MODERN MEDICINE AND PRACTICE
https://inovatus.es/index.php/ejmmp

EUROPEAN JOURNAL OF MODERNMEDICINEAND PRACTICE
Vol. 4 No. 6 (Jun - 2024) EJMMP ISSN: 2795-921X

RELATIONSHIP BETWEEN TYPE 2 DIABETES MELLITUS (T2DM), INSULIN RESISTANCE (IR) AND NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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Abstract: The field of non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH), despite the challenges posed by the coronavirus disease 2019 (COVID-19) pandemic, continued to evolve rapidly in 2020. NAFLD has been proposed to become metabolically associated fatty liver disease (MAFLD), 1 but the definition and terminology for clinical practice and clinical research require further discussion and consensus.

Nonalcoholic fatty liver disease and its subtype nonalcoholic steatohepatitis affect approximately 30% and 5% of the US population, respectively. In patients with non-alcoholic steatohepatitis, half of the deaths are due to cardiovascular disease and malignancy, but awareness remains low. Cirrhosis, the third leading cause of death in patients with nonalcoholic fatty liver disease, is expected to become the most common indication for liver transplantation. Sixty-six percent of patients over 50 years of age with diabetes or obesity are thought to have nonalcoholic steatohepatitis with advanced fibrosis. Although the ability to identify the subtype of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease still requires liver biopsy, biomarkers for detecting progressive fibrosis are becoming increasingly reliable. Lifestyle modification is the mainstay of treatment for patients with nonalcoholic steatosis. The association between nonalcoholic steatohepatitis and cardiovascular disease is clear, although causality remains to be proven in well-controlled prospective studies. The incidence of hepatocellular carcinoma associated with nonalcoholic fatty liver disease is increasing, and up to 50% of cases may occur in the absence of cirrhosis.

Key words: NAFLD, insulin resistance, adiponectin, leptin.

NAFLD ranges from simple steatosis to NASH with or without liver fibrosis in the absence of excessive alcohol consumption. While steatosis is not associated with increased liver-related morbidity or mortality, NASH can progress to more severe stages such as cirrhosis and hepatocellular carcinoma, ultimately leading to liver failure and liver transplantation 2 . Histopathological analysis remains the gold standard for diagnosing liver injury. However, invasiveness, risk and cost are concerns. In addition, low variability in liver biopsy results interobserver and moderate intra-study variability in liver biopsy results lead to suboptimal reliability of treatment effect measurements in clinical trials.

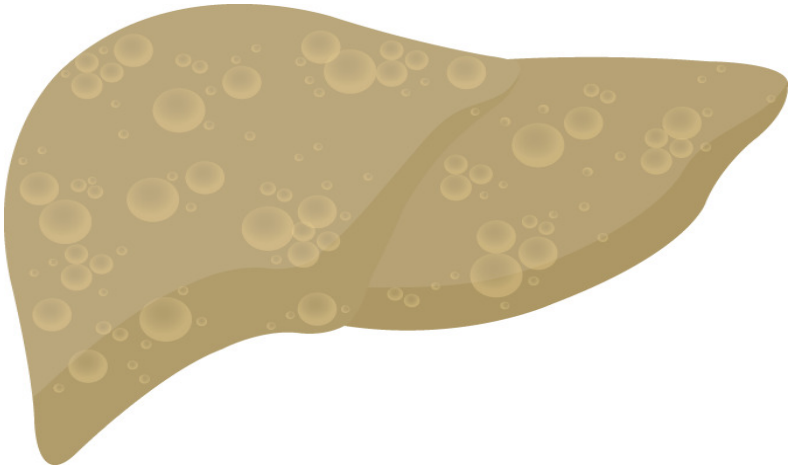
A major priority and clinical need is the ability to identify patients with NASH who are at greater risk of progression to cirrhosis and who are candidates for clinical trials and new pharmacotherapies. Also in 2020, Newsom et al 8 published the FibroScan-AST score (FAST), a score for noninvasively identifying patients with significant NASH (NAFLD activity score ≥4) and liver fibrosis (≥F2) to identify patients at increased risk of disease progression. This prospective study was conducted in a derivation cohort (n = 350) and validated in multiple global cohorts (n = 1026) from North America, Europe, and Asia. Five predictors of NAFLD and associated liver injury were examined: measurement of liver stiffness using vibration transient

elastography, controlled attenuation parameter, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and AST:ALT ratio.

There are currently no FDA-approved pharmaceutical drugs to treat NASH. However, 2020 marks a year of hope and cautious optimism as we begin to see change, despite numerous previous setbacks, in the NASH therapeutic landscape.

An estimated 75 to 100 million people in the United States have nonalcoholic fatty liver disease, and its potential incidence extends beyond the liver. It is important that primary care physicians, endocrinologists, and other specialists are aware of the extent and long-term consequences of the disease. Early identification of patients with nonalcoholic steatohepatitis may help improve patient outcomes through treatment, including transplantation, for patients with decompensated cirrhosis.

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, with a worldwide prevalence of 25%. In the United States, NAFLD and its subtype, nonalcoholic steatohepatitis, affect 30% and 5% of the population, respectively. Given the ongoing childhood obesity epidemic, rising rates of diabetes, and other factors, the prevalence of NAFLD, as well as the proportion of people with advanced liver disease, is projected to continue to rise.



The liver is one of the main houses that controls metabolic homeostasis. Metabolic diseases such as obesity, IR, T2DM, dyslipidemia and NAFLD are associated with molecular biochemical and complex immune mechanisms [1, 2]. Both diabetes and NAFLD are chronic diseases that typically cause non-worrying changes that can lead to disability and many other metabolic complications. All of them independently contribute to increased risk of mortality and morbidity, as well as overall global consumer disorders [3 – 5].

Currently, NAFLD remains one of the most common liver diseases, affecting up to 25% of the adult population [6 – 8], with an increased incidence reported in children [9]. This may soon become the most common indication for liver transplantation [10]. This multifactorial condition may result from an unhealthy lifestyle, obesity, dyslipidemia, type 2 diabetes mellitus and/or other metabolic syndromes [11, 12]. It is characterized by a wide spectrum of liver diseases that range from simple fat accumulation (benign steatosis) to inflammation (non-alcoholic steatohepatitis (NASH)), fibrosis, cirrhosis, liver failure and finally to hepatocellular carcinoma (HCC) in the absence of excessive alcohol consumption. drugs or viral etiology [3–6]. Researchers have found that people with diagnosed NAFLD have a two-fold increased risk of developing T2DM [1,7] and a higher risk of developing cancer [8], cardiovascular [1, 2] and kidney diseases [2], especially when associated with T2DM [7].

Since T2DM is defined by high serum glucose levels, IR, and damaged islet cell function, it is possible that patients with NAFLD have a higher risk of developing diabetes because they typically have abnormal glucose metabolism [26]. Interestingly, recent evidence suggests that T2DM is an independent risk factor for NAFLD [27], women with a history of gestational diabetes mellitus (GDM) have a higher risk of NAFLD and vice versa [8, 2], and that resolution of hepatic steatosis may prevent the onset of T2DM [3, 1].

The association between T2DM and NAFLD can be described by a spectrum of metabolic changes represented by IR, defective liver lipid profile, and triglyceride (TG) metabolism, which lead to fat accumulation, immune responses, and/or subsequently β-cell-mediated hyperinsulinemia. dysfunction in T2DM [6]. Normally, there is a balanced scale between lipid uptake (free fatty acids (FFA) or de novo lipogenesis (DNL) and esterification) and lipid utilization (metabolism or β-oxidation and excretion as very low-density lipoprotein). VLDL)). In NAFLD, VLDL removal cannot keep pace with the increased rate of uptake and intrahepatic TG production [7]. Thus, the immunopathogenesis of NAFLD can be described by two hypotheses. One involves increased dietary fat intake, which results in excess free fatty acids (FFA), increased DNL, and decreased hepatic TG excretion, and the other involves oxidative stress, lipid peroxidation, mitochondrial dysfunction, and release of inflammatory mediators [2].

Adipokines

Obesity is a major risk factor for the development of diseases such as T2DM, hyperlipidemia and NAFLD. This metabolic disease occurs due to imbalances in energy intake, energy consumption, and fat storage [8]. Adipose tissue is a highly endocrine organ that secretes hormones and cytokines known as adipokines. The development of IR in NAFLD is also likely associated with an imbalance between pro-insulin (adiponectin, leptin) and anti-insulin (i.e. TNFα) cytokines [7-8]. Adiponectin is a specific secretory adipokine that regulates the oxidation of fatty acids (FAs), inhibits the accumulation of FFAs, maintains glucose homeostasis throughout the body and sensitivity to hepatic insulin. Hypoadiponectinemia affects fatty acid metabolism and contributes to the development of chronic inflammation in the liver [5]. On the other hand, leptin can stimulate hepatic stellate cell activation and liver fibrosis, control energy balance and suppress appetite [1]. Elevated leptin levels were found in subjects with increased body fat and cardiometabolic disorders [5]. The authors noted in a cross-sectional study that patients with NAFLD had lower adiponectin levels, higher serum leptin levels, and a higher leptin to adiponectin (L/A) ratio [3]. Adiponectin and leptin can independently predict the occurrence of NAFLD, so they can be considered as potential prognostic biomarkers for NAFLD [4]. Recently, researchers discovered that the novel adipokine Gremlin 1 can antagonize insulin signaling, is positively correlated with body fat percentage and IR in patients with T2DM and NAFLD/NASH, and may also represent a potential biomarker or therapeutic target [5].

2.6. Insulin resistance

Insulin is an anabolic hormone that can mediate fluid homeostasis, ion transport, TG storage in adipose tissue, can promote esterification and storage of fatty acids in lipid droplets, and can also inhibit lipolysis. Under normal conditions, β-cells of the pancreas secrete insulin after meals or after the release of hormones (ie, catecholamines, glucagon). Insulin suppresses hepatic glucose production and stimulates peripheral glucose uptake, while hormones such as glucagon-like peptide-1 (GLP-1) stimulate gluconeogenesis, glycogenolysis, and hepatic glucose production. Insulin mediates glucose metabolism not only by stimulating glucose uptake into adipose tissue and liver tissue, but also by inhibiting hepatic glucose production [1,3]. Hepatic insulin clearance is reduced in patients with T2DM and correlates with the severity of the metabolic syndrome. In fact, insulin exhibits both anti-inflammatory and pro-inflammatory properties [1,4]. The term "insulin resistance" is commonly used to describe insulin-mediated glucose uptake in skeletal muscle. IR is determined by a suboptimal cellular response to physiological insulin levels in various tissues. This pioneers the idea that glycolysis is increased in critical illness, and the release of SFAS for peripheral needs, like most glucose, is directed to the brain [4, 1,5]. Subsequently,

hyperinsulinemia results from beta cells attempting to overcome IR by increasing insulin release. High calorie intake impairs insulin receptor signaling, leading to improper suppression of FFA release from fat cells as well as improper release of nitric oxide (NO) [1,6]. Consequently, IR and inflammation form a vicious circle, with each condition promoting the other and accelerating the development of NAFLD and other metabolic disorders secondary to lipotoxicity [1,7]. In both obese and lean subjects, high IR was found to be the most significant predictor of NAFLD [1,8], and studies have shown that serum insulin levels are closely associated with liver distention and lobular inflammation [1]. Complex relationship between IR, NAFLD and T2DM is based on a vicious circle. High-fat diet-induced obesity is a major precursor triggering lipotoxicity and glucotoxicity pathways, which are both mediated by insulin via IR. Figure 1.).

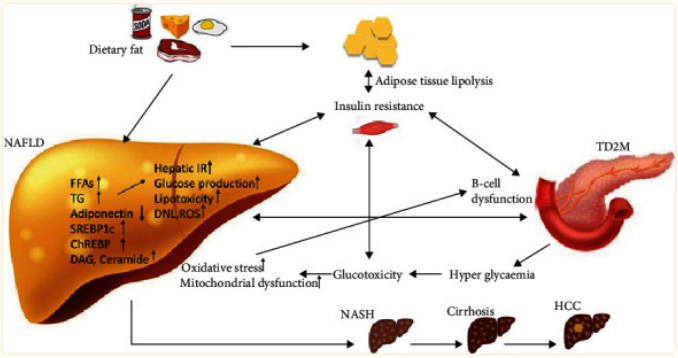


Рисунок 1

Комплексный иммунопатогенез НАЖБП, ИР и СД2. СД2: сахарный диабет 2 типа; НАЖБП: неалкогольная жировая болезнь печени; НАСГ: неалкогольный стеатогепатит; ГЦК: гепатоцеллюлярная карцинома; ИР: инсулинорезистентность; СЖК: свободные жирные кислоты; ТГ: триглицерид; ChREBP: белок, связывающий углеводный ответный элемент; SREBP1c: белок 1c, связывающий элементы, регулирующие стерол; ДАГ: диацилглицерины; АФК: высокоактивные формы кислорода;

Numerous studies are currently under development that are investigating promising new pharmacological agents for the treatment of NAFLD and testing the effects of antidiabetic drugs on liver function. We hope that in the future, larger clinical trials will evaluate and approve new therapeutic drugs for NAFLD that can be used safely in patients with T2DM.

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