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Nonalcoholic fatty liver disease is associated with an increased prevalence of distal symmetric polyneuropathy in adult patients with type 1 diabetes

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ABSTRACT

Aims: Presently, data on the association between nonalcoholic fatty liver disease (NAFLD) and distal symmetric polyneuropathy in people with diabetes are scarce and conflicting. The aim of this retrospective, cross-sectional study was to examine whether NAFLD was associated with an increased prevalence of distal symmetric polyneuropathy in type 1 diabetic adults.

Methods: We studied all white type 1 diabetic outpatients ($n = 286$, 42.3% male, mean age 43 ± 14 years, median diabetes duration 17 [10–30] years), who participated in a foot screening program at our adult diabetes clinic after excluding those who had excessive alcohol consumption and other known causes of chronic liver disease. NAFLD was diagnosed by ultrasonography. Distal symmetric polyneuropathy was detected using the Michigan Neuropathy Screening Instrument method and the biothesiometer Vibrotest.

Results: Overall, the prevalence rates of NAFLD and distal symmetric polyneuropathy were 52.4% and 35.3%, respectively. Patients with NAFLD had a substantially increased prevalence of distal symmetric polyneuropathy compared to their counterparts without NAFLD (51.0% vs. 17.1%, $p < 0.001$). In univariate analysis, NAFLD was associated with an approximately 5-fold increased risk of prevalent distal symmetric polyneuropathy (odds ratio [OR] 5.32, 95% confidence interval [CI] 3.1–9.3, $p < 0.001$). This association remained significant even after adjustment for age, sex, diabetes duration, hemoglobin A1c, diabetic retinopathy, smoking, metabolic syndrome, chronic kidney disease and carotid artery stenoses ≥ 40% (adjusted-OR 2.23, 95% CI 1.1–4.8, $p < 0.05$).

Conclusions: Our results show that NAFLD, diagnosed by ultrasonography, is strongly associated with an increased risk of distal symmetric polyneuropathy in type 1 diabetic adults, independently of several cardio-metabolic risk factors.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide (occurring in up to 30% of adults in Western countries) and has now become the second most frequent indication for liver transplantation in the United States with the worrying prospect of becoming the first indication in the coming years.[1–3]

The prevalence of NAFLD in people with diabetes is much higher, ranging from 50% to 75% in patients with type 2 diabetes and from 40% to 50% in those with type 1 diabetes.[3,4] In addition, patients with diabetes are more likely to develop the more severe histologic forms of NAFLD, including nonalcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis.[3,4] To date, convincing evidence indicates that NAFLD is associated not only with considerable liver-related morbidity and mortality, but also with an increased risk of cardiovascular disease (CVD), chronic kidney disease (CKD) and other important extra-hepatic complications both in patients without diabetes and in those with type 1 or type 2 diabetes.[5–9]

In parallel, distal symmetric polyneuropathy, a chronic, nerve-length-dependent, sensory and motor polyneuropathy, is the most common form of diabetic neuropathy that affects at least one third of patients with type 1 or type 2 diabetes.[10–12] Notably, the presence of distal symmetric polyneuropathy not only confers a predisposition to painless foot ulcers and subsequent amputations, but is also associated with an increased risk of all-cause and CVD mortality.[13–15] It is well known that poor glycemic control is the strongest risk factor for the development of diabetic peripheral

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neuropathy, but other important pathological conditions, such as dyslipidemia, hypertension, diabetic retinopathy, nephropathy and smoking, may play important roles.[10,16–18] Given that all these risk factors and pathological conditions are also strongly associated with NAFLD (irrespective of pre-existing diabetes), and that NAFLD is associated with an increased risk of diabetic nephropathy (another chronic microvascular complication of diabetes),[7,8] it is reasonable to assume that there is an association between NAFLD and diabetic distal symmetric polyneuropathy. Currently, however, published studies that have evaluated the existence of such association are very few and have produced conflicting results.[19–21]

Thus, the aim of this retrospective, observational study was to assess whether NAFLD, as diagnosed by ultrasonography, was associated with an increased prevalence of distal symmetric polyneuropathy in type 1 diabetic adults.

2. Methods

2.1. Patients

For the purpose of this study, we have retrospectively analyzed the electronic records of all white outpatients with established type 1 diabetes ($n = 563$), who regularly attended our adult diabetes clinic and accepted to participate in a foot-screening program (over the years 2004–2012). The only exclusion criteria for participating in this screening program were the presence of foot ulcers, gangrene or prior amputations. Type 1 diabetes was diagnosed by the typical presentation of disease, the absolute dependence on insulin treatment for survival, the presence of undetectable fasting C-peptide levels and the presence of anti-islet cell auto-antibodies.[10]

We have subsequently excluded all patients with: (1) missing liver ultrasound data ($n = 184$, 32.7%); (2) a history of end-stage renal disease or malignancy ($n = 6$, 1%); and (3) a documented history of cirrhosis of any etiology or chronic liver disease due to secondary causes, such as excessive alcohol consumption (i.e., defined as alcohol consumption >30 g/day for men and >20 g/day for women, respectively), viral hepatitis or use of steatogenic medications ($n = 87$, 15.4%).

As a consequence of this selection, 286 (50.8%) adult outpatients with established type 1 diabetes (mean age 43 ± 14 years; 42.3% male; median duration of diabetes 17 [10–30] years) were included in the final analysis. Details of the study design are summarized in Supplemental Fig. 1.

No significant differences were found in main demographic/laboratory variables and frequency of distal symmetric polyneuropathy between patients with ($n = 286$) and without ($n = 184$) liver ultrasound examination (data not shown). It is important to note that in our diabetes clinic an ultrasound examination of the liver is almost routinely performed among the outpatients with diabetes.

The local ethics committee approved the study protocol. The informed consent requirement for this study was exempted by the ethics committee, because researchers only accessed retrospectively a de-identified database for analysis purposes.

2.2. Clinical and laboratory data

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Blood pressure was measured in duplicate with a standard mercury manometer after a rest of at least 5 min. Patients were considered as having hypertension if their blood pressure was ≥130/85 mm Hg or if they were taking any anti-hypertensive drugs. Detailed information on smoking status, daily alcohol consumption and current use of medications was obtained from all patients via interviews during medical examinations.

Venous blood was drawn in the morning after an overnight fast. Serum lipids, creatinine (measured using a Jaffe´ rate-blanked and compensated assay), liver enzymes and other biochemical blood measurements were determined by standard laboratory procedures on Siemens Dimension Vista (Siemens, Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA). Normal ranges for serum alanine and aspartate aminotransferase levels (ALT and AST) in our laboratory were 10–40 U/l for both men and women. Normal ranges for serum gamma-glutamyltransferase (GGT) levels were 5–50 units/l for women and 5–55 U/l for men, respectively. LDL-cholesterol was calculated by the Friedewald's equation. No patients had serum triglyceride levels above 4.5 mmol/l. Hemoglobin A1c (HbA1c) was measured by a high-performance liquid chromatography analyzer on Tosoh G7 automated analyzer (Tosoh Bioscience Inc., San Francisco, CA; USA); the upper limit of normal for our laboratory was 5.6% (38 mmol/mol). The estimated glomerular filtration rate ($eGFR_{MDRD}$) was calculated by the 4-variable Modification of Diet in Renal Disease (MDRD) study equation.[23] Albuminuria was measured using an immuno-nephelometric method on a morning spot urine sample and expressed as the albumin-to-creatinine ratio (ACR) on Beckman-Coulter IMMAGE (Beckman-Coulter Instruments, Fullerton, CA; USA). The presence of CKD was defined as an $eGFR_{MDRD} < 60$ ml/min/1.73 m^2, macro-albuminuria (defined as an urinary ACR >30 mg/mmol), or both.

Metabolic syndrome was diagnosed by a modified Adult Treatment Panel (ATP)-III definition, as waist circumference was available only in few patients ($n = 89$). Accordingly with this modified ATP-III definition,[24,25] a patient with type 1 diabetes was classified as having the metabolic syndrome if he/she had at least two of the following four components: (i) BMI >28 kg/m^2 in men or >27 kg/m^2 in women; (ii) triglycerides ≥1.7 mmol/l; (iii) HDL-cholesterol <1.0 mmol/l in men and <1.29 mmol/l in women or receiving lipid-lowering drugs; and (iv) blood pressure ≥ 130/85 mm Hg or receiving anti-hypertensive drugs.

A single ophthalmologist diagnosed diabetic retinopathy using fundoscopy after pupillary dilation according to a clinical disease severity scale (no retinopathy, non-proliferative, proliferative or laser-treated retinopathy). The presence of proliferative retinopathy was confirmed by fundus fluorescein angiography. The presence of atherosclerotic plaques (i.e., stenosis ≥40%) at the level of either the internal or common carotid arteries was also detected by echo-Doppler scanning in all patients.

2.3. Assessment of diabetic peripheral neuropathy

To assess diabetic peripheral neuropathy, we applied a validated Michigan Neuropathy Screening Instrument method (MNSI), as described elsewhere.[22,26] Since this method was designed only for screening purposes, the obtained results can be referred to 'possible' distal symmetric polyneuropathy. A trained nurse administered the MNSI questionnaire to all our patients. This questionnaire consists of 15 "yes or no" questions, including one relevant to general asthenia and one relevant to peripheral vascular disease, as described by the Michigan Clinic.[27] After administration of the MNSI questionnaire, we also performed in all patients: (*i*) *a* foot inspection looking for the presence of deformities (e.g., hammer toes, overlapping toes, hallux valgus, joint subluxation, prominent metatarsal heads), dry skin, callus, infection or ulceration; (*ii*) a non-invasive, quantitative assessment of vibration sensation threshold (VPT) at the dorsum of the great toe using a biothesiometer Vibrotest instead that a 128-Hz tuning fork; and (*iii*) a grading of ankle reflexes (normal, reduced, or absent). The results of physical examination were as follows: 1 point in presence of alterations of the foot at inspection, 1 point to a pathologic ankle reflex (0.5 point when evocable with the Jendrassik maneuver), and 1 point to a VPT higher than 25 Volt. Evaluating both feet, a maximum score of 8 points for each patient was possible.

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