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Structural changes of cutaneous immune cells in patients with type 1 diabetes and their relationship with diabetic polyneuropathy

Aims: This study aims to investigate the link between cutaneous macrophages and neuropathic pain in diabetic polyneuropathy (DPN) by quantifying IBA1+ macrophages and Langerhans cells (LCs) in skin biopsies from participants with type 1 diabetes (T1DM) including those without DPN, with painless and painful DPN, and healthy controls.
Methods: 26 healthy controls and 78 participants [without DPN (n=24), painless DPN (n=29), and painful DPN (n=25)] were randomly selected and included in the study. Patients underwent neuropathy assessment including ankle reflexes, vibration threshold, mechanical detection, pinprick and temperature sensation tests, DPNCheck®, skin biopsy, and blood biomarkers. Dermal IBA1+ macrophages were visualized through immunofluorescent labelling and IBA1 area fraction was quantified within a 300 µm range from the dermal-epidermal border. LCs within the epidermis were visualized using immunohistochemical labelling of langerin (CD207+) and LC number density, soma cross-sectional area, and process level were measured.
Results: IBA1 area fraction (%) differs among groups, with healthy controls displaying the highest expression, followed by participants without DPN, those with painless DPN, and with painful DPN. There were no significant differences in LC soma cross-sectional area and process level among the groups. After adjusting for confounders, LC number density was significantly higher in patients with painless and painful DPN compared to the controls. A positive correlation was observed between IBA1 area fraction and Intraepidermal Nerve Fiber Density (IENFD), along with negative correlations with HbA1c, Michigan Neuropathy Screening Instrument questionnaire (MNSI-Q) score, MNSI-total score, Toronto Clinical Neuropathy Score (TCNS), and vibration threshold. LCs morphologies were not correlated with DPN measures.
Conclusions: The study shows the potential involvement of dermal IBA1+ macrophages in DPN. The observed variations in IBA1 area fraction among groups and, the correlations between IBA1 area fraction and neuropathy measures, especially IENFD, and HbA1c, suggest a possible association between macrophage presence and DPN severity.

Comments. This study uses a comprehensive approach to investigate the relationship between dermal IBA1+ macrophages, LCs, and DPN. The study observed significant differences in dermal IBA1+ macrophage infiltration among the groups. Patients with DPN exhibited reduced IBA1+ macrophage presence, even after accounting for confounding factors. The study's outcomes diverged from recent research in patients with type 2 diabetes (T2DM), where IBA1+ macrophage density increased in patients with painful DPN compared to controls. Differences in diabetes type, duration, and metabolic dysfunctions were proposed to account for these variations. Previous studies on LC expression in diabetes reported conflicting results. Some reported epidermal LC density reductions in T2DM, while others found either increases or decreases in LC density in T1DM and T2DM mice models. Corneal LCs reported to be increased in patients with T1DM linked to corneal nerve loss. However, this study found no differences in LC morphology or correlations with DPN or pain. The study's limitations include a relatively small sample size, a cross-sectional design, potential uncontrolled confounders, and inability to address functional alterations of immune cells. This study suggests IBA1+ macrophages potential role in T1DM DPN progression unveiling the complex interaction of immune cells and neuropathy.
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Reference. Hu X, Buhl CS, Sjogaard MB, Schousboe K, Mizrak HI, Kufaishi H, Hansen CS, Yderstræde KB, Jensen TS, Nyengaard JR, Karlsson P. Structural Changes of Cutaneous Immune Cells in Patients With Type 1 Diabetes and Their Relationship With Diabetic Polyneuropathy. Neurol Neuroimmunol Neuroinflamm. 2023 Aug 1;10(5):e200144. doi: 10.1212/NXI.0000000000200144. PMID: 37527931; PMCID: PMC10393274.
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