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A comprehensive review of non-alcoholic fatty Liver disease in a dyslipidemia.

Una revisión exhaustiva de la enfermedad del hígado graso no alcohólico en una dislipidemia.

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD), also known as metabolic-associated fatty liver disease (MAFLD), is characterized by hepatocyte abnormal buildup of triglycerides and other lipids. This frequent illness can advance from simple steatosis to steatohepatitis and, ultimately, end-stage liver disease. MAFLD is linked to problems with systemic energy metabolism, such as insulin resistance and atherogenic dyslipidemia. The Scope Of Review: The liver is the primary organ in lipid metabolism because it secretes very low-density lipoproteins (VLDL) and internalizes fatty acids and lipoproteins. This review article highlights new findings on hepatic lipid synthesis, VLDL generation, and lipoprotein internalization in the context of MAFLD, as well as lipid exchange between adipose tissue and the liver. Major Conclusion: Triglycerides and other fats build up in the liver cells to cause fatty liver. The balance between the delivery and elimination systems determines the number of fatty acids in the liver. Inflammation of the liver and liver cell death has been linked to fatty liver in certain cases (steatohepatitis). The liver normally contains a specific quantity of fat, but when exposed to certain pathological circumstances, the balance between fat production and utilization may be disrupted. NAFLD dyslipidemia is characterized by elevated blood triglycerides, elevated tiny, dense low-density lipoprotein (LDL non-type A) particles, and decreased HDL cholesterol. In many areas of the globe, including the United States, nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver condition. According to population-based abdominal imaging studies, at least 25% of American people have fatty livers. The total frequency of NAFLD in the general population in India is near to 40%.

Key words: Fatty Liver, Metabolic associated fatty liver disease, Dyslipidemia, Steatohepatitis

RESUMEN

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Antecedentes: La enfermedad del hígado graso no alcohólico (NAFLD), también conocida como enfermedad del hígado graso asociada al metabolismo (MAFLD), se caracteriza por una acumulación anormal de triglicéridos y otros lípidos en los hepatocitos. Esta enfermedad frecuente puede avanzar desde una simple esteatosis hasta una esteatohepatitis y, en última instancia, una enfermedad hepática terminal. MAFLD está relacionado con problemas con el metabolismo energético sistémico, como la resistencia a la insulina y la dislipidemia aterogénica. El alcance de la revisión: El hígado es el órgano principal en el metabolismo de los lípidos porque secreta lipoproteínas de muy baja densidad (VLDL) e internaliza ácidos grasos y lipoproteínas. Este artículo de revisión destaca nuevos hallazgos sobre la síntesis de lípidos hepáticos, la generación de VLDL y la internalización de lipoproteínas en el contexto de MAFLD, así como el intercambio de lípidos entre el tejido adiposo y el hígado. Conclusión principal: los triglicéridos y otras grasas se acumulan en las células del hígado y provocan hígado graso. El equilibrio entre los sistemas de entrega y eliminación determina la cantidad de ácidos grasos en el hígado. En determinados casos se ha relacionado la inflamación del hígado y la muerte de las células hepáticas con el hígado graso (esteatohepatitis). El hígado normalmente contiene una cantidad específica de grasa, pero cuando se expone a determinadas circunstancias patológicas, el equilibrio entre la producción y utilización de grasa puede verse alterado. La dislipidemia NAFLD se caracteriza por niveles elevados de triglicéridos en sangre, partículas elevadas de lipoproteínas de baja densidad densas y pequeñas (LDL no tipo A) y disminución del colesterol HDL. En muchas áreas del mundo, incluido Estados Unidos, la enfermedad del hígado graso no alcohólico (NAFLD) es la afección hepática crónica más común. Según estudios de imágenes abdominales poblacionales, al menos el 25% de los estadounidenses tienen hígado graso. La frecuencia total de NAFLD en la población general de la India es cercana al 40%.

Palabras clave: Hígado graso, Enfermedad del hígado graso asociada metabólicamente, Dislipidemia, Esteatohepatitis.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), also known as metabolic-associated fatty liver disease (MAFLD), is characterized by hepatocyte abnormal buildup of triglycerides and other lipids. This frequent illness can advance from simple steatosis to steatohepatitis and, ultimately, end-stage liver disease. MAFLD is linked to problems with systemic energy metabolism, such as insulin resistance and atherogenic dyslipidemia.

MAFLD Pathophysiology

LIPOPROTEINS IN LIPID METABOLISM IN THE SYSTEM

Lipoproteins are a diverse set of mixed micelles that varies in size, lipid composition, apolipoprotein (APO) concentration, and tissue of origin. APOs provide a variety of critical activities in the metabolism and control of several lipoprotein types. Lipoproteins have a monolayer of membrane lipids at the surface, mostly phosphatidylcholine and unesterified cholesterol, while the hydrophobic lipoprotein core consists primarily of triglycerides, cholesterol esters, and the lipophilic vitamins A, D, E, and K.

DYSLIPIDEMIA AND METABOLIC-ASSOCIATED FATTY LIVER DISEASE

The growth of hepatocyte lipid droplets (LDs) containing triglycerides, cholesterol esters, and other lipid species is a feature of non-alcoholic fatty liver disease. A recent consensus was reached to modify the terminology of this illness to metabolic-associated fatty liver disease (MAFLD) to better represent the metabolism-related pathogenesis. Fat accumulation at the tissue level can be benign, occurring without inflammation (hereinafter referred to as metabolic-associated fatty liver; MAFL). It can potentially escalate to a chronic inflammatory condition followed by tissue damage (steatohepatitis).

The latter condition, in particular, is usually linked with variable degrees of fibrosis, a condition defined by collagen synthesis by a transition of hepatic stellate cells to fibroblast like cells. Although steatohepatitis is not immediately fatal, patients are at a greater risk of developing the advanced liver disease (fibrosis, cirrhosis, and hepatocellular cancer) and cardiovascular disease, the latter being the leading cause of mortality among MAFLD patients.

MAFLD- associated Dyslipidemia

Most MAFLD patients have at least some metabolic syndrome characteristics, including obesity, insulin resistance, and atherogenic dyslipidemia with elevated plasma triglyceride concentrations. As a result, the plasma lipoprotein patterns seen in MAFLD are similar to or identical to those seen in metabolic syndrome and type 2 diabetes. Hypertriglyceridemia due to big VLDL particles (VLDL1), increased amounts of tiny dense LDL, and low HDL cholesterol is characteristics of MAFLD-associated dyslipidemia. CETP activity in the blood can explain this lipoprotein profile characteristic of MAFLD. Increased interchange of cholesterol ester and triglyceride molecules occurs under hypertriglycemic circumstances between LDL or HDL particles on one side and TRL particles on the other. This CETP-catalyzed lipid exchange, which is exclusively driven by mass action, results in an increase in triglycerides associated with LDL and HDL, giving these lipoprotein particles a better substrate for HL. As a result of the HL-mediated hydrolysis of triglycerides, they decrease, explaining the formation of tiny dense LDL and small HDL particles. The latter are excreted by the kidney, which explains why HDL cholesterol levels are low overall. Thus, an increase in big TRL content drives changes in small dense LDL and HDL profiles in MAFLD patients. This shift in LDL and HDL, together with the buildup of TRL remnants, is viewed as a primary cause of increased cardiovascular risk in people with MAFLD. Small dense LDL is particularly dangerous because they can easily enter the vascular intima,

accelerating cholesterol deposition in atherosclerotic plaques. The lower particle number of HDL observed in MAFLD subjects may impair cholesterol homeostasis.

Dyslipidemia in the course of MAFLD progression

Dyslipidemia is not consistent throughout the phases of MAFLD. In general, plasma concentrations of big VLDL particles (VLDL1) and tiny dense LDL particles are greater in MAFL patients than in non-steatotic controls. However, progression to severe fibrosis or cirrhosis is related with a reduction in plasma concentrations of large APOB-containing lipoproteins, a connection validated by a large population-based investigation applying a non-invasive fibrosis estimation method. Interestingly, the research found a drop in 'normal-sized' VLDL2 particles from MAFL to steatohepatitis, and then to severe fibrosis, which might be due to the gradual loss of healthy, non-steatohepatitis hepatocytes. Along these lines, in advanced fibrotic stages of MAFLD, a decrease in the liver-derived atherogenic lipoprotein Lp(a) was reported. Taken as a whole, MAFLD dyslipidemia appears to be most evident in MAFL or moderate steatohepatitis, stages defined by significant liver steatosis, and it tends to diminish in more advanced, fibrotic stages.

VLDL synthesis in MAFLD

Hepatocytes absorb circulating lipids, digest them, and integrate fatty acids not necessary for cellular metabolism into triglycerides, cholesterol esters, and membrane lipids, which are then discharged into the bloodstream as VLDL. The fatty acids required to make VLDL lipids reach the hepatocytes as FFA via the plasma membrane or as lipoprotein-borne lipids via endocytosis. Furthermore, hepatocytes use de novo lipogenesis (DNL) to manufacture fatty acids from glucose and other non-lipid substrates. When hepatocyte triglyceride production surpasses VLDL triglyceride release, liver steatosis occurs. As a result, the emergence of MAFLD is inextricably related to VLDL production. Disruptions in VLDL secretion can lead to the accumulation of not only triglycerides, but also lipotoxic lipids carried by VLDL, and thus to the development and progression of the disease. Excess lipid accumulation in MAFLD, on the other hand, stimulates VLDL.

Lipoproteins and de novo lipogenesis in MAFLD

De novo lipogenesis (DNL), the metabolic route that synthesizes saturated fatty acids (SAFAs) and monounsaturated fatty acids (MUFAs) from acetyl-CoA, accounts for only around 5% of fatty acids in the liver and VLDL [92,93] of lean, healthy adults. However, in MAFLD, the rate of hepatic DNL is greatly enhanced, and DNL can account for greater than 25% of VLDL triglycerides. This increase in MAFLD relative to healthy people can be explained in part by the stimulation of DNL enzymes, which happens mostly via sterol regulatory element binding protein-1 (SREBP1) and carbohydrate response element-binding protein-1 (CREB1) (ChREBP). These two transcription factors are activated by elevated glucose flux as well as insulin signaling. Accordingly, hyperglycemic

and hyperinsulinemic conditions caused by energy excess promote DNL by chronic SREBP1 and ChREBP activation in the liver.

MAFLD peripheral lipoprotein processing

In addition to secreting VLDL into the circulation, the liver regulates VLDL and chylomicron disposal in peripheral organs by secreting substances that alter peripheral lipoprotein processing through modifying LPL activity. APOC3, APOA5, Angiopoietin-like proteins.

MAFLD hepatic lipoprotein processing

The bulk of TRL residues formed by LPL-dependent peripheral triglyceride hydrolysis is returned to the liver, where they are endocytosed and digested by hepatocytes, releasing lipids for re-secretion as VLDL or excretion via the bile. Humans with MAFLD had greater residual lipoprotein concentrations, and the amount of fat in the liver corresponds with postprandial lipemia.

The LDL receptor is the primary receptor in hepatocytes for cholesterol-enriched APOB-containing residual lipoproteins (LDLR). Protein loss of function mutations can induce severe hypercholesterolemia and have a negative impact on cardiovascular health in people.

LDLR-related protein-1 (LRP1) is an alternative receptor for residual uptake. Both LDLR and LRP1 require APOE as a co-ligand for effective internalization. Although APOE may influence hepatic lipid balance by altering VLDL production, findings support the idea that, despite increased hepatocyte lipid burden, effective absorption of cholesterol-enriched residual lipoproteins protects against diet-induced MAFLD. Reduced extracellular production of oxidized lipoproteins, particles that can enhance MAFLD development following absorption into liver-resident Kupffer cells as well as invading macrophages, could explain the protective impact of residual clearance. Other putative processes include the activation of proteins that mediate cholesterol elimination via the biliary pathway and the facilitation of extracellular vesicles transporting the anti-inflammatory micro RNA species miR-223. It is crucial to highlight that lipid uptake does not guard against MAFLD, but rather appears to encourage it. The discovery that knocking off the VLDL receptor (VLDLR), which primarily regulates the clearance of bigger, triglyceride-rich particles, protects mice from high-fat diet-induced MAFLD suggests this. The VLDLR is expressed at low levels in healthy livers but increases with the progression of MAFLD in humans, perhaps contributing to disease development. It is worth noting, however, that PCSK9 deficit produces altered beta cell activity and lower plasma insulin levels, which might be a complicating factor impacting MAFLD development in PCSK9 deficiency. In conclusion, additional study is needed to elucidate PCSK9's pleiotropic activities, the role of various lipoprotein receptors, and the processing of internalized lipoproteins in MAFLD.

CONCLUSION AND PERSPECTIVE

Lipoprotein systemic metabolism is directly connected to lipid homeostasis in the liver and, as a result, the development and progression of MAFLD. The buildup of lipids in hepatocytes as the initial event of MAFLD development is governed first by lipid efflux, mostly by VLDL secretion, second by fatty acid and lipoprotein absorption, and third by de novo fatty acid synthesis. Genetic polymorphisms and treatments show that functional changes in single proteins in these pathways can be enough to modify MAFLD. To anticipate the consequences of certain therapies, a greater knowledge of the interplay between the branches of lipid metabolism inside the liver is required. There are significant gaps in our understanding of the subcellular compartmentalization of lipid production, storage, and secretion.

Steatosis and injury to the liver have a significant influence on plasma lipoprotein patterns, dyslipidemia, and, as a result, cardiovascular health. The effect of plasma lipoproteins on MAFLD is less obvious, and additional study is needed to understand how lipoprotein particle absorption into hepatocytes, particularly liver-resident or -infiltrating immune cells, promotes MAFLD development. Deciphering the impact of cell type-dependent lipoprotein processing on inflammation vs insulin resistance appears to be a viable research route for better understanding the role of lipoprotein metabolism in the start and progression of MAFLD.

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