Non-alcoholic fatty liver disease and hematologic manifestations (Review)

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Abstract. Non-alcoholic fatty liver disease (NAFLD) is a multisystem disease, and it is associated with numerous extra-hepatic manifestations or additional co-occurring diseases. The aim of the present review was the identification and management of the hematologic manifestations of NAFLD. One of the triggers is considered to be iron abnormalities. Increased ferritin levels, hepatic iron deposits and iron overload are associated with NAFLD. The iron overload degree and severity are associated with the level of liver fibrosis and with the risk for hepatocellular carcinoma. Excess iron deposits refers to the dysmetabolic iron overload syndrome (DIOS) and it is characterized by steatosis associated with moderate tissue iron deposition and increased levels of serum ferritin, while the serum transferrin saturation was normal. Further prospective studies are necessary to determine whether NAFLD has an independent risk for hematologic symptoms, besides the known risk factors. Future studies are also needed in order to assess the increasing impact of NAFLD on the micro- and macro-vascular complications of this systemic disease.

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Contents

1. Introduction

The prevalence of non-alcoholic fatty liver disease (NAFLD) has increased worldwide in the last decades in parallel with the increase in obesity (1-4). NAFLD is a multisystem disease that is associated with many extra-hepatic manifestations or comorbid diseases. Findings of a previous meta-analysis revealed that the prevalence of NAFLD is 25.2% worldwide, the lowest values being recorded in Africa (13.5%) and the highest in South America and the Middle East (30.5 and 31.8%, respectively) (5). Findings have also shown that 10-15% of individuals with normal weight and 70% of obese patients have a fatty liver (6). A higher level of visceral fat increases the risk of hepatic steatosis in both slim and overweight individuals (7). Patients with dyslipidemia and type 2 diabetes mellitus (T2DM) have a higher prevalence of NAFLD than the average population (6,8). The pathogenic mechanism of liver inflammation and fibrosis in patients with NAFLD is incompletely understood. An improved understanding of the pathogenesis, natural history and treatment of NAFLD is necessary (9). One of the triggers is considered to be iron abnormalities. NAFLD is characterized by deposits of triglycerides in hepatocytes without secondary causes of liver disease, and this includes significant alcohol consumption (10). NAFLD includes non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) which have the potential to progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Histologically, NAFL is present in 80% of patients and NASH is present in 20% of patients (11). The stage of fibrosis is the strongest predictor of disease-specific mortality in NAFLD (12). Patients with

elevated liver enzymes or ultrasound-proven steatosis and who have risk factors for NASH without a definitive diagnosis, require a biopsy (13,14). Biopsy is the gold standard technique for detecting liver fibrosis; some of the disadvantages include insufficient sampling, sample site pain, high costs, as well as intra- and inter-observer variability (15,16).

Matteoni *et al* presented the first diagnostic criteria for the classification of NAFLD into four different subtypes: NAFLD type 1, in which the patient presents only fatty liver; type 2, in which the patient presents fatty liver and lobular inflammation; type 3, in which the patient presents fatty liver plus ballooning degeneration; and type 4, in which the patient presents fat accumulation, ballooning degeneration, and either Mallory-Denk bodies or fibrosis (7). Subtypes 3 and 4 are considered today as NASH (17). Previous studies have assessed the extra-hepatic manifestations of NAFLD and found they were associated with cardiovascular disease (CVD), T2DM, colorectal cancer, chronic kidney disease (CKD), obstructive sleep apnea (OSA), hypothyroidism, polycystic ovarian syndrome (PCOS) as well as hematologic manifestations (18-20). Cardiovascular diseases, followed by extra-hepatic malignancies, and then liver-related mortality is the leading cause of mortality in patients with NAFLD (18-20). It has been (widely) accepted that the standard treatment of patients with NAFLD is loss of weight through diet and exercise.

2. Methods

The aim of the present review was the identification and management of the hematologic manifestations of NAFLD. In this review, a literature search was performed for the term 'non-alcoholic fatty liver disease (NAFLD)' combined with 'hematologic manifestations' and 'iron overload', in the PubMed and Scopus databases from January, 1990 to December, 2020. The inclusion criterion was articles relevant to these searches. The exclusion criteria were studies written in languages other than English, letters to the editor, editorials, comments, conference presentations, opinions, and articles where there was no free access.

3. NAFLD and hematologic disorders

Increased ferritin levels, hepatic iron deposits and iron overload are associated with NAFLD. In NAFLD patients, the iron overload degree and severity are associated with the level of liver fibrosis and with the risk for HCC (21-23).

Even if the evidence that suggests the association between increased ferritin level and liver injury in NAFLD is reasonably strong, in other studies no clear association has been identified (24,25). In one study performed among NAFLD patients, iron indices were significantly reduced by therapeutic phlebotomy; however, there was no effect on insulin resistance or hepatic histology (26). In response to phlebotomy, these patients may develop anemia, in contrast to the experience of phlebotomy in patients with primary hemochromatosis. It is not currently recommended to use serial phlebotomy to decrease the ferritin levels of NAFLD patients, unless it is associated with a well-documented investigation of iron overload. Proinflammatory activity with elevated levels of plasminogen activator inhibitor-I in NAFLD patients leads to low level activation of the coagulation cascade, and the result is an increased risk of vascular thrombosis and thrombophilia (11). NASH etiology of cirrhotic patients is the leading cause for portal vein thrombosis. Furthermore, transplant recipients diagnosed with NASH cirrhosis have a higher risk for poorer post-transplant graft and patient survival, compared to recipients who do not have pretransplant portal vein thrombosis (27).

Approximately one in three NAFLD patients has excess iron deposits. This refers to the dysmetabolic iron overload syndrome (DIOS) and it is characterized by steatosis associated with moderate tissue iron deposition (hemosiderosis) and increased levels of serum ferritin, while the serum transferrin saturation was normal (28,29). The magnitude of hyperferritinemia in patients with NAFLD and/or metabolic syndrome (MetS) overemphasizes the degree of iron overload histologically detected when compared to hemochromatosis (30).

A serum ferritin level that is 1.5-fold higher than the normal upper limit in NAFLD patients is associated with (excessive) deposits of iron in the liver, underlying NASH, and a worse histological activity (31). Elevated levels of serum ferritin are autonomously associated with a higher NAFLD activity score (NAS), even in cases of patients without (excessive) deposition of iron in the liver (31). More severe liver fibrosis is correlated with the serum levels of ferritin. Taken separately, serum ferritin levels have a low level of diagnostic accuracy when it comes to the presence or severity of liver fibrosis in patients with NAFLD (AUROC <0.60) (32).

Specific patterns of hepatic iron deposits are associated with distinct histological features in patients with NAFLD. More advanced histological features, such as NASH and fibrosis, are associated with the presence of iron in the reticuloendothelial system (as opposed to hepatocellular deposits) in cases of patients with NAFLD (33-35). The development of HCC in NASH is associated with sinusoidal iron deposition (22,36).

4. Conclusions

Patients can benefit from the use of appropriate pharmaceutical therapies, such as lipid-lowering agents and insulin sensitizers; these aid in limiting the progression of NAFLD and lower the risk of extrahepatic manifestations. Further studies, with a longer follow-up period, are needed to collect the detailed cardio-metabolic risk profiles of these patients, in order to evaluate the impact of NAFLD as a systemic disease. Additionally, it is recommended that clinical trials be carried out to examine the effect of NAFLD treatment on the risks and outcomes of its extrahepatic manifestations. The treatment for many of the extrahepatic symptoms associated with NAFLD remains a change in the lifestyle, including adequate physical activity, weight loss and diet changes. Further studies are necessary in order to investigate the effect of pharmacological treatment on the extrahepatic manifestations of NAFLD. Consequently, further prospective studies are crucial in determining whether NAFLD has an independent risk factor for hematologic symptoms, besides the known risk factors. Weight loss, diet changes and the stopping of smoking have the potential to prevent the progression of NAFLD and its extrahepatic comorbid complications. Future studies are necessary for a better understanding of the pathophysiology and to potentially

alter the natural history of these conditions. Future studies are also needed in order to assess the increasing impact of NAFLD on the micro- and macro-vascular complications of this systemic disease.

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Authors' contributions

VP, DD, AND, RP, AEM, and LN contributed equally to the acquisition, analysis and systematization of the literature data, manuscript writing and critical revision for important intellectual content. All authors read and approved the final version of the manuscript for publication.

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Competing interests

The authors declare that they have no competing interests.

References

1. Tariq R, Axley P and Singal AK: Extra-hepatic manifestations of nonalcoholic fatty liver disease: A review. J Clin Exp Hepatol 10: 81-87, 2020.
2. Nobili V, Alkhouri N, Alisi A, Della Corte C, Fitzpatrick E, Raponi M and Dhawan A: Nonalcoholic fatty liver disease: A challenge for pediatricians. JAMA Pediatr 169: 170-176, 2015.
3. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL and Harrison SA: Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: A prospective study. Gastroenterology 140: 124-131, 2011.
4. Wijarnpreecha K, Aby ES, Ahmed A and Kim D: Evaluation and management of extrahepatic manifestations of nonalcoholic fatty liver disease. Clin Mol Hepatol 27: 221-235, 2021.
5. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L and Wymer M: Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 64: 73-84, 2016.
6. Vernon G, Baranova A and Younossi ZM: Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 34: 274-285, 2011.
7. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC and McCullough AJ: Nonalcoholic fatty liver disease: A spectrum of clinical and pathological severity. Gastroenterology 116: 1413-1419, 1999.
8. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E and Gastaldelli A: Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 5: 1544-1560, 2013.
9. Younossi ZM, Rinella ME, Sanyal AJ, Harrison SA, Brunt EM, Goodman Z, Cohen DE and Loomba R: From NAFLD to MAFLD: Implications of a premature change in terminology. Hepatology 73: 1194-1198, 2021.
10. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM and Sanyal AJ: The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American association for the study of liver diseases. Hepatology 67: 328-357, 2018.
11. Byrne CD and Targher G: NAFLD: A multisystem disease. J Hepatol 62 (Suppl 1): S47-S64, 2015.
12. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S and Hultcrantz R: Fibrosis stage is the strongest predictor for disease specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 61: 1547-1554, 2015.
13. Rinella ME: Nonalcoholic fatty liver disease: A systematic review. JAMA 313: 2263-2273, 2015.
14. Li AA, Ahmed A and Kim D: Extrahepatic manifestations of nonalcoholic fatty liver disease. Gut Liver 14: 168-178, 2020.
15. Sebastiani G and Alberti A: Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. World J Gastroenterol 12: 3682-3694, 2006.
16. West J and Card TR: Reduced mortality rates following elective percutaneous liver biopsies. Gastroenterology 139: 1230-1237, 2010.
17. Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T and Younossi ZM: Long-term follow-up of patients with nonalcoholic fatty liver. Clin Gastroenterol Hepatol 7: 234-238, 2009.
18. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A and Angulo P: The natural history of nonalcoholic fatty liver disease: A population-based cohort study. Gastroenterology 129: 113-121, 2005.
19. VanWagner LB and Rinella ME: Extrahepatic manifestations of nonalcoholic fatty liver disease. Curr Hepatol Rep 15: 75-85, 2016.
20. Kim D, Kim WR, Kim HJ and Therneau TM: Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology 57: 1357-1365, 2013.
21. Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, Sanyal AJ and Nelson JE; NASH Clinical Research Network: Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatology 55: 77-85, 2012.
22. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, Leone N, Massarenti P, Piga A, Marchesini G and Rizzetto M: Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. Hepatology 39: 179-187, 2004.
23. Sorrentino P, D'Angelo S, Ferbo U, Micheli P, Bracigliano A and Vecchione R: Liver iron excess in patients with hepatocellular carcinoma developed on non-alcoholic steato-hepatitis. J Hepatol 50: 351-357, 2009.
24. Valenti L, Fracanzani AL, Bugianesi E, Dongiovanni P, Galmozzi E, Vanni E, Canavesi E, Lattuada E, Roviaro G, Marchesini G and Fargion S: HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with non-alcoholic fatty liver disease. Gastroenterology 138: 905-912, 2010.
25. Duseja A, Das R, Nanda M, Das A, Garewal G and Chawla Y: Nonalcoholic steatohepatitis in Asian Indians is neither associated with iron overload nor with HFE gene mutations. World J Gastroenterol 11: 393-395, 2005.
26. Adams LA, Crawford DH, Stuart K, House MJ, St Pierre TG, Webb M, Ching HL, Kava J, Bynevelt M, MacQuillan GC, *et al*: The impact of phlebotomy in nonalcoholic fatty liver disease: A prospective, randomized, controlled trial. Hepatology 61: 1555-1564, 2015.
27. Agbim U, Jiang Y, Kedia SK, Singal AK, Ahmed A, Bhamidimarri KR, Bernstein DE, Harrison SA, Younossi ZM and Satapathy SK: Impact of nonmalignant portal vein thrombosis in transplant recipients with nonalcoholic steatohepatitis. Liver Transpl 25: 68-78, 2019.
28. Mendler MH, Turlin B, Moirand R, Jouanolle AM, Sapey T, Guyader D, Le Gall JY, Brissot P, David V and Deugnier Y: Insulin resistance-associated hepatic iron overload. Gastroenterology 117: 1155-1163, 1999.

29. Mihailovici AR, Padureanu V, Albu CV, Dinescu VC, Pirlog MC, Dinescu SN, Malin RD and Calborean V: Myocardial Noncompaction. Rev Chim (Bucharest) 69: 2209-2212, 2018.
30. Moirand R, Mortaji AM, Loreal O, Paillard F, Brissot P and Deugnier Y: A new syndrome of liver iron overload with normal transferrin saturation. Lancet 349: 95-97, 1997.
31. ForŢofoiu MC, Popescu DM, Pădureanu V, Dobrinescu AC, Dobrinescu AG, Mită A, Foarfă MC, Bălă VS, Muşetescu AE, Ionovici N and ForŢofoiu M: Difficulty in positive diagnosis of ascites and in differential diagnosis of a pulmonary tumor. Rom J Morphol Embryol 58: 1057-1064, 2017.
32. Angulo P, George J, Day CP, Vanni E, Russell L, De la Cruz AC, Liaquat H, Mezzabotta L, Lee E and Bugianesi E: Serum ferritin levels lack diagnostic accuracy for liver fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 12: 1163-1169.e1, 2014.
33. Nelson JE, Wilson L, Brunt EM, Yeh MM, Kleiner DE, Unalp-Arida A and Kowdley KV; Nonalcoholic Steatohepatitis Clinical Research Network: Relationship between the pattern of hepatic iron deposition and histological severity in nonalcoholic fatty liver disease. Hepatology 53: 448-457, 2011.
34. Forţofoiu M, Forţofoiu MC, Comănescu V, Dobrinescu AC, Pădureanu V, Vere CC, Streba CT and Ciurea PL: Hepatocellular carcinoma and metabolic diseases - histological perspectives from a series of 14 cases. Rom J Morphol Embryol 56: 1461-1465, 2015.
35. Găman AE, Ungureanu AM, Turculeanu A, Gheonea DI, Drocaş AI, Mitroi G, DobriŢoiu M, Comănescu MV, Stănculescu AD, Cioboată R, *et al*: The impact of liver steatosis on early and sustained treatment response in chronic hepatitis C patients. Rom J Morphol Embryol 58: 107-113, 2017.
36. Furtunescu F, Minca DG, Vasile A and Domnariu C: Alcohol consumption impact on premature mortality in Romania. Rom J Leg Med 17: 296-302, 2009.