Is nonalcoholic fatty liver disease the hepatic expression of the metabolic syndrome?

Yusuf Yilmaz

Abstract
Nonalcoholic fatty liver disease (NAFLD) is generally considered as the hepatic manifestation of the metabolic syndrome (MS). Although there is no doubt that NAFLD is tightly linked to the MS, the diagnosis of NAFLD encompasses a broad range of histological entities and as a composite phenotype may be hindering attempts to understand the mechanistic basis of these variants. The awareness that NAFLD is not solely and invariably associated with the MS is a useful means to help direct future studies. We should be aware that mechanisms other than insulin resistance may contribute to the chronic inflammatory processes that underpin the development of liver fat accumulation and the subsequent architectural distortion of the liver. Further studies with special focus on hemoglobin as a risk factor for the development of NAFLD in the absence of MS should be performed.

© 2012 Baishideng. All rights reserved.

Key words: Nonalcoholic fatty liver disease; Metabolic syndrome; Insulin resistance; Fibrosis; Hemoglobin

Peer reviewers: Rachel Mary Hudacko, MD, Department of Pathology and Laboratory Medicine, Medical Education Building, Rm 212, Robert Wood Johnson Medical School, 1 Robert Wood Johnson Place, New Brunswick, NJ 08901, United States; Juan Carlos Perazzo, MD, PhD, Professor, Department of Biological Sciences, Pathophysiology School of Pharmacy and Biochemistry, UBA, Junin 950, 5, Buenos Aires 1113, Argentina

Yilmaz Y. Is nonalcoholic fatty liver disease the hepatic expression of the metabolic syndrome? World J Hepatol 2012; 4(12): 332-334 Available from: URL: http://www.wjgnet.com/1948-5182/full/v4/i12/332.htm DOI: http://dx.doi.org/10.4254/wjh.v4.i12.332

INTRODUCTION
The epidemic of obesity is now a global and seemingly unstoppable phenomenon. Worldwide, the World Health Organization states that there are now over one billion overweight adults, of whom at least 300 million are obese[1]. In the wake of the obesity epidemic follow numerous comorbidities, including nonalcoholic fatty liver disease (NAFLD)[2]. NAFLD, which comprises a range of conditions from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis, is the most common liver disease identified in Western countries[3]. The metabolic syndrome (MS), a potent risk factor for NAFLD, may represent a state in which the disturbances of metabolism that characterize fatty liver infiltration are already occurring prior to disease manifestation. However, debate rages as to whether the MS is, in fact, a useful concept in view of the lack of a unifying pathophysiology and issues of whether the sum of the components of the MS represent any greater risk than the components alone[4,5]. In addition, the fact that there is still no single internationally recognized definition of the MS reflects the diversity of opinion as to the purpose of defining the MS and whether there is a single principal underlying metabolic abnormality[6]. One widely held belief is that insulin resistance represents the unifying underlying pathological process resulting in both MS and NAFLD[7,8]. An alternative hypothesis is that the disturbances of lipid metabolism...
seen in the MS result in a variety of secondary pathological processes which ultimately lead to fatty liver infiltration. Therefore, an important issue in the assessment of the risk of NAFLD in patients with the MS is dependent on the criteria used to identify the MS itself. However, there is another issue of utmost relevance that merits consideration. Although NAFLD is intricately intertwined with the MS, the definition of NAFLD includes only one component, i.e., liver fat content > 5%-10% by weight in the absence of excess alcohol consumption or any other liver disease. Even more importantly, only 20% to 80% of patients with NAFLD fulfill the criteria for the MS. Therefore, the presence of the MS alone does not sufficiently explain why some adults do have NAFLD. Starting from these premises, the identification of other factors that may explain this unexpected finding has key clinical implications.

**NAFLD UNRELATED TO THE MS: HEMOGLOBIN AS THE KEY RISK FACTOR**

To shed more light on the clinical and biochemical features of NAFLD unrelated with the MS, we have recently conducted a multicenter cross-sectional study in Turkey. The purpose of the research was to determine if there were differences between patients with biopsy-proven NAFLD with and without a diagnosis of the MS. Our original hypothesis was that a detailed characterization of NAFLD patients without a diagnosis of the MS would be useful for identifying novel mechanisms of hepatic fat accumulation. Of a total of 357 consecutive patients with NAFLD recruited in the study, 214 met the ATP-III criteria for the MS while the remaining 143 did not. In NAFLD patients with the MS, insulin resistance and diabetes were independent predictors of NASH. Very intriguingly, the only variable independently associated with both NASH and severe moderate-to-severe fibrosis in NAFLD patients without the MS was hemoglobin. Receiver operating characteristic curve analysis also demonstrated that 144 g/L was the optimal hemoglobin cutoff value for a diagnosis of NASH in NAFLD patients without the MS, with a sensitivity and specificity of 75.5% and 71.3%, respectively. If these results will be independently validated by future studies, we anticipate that liver biopsy should be recommended for patients with ultrasound-diagnosed NAFLD, no evidence of the MS, and hemoglobin levels higher than 144 g/L.

As expected, our data indicated that insulin resistance was significantly related to the presence of NASH and severe fibrosis in patients with biopsy-proven NAFLD; however, this association was chiefly confined in the subgroup of NAFLD patients with the MS. In contrast, hemoglobin levels were the most important independent predictor of both NASH and severe fibrosis in NAFLD patients without a diagnosis of MS. These findings are of interest and in keeping with a recent proteomic study which showed that free hemoglobin subunits positively associated with the severity of liver lesions in NAFLD.

In another large epidemiological study of 8985 Chinese subjects, Xu et al. reported that the prevalence rate of NAFLD increased with progressively higher hemoglobin concentrations. Notably, Yu et al. have also shown in an epidemiological study of 6944 apparently healthy subjects that increased baseline hemoglobin levels predict the incidence of NAFLD at a 3-year follow-up. Our study is the first to demonstrate that hemoglobin is the main independent predictor of the severity of the liver lesions in patients with biopsy-proven NAFLD without MS. However, the exact mechanisms underlying this association remain to be determined. Previous studies have demonstrated that increased hemoglobin concentrations lead to increased blood viscosity, thereby raising peripheral resistance and reducing blood flow and perfusion. In turn, a reduced blood perfusion to the liver has been suggested to accelerate fibrosis. Furthermore, increased iron itself can increase liver damage by oxidative stress and lipid peroxidation. The possible mechanisms leading to increased hemoglobin levels in NASH and in NAFLD subjects with advanced fibrosis need additional study, but it might be a consequence of hepatic hypoxia resulting in a stimulation of erythropoietin production.

**CONCLUSIONS AND PERSPECTIVES**

Is NAFLD just the mirror of the MS at the hepatic level? Clinical studies have clearly shown that the answer to this key question is “no”. Although there is no doubt that NAFLD is tightly linked to the MS, the diagnosis of NAFLD encompasses a broad range of histological entities and as a composite phenotype may be hindering attempts to understand the mechanistic basis of these variants. The awareness that NAFLD is not solely and invariably associated with the MS is a useful means to help direct future studies. We should be aware that mechanisms other than insulin resistance may contribute to the chronic inflammatory processes that underpin the development of liver fat accumulation and the subsequent architectural distortion of the liver.

Inferring clinically relevant insights from the complex picture of the quantitative changes in expression levels of circulating molecules remains a major challenge in NAFLD. Ideally, NAFLD biomarkers should be accessible in a minimally invasive way through assaying the serum, plasma, or blood. Initial exploratory studies aimed at the discovery of biomarkers are frequently performed using high-throughput proteomics-based platforms. Currently, hemoglobin is clearly the most widely replicated proteomic biomarker of NAFLD. Accordingly, it has been identified as a biomarker of NAFLD in two independent proteomic studies and then validated using distinct analytical methods in large and independent replication cohorts. In our previous study, we have also shown that high hemoglobin levels were associated not only with the presence of NASH but also with the extent of hepatic fibrosis. Decreased blood flow to the liver due to increased hemoglobin levels may indeed in-
duce hepatic hypoxia and a profibrotic response\textsuperscript{[23]}. Further studies with special focus on hemoglobin as a risk factor for the development of NAFLD in the absence of MS should be performed. Additional research will also be required to determine whether or not treatment strategies chiefly focused on reducing hemoglobin may contribute to the modulation of systemic inflammatory response or the development of common metabolic diseases. An important objective of such studies will be also to assess the diagnostic accuracy of hemoglobin for predicting NASH and liver fibrosis while properly adjusting for confounding effects from clinical risk factors and drug exposures.

REFERENCES

1. McAllister EJ, Dhurandhar NV, Keith SW, Aronne LJ, Bargher J, Baskin M, Benca RM, Biggio J, Boggiano MM, Eisenmann JC, Elobeid M, Fontaine KR, Gluckman P, Hanlon EC, Katzmarzyk P, Pietrobelli A, Reddon DT, Ruden DM, Wang C, Waterland RA, Wright SM, Allison DB. Ten putative contributors to the obesity epidemic. Crit Rev Food Sci Nutr 2009; 49: 868-913
2. Ismail MH. Nonalcoholic fatty liver disease and type 2 diabetes mellitus: the hidden epidemic. Am J Med Sci 2011; 341: 485-492
3. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. Science 2011; 332: 1519-1523
4. Daskalopoulou SS, Mikhailidis DP, Elisaf M. Prevention and treatment of the metabolic syndrome. Angiology 2004; 55: 589-612
5. Sookoian S, Pirola CJ. Metabolic syndrome: from the genetics to the pathophysiology. Curr Hypertens Rep 2011; 13: 149-157
6. Kassi E, Pervanidou P, Kaltas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med 2011; 9: 48
7. Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Järvinen H, Svegliati-Baroni G. From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis 2010; 42: 320-330
8. Moore JB. Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. Proc Nutr Soc 2010; 69: 211-220
9. Zimmermann A, Zimmermann T, Schattenberg J, Pöttgen S, Lotz J, Rossmann H, Roeddiger R, Biesterfeld S, Geiss HC, Schuchmann M, Galle PR, Weber MM. Alterations in lipid, carbohydrate and iron metabolism in patients with non-alcoholic steatohepatitis (NASH) and metabolic syndrome. Eur J Intern Med 2011; 22: 305-310
10. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol 2010; 16: 5286-5296
11. Green RM. NASH–hepatic metabolism and not simply the metabolic syndrome. Hepatology 2003; 38: 14-17
12. Yilmaz Y, Senates E, Ayyildiz T, Colak Y, Tuncer I, Ovunc AO, Dolar E, Kalayci C. Characterization of nonalcoholic fatty liver disease unrelated to the metabolic syndrome. Eur J Clin Invest 2012; 42: 411-418
13. Grundy SM, Cleeman JJ, Merz CN, Brewer HB, Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-239
14. Trak-Smarya V, Dargere D, Noun R, Albuquerque M, Zagury O, Mahieux L, Daskalopoulou SS, Michel G, Dargere D, Noun R, Albuquerque M, Zagury O, Mahieux L, Daskalopoulou SS, Michel G. Endothelial nitric oxide synthase is a critical factor in experimental liver fibrosis. Antioxid Redox Signal 2004; 6: 451-458
15. Yu C, Xu C, Xu L, Yu J, Miao M, Li Y. Serum proteomic analysis revealed diagnostic value of hemoglobin for nonalcoholic fatty liver disease. J Hepatol 2012; 56: 241-247
16. Alayash AI, Patel RP, Cashon RE. Redox reactions of hemoglobin and myoglobin: biological and toxicological implications. Antioxid Redox Signal 2001; 3: 313-327
17. Kwaan HC, Wang J. Hyperviscosity in polycythemia vera and other red cell abnormalities. Semin Thromb Hemost 2003; 29: 451-458
18. Leung TM, Tipoe GL, Liow EC, Lau TY, Fung ML, Nanji AA. Endothelial nitric oxide synthase is a critical factor in experimental liver fibrosis. Int J Exp Pathol 2008; 89: 241-250
19. Saher AT, Musallam KM, Inati A. Iron overload: consequences, assessment, and monitoring. Hemoglobin 2009; 33 Suppl 1: 546-557
20. Yilmaz Y. Serum proteomics for biomarker discovery in nonalcoholic fatty liver disease. Clin Chim Acta 2012; 413: 1190-1193
21. Yilmaz Y. NAFLD in the absence of metabolic syndrome: different epidemiology, pathogenetic mechanisms, risk factors for disease progression? Semin Liver Dis 2012; 32: 14-21