of FFA, and then steatosis liver. The fabric fat secretes adipokines such as leptin, able to adjust the adipocyte metabolism and numerous insulin-mediated processes. Adiponectin plays a role in anti-inflammatory and anti-steatotic; its secretion It is in part regulated by TNF-α under the control of NF-kB.

Adipose tissue in the pathogenesis of NAFLD

In patients with NAFLD, the total amount of triglyceride pool in the liver originates from three sources: i) adipose tissue (60%); ii) remnant chylomicrons (15%) mostly from dietary fats; iii) hepatic lipogenesis or *de novo lipogenesis* (approximately 25%). Regarding the aliquot from adipocytes, 75-80% of triglyceride originates from the subcutaneous adipose tissue whereas the remaining portion is derived from the visceral adipose tissue and conveyed to the liver via the portal vein (the *portal hypothesis*) [27,28]. According to this hypothesis, the omental fat, which drains directly into the portal vein, contributes significantly to the flow of FFA to the liver as a consequence of the high lipolytic activity of the fat present therein. From the pathogenic point of view, the portal hypothesis is intriguing for several reason. For example, the visceral adipose tissue has a secretory profile different from that of subcutaneous adipose tissue characterized by abundant release of inflammatory cytokines. These cytokines are drained directly from the portal vein and poured out in the liver before reaching any other organ [29]. Therefore, the anatomical contiguity places the liver as the first barrier to the visceral adipose tissue. In physiological conditions, the liver is already subject to a high metabolic activity from which derives a large release of free radicals. In the presence of fatty liver, the oxidative metabolism increases further and even more if hyperglycemia and insulin resistance are present. The abnormal release of free radicals can be compensated until saturation is reached by the antioxidant barrier [30]. When the protective systems are exhausted, ROSs begin to oxidize hepatocytes and other hepatic cells, which in turn activate protective mechanisms by triggering the inflammatory response [31]. This results in an increased expression of TNF-α, IL-1, IL-6 and other inflammatory cytokines which contribute to acceleration of the damage and the more rapid progression of the disease [32,33].

NAFLD and cancer: the adipocytokine network

Based on their effect on NAFLD, adipokines are generally divided into adipokines promoting the onset of NAFLD and adipokines inhibiting the development of NAFLD. A crosstalk between these two groups of adipokines can result either in a beneficial or harmful effect on NAFLD progression [34,35]. However, the ultimate effect is generally temporary because both endogenous factors (e.g. genetic components) and exogenous factors (e.g. eating habits and lifestyles) determine continuous changes in the metabolic environment followed by dynamic changes of the adipokine profile with different effects on NAFLD evolution. For example, an antagonist relationship exists between adiponectin (with *inhibitory action*) and TNF-α (with *promoting action*) showing opposite effects on insulin resistance and NAFLD [36,37]. Under normal conditions, there is an equilibrium between the two adipokine groups. This homeostatic equilibrium can be altered by hypertrophy or hyperplasia of adipocytes, and can lead to a chronic state of inflammation, insulin resistance and development of NAFLD [38]. The expansion of adipose tissue, independently of other concomitant factors, deprives patients with NAFLD of the anti-inflammatory and antifibrotic effects of adiponectin, effects which are inversely related to total adiposity [39]. Adiponectin is a potent cytokine exerting insulin sensitizing, anti-inflammatory and anti-steatotic activity in hepatocytes through increasing oxidation of free fatty acids and decreasing gluconeogenesis, FFA flow and *de novo* lipogenesis [40,41]. In addition, adiponectin protects hepatocytes from apoptosis in the NAFLD-associated hepatic inflammatory microenvironment [42]. TNF-α is another important pro-inflammatory cytokine in NAFLD which promotes insulin resistance [43]. The excessive release of TNF-α from both the hypertrophic adipocytes and Kuppfer cells is one of the early events of hepatic damage. In fact, TNF-α stimulates the production of other chemo-attractant cytokines in the hepatocytes, which in turn recruit inflammatory cells [44,45]. High levels of TNF-α and low levels of adiponectin are favorable conditions for the development of insulin resistance and NAFLD [46]. These two adipokines involved in the pathogenesis of NAFLD mutually inhibit the synthesis and activity of each other by targeting metabolic equilibrium [47]. However, these adipokines are thought to be involved in the link between obesity, NAFLD and development of both intra and extra hepatic tumors [48-50]. In particular, adiponectin exerts antitumor activity by activating the AMP protein kinase (AMPK), an inhibitor of tumor cell growth that stimulates the caspase signaling pathway leading to apoptosis of endothelial cells [51,52]. In addition, adiponectin exerts its anti-tumor action by inhibiting TNF-α, involved in both tumor proliferation and angiogenesis [53,54]. Accordingly, insulin is becoming a relevant factor in the regulation of cell proliferation, apoptosis and tumor angiogenesis [55,56]. Leptin is another adipocitokine involved in the onset of NAFLD [57]. Leptin plays a dual role in NAFLD. On one hand, it seems to have a protective role for hepatic steatosis, especially in the early stages of the disease. On the other hand, it could

act as an inflammatory and fibrinogenic factor as the disease progresses. As visceral adipose tissue increases, leptin levels concomitantly increase. This should limit the expansion of fat mass in order to avoid the formation of insulin resistance. In this sense, leptin should exert an anti-steatotic effect on the hepatocytes [58,61]. If adipose tissue expands, a state of leptin resistance occurs. Accordingly, leptin is no longer able to compensate insulin resistance and the progression of steatosis [62]. In this context, leptin may exert non-beneficial effects by acting as a fibrinogenic and pro-inflammatory adipokine. Leptin is considered an adipocytokine acting as molecular link between obesity and cancer [63-65]. Low levels of adiponectin and high levels of leptin are associated with the processes of mitogenesis, tumor growth and cell motility when adipose tissue dysfunction occurs. Furthermore, an increase in leptin stimulates the release of pro-inflammatory cytokines such as TNF-α and IL-6, which in turn give rise to an inflamed microenvironment which favors tumor development and up-regulation of angiogenesis promoting factors (i.e. VEGF and HIF-1α) [66-68].

Conclusion

The incidence of NAFLD is increasing in accordance with the increasing prevalence of metabolic syndrome and obesity. In addition, NAFLD and predisposition to cancer is still matter of debate. Consequently, the question arises as to whether the increasing NAFLD incidence accounts for the increase of certain type of cancer (particularly liver and colon cancer). NAFLD is frequently associated with visceral obesity, diabetes and dyslipidemia, and it is related to clinical and biological markers of insulin resistance. Insulin resistance associated with the metabolic syndrome and the consequent activation of the inflammatory cascade underlying the development of NAFLD represents a favorable background for cancer development (Fig. 3). The prevention of an excessive increase of adipose tissue is therefore important to avoid the promotion of a pro-inflammatory activity sustained by an adverse adipokine profile predisposing to an increased risk of cancer. In conclusion, in overweight or obese patients with NAFLD, a program of cancer prevention aimed at quenching the inflammatory cascade and improve insulin sensitivity should be mandatory. It is therefore advisable for these subjects to adopt correct lifestyles including healthy eating habits and avoid sedentariness.

Competing Interests

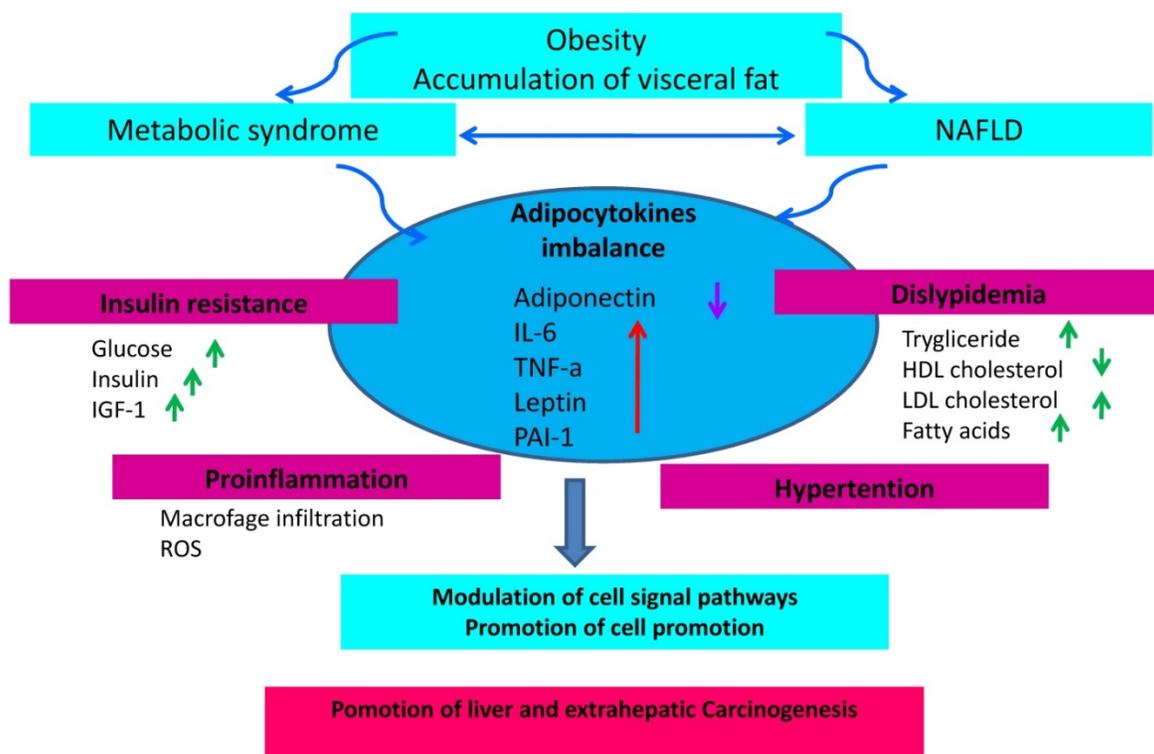The authors have declared that no competing interest exists.

Figure 3. The state of chronic low-grade inflammation due to obesity and the presence of NAFLD leads to the emergence of a micro-environment favorable to the development of cancer and the onset of insulin resistance due to activation of the axis that regulates the insulin growth factor-1 IGF-1 and insulin resulting in hyperinsulinemia. Through its proliferative and anti-apoptotic effects, this process can increase mutations that promote carcinogenesis.

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