Sambataro M, Pitzalis F, Fassan M, Segatto M. Commentary to Neuroinflammation and osteomyelitis in adults with Type 2 diabetes mellitus and peripheral neuropathy without and with foot lesions. What comes first?. J Neurol Neuromedicine (2026) 10(1): 1-4

www.jneurology.com

Journal of Neurology & Neuromedicine

Commentary Open Access

Commentary to Neuroinflammation and osteomyelitis in adults with Type 2 diabetes mellitus and peripheral neuropathy without and with foot lesions. What comes first?

Maria Sambataro[1]*, Francesca Pitzalis[1], Matteo Fassan[2], Marco Segatto[3]

[1]Endocrine, Metabolism and Nutrition Disease Unit, Santa Maria di Ca' Foncello Hospital, Treviso, Italy
[2]Department of Pathology, University of Padua and Veneto Institute of Oncology IRCCS, Italy
[3]Department of Biosciences and Territory, University of Molise, Italy

Article Info

Article Notes
Received: February 10, 2026
Accepted: May 28, 2026

***Correspondence:**
*Dr. Maria Sambataro, Endocrine, Metabolism and Nutrition Disease Unit, Santa Maria di Ca' Foncello Hospital, Treviso, Italy; Email: maria.sambataro@aulss2.veneto.it

©2026 Sambataro M. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License

Keywords
Diabetic Foot
Neuropathy
Osteomyelitis
Fractalkine CXC3L1/CXC3R1 axis

In the paper "Neuroinflammation and osteomyelitis in adults with Type 2 Diabetes Mellitus (T2DM) and peripheral neuropathy without and with foot lesions. What comes first?" published in September 2025[1], diabetic foot disease (DFD) was examined as a complex process involving peripheral nerve dysfunction, inflammatory activation and tissue injury (Figure 1 A-B-C-D-E-F). Within this framework, chronic oxidative stress associated with hyperglycemia was proposed as a factor potentially contributing to epigenetically mediated neuronal apoptosis in post-mitotic cells. This interpretation is consistent with the possibility that neuronal injury represents one component of a broader pathophysiological network involving innervated peripheral tissues, including bone, and associated with advanced clinical manifestations such as neuro-ischemic gangrene or infected necrosis. Similar patterns of tissue damage observed in myocardial ischemia, heart failure, diabetic retinopathy and end-stage renal disease, may reflect convergent mechanisms across different organ systems.

The updated IWGDF definition (2023[2]) frames DFD as a condition with coexisting multiple clinical components, providing an operational approach for identification and management. Our commentary does not aim to redefine this clinical construct but proposes a complementary pathobiological model that may help to interpret the relationship among these features.

We hypothesize that hyperglycemia may be associated with alterations in the mitochondrial milieu, potentially contributing to the generation of danger-associated molecular signals, such as non-clivated protoneurotropins, that could affect central and peripheral neuronal function on satellite innervated tissues. Recently, it has been demonstrated that, in adverse conditions, proneurotrophins can be secreted to the extracellular neuron space where they acquire apoptotic capacities versus different neuronal populations with direct/indirect glia-mediated effects[3]. Distal sensory and autonomic neuropathy may amplify neuroischemic and endothelial signaling, inflammatory responses and bone cell apoptosis, potentially contributing to tissue vulnerability.

Fractalkine (CX3CL1), a transmembrane chemokine with neurovascular distribution and cleavage-dependent signaling properties, emerged as a candidate marker[4]. Under basal conditions, neuronal CX3CL1 is involved in signaling interactions with its receptor (CX3CR1) in glial cell populations. *In vitro* animal models of hippocampal

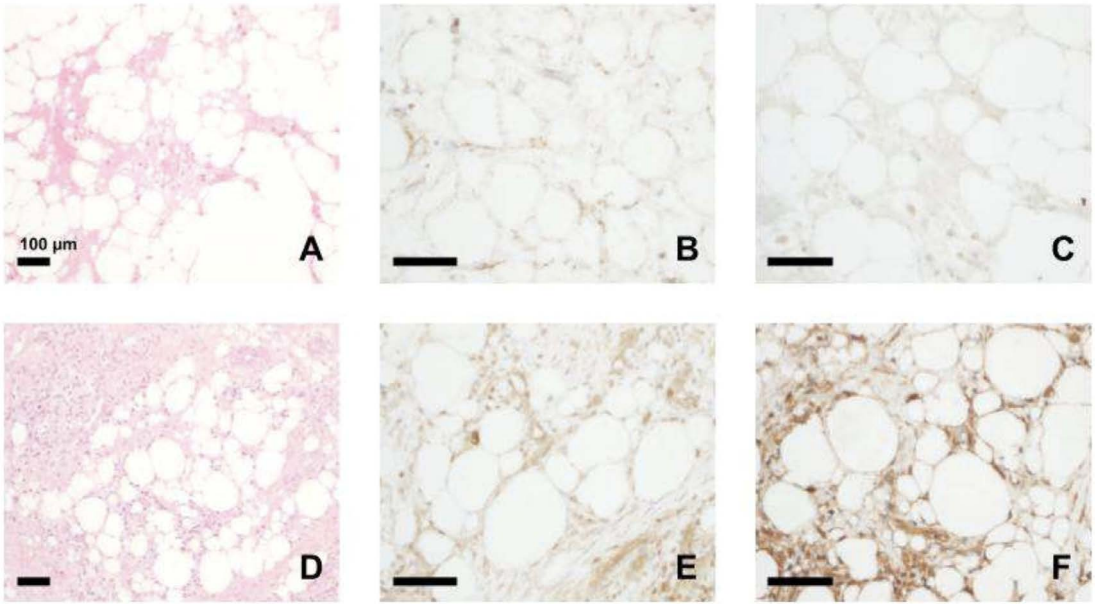

Figure 1: Hematoxylin/eosin staining and CX3CL1 and RORγ immunohistochemical co-expression in femoral head controls (A-B-C) versus foot bone of diabetic patients with HIOM ("highly infected osteomyelitis"; D-E-F). Magnification A-D 200X, for B-C-E-F 400X (main paper[1]; Figure 6)

Table 1: Description of clinical characteristics of patients' subgroups (for more clinical details, see main paper[1])

Clinical data	NC (53)	DNp (106)	DNpU (119)	DNpUV (149)
Age (years)	54 ±2	65±1**	61±1**$$	68±1**$$§§
Body mass index (BMI) (kg/m^2)	22.6±0.3	31.2±0.6**	31.5±0.6**	30.6±0.6**
Duration of disease (years)	0	13±1**	13±1**	16±1**$$§§
HbA1c (%)	5.6±0.2	7.9±0.2*	7.9±0.2*	7.9±0.15*
HbA1c mmol/mol	37.7±2.3	62.7±1.8*	62.5±1.9*	62.6±1.5*
Glycaemia (mg/dL)	90.4±1.9	162±6.4**	157.6±6.2**	151.1±4.9**

*p < 0.05 **p < 0.01 vs NC; $ p < 0.05 vs DNp; $$ p < 0.01 vs DNp; § p < 0.05 vs DNpU; §§ p <0.01 vs DNpU

neurotoxicity have shown that the CX3CL1/CX3CR1 axis may be associated with Brain-Derived Neurotrophic Factor (BDNGF) and Tropomyosin receptor kinase B (TrkB)[5] signaling, as well as with neuronal plasticity.

However, elevated concentrations of soluble CX3CL1 have been reported to enhance CX3CR1-mediated inflammatory cell recruitment and activation through mechanisms distinct from its membrane-bound form[6]. Evidence from vascular models, including rat aorta systems[7] and clinical contexts such as NSTEMI[8], suggests that CX3CL1 may also be associated with vascular dysfunction. In these settings, CX3CL1 has been linked to increased production of reactive oxygen species (ROS) and reduced nitric oxide (NO) bioavailability in vascular smooth muscle cells[7], as well as to fibrotic cardiovascular tissue remodeling[8].

The role of neuroinflammatory mechanisms within this complex signaling network remains to be fully elucidated.

We analyzed of 374 patients with T2DM patients and neuropathy, stratified into subgroups based on the presence of foot lesions and vascular status: diabetic neuropathic subjects without lesions (DNp, n=106); non-macrovascular diabetic neuropathic subjects with ulcers/lesions/osteomyelitis (DNpU, n=119); revascularized diabetic neuropathic subjects with ulcers/lesions/osteomyelitis (DNpUV, n=149) and healthy controls (NC, n=53).

Focus on T2DM ensured pathophysiological homogeneity, avoiding confounding from Type 1 Diabetes Mellitus (T1DM) autoimmune mechanisms. Glycemic control (HbA1c, fasting glucose) showed no differences among diabetic groups but differed from controls (Table 1, main paper[1]), suggesting that the observed biological alterations are unlikely to be solely driven by differences in glycemic status.

We evaluated CX3CL1-related markers in relation to electrophysiological parameters of neuropathy and characterized circulating inflammatory mediators and immune cell populations. Clinical osteomyelitis was defined based on probe-to-bone testing, X-ray and histological evidence of trabecular disruption (main paper[1] Figure

4-5), suggesting that non-infectious mechanisms, including osteonecrotic processes, may contribute to the observed tissue changes. Bone biopsies were obtained from exposed bone (TUC III) and osteomyelitis severity was graded based on monocyte/fibrosis infiltration. Autophagic and apoptotic markers were evaluated in infected/non-infected samples (main paper[1] Figure 8 for details). Electrophysiological parameters, including sural nerve conduction velocity (sural CV) and sensory action potential amplitude (sAP) confirmed the presence and severity of neuropathy.

Worsening neuronal function and increased nerve-growth factor precursor (proNGF) levels were associated with lesion depth (with/without ischemia) and with higher numbers of 6-sulfo LacNac (SLAN)$^+$ monocytes co-expressing CX3CR1. Immunofluorescence analyses revealed co-expression of CX3CL1 with high frequency of p75 neurotrophin receptors in tyrosine hydroxylase (TH)$^+$ nerves; this observation is of interest, as p75 is commonly associated with proNGF-related apoptotic signaling[3]. Moreover, altered vibration perception threshold (VPT) and bone NGF levels were associated with cleaved caspase-3 and Bcl2 associated X protein (BAX) expression, as well as with the abundance of SLAN$^+$CX3CR1$^+$ inflammatory monocytes, and inversely associated with circulating NK cells levels.

Taken together, these findings are consistent with a potential association between altered neuronal pathways, intrabone neurotrophin signaling and neuroimmune and ischemia-related processes. Within this framework, these alterations may be linked to apoptotic and osteoclastogenic signatures observed in bone tissue, including in the absence of overt microbiological evidence of infection.

The hypothesis-generating model suggests the possibility that neuropathy may be associated with a broader neuroinflammatory milieu involving vascular, immune and bone compartments. Sensory loss and autonomic dysregulation may be linked to alterations in tissue homeostasis, including changes in neurotrophin signaling, vascular function and immune cell recruitment. Within this model, CX3CL1/CX3CR1 signaling may represent a potential interface between neural and immune responses, associated with apoptotic and autophagic signatures observed in bone tissue. This model may inform revised interpretations of pathogenic events and targeted therapies.

Future Perspectives

Future longitudinal and prospective studies should further explore associations observed in early neuropathy/pre-lesional phases, including the characterization of CX3CR1$^+$ immune cell populations across different tissues, which may provide additional insight into their potential role in disease progression. These studies are necessary to demonstrate if hyperglycemia directly impairs bone structure before foot lesions or by nerve dysfunction, potentially predisposing apoptotic intracellular signals. In particular, “early identification” of neuropathic and neuroinflammatory alteration is crucial before clinically evident and irreversible neuroischemic foot lesions. Such approaches could integrate serial assessments of peripheral nerve function, circulating biomarkers and tissue-specific markers, where feasible.

Particular attention should be given to proNGF-related p75 receptor expression and its association with CX3CR1$^+$ monocyte behavior under conditions of hyperglycemia-related oxidative stress. These approaches may help to clarify whether specific neuroimmune profiles are associated with increased susceptibility to clinically relevant complications.

Clinically relevant outcomes should include the development of foot ulcers, progression to osteomyelitis and the need for revascularization, allowing the correlation of early molecular/cellular alterations and subsequent clinical management.

Strengths and Limitations

This study integrates clinical, electrophysiological, immunological, and molecular data, providing multidimensional characterization of diabetic neuropathy and associated tissue alterations.

However, some limitations should be acknowledged. The restriction to T2DM patients may limit generalizability to other forms of diabetes. Sample size limitations in subgroup analyses may affect statistical power. In addition, clinical heterogeneity across patient groups, including differences in vascular status and treatment pathways, may influence the observed findings.

Bone biopsies were obtained from different anatomical sites, in line with previously reported approaches[9], which may introduce variability in tissue-level observations.

Moreover, concomitant conditions and therapeutic interventions (Table 1, main paper[1]) may have contributed to heterogeneity in inflammatory and molecular profiles.

Despite these limitations, the consistency of findings across independent analytical approaches supports the internal coherence of the proposed framework and highlights the need for further investigations in longitudinal settings.

Acknowledgements

Treviso (Italy) Diabetics Association OdV provided financial support for the conduct of the research.

Abbreviations

BAX: Bcl2 associated X protein

Bcl2: B-cell lymphoma 2

BDNGF: Brain-Derived Neurotrophic Factor

BMI: Body Mass Index

CV: Conduction velocity

CX3CL1: Chemokine (C-X3-C motif) ligand 1

CX3CR1: C-X3-C motif chemokine receptor 1

DFD: Diabetic Foot Disease

DNp: Subjects with Diabetic Neuropathy without foot lesions

DNpU: Subjects with Diabetic Neuropathy with ulcers/lesions/osteomyelitis

DNpUV: Revascularized Subjects with Diabetic Neuropathy with ulcers/lesions/osteomyelitis

HbA1c: Glycated Hemoglobin

HIOM: Highly Infected Osteomyelitis

IWGDF: International Working Group on the Diabetic Foot

sAP: sensory action potential

proNGF: precursor Nerve Growth Factor

NC: Normal control

NGF: Nerve Growth Factor

NK: Natural killer cell

NO: Nitric Oxide

p75 NTR: p75 neurotrophic receptor

ROS: Reactive Oxygen Species

SLAN: 6-sulfo LacNAc

T1DM: Type 1 diabetes mellitus

T2DM: Type 2 diabetes mellitus

TH: Tyrosine hydroxylase

TrkB: Tropomyosin receptor kinase B

TUC: University of Texas wound classification

VPT: Vibration Perception Threshold

References

1. Sambataro M, Sambado L, Colardo M, et al. Neuroinflammation and osteomyelitis in adults with Type 2 diabetes mellitus and peripheral neuropathy without and with foot lesions. What comes first? J Diabetes Complications. 2025; 39(11): 109176. doi: 10.1016/j.jdiacomp.2025.109176. PMID: 41056698.

2. Schaper NC, van Netten JJ, Apelqvist J, et al. Practical guidelines on the prevention and management of diabetes-related foot disease (IWGDF 2023 update). Diabetes Metab Res Rev. 2024; 40(3): e3657. doi: 10.1002/dmrr.3657. PMID: 37243927.

3. Costa RO, Perestrelo T, Almeida RD. PROneurotrophins and CONSequences. Mol Neurobiol. 2018; 55(4): 2934-2951. doi: 10.1007/s12035-017-0505-7. PMID: 28456935.

4. Umehara H, Bloom ET, Okazaki T, et al. Fractalkine in vascular biology: from basic research to clinical disease. Arterioscler Thromb Vasc Biol. 2004; 24(1): 34-40. doi: 10.1161/01.ATV.0000095360.62479.1F. PMID: 12969992.

5. Chen Y, Liu J, Zhang S, et al. Advances in the multifunctional roles of CX3CL1 in the central nervous system. Front Aging Neurosci. 2026; 18: 1696689. doi: 10.3389/fnagi.2026.1696689. PMID: 41669249; PMCID: PMC12883738

6. He Q, Zhou T, He Q. Targeting CX3CR1 Signaling Dynamics: A Critical Determinant in the Temporal Regulation of Post-Stroke Neurorepair. Brain Sci. 2025; 15(7): 759. doi: 10.3390/brainsci15070759. PMID: 40722349; PMCID: PMC12293467.

7. Stangret A, Sadowski KA, Jabłoński K, et al. Chemokine Fractalkine and Non-Obstructive Coronary Artery Disease-Is There a Link? Int J Mol Sci. 2024; 25(7): 3885. doi: 10.3390/ijms25073885. PMID: 38612695; PMCID: PMC11012077.

8. Schäfer A, Schulz C, Fraccarollo D, et al. The CX3C chemokine fractalkine induces vascular dysfunction by generation of superoxide anions. Arterioscler Thromb Vasc Biol. 2007; 27(1): 55-62. doi: 10.1161/01.ATV.0000251535.30191.60. PMID: 17082482.

9. Dang Z, Maselli D, Spinetti G, et al. Sensory neuropathy hampers nociception-mediated bone marrow stem cell release in mice and patients with diabetes. Diabetologia. 2015; 58(11): 2653-62. doi: 10.1007/s00125-015-3735-0. PMID: 26358583; PMCID: PMC4589553.