

Female sex is a risk factor for painful diabetic neuropathy: the first prospective evidence

Aims: To analyze the incidence and risk factors of painful diabetic peripheral neuropathy (DPN) in the EURODIAB Prospective Complications Study taking into consideration the influence of gender.

Methods: The EURODIAB Prospective Complications Study recruited 3250 participants with type 1 diabetes who were followed up for 7.3 ± 0.6 years. A standardized protocol was used to evaluate DPN, including clinical assessment, quantitative sensory testing, and autonomic function tests. Painful DPN (defined as painful neuropathic symptoms in the legs - deep aching or burning pain - in participants with confirmed DPN) was assessed at baseline and follow-up.

Results: At baseline, 234 (25.2%) out of 927 participants with DPN had painful DPN. At follow-up, newly diagnosed DPN developed in 276 (23.5%) of 1172 participants without DPN at baseline. Of these, 41 (14.9%) had incident painful DPN. Comparing participants with painless and painful DPN, most of those who developed incident painful DPN were female (73% vs 48% painless DPN, $p=0.003$) and this remained significant after adjustment for duration of diabetes and HbA_{1c} (OR 2.69 [95% CI 1.41, 6.23], $p=0.004$). The proportion of participants with macro- or microalbuminuria was lower in those with painful DPN compared with painless DPN (15% vs 34%, $p=0.02$), and this association remained after adjusting for HbA_{1c}, diabetes duration, and sex ($p=0.03$).

Conclusions: This study definitively demonstrates that female sex is a risk factor for painful DPN. Additionally, there is less incidence of diabetic nephropathy in painful, compared with painless DPN. Thus, painful DPN is not driven by cardiometabolic factors traditionally associated with microvascular disease. Gender differences might therefore play an important role in the pathophysiology of neuropathic pain in diabetes.

Comments. Painful diabetic neuropathy affects up to 25% of individuals with diabetes and has many medical and social consequences. The EURODIAB Prospective Diabetes Complications Study is the first prospective observation to reveal that the female gender is a risk factor for painful DPN. Patients with type 1 diabetes with a mean duration of the disease of 15 years were followed for the next 7.3 years. The painful DPN was diagnosed in 41 subjects. The percentage of women in the painful group was high (73%). The mechanisms underlying sex differences in chronic pain are incompletely understood. Sex hormones are known to contribute to sexual differentiation of the nervous system and are hypothesized to be involved in pain modulation. Moreover, key regions of the brain responsible for the detection and processing of nociception have been found to have altered structure and function in women. Interestingly, the groups with painful and painless DPN were not distinguished by an increased occurrence of other diabetes complications or a more frequent diagnosis of dyslipidemia and hypertension. In fact, albuminuria was less common in painful groups. Thus, the development of painful DPN may be driven by psychological, social, cultural, genetic, hormonal, and other factors and the findings require further research.

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Reference. Elliott J, Sloan G, Stevens L, Selvarajah D, Cruccu G, Gandhi RA, Kempler P, Fuller JH, Chaturvedi N, Tesfaye S; EURODIAB Prospective Complications Study Group. Female sex is a risk factor for painful diabetic peripheral neuropathy: the EURODIAB prospective diabetes complications study. *Diabetologia*. 2023 Oct 23. doi: 10.1007/s00125-023-06025-z. Epub ahead of print. PMID: 37870649.

<https://link.springer.com/article/10.1007/s00125-023-06025-z>