

Non-cardiometabolic comorbidities of non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of disorders which affect the liver, but were proven to have implications in many other organs and systems. It is now widely accepted that NAFLD has many comorbidities, mainly metabolic and cardio-vascular. Even if much comorbidity are well-explained, there are many other diseases associated with NAFLD in which the pathophysiological pathways are not completely understood. Research is conducted nowadays with the goal of completely elucidate the pathogenesis of NAFLD and its comorbidities, in order to eventually find a targeted cure for this "epidemic" liver disease. The purpose of this review is to present the non-cardiometabolic comorbidities of NAFLD, by using epidemiological and , physiopathological data, and to bring updated information on their treatment.

Key words: *non-alcoholic fatty liver disease, steatohepatitis, osteoporosis, psoriasis, chronic kidney disease*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of liver damage worldwide, becoming a global burden which grows in incidence alongside with obesity [1]. NAFLD is associated with the metabolic syndrome and presents a large variability in evolution between patients [2], especially in those who express a more aggressive form of NAFLD, the non-alcoholic steatohepatitis (NASH).

The pathophysiological consequences of NAFLD and NASH extend beyond the liver. Nowadays, it is widely accepted that NAFLD is closely associated (besides the metabolic syndrome) with cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). However, these are not the only conditions linked to NAFLD [2]. For example, osteoporosis is strongly associated with NAFLD [3]. Also, an interesting statistics indicates the fact that extrahepatic malignancies are the second cause of mortality in NAFLD patients, after CVD [4, 5]. By comparison, liver-related complications are only the third cause in NAFLD patients` mortality [2, 5].

The purpose of the present paper is to review the so far proven extra-hepatic comorbidities of NAFLD, other than the cardio-vascular and metabolic ones. We will leave for a further discussion the association between NAFLD and T2DM, metabolic syndrome, cardiovascular events and the endocrinopathies (hypothyroidism and polycystic ovary syndrome) [6, 7].

Thus, we will focus on CKD, osteoporosis, psoriasis, extrahepatic malignancies and obstructive sleep apnea, which are also known to be associated with NAFLD.

The links between NAFLD and chronic kidney disease

Chronic kidney disease (CKD) is defined as glomerular filtration rate (GFR) <60 mL/min/1.73 m² or kidney damage, for a minimum of 3 months, irrespective of the etiology [8]. It is now stated that 20-50% of patients with NAFLD can present various degrees of CKD, especially those with NASH [9]. Since the studies published by Targher et al. [10, 11], there is a growing interest in finding whether there is a causative link between NAFLD/NASH and CKD [6]. A meta-analysis published in 2014 showed that NAFLD increases 2-fold the prevalence (OR 2.12, 95% CI 1.7–2.7) and nearly 2-fold the incidence (HR 1.79, 95% CI 1.7–1.9) of CKD. In the same study, it was proven that the incidence and prevalence of CKD were higher in patients with advanced liver fibrosis and NASH [12]. It is important to mention that this increased risk for CKD in NAFLD patients persisted after adjustment for the traditional risk factors for CKD (e.g. diabetes mellitus, hypertension) [13]. In a large cohort study on Korean population, the authors emphasized that NAFLD is associated with decline in renal function and careful monitoring is required in those situations [14].

The pathophysiology of CKD in patients with NAFLD is very complex. There are risk factors that

influence only one of these diseases and other risk factors that might influence both conditions. Also, if CKD starts evolving, it will ultimately influence the liver function [13]. An important pathway that is altered in CKD pathogenesis is the up-regulation of the renin-angiotensin system, usually in subjects with impaired anti-oxidant defenses and insulin resistance [6, 15]. Increased fructose intake is another blamed cause of liver accumulation of lipids and accelerated progression of CKD [16, 17]. Adiponectin [18] and galectin-3 [19] have implications in liver-kidney damage. Adiponectin is a hormone which inhibits atherogenic dyslipidemia and promotion of NAFLD, while galectin-3 is a protein that is up-regulated in cases of liver and kidney fibrosis [18, 19]. Intestinal dysbiosis as well causes inflammation due to an increased number of Gram-negative bacteria in the gut and an increased production of secondary bile acids, which act on the farnesoid X receptor (FXR). This nuclear receptor has been recently studied as a potential target for NASH treatment, with promising results [20]. Other nuclear receptors with potential implications in NAFLD-CKD pathogenesis are the peroxisome proliferator-activated receptors (PPARs), mainly due to their capacity of modulating inflammation and metabolic homeostasis. A study by Ratziu et al. published in 2016 showed that an agonist of PPAR α and δ (Elafibranor) induced resolution of NASH and improved the cardiometabolic risk profile of patients [21]. Chemokines are molecules with homeostatic or inflammatory functions which were proven to initiate proteinuria and CKD [22]. Many other putative mechanisms have relevance in the pathogenesis of both NAFLD and CKD. It is worth to mention two of them, already targeted for the treatment of T2DM: the decreased incretins, such as glucagon-like peptide-1 (GLP-1) agonists, and the increased activity of sodium-glucose co-transporter 2 (SGLT2) [13]. These alterations lead to impaired fasting glucose and eventually T2DM, and are blocked by the using of synthetic GLP-1 receptor agonists and SGLT2 inhibitors. Recently, there are voices advocating that a combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor has a clear potential benefit on metabolic-cardiovascular-renal disease in patients with T2DM [23, 24]. From all of those proven pathways, it is evident that NAFLD may play an important role in the pathogenesis of CKD [25].

NAFLD and osteoporosis

Questions have been raised in the last decade whether we should add osteoporosis as an important comorbidity in patients with metabolic syndrome and NAFLD [26, 27]. It is known that bone mineral density is impaired in patients with chronic liver diseases [28], both in children and adults [6]. Multiple factors are associated with decreased bone mineral density (BMD) and NAFLD, including chronic inflammation, obesity, insulin resistance, T2DM and vitamin D₃ deficiency [2]. However, whether osteoporosis and NAFLD are etiologically linked to each other or not is a question to which it is impossible at this moment to offer a clear answer [29, 30]. A study on 216 premenopausal and 265 postmenopausal women showed that postmenopausal women with NAFLD may be at higher risk of osteoporosis, even after adjustment for the presence of the metabolic syndrome [29]. In a study on middle-aged and elderly Chinese women, it was shown that NAFLD was significantly associated with history of osteoporotic fracture [31]. Another study on Chinese adults (99 males and 125 postmenopausal women) showed that NAFLD seems to alter BMD in both males and females [32]. Upala's recent meta-analysis did not show a significant difference in BMD between patients with NAFLD and controls, but he admits that the study has limitations and there is a need for further observational studies, which exclude the effects of body-mass index (BMI) [30].

The possible pathogenic mechanisms linking NAFLD to decreased BMD and osteoporosis are still unclear. Multiple hypothesis have emerged, but the most promising are related to insulin resistance, systemic inflammation, bone-specific molecules influencing bone turnover and the metabolism of calcium and vitamin D [33, 34]. Insulin resistance and diabetic nephropathy were shown to be an important cause of osteoporosis in patients with T2DM [35]. Insulin resistance is incriminated as the central mechanism for production of both T2DM and NAFLD, and is independently associated with the stage of hepatic fibrosis in these patients [27]. The presence of liver fibrosis and its severity is independently associated with low BMD and osteoporosis in patients with NAFLD, as a recent study concludes [36]. Systemic inflammation is known to influence NAFLD and, particularly, NASH. Growing level of evidence supports the theory that inflammation contributes also to the pathogenesis of

osteoporosis [37, 38]. Among the incriminated cytokines, interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) play an important role in estrogen-deficiency related bone loss [38]. In a recent study, IL-6 and TNF- α were found at high levels in serum of patients with NASH [39], but the presence of osteoporosis was not assessed on the study population. Bone metabolism and turnover is influenced by many molecules, mainly osteopontin, osteocalcin and osteoprotegerin [33, 34, 40]. These hormones were incriminated recently in affecting glucose metabolism and leading to prediabetes [41]. This mechanism could be a trigger for insulin resistance exacerbation and NAFLD, added to the known inflammatory and fibrotic actions of osteopontin [42].

Finally, even the treatment for NASH may promote osteoporosis. Thiazolidinediones (PPAR- γ agonists) are insulin sensitizers which slow down liver fibrosis progression, but were shown to promote loss of BMD and fractures [27]. The treatment of osteoporosis, including bisphosphonates and denosumab [43], is not known to date to induce NAFLD.

Data linking NAFLD to psoriasis and psoriatic arthritis

Psoriasis is a chronic inflammatory, immune-mediated disease, which is frequently associated to comorbidities. The most well-known "psoriatic comorbidities" are the psoriatic arthritis, uveitis, inflammatory bowel diseases and metabolic syndrome (MS) [44]. After the age of 40, the patient with psoriasis is more predisposed to develop MS [45]. Furthermore, there is an increased prevalence of the MS in patients with moderate to severe forms of psoriasis, and this finding is independent from the presence of obesity [46]. It should be not a surprise that psoriasis and NAFLD can coexist, given the relationship between MS and both NAFLD and psoriasis [47]. The study of Gisoni et al. [48] showed that NAFLD prevalence was significantly higher in psoriatic patients versus controls (47% vs. 28%, $p < 0.001$). Also, NAFLD was associated with a higher Psoriasis Area and Severity index (PASI), even after adjustment for the cardio-metabolic risk factors [48]. Similar results were found in other cross-sectional studies [49, 50, 51, 52]. Furthermore, psoriasis was shown to be associated with other liver conditions besides NAFLD, such as chronic hepatitis and alcoholic liver disease [53]. In 2015, Candia et al.

conducted a systematic review and meta-analysis, concluding that psoriatic patients had an increased risk of NAFLD compared to controls. This risk was higher in patients with moderate-to-severe psoriasis and psoriatic arthritis [47, 54].

The mechanism incriminated in linking NAFLD to psoriasis is inflammation. The backbone of the problem is the dysfunctional (inflamed) visceral adipose tissue, which plays a key role in promoting insulin resistance, inflammation and, consequently, NAFLD and its aggressive form, NASH [47]. The processes incriminated in promoting this sequence are the increased release of non-esterified fatty acids to the liver, the decreased production of adiponectin and the increased production of pro-inflammatory adipocytokines (TNF- α , IL-6, leptin), all of above being triggers for liver and psoriatic tissue to release more pro-inflammatory cytokines [47, 55, 56]. A fatty liver will generate itself a lot of other damaging molecules (pro-fibrogenic, pro-coagulant, pro-oxidant mediators) that may play an important role in the pathogenesis of psoriasis [25, 47].

The treatment of psoriasis and particularly of psoriatic arthritis can also influence the natural course of NAFLD [57]. Systemic treatment with methotrexate and cyclosporine should be used very careful on patients with metabolic syndrome with obesity and NAFLD, for they can worsen each of the components of the metabolic syndrome and even induce liver fibrosis [46, 56]. The therapies with biologic drugs for severe forms of psoriasis and psoriatic arthritis (infliximab, adalimumab and etanercept) can increase body fat mass or elevate the serum levels of transaminases, among other negative effects [47, 58, 59, 60].

Data linking NAFLD to extra-hepatic malignancies

Besides the risk of progression of NASH to cirrhosis and, subsequently, to hepatocellular carcinoma [61], NAFLD was found to be associated with other neoplasia, notably the colorectal cancer (CRC) [2, 6, 7]. The gastrointestinal malignancies linked to NAFLD have as primary sites the liver, the colon, the esophagus, the stomach and the pancreas. The extra-intestinal sites are the breast in women and the kidney in men [62, 63]. In a prospective study conducted by Adams et al. (on 337 subjects with NAFLD and T2DM) [64], the authors observed that 33% of deaths were caused by malignancies. Recent data showed a

connection between NAFLD and CRC [65]. The colorectal cancer which appears in individuals with little or no genetic risk is associated with their diet, physical inactivity and abdominal obesity. To date, it is proven that the presence of metabolic syndrome increases the risk for CRC. This sequence of obesity-metabolic syndrome-T2DM-adenomatous polyps-CRC can imply also the presence of NAFLD, mainly due to harms induced by insulin resistance [65, 66]. Many recent studies were conducted on Asian population, and there were few cohort studies and mostly cross-sectional studies [2]. A recent meta-analysis showed that NAFLD was significantly associated with colorectal adenoma, better seen in Asian population vs. European/North American population [6].

The putative mechanism linking NAFLD to higher risk for CRC is the axis obesity-insulin resistance-metabolic syndrome. From the known studies, there cannot be drawn a true causal relationship between NAFLD and CRC. There is a need for large, prospective studies with long follow-up of patients with NAFLD/NASH in order to establish a clear relationship with their disease and various malignancies [2, 6, 62].

Data linking NAFLD to obstructive sleep apnea

Obstructive sleep apnea (OSA) is a condition defined by events of upper airway occlusion occurring in repetition during sleep, leading to chronic intermittent hypoxia (CIH) [67, 68]. OSA is known to be associated with obesity, hypertension, dyslipidemia and insulin resistance [68, 69]. Studies in rodents and humans have shown that CIH/OSA is leading to alteration in transaminases and liver injury [6, 70]. Significant body of evidence is suggesting that OSA is associated with NAFLD, particularly in obese patients [71]. Also, the severity of OSA and CIH is correlated with the presence and the severity of NASH [72, 73]. These findings were shown in both adult population and, more alarming, in pediatric population [6]. A 2013 systematic review of the literature established that OSA is associated with an increased risk for NAFLD, NASH and advanced fibrosis (independent of age, gender and BMI) [74]. The most recent systematic review found OSA to be significantly correlated with liver steatosis, lobular inflammation, hepatocytes` ballooning, fibrosis and ALT levels [75].

The main mechanism by which OSA increases insulin resistance and precipitates the NAFLD is chronic intermittent hypoxia [70]. CIH is promoting lipolysis in the adipose tissue, thus raising the free fatty-acids influx to the liver, ultimately leading to hepatic steatosis [68]. Furthermore, CIH induces dyslipidemia and insulin resistance, and also increases the expression of hypoxia-inducible transcription factor 1 α (HIF1 α), which exacerbates liver oxidative stress and increases lipogenesis [76]. The lysyl oxidase (LOX) enzyme serum levels were also found high in OSA patients. This enzyme is a known promoter of fibrosis in various tissues, and could be involved in CIH-NAFLD pathogenesis. Also, mitochondrial dysfunction (during hypoxia) and disruptions in the gut-liver axis (due to intestinal dysbiosis) are also proven pathophysiological mechanisms by which OSA-NAFLD association can be explained [68, 69, 76].

To date, the OSA treatment with CPAP is known to reduce arterial blood pressure, but seems to have no influence in improving insulin sensitivity and showed no impact on NAFLD regression [76].

Conclusion

Non-alcoholic fatty liver disease has complex pathogenetic mechanisms by which it connects with some comorbidities. The core process that seems to induce NAFLD and many of its comorbidities is insulin resistance, altogether with its consequences, mainly the metabolic syndrome. Further studies are required to reach a level of fully understanding of NAFLD pathogenesis, in order to be able to provide a much-needed target therapy for this liver condition.

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