Nonalcoholic Fatty Liver Disease and Peripheral Diabetic Polyneuropathy

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Peripheral diabetic polyneuropathy (DPN) is a microvascular complication of diabetes mellitus (DM), representing the most clinically relevant manifestation of typical forms of diabetic neuropathy (DN). DPN has been associated with another pathological condition linked to DM and obesity, the nonalcoholic fatty liver disease (NAFLD). NAFLD is a metabolically derangement-based liver disease, defined by the presence of steatosis in more than 5% of hepatocytes, in association with metabolic risk factors (such as obesity, diabetes, and dyslipidemia) and in the absence of excessive alcohol consumption or other chronic liver diseases.

Keywords: NAFLD ; diabetes mellitus ; peripheral polyneuropathy

1. Introduction

Peripheral diabetic polyneuropathy (DPN) is a microvascular complication of diabetes mellitus (DM), representing the most clinically relevant manifestation of typical forms of diabetic neuropathy (DN). DPN has been defined by the Toronto Expert Panel on Diabetic Neuropathy as a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvascular alterations, resulting from the chronic hyperglycemia typical of diabetes and cardiovascular risk covariates [1]. DPN occurs in at least 20% of people with type 1 DM (T1DM) after 20 years of disease duration, as suggested by large observational cohorts [2][3] and the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study [4][5]. Considering type 2 DM (T2DM), DPN has been detected in at least 10–15% of newly diagnosed patients with T2DM [6][7], and up to 50% after 10 years of disease duration [8][9]. Moreover, DPN has been identified in 11% to 23% of people with prediabetes [10]. From a clinical point of view, the DPN diagnosis is extremely relevant in DM management, since it confers a predisposition to pain, numbness, ulceration, and amputation of the distal extremities, increasing the risk of all-cause and cardiovascular disease mortality [11][12][13].

Starting from the clinical relevance of DPN, many authors tried to identify factors able to predict DPN in DM. Till now, diabetes duration and glycemic control, expressed by glycated hemoglobin (HbA1c), represent the main predictive factors [14]. Moreover, metabolic syndrome components, such as hypertriglyceridemia, hypertension, abdominal obesity, and low high-density lipoprotein (HDL) serum levels, are consistently associated with DPN in both T2DM and T1DM [15][16]. Alongside metabolic variables, several lifestyle habits have been detected as further correlates, such as smoking, alcohol abuse, height, and older age [15]. In general, many studies suggested that DPN prevalence was higher in cases of concomitant comorbid conditions, such as micro- (nephropathy or retinopathy), macro- vascular disease (peripheral arterial disease or cardiovascular disease) and depression [17]. Finally, new biochemical markers have been investigated as potential predictive markers of DPN. In particular, novel systemic biomarkers of oxidative stress (i.e., reactive oxygen species), inflammation (interleukin (IL)-6, and tumor necrosis factor (TNF)-a), and vascular activation, have been linked to distal DPN development [16].

Recently, DPN has been associated with another pathological condition linked to DM and obesity, the nonalcoholic fatty liver disease (NAFLD). NAFLD is a metabolically derangement-based liver disease, defined by the presence of steatosis in more than 5% of hepatocytes, in association with metabolic risk factors (such as obesity, diabetes, and dyslipidemia) and in the absence of excessive alcohol consumption or other chronic liver diseases [18][19]. NAFLD affects more than 25% of the global population [20] and is largely demonstrated as highly prevalent in patients with T2DM (60–75%) [21]. Many studies proved that NAFLD is associated with an increased risk of macro- and micro-vascular complications in diabetic patients [22][23][24], notably including albuminuria [25] and retinopathy [26]. Currently, there is little information about the association between NAFLD and DPN, and the available data are scarce and conflicting.

2. Current Insights

Several studies have been designed to explore the impact of NAFLD on DPN prevalence in both T1DM and T2DM patients so far, but this is the first attempt to systematically combine these results together in a meta-analysis. We demonstrate that DPN is more frequent when NAFLD is associated to DM, evaluating more than 9000 diabetic subjects. This result has an immediate clinical translation. Indeed, we clearly demonstrate that a diabetic patient must be carefully evaluated for the onset of peripheral neurological complications, especially when NAFLD is associated with diabetes. This is particularly true in T2DM or in T1DM and advancing age. Indeed, we demonstrate that DPN risk in T1DM is higher when the diabetes duration is longer, confirming that the long disease duration could be a confounding factor for DPN development. Moreover, here we highlight how NAFLD in DM is strictly related to high BMI and diabetes duration, confirming how the prevention of the DM complications must necessarily involve attention to weight gain. In details, NAFLD determines a complex array of metabolic and extra-hepatic consequences, which result from the intra-hepatic deposition of ectopic fat. This condition strongly correlates with abdominal obesity, insulin resistance, and all components of metabolic syndrome. Notably, obesity is one of the clinical correlates of PND in DM2 people. Therefore, obesity itself could represent a confounding factor of the association between NAFLD and PND, at least in DM2.

The link between NAFLD and microvascular complications in diabetic patients is based so far only on association studies, but the cause-effect relationship is far from being completely elucidated. In particular, NAFLD has been suggested as an independent predictor for diabetic kidney disease and proliferative diabetic retinopathy in patients with T2DM [27][28], while the association with DPN is more debated. Thus, NAFLD has been considered as a risk factor for organ-specific complications of DM. What is largely supposed is that NAFLD could exacerbate insulin resistance, impairs dyslipidemia, and predisposes vessels to atherogenic damages, throughout the release of pro-inflammatory, pro-coagulant, and pro-atherogenic factors [29][30][31]. Moreover, NAFLD induces those damages leading to endothelial dysfunction, predisposing to vascular diseases [32].

In particular, considering DPN, the pathogenetic relationship with NAFLD is still under debate. From one side, the metabolic asset leading to NAFLD is largely considered among the risk factors for DPN development. Moreover, in addition to the known metabolic correlates, the possible molecular mediators linking NAFLD with DPN could include the increased release of some pathogenic mediators from the liver, such as advanced glycation end-products, reactive oxygen species, C reactive protein, IL-6, and TNF-α, as also suggested for retinopathy and chronic kidney disease [28].

NAFLD natural history describes early stages, typically asymptomatic, with only incidental finding of abnormal liver enzymes, such as raised plasma alanine aminotransferase (ALT), aspartate transaminase (AST), and/or gamma-glutamyltransferase (γGT) [33]. However, since liver enzymes largely fluctuate in NAFLD patients, they are not routinely considered as clinical markers of NAFLD diagnosis or severity [18][34][35]. Thus, the use of imaging techniques, such as ultrasound, is generally applied as a first line diagnostic step in evaluating hepatic steatosis, also considering its safety and availability, and low cost [36]. With this in mind and considering the main result of our meta-analysis, it is clear that diabetic patients must undergo hepatic ultrasound evaluation in order to precociously detect the presence of NAFLD. However, NAFLD severity could also have a role in comorbidities development. The gold standard to detect NAFLD severity, in terms of steatosis amount, necro-inflammation, and fibrosis is represented by liver biopsy [18] that is not suitable for large-scale screening purposes, due to invasiveness and costs. Several emerging non-invasive techniques, notably including composite biomarkers, ultrasound elastography, or magnetic resonance, display good performance in evaluating NAFLD severity and have been proposed for widespread use in clinical practice. Unfortunately, only a minority of studies enrolled in our meta-analysis evaluated NAFLD severity, preventing us from a reliable analysis of such data. Future studies should be designed to identify whether NAFLD severity could predict the DPN development.

The result of this meta-analysis provides a clear snapshot on what we know about the association among DM, NAFLD, and peripheral DPN. This setting, however, is very heterogeneous. Indeed, all studies enrolled are population-based matched case-control studies, with a clear difference among inclusion and exclusion criteria. Moreover, only in 7 out of 13 studies the aim of the study was the evaluation of the prevalence of micro-vascular complications in diabetic patients. In the remaining part, the peripheral DPN has been assessed in relation to specific clinic or biochemical characteristics of enrolled patients, such as uric acid or liver fibrosis. Thus, the approach to our study question (i.e., whether NAFLD predisposes to peripheral DPN in patients with DM) is widely different, limiting the robustness of a comprehensive evaluation. Moreover, the peripheral DPN can be probable and confirmed, according to the diagnostic path followed. In particular, only when NCS is performed, a confirmed diagnosis should be reached. Our meta-analysis collected only six studies in which a confirmed DPN could be verified, increasing the heterogeneity among studies. Furthermore, the clinical management of patients enrolled in each study is extremely variable. In particular, diabetic comorbidities and complications management could have a significant role in DPN development. Here, however, we could not adjust the

meta-analytic approach with the therapies applied to enrolled patients. This could lead to confounding results considering secondary endpoints. As a confirmation, we highlight that lipid profile does not change between the study and control group, although several studies suggested a worse lipid profile in patients with NAFLD [37][38][39]. Thus, we could not speculate in favour or in contrast to dyslipidaemia as a factor linking NAFLD and peripheral neuropathy in diabetic patients.

3. Conclusions

The present meta-analysis suggests a significantly increased DPN prevalence among diabetic patients with NAFLD, in particular in the case of T2DM. Indeed, T2DM combined with NAFLD demonstrated a higher prevalence of peripheral DPN than the T2DM-alone group. This result has not been confirmed in T1DM, likely due to the longer duration of disease as a confounding factor. Moreover, our findings confirm that NAFLD in DM is strictly related to high BMI and also to diabetes duration. In conclusion, these results suggest that physicians should pay more attention to the early detection of DPN, especially in patients with NAFLD. Lastly, large-scale prospective studies are required to elucidate causal associations between NAFLD and the microvascular complications, including DPN, in diabetic people.

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