World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/esps/
wjh@wjgnet.com
doi:10.4254/wjh.v4.i12.332

World J Hepatol 2012 December 27; 4(12): 332-334
ISSN 1948-5182 (online)

EDITORIAL

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

Yusuf Yilmaz

Yusuf Yilmaz, Department of Gastroenterology, School of Medicine, Marmara University, 34840 Istanbul, Turkey
Yusuf Yilmaz, Institute of Gastroenterology, Marmara University, 34840 Istanbul, Turkey
Author contributions: Yilmaz Y conceived and wrote the paper.
Correspondence to: Yusuf Yilmaz, MD, Institute of Gastroenterology, Marmara University, Basibuyuk Yerleskesi, Maltepe, 34840 Istanbul, Turkey. dryusufyilmaz@gmail.com
Telephone: +90-533-4403995 Fax: +90-216-6886681
Received: November 8, 2011 Revised: October 6, 2012
Accepted: November 14, 2012
Published online: December 27, 2012

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.

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[9]. 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[6]. 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[10]. Even more importantly, only 20% to 80% of patients with NAFLD fulfill the criteria for the MS[11]. 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[12]. 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[13] 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[12]. 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[12].

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[14].

In another large epidemiological study of 8985 Chinese subjects, Xu *et al*[15] reported that the prevalence rate of NAFLD increased with progressively higher hemoglobin concentrations. Notably, Yu *et al*[16] 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[12]. 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[17,18]. In turn, a reduced blood perfusion to the liver has been suggested to accelerate fibrosis[19]. Furthermore, increased iron itself can increase liver damage by oxidative stress and lipid peroxidation[20]. 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[21]. 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[14,16] and then validated using distinct analytical methods in large and independent replication cohorts[12,15,16]. In our previous study[12], 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[22].

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, Barger J, Baskin M, Benca RM, Biggio J, Boggiano MM, Eisenmann JC, Elobeid M, Fontaine KR, Gluckman P, Hanlon EC, Katzmarzyk P, Pietrobelli A, Redden 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, Kaltsas 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 JI, 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-Smayra V**, Dargere D, Noun R, Albuquerque M, Yaghi C, Gannagé-Yared MH, Bedossa P, Paradis V. Serum proteomic profiling of obese patients: correlation with liver pathology and evolution after bariatric surgery. *Gut* 2009; **58**: 825-832

15 **Xu L**, Xu CF, Yu CH, Miao M, Li YM. Haemoglobin and non-alcoholic fatty liver disease: further evidence from a population-based study. *Gut* 2009; **58**: 1706-1707

16 **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

17 **Alayash AI**, Patel RP, Cashon RE. Redox reactions of hemoglobin and myoglobin: biological and toxicological implications. *Antioxid Redox Signal* 2001; **3**: 313-327

18 **Kwaan HC**, Wang J. Hyperviscosity in polycythemia vera and other red cell abnormalities. *Semin Thromb Hemost* 2003; **29**: 451-458

19 **Leung TM**, Tipoe GL, Liong 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

20 **Taher AT**, Musallam KM, Inati A. Iron overload: consequences, assessment, and monitoring. *Hemoglobin* 2009; **33** Suppl 1: S46-S57

21 **Yilmaz Y**. Serum proteomics for biomarker discovery in nonalcoholic fatty liver disease. *Clin Chim Acta* 2012; **413**: 1190-1193

22 **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

S- Editor Li JY **L- Editor** A **E- Editor** Li JY