Serum lipidomic determinants of incident neuropathy in type 2 diabetes

Aim: In this study, lipidomic profiles in early type 2 diabetes were evaluated as possible predictors of diabetic neuropathy.
Methods: This study is an observational study of participants with type 2 diabetes (N=69) who were initially participants of randomized controlled trial assessing the efficacy of angiotensin receptor blockers in halting the progression of diabetic kidney disease (DKD) (1996-2001) and are now enrolled in a longitudinal follow-up evaluating complication development. Lipidomic profiles were evaluated in participants who then developed diabetic neuropathy 10 years later. Lipidomic profiles were measured from stored serum samples that were analyzed via mass spectrometry, generating 236 unique lipids (including 6.8% free fatty acids, 32.2% glycerolipids, 5.1% cholesteryl-esters, 35.1% phospholipids, 8.5% sphingomyelins, and 12.3% acylcarnitines). Neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) Index (combined examination and questionnaire; a score ≥2.5407 indicated the presence of neuropathy). Logistic regression was used to compare the standardized relative abundance of each lipid species to the presence or absence of neuropathy (adjusted for age, sex, BMI, systolic and diastolic blood pressure, hemoglobin A1c, statin use, use of other lipid-lowering agents, chain length, and saturation status).
Results: Using the MNSI Index, n=27 participants had diabetic neuropathy and n=42 participants were neuropathy-free at the 10-year follow-up. Neuropathy participants were noted to have higher systolic and diastolic blood pressure and higher urine albumin creatinine ratio. Lower medium-chain acylcarnitines, higher free fatty acids, lower phosphatidylcholines, and higher lysophosphatidylcholines were associated with higher MNSI indices.
Conclusions: Lower medium-chain acylcarnitines, higher free fatty acids, lower phosphatidylcholines, and higher lysophosphatidylcholines are associated with the development and severity of diabetic neuropathy in type 2 diabetes.

Comments. Metabolic syndrome components have long been recognized as likely risk factors for diabetic neuropathy. The authors of this study have previously assessed lipidomic profiles of incident DKD (Afshinnia F et al, *JCI Insight*, 2019; 4:e3130317) in the same cohort of type 2 diabetes participants, with similar findings in those with and without DKD. Cross-sectional studies assessing the lipidomic profiles of concurrent diabetic neuropathy suggest that free fatty acids, acylcarnitines and complex lipids may also play a role in neuropathy development as well (Rumora AE et al *Ann Clin Transl Neurol. 2021;8:1292-1307*). This study is the first to evaluate lipidomic profiles with incident neuropathy.
The investigators of this study found that decreased medium-chain acylcarnitines, increased free fatty acids, decreased phosphatidylcholines, and increased lysophosphatidylcholines are associated with the development of MNSI-defined diabetic neuropathy, suggesting that impaired β-oxidation plays a significant role in neuropathy development. The strengths of this study are: 1) the novel approach; and 2) the longitudinal follow-up, suggesting more of a causal role of lipids in incident neuropathy. The limitations are: 1) the baseline assessment of neuropathy was a risk-prediction tool rather than the MNSI index used at the 10-year follow-up, and 2) the lack of more comprehensive neuropathy assessment measures (i.e., nerve conduction studies). This study is the first to demonstrate differences in the lipidome in incident neuropathy. Larger studies are needed to confirm these findings.
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Reference. Afshinnia F, Reynolds EL, Rajendiran TM, Soni T, Byun J, Savelieff MG, Looker HC, Nelson RG, Michailidis G, Callaghan BC, Pennathur S, Feldman EL. Serum lipidomic determinants of human diabetic neuropathy in type 2 diabetes. Ann Clin Transl Neurol. 2022 Sep;9(9):1392-1404. doi: 10.1002/acn3.51639. Epub 2022 Aug 3. PMID: 35923113; PMCID: PMC9463947.
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