Diabetic Neuropathies in the Era of Precision Medicine: Unravelling Complex Mechanisms Through Multimodal Approaches

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AT THE European Association for the Study of Diabetes (EASD) Annual Meeting, held in Vienna, Austria, from 15th–19th September 2025, the session 'Diabetic Neuropathies in the Era of Precision Medicine' offered a comprehensive and forward-looking examination of sensory, autonomic, and inflammation-driven neuropathic complications in diabetes. Chaired by Leszek Czupryniak, Central University Hospital, Warsaw, Poland; and Anca Pantea-Stoian, INDNBM Paulescu, Bucharest, Romania, the symposium brought together experts who highlighted emerging pathomechanisms, advanced diagnostic technologies, and the promise of tailored therapeutic strategies.

ACKNOWLEDGING PREDIABETIC POLYNEUROPATHY

Julia Szendroedi, University Hospital Heidelberg, Germany, opened the session by emphasising the substantial morbidity and mortality associated with diabetic sensorimotor polyneuropathy (DSPN). Affecting more than half of individuals with Type 2 diabetes (T2D), DSPN markedly increases the risk of foot ulceration, major amputation, and mortality by nearly 3.6-fold in Type 1 diabetes (T1D) and 1.6-fold in T2D.[1] Yet, as Szendroedi noted, determining the true prevalence of neuropathy in prediabetes remains challenging. Definitions of prediabetes vary, and screening methods for neuropathy differ significantly between studies, resulting in widely divergent prevalence estimates ranging from greater than 10% in most studies,[2] to as high as 70–80%. This variability has prevented robust meta-analyses, leaving individual studies to shape the field.

Early Small-Fibre Injury and Phenotype Progression

Szendroedi contrasted studies showing minimal sensory changes in normoglycaemic individuals with others reporting unexpectedly high neuropathy rates, underscoring both the sensitivity and the limitations of quantitative sensory testing (QST). The accumulating evidence suggests that neuropathy in prediabetes begins with early metabolic and vascular injury to small fibres. As individuals progress to T2D, large-fibre dysfunction and central sensitisation become more prominent, with age and nephropathy acting as amplifiers of risk, while HbA1c alone does not fully account for the observed sensory patterns.[3]

Longitudinal QST phenotyping has revealed dynamic transitions across sensory subtypes. Patients may evolve from profiles dominated by thermal hyperalgesia to mechanical hyperalgesia, and eventually to sensory loss, reflecting distinct and measurable clinical trajectories.[4]

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Defining Prediabetes Matters: Divergent Risk Hierarchies

Szendroedi emphasised that how prediabetes is defined substantially influences neuropathy risk prediction. An HbA1c-based approach, while convenient, is the least predictive for DSPN. In contrast, an oral glucose tolerance test-based hierarchy, where impaired glucose tolerance predicts risk more strongly than impaired fasting glucose, and both of these predict risk more strongly than HbA1c, better reflects true DSPN susceptibility (unpublished data). She also discussed the emerging prediabetes clusters (cluster 1-6), highlighting that individuals in cluster 5 have a notably elevated risk of neuropathy, demonstrating the biological heterogeneity present even before diabetes onset.[5]

Metabolic Drivers and Patchy Small-Fibre Damage

Applying QST to individuals without overt neuropathy has shown that insulin resistance is a key driver of early preclinical neuropathy in those without diabetes. Among people with T2D, further metabolic syndrome components and accumulation of skin advanced glycation end-products (AGE) contribute to progression.[6] Early investigations using corneal confocal microscopy and skin biopsy have revealed small-fibre loss shortly after diabetes diagnosis. Yet, the overlap between corneal and skin findings was present in only 3% of individuals, indicating a 'patchy', organ-specific pattern of nerve involvement.[7] "This is evidence we need more longitudinal studies," Szendroedi remarked.

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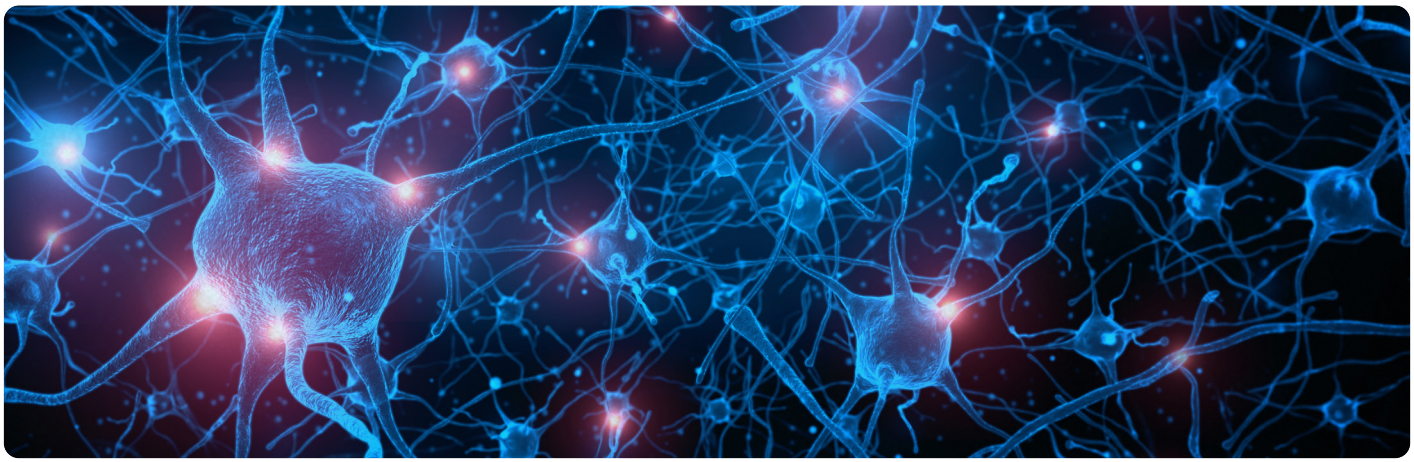
Ischaemia, Oxidative Stress, and Neuroimmune Alterations

Peripheral nerve ischaemia is emerging as a major contributor to DSPN, with dynamic contrast-enhanced magnetic resonance neurography (MRN) revealing that microvascular permeability correlates strongly with age, BMI, and neuropathy severity.[8] Skin biopsy analyses indicate early oxidative stress, reflected in increased dermal superoxide dismutase 2 (SOD2) expression, while the markedly reduced Langerhans cell density in newly diagnosed T2D points to early neuro-immune dysregulation that appears independent of intraepidermal nerve fibre density.[9]

Individuals in cluster 5 have a notably elevated risk of neuropathy

Proximal Nerve Involvement and Distinct Patterns in Type 1 Versus Type 2 Diabetes

Advanced MRN has shed light on early microstructural remodelling in the proximal sciatic nerve, extending understanding beyond distal small-fibre pathology. Comparative analyses between T1D and T2D indicate distinct remodelling patterns, with glycaemia more influential in T1D and dyslipidaemia playing a stronger role in T2D. These findings support the emerging



'patch hypothesis', suggesting that different mechanisms may drive neuropathy in different nerve regions.[10] Neuron-specific biomarkers, including neurofilament light chain protein and circulating myelin-related mRNA, have shown predictive value for both hypoalgesic and hyperalgesic phenotypes, emphasising their utility for mechanistic longitudinal studies.[11] Szendroedi concluded her talk by emphasising that DSPN is not a linear disease but a mosaic, in which compensated segments, immune-active regions, and ischaemic lesions coexist within the same nerve. Because different mechanisms dominate in different regions and patients, multimodal assessment, using QST, MRN, biopsy markers such as SOD2, and circulating biomarkers like neurofilament light chain, is essential. She called for early screening, including in prediabetes, and phenotype-guided management strategies in the future.

UPDATE ON CARDIOVASCULAR AUTONOMIC NEUROPATHY

In the second talk, Péter Kempler, Semmelweis University, Budapest, Hungary, delivered an "unorthodox perspective" on cardiovascular autonomic neuropathy (CAN), starting his talk by invoking the words of the late Aaron Vinik: "Know autonomic neuropathy and you will know the whole of medicine."

Mortality Risk and Long-Term Data

CAN has been recognised for decades, and early data suggested a fivefold increase in mortality among affected individuals.[12] More recent 20-year follow-up data in T2D indicated a 1.5-fold increase in mortality risk, bringing it closer to that seen in sensory neuropathy and refining earlier estimates.[13] Additional pooled analyses have shown that having more than two CAN abnormalities confers a 3.5-fold increased risk of mortality.[14]

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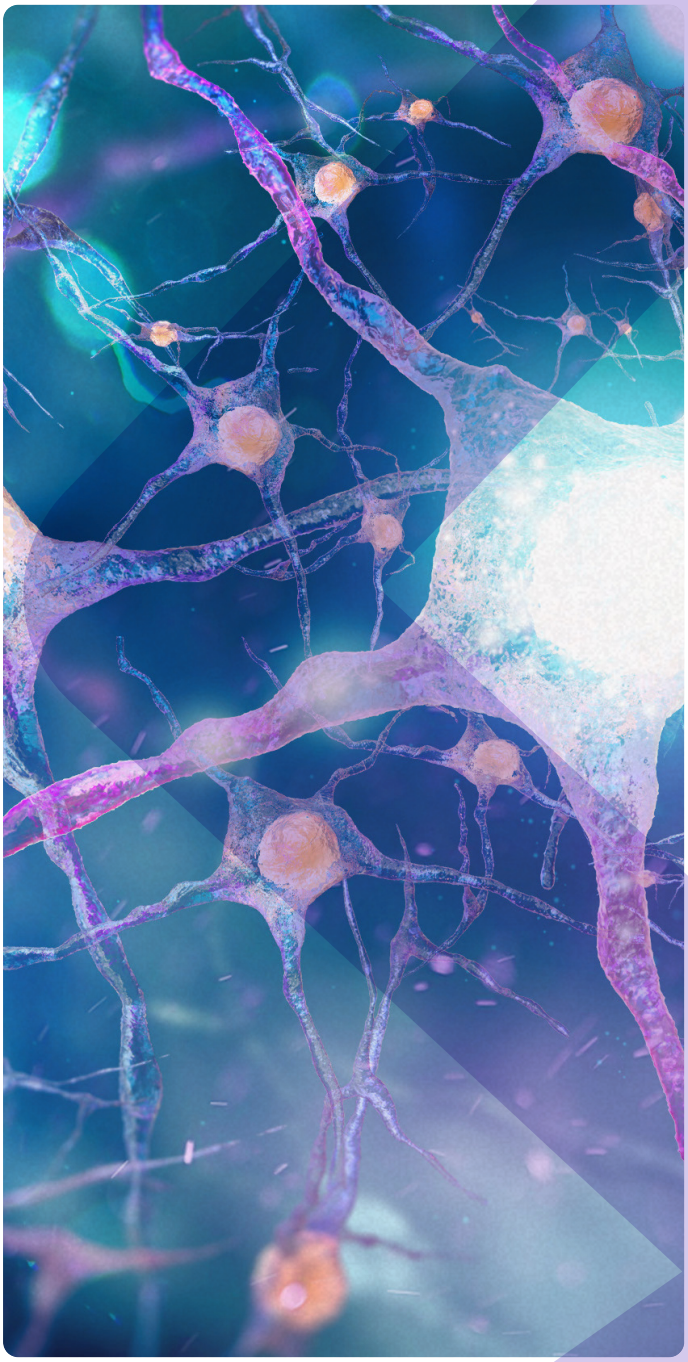
x 3.5

mortality in the intensive glucose-lowering arm. Notably, a self-reported history of neuropathy, despite the absence of formal neuropathy assessment in the study, emerged as the strongest independent predictor of mortality under intensive treatment. Newly presented 2025 analyses revealed striking sex differences: women with CAN exhibited significantly higher risks of both all-cause and cardiovascular mortality, while men did not show this association.[16] These findings echo signals from the original ACCORD dataset that had previously gone unrecognised.



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Pathogenic Therapies and Cardiometabolic Protection

He continued by outlining the mechanisms by which hyperglycaemia induces micro- and macrovascular endothelial injury, including glucose toxicity, oxidative stress, inhibition of glyceraldehyde-3-phosphate dehydrogenase, and activation of harmful alternative pathways such as AGE formation. These pathways underpin the rationale for agents such as benfotiamine, which reduces AGE formation and diverts glucose into non-harmful pathways, and alpha-lipoic acid, mitigating oxidative stress. Although widely used in Germany, Austria, and parts of Central Europe for decades, these agents remain underutilised in the UK, France, and the USA due to a lack of recent large trials.

Finally, Kempler presented compelling real-world evidence from a Hungarian study of nearly 24,000 patients comparing pathogenically oriented alpha-lipoic acid therapy with symptomatic treatments. Individuals receiving alpha-lipoic acid showed approximately 30% fewer myocardial infarctions requiring percutaneous coronary intervention, improved stroke outcomes, a 30% reduction in hospitalisations for heart failure, a 17% reduction in cancer events, and a 45% decrease in all-cause mortality, with no significant difference in lower-limb amputation rates.[17] He closed with quotations from writer and philosopher, Aldous Huxley, and Murphy's Law to highlight the consequences of ignoring complex, multifactorial evidence in favour of overly simplistic explanations, leaving the audience a moment to reflect.

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INFLAMMATION, DIABETES HETEROGENEITY AND POLYNEUROPATHY

The final talk, delivered by Christian Herder, German Diabetes Center, Düsseldorf, Germany, explored the interplay between inflammation, diabetes heterogeneity, and DSPN risk.

Inflammatory Biomarkers and Neuropathy Incidence

Using data from the KORA cohort (a subgroup of over 500 participants aged 61–82 years), Herder described the first prospective evidence linking inflammatory biomarkers with incident DSPN. Elevated levels of high sensitivity C-reactive protein, IL-6, and TNF-α were associated with greater neuropathy risk, while adiponectin showed an inverse association.[18] To capture a broader view of inflammatory processes, the team analysed 71 high-quality serum biomarkers using the OLINK Inflammation Assay (OLINK Proteomics, Uppsala, Sweden). Twenty-six proteins were positively associated with future DSPN, reflecting coordinated signalling across innate and adaptive immune pathways. Upstream regulatory analysis identified TNF-α and IL-1β as key drivers, reinforcing their therapeutic potential.[19]

Diabetes Subtypes and Differential Risk

Herder examined heterogeneity within diabetes and prediabetes using data from the German Diabetes Study,[20] Europe's largest prospective cohort of individuals with recent-onset diabetes. Significant differences in inflammatory biomarker profiles emerged across diabetes subtypes. The severe insulin-resistant diabetes phenotype exhibited the highest inflammatory load, accompanied by elevated leukocyte counts and increased neutrophil-lymphocyte ratios, while the severe insulin-deficient diabetes subtype displayed the lowest inflammatory burden.[19] Parallels were observed in prediabetes. In a call back to Szedroedi's earlier discussion of clusters, Herder explained that cluster 5, marked by high visceral adiposity, hepatic fat accumulation, and pronounced

insulin resistance, had both the highest inflammatory load and the greatest DSPN risk. In contrast, cluster 2 showed the lowest inflammatory burden.[5]

Inflammasome Inhibition: A Targeted Therapeutic Pathway

Herder highlighted the role of NLRP3 inflammasome activation in generating IL-1β, a potent pro-inflammatory cytokine. Within the INTERCEPT-T2D consortium, an ongoing RCT is testing an inflammasome inhibitor in individuals with T2D and elevated inflammatory markers, with neuropathy outcomes designated as a key secondary endpoint.[21] Results are anticipated within the next few years and may help pave the way for targeted anti-inflammatory therapies.

Key Takeaways

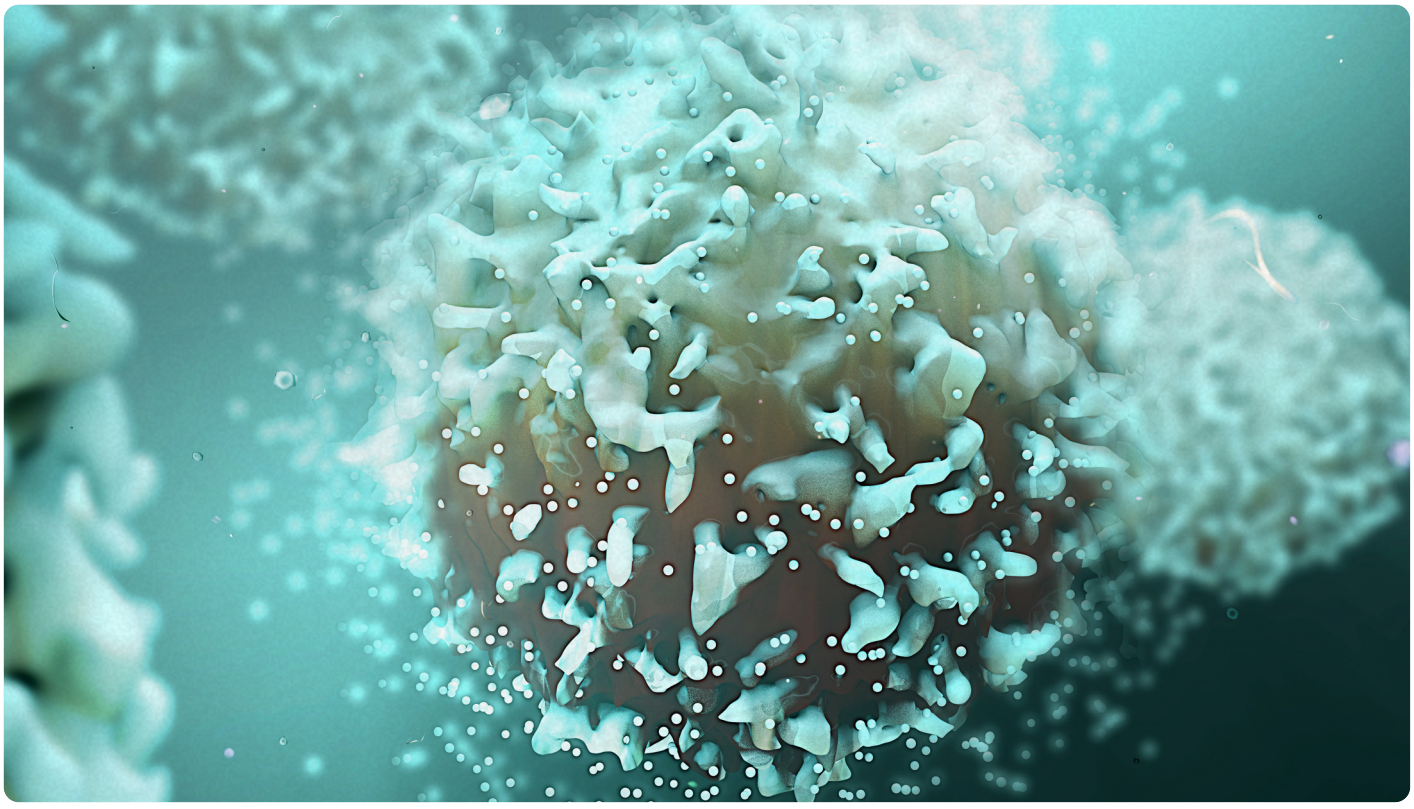
Herder concluded by emphasising that DSPN risk is strongly linked to multi-marker inflammatory signatures, that diabetes and prediabetes subtypes differ markedly in inflammatory burden, and that identifying high-inflammation subgroups may facilitate precision medicine approaches to neuropathy prevention and management.

CONCLUSION

Across all three talks, a clear narrative emerged: diabetic neuropathies are mechanistically heterogeneous, multifactorial, and ill-suited to one-size-fits-all approaches. Early small-fibre injury, proximal nerve remodelling, vascular dysfunction, inflammation, and metabolic diversity each contribute to a mosaic of pathology rather than a linear progression.

The speakers collectively emphasised the importance of early and multimodal screening, including in prediabetes, along with phenotype-guided assessment and treatment, better recognition of autonomic and inflammatory contributors, and the promise of targeted therapies spanning metabolic, vascular, and inflammatory pathways.

As precision medicine evolves, integrating multimodal diagnostics with mechanistic understanding offers a path towards genuinely individualised care, with the potential to alter the natural history of diabetic neuropathies in the years ahead.



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