Serum Visfatin Levels in NAFLD

Subjects: Gastroenterology & Hepatology

Contributor: Abdulrahman Ismaiel

Adipokines, including visfatin, have been studied in nonalcoholic fatty liver disease (NAFLD). Several studies evaluated visfatin levels in NAFLD, the presence and severity of hepatic steatosis, liver fibrosis, lobar inflammation, nonalcoholic steatohepatitis (NASH), and gender differences.

Keywords: visfatin ; adipokines ; NAFLD ; hepatic steatosis ; liver fibrosis ; NASH

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is primarily a liver pathology associated with structural and functional liver modifications, increased liver-related morbidity and mortality due to possible progression to cirrhosis, liver failure, and ultimately, hepatocellular carcinoma, as well as several extrahepatic manifestations [1][2][3][4]. Until the present, NAFLD remains without currently approved therapies [5][6][7]. The worldwide prevalence of associated metabolic diseases such as NAFLD, type 2 diabetes mellitus, dyslipidemia, and obesity has dramatically increased over the last decades [8].

The development and progression of NAFLD are based on a complex and multifactorial mechanism, explained by a recent hypothesis known as the “multiple-hit model” that has now been more widely accepted, describing a prominent metabolic dysfunction due to several genetic and environmental interactions, in addition to changes in crosstalk between several organs and tissues such as adipose tissue, liver, pancreas, and gut [9].

Adipose tissue is considered because of highly active endocrine tissue-producing peptides known as adipokines that exert autocrine, paracrine, and endocrine functions. Despite conflicting evidence, adipokines have gained increasing interest in several obesity-related diseases, including NAFLD [8][10]. However, the pathogenic effects exerted by adipokines in NAFLD remain under investigation.

Among these adipokines is visfatin, a highly conserved 52-kDa protein that is found in all living species, also known as nicotinamide phosphoribosyltransferase (NAMPT) and pre-B-cell colony-enhancing factor 1 (PBEF-1). Visfatin has several main sources, including adipocytes, lymphocytes, monocytes, neutrophils, hepatocytes, and pneumocytes [11]. Various pathways affected by visfatin include oxidative stress response, apoptosis, lipid, and glucose metabolism, as well as insulin resistance and inflammation, possibly playing a role in the pathogenesis of NAFLD [12][13][14]. The expression of visfatin is regulated by several cytokines such as tumoral necrosis factor-alpha (TNF α), interleukin-6 (IL-6), and lipopolysaccharide that are known to promote insulin resistance [15]. Furthermore, increased visfatin levels were found to be associated with atherosclerotic disease and coronary artery disease, pathologies demonstrated to be among the main mortality causes in NAFLD [16][17][18][19].

2. Current Insights on Serum Visfatin Levels in NAFLD

Lately, there has been a growing interest in evaluating several adipokines that are possibly associated with NAFLD, including visfatin. Although the current literature contains several published systematic reviews and meta-analyses evaluating adipokines in NAFLD, none evaluated serum visfatin levels in NAFLD [20][21][22]. To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the association between serum visfatin levels and NAFLD, the presence and severity of hepatic steatosis, as well as liver fibrosis, lobar inflammation, NASH, and gender differences. We included 21 articles in our qualitative synthesis with a total study population of approximately 1900 subjects from different races and backgrounds who participated in 10 cross-sectional studies, 9 case-control studies, and 2 prospective studies that were conducted in Europe, the Middle East, Asia and America. Moreover, we included 14 articles in our quantitative synthesis. We demonstrated that serum visfatin levels are not significantly associated with NAFLD, the presence or severity of hepatic steatosis, liver fibrosis, lobar inflammation, NASH, and gender differences.

We reported several results that need to be further discussed. Firstly, the term NAFLD was recently updated to metabolic-dysfunction-associated fatty liver disease (MAFLD) with new criteria for diagnosis. MAFLD is characterized by the presence of hepatic steatosis, in addition to one of the following three criteria, including overweight/obesity, type 2 diabetes mellitus (DM), or confirmed metabolic dysregulation [23][24]. Therefore, NAFLD and MAFLD should not be used interchangeably because of the difference in diagnostic criteria between the two terms. The current literature lacks studies evaluating serum visfatin levels in MAFLD. Hence, all studies included in our systematic review and meta-analysis used the diagnostic criteria for NAFLD, and not MAFLD, reflecting findings associated with NAFLD and not MAFLD. Therefore, future studies are required to evaluate serum visfatin levels using the MAFLD criteria.

Secondly, we reported a prevalence of NAFLD in our sample study of approximately 50%, with an almost equal sex distribution. These findings might be explained by sampling methods used in the included studies. Included studies were from various continents involving participants from several backgrounds. As several risk factors and pathologies have been demonstrated to be associated with specific races and ethnicities, including studies involving subjects from multiple races allows us to report more reliable and generalizable results that are based on findings involving participants from different backgrounds.

Thirdly, we included studies that used a variety of methods to evaluate the presence and severity of hepatic steatosis. Diagnosing NAFLD can be confirmed by the presence of hepatic steatosis through a liver biopsy (which is the current gold standard), in addition to several other imaging methods, including ultrasonography (which is currently the most commonly used investigation to evaluate hepatic steatosis), as well as CT scans, MRI, and noninvasive biomarkers [1][25][26]. Almost half of the included studies in our review performed a liver biopsy to assess for hepatic steatosis, while the rest of the studies used ultrasonography. We did not include studies that confirmed the diagnosis of NAFLD through the sole use of liver enzymes such as ALT levels [27][28].

Fourthly, in addition to visfatin, several other adipokines have been studied in NAFLD, including leptin, adiponectin, resistin, and chemerin. Current studies reported controversial potential effects of visfatin in regard to insulin resistance, hepatic steatosis, and fibrosis. However, one of the most studied adipokines, adiponectin, was reported to be associated with potential effects leading to an improvement in insulin resistance, as well as hepatic steatosis, inflammation, and fibrosis [20]. Moreover, although leptin was demonstrated to improve insulin resistance and liver fat, it was also reported to deteriorate hepatic inflammation and fibrosis [20].

Fifthly, interestingly, although our findings demonstrated that visfatin is not associated with NAFLD, the presence and severity of hepatic steatosis, liver fibrosis, lobar inflammation, NASH, and gender differences, a couple of recently published studies reported a significant association between visfatin and hepatocellular carcinoma (HCC), suggesting that visfatin plays an essential role in the proliferation of HCC cells and may also be associated with disease progression [29][30][31][32]. Further future studies are required in order to understand the principles and possible mechanisms through which visfatin could possibly lead to an increased risk of HCC without leading to an increased hepatic steatosis severity or inflammation in NAFLD. Understanding how the signaling pathways that potentially play a role in controlling the expansion of adipose tissue and inflammation is considered crucial in order to prevent obesity-associated comorbidities [33].

Sixthly, NAFLD is mainly a hepatic pathology with several extrahepatic manifestations, including cardiovascular complications, which are the main leading cause of death in NAFLD patients, mostly attributed to ischemic heart disease [34][35][36]. Increased visfatin levels were reported in patients with atherosclerotic and coronary artery disease, both diseases demonstrated to be among the main mortality causes in NAFLD [16][17][18][19]. Current literature lacks studies evaluating CVD (mainly atherosclerotic disease) and visfatin levels in NAFLD patients. It remains to be demonstrated in future studies if NAFLD patients who have concomitant atherosclerotic or coronary artery disease will have increased visfatin levels. Emerging evidence points to the existence of several obesity phenotypes being associated with different CV risk factors, suggesting a relation to the physical and lifestyle features [37]. This might explain how CV prognosis might be improved in certain overweight and obese subjects compared to leaner ones, also known as the obesity paradox. Due to the limited number of available studies evaluating serum visfatin levels in portal inflammation, in addition to visceral adipose tissue and liver visfatin levels in NAFLD and liver fibrosis, we were not able to conduct a meta-analysis for further assessment of these associations.

Seventhly, according to the quality assessment of included studies in our systematic review and meta-analysis, almost half of the studies were rated as “fair”, while five studies were rated as “good” and “poor” each. Hence, results obtained from studies rated as “fair” and “poor” should be cautiously interpreted. As global quality assessment measures are not considered clear enough to identify specific biases in articles, we detailed the description of the items that help with this understanding. Thus, almost half might be subject to selection bias (the population was not clearly specified, or the

controls were not selected from a similar population as the cases for sure). The exposure was valid and reliable in all of the studies. Almost half of the studies used ultrasonography for disease diagnostic, instead of liver biopsy, due to associated risk for the latter technique. Ultrasonography is a technique with high specificity but low sensitivity for fatty liver disease diagnostic; thus, directional misclassification might have occurred, which could contribute to the reduction of the relation between the exposure and the outcome (a bias towards the null) [38][39]. Although few studies used blinding, due to the objective measured used, this could not negatively impact the study findings. Another important negative issue is the fact that almost half of the studies did not control for confounding. Last, due to the study design used, where the timeframe between the exposure and the outcome measure was short and in the absence of the possibility to establish precedence between the two, we cannot know which was first, the exposure of the disease or the outcome.

Our systematic review and meta-analysis has several limitations. Due to the observational design of the included studies in this review, causality between visfatin and NAFLD, hepatic steatosis, liver fibrosis, lobar inflammation, and NASH cannot be confirmed or negated. Although almost half of the included studies used liver biopsy, which is the current gold standard to diagnose NAFLD, the remaining half used ultrasonography, which might possibly lead to underestimation in NAFLD prevalence. Almost half of the studies might be at some risk of selection bias. Also, nearly half of the studies did not control for confounding such as pharmacological treatment or associated comorbidities, which affect metabolic pathways and potentially confound visfatin synthesis, and even for them, residual confounding might exist due to the observational nature of the studies. Moreover, there is heterogeneity among studies with respect to BMI, where adipose tissue may have a significant impact on visfatin levels. However, due to incomplete characteristics of patients in analyzed studies, we were not able to perform further detailed subgroup analysis. Furthermore, due to the limited number of published studies evaluating visfatin levels in NASH, liver fibrosis, lobar inflammation, and hepatic steatosis severity, we were able to assess only a few studies, about two or three studies for each association. Therefore, further studies evaluating these associations are considered necessary. Results should be interpreted with caution due to possible methodological flaws in included studies.

Nevertheless, our systematic review and meta-analysis also has several important strengths. The topic of this review is of important clinical significance, mainly due to the rapid global increase in the prevalence of NAFLD, as well as the associated increased morbidity and mortality rates. We believe that our review points out the missing required data that requires further assessment in future studies while summarizing the current literature in a nonbiased manner. Moreover, we conducted the search strategy in a comprehensive manner using several medical databases, which allowed us to assess the studied association in a systematic manner. We included studies involving participants from several races and backgrounds, which allowed us to have more generalizable results. To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the association between visfatin levels and NAFLD, hepatic steatosis presence and severity, liver fibrosis, lobar inflammation, NASH, and gender differences.

3. Conclusions

In conclusion, we could not find evidence to sustain that visfatin levels are associated with NAFLD, the presence or severity of hepatic steatosis, liver fibrosis, lobar inflammation, NASH, and gender differences. Nevertheless, obtained results should be interpreted with caution due to the imperfect methodological quality of the assessed studies.

References

1. Dumitrascu, D.L.; Neuman, M.G. Non-alcoholic fatty liver disease: An update on diagnosis. Clujul Med. 2018, 91, 147–150.
2. Sporea, I.; Popescu, A.; Dumitrașcu, D.; Brisc, C.; Nedelcu, L.; Trifan, A.; Gheorghe, L.; Braticevici, C.F. Nonalcoholic F atty Liver Disease: Status Quo. J. Gastrointestin. Liver Dis. 2018, 27, 439–448.
3. Mantovani, A.; Scorletti, E.; Mosca, A.; Alisi, A.; Byrne, C.D.; Targher, G. Complications, morbidity and mortality of nonal coholic fatty liver disease. Metabolism 2020, 111, 154170.
4. Francque, S.M.; van der Graaff, D.; Kwanten, W.J. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysi ological mechanisms and implications. J. Hepatol. 2016, 65, 425–443.
5. Blond, E.; Disse, E.; Cuerq, C.; Drai, J.; Valette, P.-J.; Laville, M.; Thivolet, C.; Simon, C.; Caussy, C. EASL-EASD-EAS O clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: Do they lead to over-referral? Diabetologia 2017, 60, 1218–1222.

6. Patel, A.; Gawrieh, S.; Rizvi, S.; Xiang, Q.; Szabo, A.; Saeian, K. Management strategies used for nonalcoholic fatty liv er disease: Survey of AASLD members. Gastroenterology 2009, 136, A847.
7. Chan, W.K.; Treeprasertsuk, S.; Imajo, K.; Nakajima, A.; Seki, Y.; Kasama, K.; Kakizaki, S.; Fan, J.-G.; Song, M.J.; Yoo n, S.K.; et al. Clinical features and treatment of nonalcoholic fatty liver disease across the Asia Pacific region—The GO ASIA initiative. Aliment. Pharmacol. Ther. 2018, 47, 816–825.
8. Mirza, M.S. Obesity, Visceral Fat, and NAFLD: Querying the Role of Adipokines in the Progression of Nonalcoholic Fatt y Liver Disease. ISRN Gastroenterol. 2011, 2011, 592404.
9. Fang, Y.-L.; Chen, H.; Wang, C.-L.; Liang, L. Pathogenesis of non-alcoholic fatty liver disease in children and adolesce nce: From “two hit theory” to “multiple hit model”. World J. Gastroenterol. 2018, 24, 2974–2983.
10. Funcke, J.B.; Scherer, P.E. Beyond adiponectin and leptin: Adipose tissue-derived mediators of inter-organ communicat ion. J. Lipid Res. 2019, 60, 1648–1684.
11. Samal, B.; Sun, Y.; Stearns, G.; Xie, C.; Suggs, S.; Mcniece, I. Cloning and characterization of the cDNA encoding a no vel human pre-B-cell colony-enhancing factor. Mol. Cell Biol. 1994, 14, 1431–1437.
12. Wang, T.; Zhang, X.; Bheda, P.; Revollo, J.R.; Imai, S.-I.; Wolberger, C. Structure of Nampt/PBEF/visfatin, a mammalia n NAD+ biosynthetic enzyme. Nat. Struct. Mol. Biol. 2006, 13, 661–662.
13. Revollo, J.R.; Grimm, A.A.; Imai, S. The NAD biosynthesis pathway mediated by nicotinamide phosphoribosyltransfera se regulates Sir2 activity in mammalian cells. J. Biol. Chem. 2004, 279, 50754–50763.
14. Adolph, T.E.; Grander, C.; Grabherr, F.; Tilg, H. Adipokines and Non-Alcoholic Fatty Liver Disease: Multiple Interactions. Int. J. Mol. Sci. 2017, 18, 1649.
15. Ognjanovic, S.; Bao, S.; Yamamoto, S.Y.; Garibay-Tupas, J.; Samal, B.; Bryant-Greenwood, G.D. Genomic organizatio n of the gene coding for human pre-B-cell colony enhancing factor and expression in human fetal membranes. J. Mol. Endocrinol. 2001, 26, 107.
16. Duman, H.; Özyıldız, A.G.; Bahçeci, İ.; Duman, H.; Uslu, A.; Ergül, E. Serum visfatin level is associated with complexity of coronary artery disease in patients with stable angina pectoris. Ther. Adv. Cardiovasc. Dis. 2019, 13, 1–7.
17. Zheng, L.-Y.; Xu, X.; Wan, R.-H.; Xia, S.; Lu, J.; Huang, Q. Association between serum visfatin levels and atheroscleroti c plaque in patients with type 2 diabetes. Diabetol. Metab. Syndr. 2019, 11, 60.
18. Hognogi, L.D.M.; Simiti, L.V. The cardiovascular impact of visfatin—An inflammation predictor biomarker in metabolic s yndrome. Clujul Med. 2016, 89, 322–326.
19. Romacho, T.; Sánchez-Ferrer, C.F.; Peiró, C. Visfatin/Nampt: An adipokine with cardiovascular impact. Mediat. Inflam m. 2013, 2013, 946427.
20. Polyzos, S.A.; Kountouras, J.; Mantzoros, C.S. Adipokines in nonalcoholic fatty liver disease. Metabolism 2016, 65, 106 2–1079.
21. Boutari, C.; Perakakis, N.; Mantzoros, C.S. Association of Adipokines with Development and Progression of Nonalcohol ic Fatty Liver Disease. Endocrinol. Metab. 2018, 33, 33–43.
22. Bekaert, M.; Verhelst, X.; Geerts, A.; Lapauw, B.; Calders, P. Association of recently described adipokines with liver hist ology in biopsy-proven non-alcoholic fatty liver disease: A systematic review. Obes. Rev. 2016, 17, 68–80.
23. Eslam, M.; Newsome, P.N.; Anstee, Q.M.; Targher, G.; Gomez, M.R.; Zelber-Sagi, S.; Wong, V.W.; Dufour, J.F.; Schatte nberg, J.; Arrese, M.; et al. A new definition for metabolic associated fatty liver disease: An international expert consens us statement. J. Hepatol. 2020.
24. Eslam, M.; Sanyal, A.J.; George, J. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fat ty Liver Disease. Gastroenterology 2020.
25. Leoni, S.; Tovoli, F.; Napoli, L.; Serio, I.; Ferri, S.; Bolondi, L. Current guidelines for the management of non-alcoholic fa tty liver disease: A systematic review with comparative analysis. World J. Gastroenterol. 2018, 24, 3361–3373.
26. Ismaiel, A.; Leucuta, D.C.; Popa, S.L.; Fagoonee, S.; Pellicano, R.; Abenavoli, L.; Dumitrascu, D.L. Non-invasive bioma rkers in predicting non-alcoholic steatohepatitis and assessing liver fibrosis: Systematic review and meta-analysis. Pan minerva Med. 2020.
27. Dyson, J.K.; Anstee, Q.M.; McPherson, S. Non-alcoholic fatty liver disease: A practical approach to diagnosis and stagi ng. Frontline Gastroenterol. 2014, 5, 211–218.
28. Targher, G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: The plot th ickens. Diabet. Med. 2007, 24, 1–6.

29. Ninomiya, S.; Shimizu, M.; Imai, K.; Takai, K.; Shiraki, M.; Hara, T.; Tsurumi, H.; Ishizaki, S.; Moriwaki, H. Possible Role of Visfatin in Hepatoma Progression and the Effects of Branched-Chain Amino Acids on Visfatin-Induced Proliferation in Human Hepatoma Cells. Cancer Prev. Res. 2011, 4, 2092–2100.
30. Pazgan-Simon, M.; Kukla, M.; Zuwała-Jagiełło, J.; Derra, A.; Bator, M.; Menżyk, T.; Lekstan, A.; Grzebyk, E.; Simon, K. Serum visfatin and vaspin levels in hepatocellular carcinoma (HCC). PLoS ONE 2020, 15, e0227459.
31. Tsai, I.T.; Wang, C.-P.; Yu, T.-H.; Lu, Y.-C.; Lin, C.-W.; Lu, L.-F.; Wu, C.-C.; Chung, F.-M.; Lee, Y.-J.; Hung, W.-C.; et al. Circulating visfatin level is associated with hepatocellular carcinoma in chronic hepatitis B or C virus infection. Cytokine 2017, 90, 54–59.
32. Liang, N.; Chen, Y.; Yang, L.; He, S.; Liu, T. Visfatin increases miR-21 to promote migration in HCC. Cell Mol. Biol. 201 8, 64, 48–52.
33. Catalán, V.; Gómez-Ambrosi, J.; Rodríguez, A.; Pérez-Hernández, A.I.; Gurbindo, J.; Ramírez, B.; Méndez-Giménez, L.; Rotellar, F.; Valentí, V.; Moncada, R.; et al. Activation of Noncanonical Wnt Signaling Through WNT5A in Visceral Ad ipose Tissue of Obese Subjects Is Related to Inflammation. J. Clin. Endocrinol. Metab. 2014, 99, E1407–E1417.
34. Targher, G.; Day, C.P.; Bonora, E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N. En gl. J. Med. 2010, 363, 1341–1350.
35. Ismaiel, A.; Colosi, H.A.; Rusu, F.; Dumitrascu, D.L. Cardiac Arrhythmias and Electrocardiogram Modifications in Non-A lcoholic Fatty Liver Disease. A Systematic Review. J. Gastrointestin. Liver Dis. 2019, 28, 483–493.
36. Byrne, C.D.; Targher, G. NAFLD: A multisystem disease. J. Hepatol. 2015, 62, S47–S64.
37. Vecchié, A.; Dallegri, F.; Carbone, F.; Bonaventura, A.; Liberale, L.; Portincasa, P.; Frühbeck, G.; Montecucco, F. Obesit y phenotypes and their paradoxical association with cardiovascular diseases. Eur. J. Intern. Med. 2018, 48, 6–17.
38. Hernaez, R.; Lazo, M.; Bonekamp, S.; Kamel, I.; Brancati, F.L.; Guallar, E.; Clark, J.M. Diagnostic accuracy and reliabili ty of ultrasonography for the detection of fatty liver: A meta-analysis. Hepatology 2011, 54, 1082–1090.
39. Dasarathy, S.; Dasarathy, J.; Khiyami, A.; Joseph, R.; Lopez, R.; McCullough, A.J. Validity of real time ultrasound in the diagnosis of hepatic steatosis: A prospective study. J. Hepatol. 2009, 51, 1061–1067.
