

Glycaemic status modifies differently microvascular permeability of peripheral nerves in patients with type 2 diabetes with and without diabetic neuropathy

Aim: To measure microvascular permeability to the sciatic nerve by dynamic contrast-enhanced magnetic resonance neurography (DCE-MRN) in individuals with type 2 diabetes (DM2) with and without diabetic polyneuropathy (DPN) and to evaluate associations between MRN perfusion and blood glucose and HbA1c levels.

Methods: A total of 58 individuals with DM2, of whom 20 individuals had confirmed DPN applying the Toronto criteria, were included in this cross-sectional single center study. MRN was performed of the sciatic nerve at the right distal thigh in a 3T MR-scanner. The nerve's capillary permeability was calculated as a volume transfer constant (K^{trans} , min^{-1}) determined based on the shift in concentration of a small contrast agent in plasma and extravascular compartments over time (Jende JME et al *Ann Clin Transl Neurol* 2022;9:830-840). Serological testing was performed in a fasting state directly prior to MR-examination.

Results: Groups with and without DPN were similar on age, BMI, HbA1c, diabetes duration, and renal function. Microvascular perfusion was lower in individuals with DPN compared to individuals without DPN (DPN: $0.035 \pm 0.006 \text{ min}^{-1}$ Vs. no DPN: $0.041 \pm 0.014 \text{ min}^{-1}$, $p=0.036$). In individuals without DPN an inverse correlation was observed between microvascular perfusion and HbA1c ($r=-0.43$, $p=0.012$). In individuals with DPN a positive correlation was observed between microvascular perfusion and fasting glucose ($r=0.46$, $p=0.04$) as well as HbA1c ($r=0.55$, $p=0.015$).

Conclusions: MRN derived microvascular perfusion of the sciatic nerve points to differing effects of glucose control on the capillary permeability of peripheral nerves in individuals with DM2 depending on the presence of DPN.

Comments. Glycaemic control has proven little to no benefits in preventing the development and progression of DPN in individuals with DM2. Moreover, the pathophysiology of DPN with DM2 is complex and not fully understood. Hyperglycemia is considered an important risk factor of developing DPN, yet a better understanding of how glycaemic status may affect nerve function in DM2 is clearly needed. The present study presents a novel method to assess the microcirculation of peripheral nerves in-vivo in relation to glycaemic status. Interestingly, MRN of microvascular perfusion indicates contrasting effects of hyperglycemia depending on the presence of DPN. The study indicates that individuals with DM2 without DPN could benefit from improved glycaemic control by improving microvascular permeability, whilst individuals with confirmed DPN do not seem to experience the same effect. The study has several limitations including performing numerous statistical tests without correction for multiple comparisons. Moreover, the significance of the microvascular permeability assessed by the contrast agent remains to be studied, since the contrast's perfusion does not allow us to directly draw conclusions to the microvascular permeability of oxygen and nutrients. Mooshage CM et al present a promising method for assessment of capillary permeability of peripheral nerves. The study generates several interesting hypotheses, including how individuals with DM2 without DPN may benefit from glycaemic control in preventing DPN by improving microvascular permeability. Yet, whether improved microvascular perfusion by glycaemic control poses a clinical significance in preventing DPN remains to be determined in future studies.

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Reference. Mooshage CM, Schimpfle L, Kender Z, Szendroedi J, Heiland S, Nawroth P, Bendszus M, Kopf S, Kurz FT, Jende JME. Diametrical Effects of Glucose Levels on Microvascular Permeability of Peripheral Nerves in Patients With Type 2 Diabetes With and Without Diabetic Neuropathy. *Diabetes*. 2023 Feb 1;72(2):290-298. doi: 10.2337/db22-0548. PMID: 36326808.

<https://diabetesjournals.org/diabetes/article/72/2/290/147851/Diametrical-Effects-of-Glucose-Levels-on>