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MINIREVIEWS

Insulin resistance and adipose tissue interactions as the cornerstone of metabolic (dysfunction)-associated fatty liver disease pathogenesis

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Abstract

The relationship between metabolic derangements and fatty liver development are undeniable, since more than 75% of patients with type 2 diabetes mellitus present with fatty liver. There is also significant epidemiological association between insulin resistance (IR) and metabolic (dysfunction)-associated fatty liver disease (MAFLD). For little more than 2 years, the nomenclature of fatty liver of non-alcoholic origin has been intended to change to MAFLD by multiple groups. While a myriad of reasons for which MAFLD is thought to be of metabolic origin could be exposed, the bottom line relies on the role of IR as an initiator and perpetuator of this disease. There is a reciprocal role in MAFLD development and IR as well as serum glucose concentrations, where increased circulating glucose and insulin result in increased *de novo* lipogenesis by sterol regulatory element-binding protein-1c induced lipogenic enzyme stimulation; therefore, increased endogenous production of triglycerides. The same effect is achieved through impaired suppression of adipose tissue (AT) lipolysis in insulin-resistant states, increasing fatty acid influx into the liver. The complementary reciprocal situation occurs when liver steatosis alters hepatokine secretion, modifying fatty acid metabolism as well as IR in a variety of tissues, including skeletal muscle, AT, and the liver. The aim of this review is to discuss the importance of IR and AT interactions in metabolic altered states as perhaps the most important factor in MAFLD pathogenesis.

Key Words: Metabolic (dysfunction)-associated fatty liver disease; Insulin resistance; Adipose tissue; Fatty liver; Metabolic syndrome; Adipokine

Core Tip: In this review, we outline the main arguments that support the importance of insulin resistance (IR) in fatty liver pathogenesis, stressing its role in metabolic dysfunction. IR and other genetic and molecular mechanisms play a pivotal role not only in metabolic dysfunction–associated fatty liver disease development but also in some of its complications and comorbidities, such as chronic kidney disease.

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INTRODUCTION

The term non-alcoholic fatty liver disease (NAFLD) was initially used by Klatskin and colleagues in 1979[1], while Ludwig coined the term non-alcoholic steatohepatitis after witnessing similar clinical features in patients with liver steatosis[2]. Even though this nomenclature has been used for almost four decades, in 2020 a group of experts suggested a change of nomenclature from NAFLD to metabolic (dysfunction)-associated fatty liver disease (MAFLD) due to the large multifactorial basis for the disease and the fact that non-alcoholic does not accurately describe the disease pathogenesis[3-5]. By contrast, metabolic dysfunction accounts for a great deal of the pathogenesis of fatty liver whenever large alcohol consumption amounts are not present. MAFLD diagnosis is based on the presence of hepatic steatosis in addition to one of the following: obesity or overweight, type 2 diabetes mellitus (T2DM), or metabolic dysregulation. Metabolic dysfunction (in this context) accounts for the following conditions: increased waist circumference, systemic hypertension, dyslipidemia, prediabetes and insulin resistance (IR) (measured through the homeostatic model assessment [HOMA] > 2.5).

The development of MAFLD is linked to dyslipidemia, obesity, and IR. These are also the main features of metabolic syndrome (MetS). MetS constitutes a cluster of metabolic abnormalities which stem from IR and chronic low grade inflammation and on the long run increase the risk for cardiovascular disease (CVD) and T2DM[6]. The criteria for diagnosing MetS have changed since they were first established by the World Health Organization in 1988[7], evolving since the knowledge of the pathogenesis and its implications expanded. The criteria include the presence of visceral adiposity, IR, atherogenic dyslipidemia, and endothelial dysfunction, among others[8].

On a very important note, the change of nomenclature to MAFLD is very well justified by the sole fact that about 90% of NAFLD patients have one or more MetS component[9]. Furthermore, Marchesini *et al*[10] showed that the presence of MetS among patients with hepatic steatosis carry a significantly increased risk of developing steatohepatitis and fibrosis, with odds ratios of 3.2 and 3.5, respectively [10]. Also, MetS is a useful index for the prediction of the severity of obesity-related fatty liver[11].

One way in which we can argue in favor of IR's importance in MAFLD pathogenesis is by analyzing the causes of the established items in the metabolic risk abnormalities checklist. Another way is by refuting the counterarguments for the use of this new term. In this review, we will cover both issues.

One of the most valid points involves the fact that given MAFLD is a heterogeneous and complex disease, considering a single postulation to explain is pathogenesis is absurd. We agree that MAFLD is a multifactorial disease, and similar to diabetes, systemic hypertension and many more involve genetic and environmental mechanisms. In fact, there is progressively more data proving the influence of different environmental factors on fatty liver genesis, including air pollution and cigarette smoke. However, in MAFLD as a multifactorial disease, there is one specific overarching concept that accounts for most of the cases and pathogenesis of MAFLD, which is metabolic dysfunction.

To give an educated opinion on the subject, we must first understand what IR is, how it manifests on different endocrine organs, how it influences triglyceride (TG) metabolism in the liver, and its role in metabolic dysfunction.

IR: The basis

Insulin is the main anabolic hormone in the body, primordial for glucose homeostasis as well as other functions in tissue growth and development. Glucose homeostasis is maintained by regulating gluconeogenesis and glycogenolysis in the liver, as well as by inducing insulin-mediated glucose uptake in skeletal and cardiac muscle, as well as in adipose tissue (AT)[12]. IR refers to the impaired response of target tissues to insulin stimulation. This abnormality can be a result of altered number of receptors, or malfunction of the existing ones. In reality, there is not a single cause for IR development; instead

multiple factors together lead to this metabolic abnormality. These include the mentioned receptor abnormalities, as well as defects in the insulin signaling cascade, negative regulation of the cascade by inhibitors, or the presence of a proinflammatory internal milieu. There has even been a proposal regarding the induction of IR by fatty acids, which because of their abnormal metabolism lead to lipid accumulation in the muscle and liver. In any given case, whenever there is a decreased sensitivity of a hormonal stimulus, the result is a positive feedback loop that increases the concentration of the effect-lacking hormone (in this case, insulin). Increased insulin serum concentrations have a variety of effects due to its trophic effects on various tissues. Insulin serum concentrations are the basis for determining the presence of IR in an individual, principally through the use of the HOMA.

During the past decade, the "glucocentric" view of IR has shifted to the "lipocentric" view, regarding its pathogenesis and associated mechanisms. We can appreciate how much the focus of IR effect on glucose metabolism prevailed before the year 2000 in any scientific literature, even if we don't look in depth. For instance, IR had been included within a concept denominated the "IR syndrome", which considered the presence of dyslipidemia, hypertension and impaired glucose tolerance as factors leading to increased cardiovascular risk, however, that's the farthest lipids' involvement got[13]. Chronic hyperglycemia leads to glucotoxicity, directly inducing IR and the IR degree is one of the strongest predictors for T2DM onset in populations at risk[14,15]. While all of this is a fact, the role of fatty acid metabolism had been overlooked since in 1965 Randle and colleagues first suggested increased serum free fatty acids (FFAs) as one of the primary causes for decreased glucose oxidation and IR development[16]. The last decade has had an increased body of research supporting this fact, centering the role of lipids, along with that of glucose, in the development of fatty liver.

IR is present in a variety of metabolic disorders, such as MetS and T2DM. IR in the liver presents as increased gluconeogenesis and decreased hepatic glycogenesis, resulting in increased glucose production and release[17].

Adipose tissue IR-Which came first: The resistance or the fat?

AT has long been known to be an endocrine organ, both by releasing hormones such as leptin and adiponectin (adipokines), and by regulating proinflammatory mediator secretion and metabolic processes. AT IR refers to the impaired suppression of lipolysis in the presence of high insulin serum levels (Figure 1). One of the key hormones involved in AT-IR is adiponectin, which contributes to the development of obesity-related IR and CVD[18]. While in this case adiponectin levels are lower, other adipokines such as leptin are increased[19], the former one acting as a protective factor for hepatic steatosis development[20].

Whenever IR ensues, there is a disinhibition of lipolysis in the AT, which results in higher breakdown of stored triglycerides in AT and higher release of FFA into the blood. The circulating FFAs lead to activation of the proinflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway in the liver, ultimately resulting in lipotoxicity. Lipotoxicity, however, is not the end result of a single pathway, but rather the combination of the role of FFAs, TGs, biliary acids (BAs), free cholesterol, ceramides, and lysophosphatidyl cholines[21].

When it comes to metabolic health, AT is the major determinant given the ability of subcutaneous AT (SAT) to store excess fat (through adipocyte *de novo* lipogenesis [DNL] instead of allowing it to deposit in the non-fatty tissues, otherwise known as "ectopic" deposition of fat. Whenever this ability becomes impaired, aberrant adipocyte tissue develops, where the adipocytes undergo hypertrophy along with decreased number of glucose transporter-4 (GLUT-4) receptors. Under physiologic conditions, adipocytes carry out recruitment of adipogenic precursor cells, along with adequate angiogenesis. Dysregulation of the signaling pathway between the wingless-related integration site (WNT) and the bone morphogenetic protein 4 (BMP-4) results in alterations in the recruitment, proliferation and differentiation of the precursors. BMP-4 has also been found to contribute to "browning" of white AT in mice, where brown AT (BAT) tallies to the oxidative phenotype of lipid-storing adipocytes[22]. The alteration in AT expansion means that not only do pathologic adipocytes have decreased number of GLUT-4 receptors but they also have altered blood supply, leading to hypoxia and consequently to activation of hypoxia-inducible factor 1 alpha (HIF-1α). By having a reduced number of GLUT-4 receptors, glucose influx is impaired, which in turn limits DNL. The induction of HIF-1α factor in this pathological AT state increases systemic inflammatory conditions. Transcriptome analysis of AT macrophages in obese mice revealed rewiring of the metabolic pathways within these macrophages with increased glycolysis and oxidative phosphorylation, rendering them as inflammatory macrophages[23]. Macrophage HIF-1α is involved in the formation of crown-like structures, which lead to maintenance of inflammatory processes and inhibition of angiogenesis in preadipocytes, leading to a vicious circle of added hypoxia and expansion of the aberrant AT[24] (Figure 2). Pathologic expansion of AT leads to systemic IR, as mentioned throughout this review.

Briefly expanding upon the importance of BAT, a 2011 paper proved how cold-induced browning of AT in rats controlled TG rich lipoprotein metabolism by boosting their turnover and channeling lipids into AT browning[25]. There has been a number of studies proving that the presence of BAT in adulthood is independently associated with lower probability of developing liver steatosis[26,27], for which multiple mechanisms have been uncovered. For instance, the uncoupling protein 1 (UCP-1) expressed specifically in BAT reverses obesity and also antagonizes liver inflammation and pathology

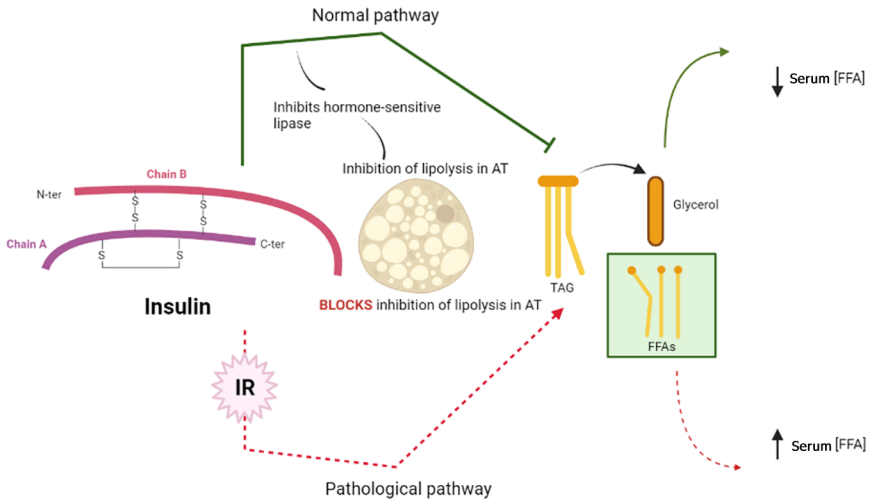

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Figure 1 Effect of insulin resistance on adipose tissue lipolysis. Under normal circumstances, insulin inhibits lipolysis in adipose tissue by inducing the hormone sensitive lipase, thus decreasing the release of excessive free fatty acids (FFAs) into the serum. However, in an insulin resistance state, inhibition of lipolysis is blocked, increasing serum FFAs, which eventually increase the influx of lipids into the liver. All the figures were created using BioRender. AT: Adipose tissue; IR: Insulin resistance.

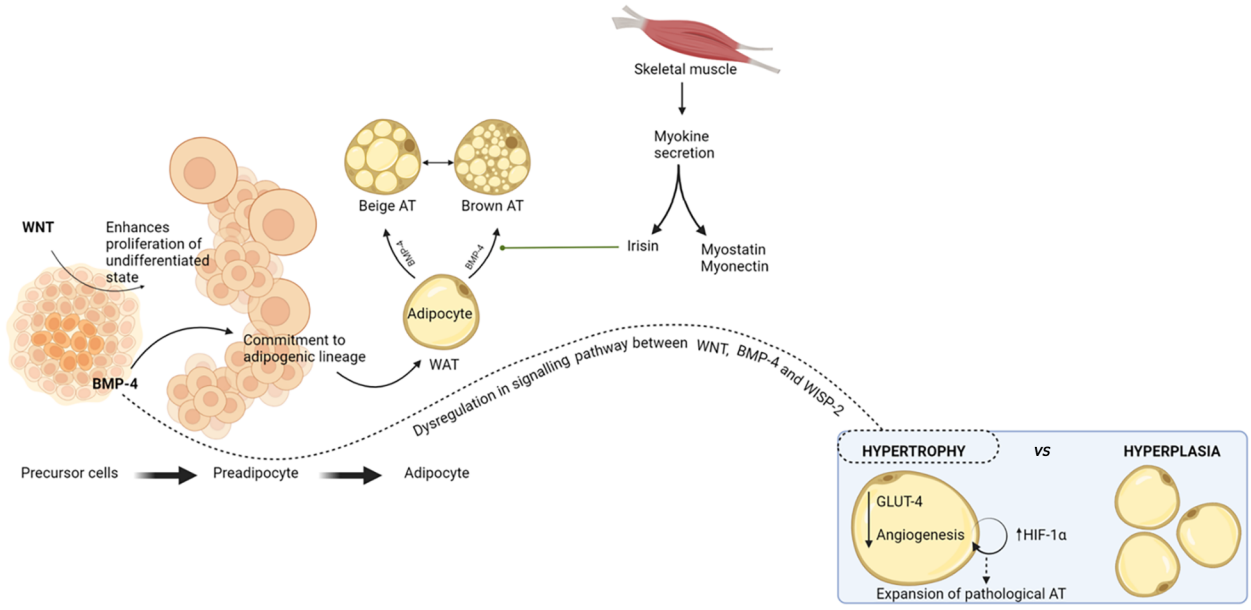

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Figure 2 Adipose tissue dysfunction in metabolic dysfunction–associated fatty liver disease. Adipocyte precursor cells undergo initial proliferation through the wingless-related integration site (WNT) signaling pathway and thereafter commitment to the adipogenic lineage by bone morphogenetic protein 4 (BMP-4) stimulus, until its conversion to preadipocytes and later on to mature adipocytes. White adipose tissue can undergo beiging or browning under the influence of two main stimuli: BMP-4 and irisin. Browning of adipose tissue (AT) implies higher catabolic and oxidation rates, In the case of WNT, BMP-4, and WNT-1 inducible signaling pathway protein 2 pathway dysregulation, there is hypertrophy of AT. Physiologically, hyperplasia through the proliferation process mentioned is the appropriate mechanism for AT expansion. Pathologically, however, hypertrophy of AT leads to decreased levels of intracellular glucose transporter 4 and limited angiogenesis. Limited angiogenesis stimulates the hypoxia inducible factor 1 alpha (HIF-1a), stimulating further AT hypertrophy, creating a vicious cycle in the expansion of pathological AT. WAT: White adipose tissue; WISP-2: WNT-1 inducible signaling pathway protein 2; GLUT-4: Glucose transporter 4.

[28]. Interestingly, uric acid transporters have been seen to influence fatty liver[19]; a study carried out by Tanaka *et al*[29] found that the use of dotinurad (urate reabsorption inhibitor) showed amelioration of IR in rats by reducing liver steatosis and promoting rebrowning of AT[29].

Novel discovery of a group of lipids known as the fatty acid esters of hydroxy fatty acids (FAHFAs) released from the AT when appropriate levels of GLUT-4 and adipogenesis are present shed light to another pathway through which AT, and specially SAT, regulates systemic IR and inflammation[30]. FAHFAs induce metabolic health by stimulating insulin-dependent glucose transport in various tissues, as well as glucagon-like peptide 1 and insulin release from the gut enteroendocrine cells and the

pancreatic β-cells, respectively. Important anti-inflammatory effects have also been shown by studying docosahexaenoic acid (DHA)-derived FAHFAs' effects in cultured human hepatoma-derived cells, finding potent activation of nuclear factor erythroid 2-related factor 2 with tenable antioxidant function [31].

The answer to the question "what came first: the resistance or the fat?" could go both ways, *i.e.* liver fat build-up could be attributed to some degree to IR and hyperinsulinemia or directly from excessive FFA availability, which consequently brings about IR. Amount of AT, hepatic steatosis, and low-grade subacute inflammation are all correlated with the development of IR and MetS[32]. For this reason, the interaction between fat and IR is not causal, but rather reciprocal.

Skeletal muscle IR

Skeletal and cardiac muscle play important roles in glucose metabolism. Studies in humans have shown that it is the principal insulin-stimulated glucose uptake site (about 75% of postprandial serum glucose), whereas AT presents with relatively lower uptake[33]. Similar to hepatic IR, one of the ways skeletal muscle IR develops is by increased FFA supply, which cannot be processed by the tissue.

The association between skeletal muscle dysfunction and the progression of MAFLD has been widely recognized. There are several muscular conditions that are directly related to fatty liver, such as myosteatosis and sarcopenic obesity. We briefly touched upon the fact that AT releases adipokines key to metabolic regulatory systems. However, skeletal muscle also has the capacity to release hormonally active molecules termed myokines, which exert their function in an autocrine, paracrine, or endocrine fashion[34]. There are hundreds of myokines and the specific function of most has not been fully elucidated; however, many have shown effects in a multisystemic manner, including cognition, bone composition, AT "browning," as well as lipid and glucose metabolism. Myostatin, myonectin, irisin and a series of interleukins are among the most important myokines. Myostatin has a negative effect on MAFLD progression, given that it enhances liver inflammation and fibrogenesis by hepatic stellate cell stimulation[35]. Irisin, on the other hand, has the opposite effect by stimulating white AT browning and UCP-1 expression reducing adipose IR. This is key, given that one of the hallmarks of treatment for MAFLD is physical exercise. Irisin, among others, is an exercise-inducible myokine; this represents one of the few pathways through which moderate or rigorous exercise can reduce progression in MAFLD by targeting IR in the liver and AT (Figure 2). An additional feature of irisin is FFA oxidation, which is a method for lipid removal from ectopic tissue; this will later be explained in the intrahepatic triglyceride content section. Lastly, myonectin plays a role in FFA oxidation in the AT and the liver, as well as thermogenesis. Therefore, we already see how different myokines can have both beneficial or detrimental effects on metabolic health depending on the collective organ characteristics. A specific phenotype based on lifestyle characteristics defines the myokines that will be released, *e.g.*, irisin, and therefore the IR in other tissues that affects the development of liver steatosis.

Lean MAFLD

The absence of overt metabolic dysfunction in the lean population with MAFLD does not exclude the presence of metabolic abnormalities at cellular level. An important measurement of our hypothesis would be measuring the presence or absence of overt IR (*e.g.*, as per international criteria, mainly the HOMA) in a follow-up period of the population.

IR causes fatty liver from the inside out and not the other way around. In other words, cellular level alterations can, on their own, cause increased TG accumulation in the liver, even if obesity, acanthosis nigricans or even HOMA are not present or are within out of normal range in the latter case.

Individuals with normal body mass index (BMI) also develop MAFLD, and many studies (mainly in non-Caucasian populations) have shown a lack of IR in patients with MAFLD. A study conducted by Ahmed *et al*[27] studied the presence of NAFLD in patients with different BMI (non-obese, overweight, and obese) and evaluated whether these NAFLD individuals presented with IR. The results showed that a significant number of individuals without IR had NAFLD; however, there was no analysis of whether the NAFLD individuals without IR had non-obese BMI. This small aspect could be quite significant, given that we claim that the two main contributors to MAFLD development are IR and AT dysfunction. Furthermore, regarding lean MAFLD, it is known that IR unrelated to obesity can occur in various hyperglycemic states.

It is important to establish that IR drives DNL in the liver. Fatty liver diagnosis is defined based on the total amount of intrahepatic TG (IHTG). A recent study showed that hepatic DNL is an important regulator of IHTG content, concluded after correcting for the potential confounding contribution of AT in DNL. It was also noted that increases in serum glucose and insulin stimulate hepatic DNL. Glucose and insulin promote DNL by inducing the carbohydrate response element binding protein, as well as the sterol regulatory element binding protein 1c (SREBP 1c) and the acetyl CoA carboxylase, respectively[36]. Increased serum insulin is a compensatory mechanism during IR when there is appropriate endocrine pancreas activity, by having increased insulin release, DNL is stimulated further.

Thus, one of the most important arguments in favor of IR as the base of pathogenesis is the fact that it directly stimulates DNL. The question here would be: can DNL alone be contribution enough to increase IHTG up to MAFLD levels? The answer is no, even though DNL contributes about 26% to total IHTG content, while most of it originates from increased influx of FFA and their esterification in the

liver, accounting for 59% of total lipid content[37]. A smaller percentage, 15%, is attributable to diet TG consumption, as shown by Donnelly *et al*[37].

Mechanisms of IHTG accumulation

Increased lipid content in the liver originates from an imbalance between FFA uptake by the liver, DNL, lipid oxidation, and hepatic very low density lipoprotein (VLDL) export rate[38]. TG synthesis and lysis are the main ways in which the liver regulates the storage of FFA in serum when levels are high, whereas in the case of energy expenditure, it releases VLDL particles containing FFA to the muscle and fat tissue[39]. There was a previous misconception on the role of hepatic TG storage as a cause of lipotoxicity; it is now known that TG storage and secretion of VLDL particles are protective mechanisms against FFA-induced lipotoxicity. An elegant study by Listenberg *et al*[40] proved that through unsaturated fatty acid supplementation in CHO an 25RA cells, a protective effect against lipotoxicity through TG synthesis induction was achieved[40].

TG storage in the liver is carried out through the conversion of FFAs into glycerol-3-phosphate. TGs, along with cholesterol esters are neutral lipid particles which can be stably stored in the liver or can be released as VLDL particles[41]. There are a number of mechanisms involved in FFA oxidation and lipid metabolism. As we briefly touched upon, irisin is one of hundreds of exercise-induced myokines secreted by skeletal muscle, which plays an important role in the AT-muscle-liver axis. It also regulates the adenosine monophosphate-activated protein kinase signaling pathway, thus increasing FFA oxidation in myocytes[42].

Another mechanism that helps keep the balance between the IHTG is fatty acid β-oxidation in the mitochondria or peroxisomes. This process leads to the production of adenosine triphosphate or in the case of excess FFAs, the production of ketone bodies[43]. Alterations in β-oxidation contribute to the development of hepatic steatosis. For instance, downregulation in peroxisome proliferator-activated receptor alpha (PPAR-α), which serves as an FFA sensor, leads to decreased fatty acid catabolism and intrahepatic lipid accumulation. These alterations also determine the severity to which steatosis will develop depending on the nutritional status of an individual[44]. Stimulation of PPAR-α in mice enhances the expression of cytochrome P450 4A and enhances lipid turnover in the liver, decreasing the risk of developing dietary steatohepatitis[45]. Furthermore, PPAR-α activation increases peroxisomal fatty acid β-oxidation by inducing acyl-coenzyme A oxidase (Acox1), the rate-limiting enzyme in the oxidation of very long-chain fatty acids[46,47]. Acox1 is also associated with spontaneous liver damage in humans, as well as spontaneous steatosis, steatohepatitis, and hepatocellular carcinoma development in mice[46]. Despite what we discussed, alterations in PPAR-α are not the only ones leading to hepatic steatosis. Instead, a number of altered function in nuclear receptors such as the pregnane and xenobiotic receptors, the liver X receptor, and the farnesoid X receptor (FXR) contribute to the pathogenesis of MAFLD[48].

What about the comorbidities in MAFLD? Let's not forget CKD: The multiple effects of gene mutations

We have already discussed two primordial concepts in the understanding of MAFLD: AT dysfunction and IR. Even though these attributes explain a great deal of the pathogenic mechanisms involved in MAFLD, saying that overseeing genetic alterations involved is a mistake would hardly be an overstatement.

As it has been already reviewed in multiple studies and around a number of countries, there is a significant amount of genetic mutations that highly predispose populations to MAFLD. Even though there are multiple genetic mutations, the most common involves the gene patatin-like phospholipase domain-containing protein 3 (PNPLA3), which encodes for a protein called adiponutrin that exerts lipolytic action on TGs and reduces DNL within the liver. The PNPLA3 gene is present in many tissues in the body; however, it is most highly expressed in the liver and the kidney.

MAFLD is known for its large range of associated comorbidities; it is not only the hepatic manifestation of MetS but is a rather multisystemic disease on its own. A recent meta-analysis evaluated the risk of having NAFLD (previous nomenclature) and the risk of developing chronic kidney disease (CKD). In total, the data from more than a million patients were analyzed, and the study concluded that pre-existing NAFLD is associated with about a 1.45-fold increased risk of incident CKD stage ≥ 3[49]. The same team carried out a meta-analysis in 2017 showing 40% increased risk of CKD in patients with NAFLD[50]. Another group of researchers reached the same conclusions, showing that the presence and severity of NAFLD are associated with an increased risk and severity of CKD[51]. However, another group concluded that the association was not because of a causal relationship between MAFLD and CKD but was due to shared risk factors between them, namely diabetes, age, hypertension, and hyperuricemia[52]. This recent cross sectional study from The National Health and Nutrition Examination Survey 2017-2018 showed that MAFLD and CKD were not independently related after propensity score matching[52].

We propose an explanation for this, which might account for the high prevalence of CKD in people with MAFLD, and also shed light on the reason why these two diseases, even when highly correlated, are not independently related.

As previously mentioned, the PNPLA3 gene is most highly expressed in two tissues: the liver and kidney. Mutations in the PNPLA3 gene, especially the PNPLA3 I148M variant, leads to CKD in a similar pattern as how the mutation predisposes to MAFLD. Montovani and his team followed this line of thought and by studying 157 patients with T2DM, found that the presence of this mutation (especially in the podocytes on the renal cortex) was associated with lower glomerular filtration rates (GFR) and higher risk of CKD, 63.6% *vs* 24.2% risk in people without homozygous mutation[53]. It is important to establish that the association between the PNPLA3 I148M variant and the risk of lower GFR and CKD development is independent of liver disease severity as well as other factors[53]. This association has also been found among children with MAFLD, where the PNPLA3 G/G genotype leads to decreased kidney function and increased 24-h proteinuria[54].

By having established this, we can understand the multifactorial nature of MAFLD and its comorbidities, as in this case, CKD's. Whether or not MAFLD predisposes to kidney malfunction could be studied in a group of patients who develop both entities but lack mutations in the PNPLA3 gene.

While PNPLA3 gene mutations might be a common factor in the predisposition for both CKD and MAFLD, there are a number of nuclear transcription factors that contribute to the pathogenesis of both diseases. These factors include the peroxisome proliferator-activated receptor (PPAR) family, FXR, and SREBP2, which modify their respective molecular pathways and influence the progression of both CKD and hepatic steatosis[55]. For instance, the downregulation of PPAR-α, PPAR-δ, and PPAR-γ causes a myriad of cellular alterations in the nephron, including increased podocyte apoptosis leading to altered glomerular barrier integrity, increased mesangial cell hypertrophy and enhanced matrix deposition, as well as NF-κB activation with consequent proinflammatory cytokine secretion in the glomerular endothelium[56]. These same factors under physiologic circumstances suppress fibrogenesis by inhibiting the transforming growth factor β in stellate cells, lower the M1/M2 Kupffer cell phenotype ratio (thus decreasing inflammatory stimulus in the liver) and increases catalase activity in hepatocytes, among other functions. It is clear how downregulation of the PPAR family of factors hinders these protective mechanisms in the liver and promotes the development of fatty liver, as well as CKD. The same situation of multiorgan damage comes about with decreased expression of FXR and upregulation of SREBP-2, given that FXR inhibits SREBP-1c-mediated DNL in hepatocytes while decreasing reactive oxygen species formation in mesangial cells and increasing endothelial nitric oxide synthase in the glomerular epithelium[55]. Finally, SREBP-2 upregulation leads to increased cholesterol synthesis and decreased excretion in both liver and renal cells[57,58]. With this brief compilation of the molecular pathway similarities between CKD and fatty liver development, it would be of no surprise to find in the near future novel discoveries on further overlapping mechanisms and genetic predisposition for both diseases.

CONCLUSION

In conclusion, although MAFLD pathogenesis is multifactorial and complex, we consider IR to be the basis for the development of the disease, the abnormal metabolic profile in patients, and disease complications. Further research is required to fully understand and test this hypothesis along with others that may develop. Understanding the basis of the disease and the many variables that play a role in its development will lead to appropriate targeted therapies for MAFLD.

FOOTNOTES

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