

Association of Non-Alcoholic Fatty Liver Disease with Peripheral Diabetic Polyneuropathy: a systematic review and meta-analysis

Aims: There is conflicting documentation of a relationship between non-alcoholic fatty liver disease (NAFLD) and diabetic polyneuropathy (DPN). The aim of this meta-analysis is to estimate the DPN risk among NAFLD patients according to the available data.

Methods: We performed a comprehensive literature review until 4 June 2021 and considered clinical trials analysing the association between NAFLD and DPN.

Results: Thirteen studies (9614 participants) were included. DPN prevalence was significantly higher in patients with NAFLD, compared to those without NAFLD [odds ratio (OR) (95%CI) 2.48 (1.42-4.34), $p=0.001$; I^2 96%]. This result was confirmed in type 2 diabetes (DPN prevalence 43% Vs 24%, OR 2.51 (1.33-4.74), $p=0.005$; I^2 97%), but not in type 1 diabetes [OR 2.44 (0.85-6.99), $p=0.100$; I^2 77%]. In addition, NAFLD subjects showed higher body mass index and diabetes duration compared to non NAFLD subjects ($p<0.001$) in both type 2 and type 1 diabetes.

Conclusions: This meta-analysis shows a greater prevalence of DPN in subjects with type 2 diabetes and NAFLD despite a high heterogeneity among studies (mainly regarding population characteristics and diagnostic methods for DPN and NAFLD). This was not true in type 1 diabetes, probably due to the confounding role of the longer diabetes duration. These results support the need for an early detection of DPN, especially in patients with NAFLD.

Comments. NAFLD is a metabolically derangement-based liver disease, characterised by the presence of steatosis in more than 5% of hepatocytes, in association with metabolic risk factors and in the absence of excessive alcohol consumption or other chronic liver diseases. NAFLD is present in >25% of the global population and is highly prevalent in patients with type 2 diabetes (60-75%). NAFLD is associated with an increased risk of macro- and micro-vascular complications in patients with diabetes in particular albuminuria and retinopathy, while scarce and conflicting information exists about the association between NAFLD and DPN. NAFLD is the next big thing in diabetes research both in terms of relevance (i.e., disease burden) and relative lack of predictive algorithms. Amongst researchers involved in diabetic neuropathy, this study brings into discussion research opportunities into aspects of small and large fibre neural involvement in NAFLD. There is already some evidence that large fibre involvement is pre-existing in type 2 subjects with NAFLD (Huang J et al. *J Diabetes Investig.* 2021;12:2019-2027; Williams KH et al. *J Diabetes Complications.* 2015;29:1240-7). The research question that is very interesting to scope is if abnormal indices for small fibre neuropathy (structure and function) can *predict* the development of NAFLD in such patients and if so, such measures could have further importance as diagnostic methods in clinical areas apart from diabetes neuropathy. Perhaps this would be of interest to discuss amongst interested stakeholders at Neurodiab 2022?

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Reference. Greco C, Nascimbeni F, Carubbi F, Andreone P, Simoni M, Santi D. Association of Nonalcoholic Fatty Liver Disease (NAFLD) with Peripheral Diabetic Polyneuropathy: A Systematic Review and Meta-Analysis. *J Clin Med.* 2021 Sep 28; 10(19):4466. doi: 10.3390/jcm10194466
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