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Metabolic impact on early peripheral sensory dysfunction

Aims: To assess the association between early peripheral sensory dysfunction (EPSD) and dysmetabolic factors in patients with and without type 2 diabetes (T2DM) without peripheral neuropathy (PN), and the impact of those features on PN development.
Methods: This is an analysis of data from the Heidelberg Study of Diabetes and its Complications (HEIST-DiC). 225 participants (117 without and 108 with T2DM) were enrolled. All participants performed biochemical evaluation, calculation of insulin resistance (IR) indexes [Homeostatic Model Assessment for Insulin Resistance (HOMA-R) and McAuley index], bioelectrical impedance analysis and skin autofluorescence [for skin advanced glycation end products (AGEs) evaluation]. The neurological assessment included symptom evaluation, physical examination, quantitative sensory testing (QST), according to the protocol of the German Research Network on Neuropathic Pain, and electrophysiological testing. EPSD was defined as the presence of mild sensory deficits not fulfilling clinical or electrophysiological criteria for PN and categorized into three neuropathic phenotypes (thermal hyperalgesia, mechanical hyperalgesia, or sensory loss) based on QST and the algorithm by Vollert J et al (*Pain 2017;158:1446-1455*). The "healthy" (H) phenotype was defined in absence of PN and ESPD. Cross-sectional analysis between H and EPSD was carried out separately for those without and with T2DM. Then, 196 patients (106 without and 90 with T2DM) were followed-up over a mean of 2.64 years for PN occurrence.
Results: In the group without T2DM, EPSD patients had greater waist circumference (99.3 vs. 92.9, p=0.037) and higher IR, compared to H and, in multivariate analysis, EPSD was associated with male gender, higher fat mass, lower lean mass and higher IR (HOMA-R: OR 1.70, McAuley index OR: 0.62). In T2DM cohort, EPSD patients presented a higher prevalence of metabolic syndrome (93.4 vs. 70.5%) and higher skin AGEs compared to H, while, in multivariate models, metabolic syndrome (OR 18.32) and skin AGEs (OR 5.66) were independent predictors of EPSD. In longitudinal evaluation, T2DM (HR 3.32 vs. no T2DM, p<0.001), EPSD (aHR 1.88 vs.H, p=0.049, adjusted for T2DM and gender), higher IR and AGEs predicted PN occurrence. HbA1c was not associated with PN development. Moreover, the presence of thermal hyperalgesia and sensory loss (aHR 4.35, p=0.011) were associated with a higher PN occurrence, after adjustment for T2DM diagnosis. No association was observed with mechanical hyperalgesia phenotype.
Conclusions: Standardized QST-based approach can identify EPSD, in individuals with and without T2DM, and these alterations and their evolution are associated with a dysmetabolic profile.

Comments. EPSD represents a sensory alteration with high risk of PN development and, also, a critical window in which preventive interventions should be reinforced. QST is one of the few non-invasive methods for small-fiber assessment, that could help to detect this timeframe. Despite some limitation, such as the missing identification of other causes of PN in H, these data strengthen the key role of early detection of the nerve damage, in particular of phenotypes at high risk of evolution, and the importance of therapeutic interventions targeting metabolic variables to prevent PN development.

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Reference. Tsilingiris D, Schimpfle L, von Rauchhaupt E, Sulaj A, Seebauer L, Bartl H, Herzig S, Szendroedi J, Kopf S, Kender Z. Dysmetabolism-related early sensory Deficits and their Relationship with peripheral Neuropathy Development. J Clin Endocrinol Metab. 2023 May 4:dgad248. doi: 10.1210/clinem/dgad248. Epub ahead of print. PMID: 37139855.
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