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LETTER

Letter to the Editor Regarding: Diabetic Peripheral Neuropathy as a Predictor of Asymptomatic Myocardial Ischemia in Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Diabetes mellitus (DM) frequently affects the nervous system [1]. This holds true both for the peripheral and for the autonomic nervous system [2]. Diabetic polyneuropathy (or distal symmetrical polyneuropathy [DPN] or, simply, peripheral neuropathy) is the most common manifestation of DM in the nervous system [3, 4]. Of the autonomic nervous system, gastrointestinal autonomic neuropathy [5] and cardiovascular autonomic diabetic neuropathy (CAN) are those most widely studied. Importantly, CAN is a recognised harbinger of cardiovascular mortality [6–8].

What is known about the impact of diabetic polyneuropathy (DPN) on mortality? First, DPN is shown to be independently associated with mortality in a number of studies [9–11]. Second, neuropathic diabetic foot ulcers have also been associated with a 5-year mortality rate that approaches the amazing 50% [12–14], exceeding the rate of several cancer types, including breast, prostate, colon, and Hodgin's disease [14]. In addition, Charcot osteoarthropathy may also be associated with increased mortality [15], more recently attributable to coronary artery disease [16–18].

In this issue of the journal, Baltzis et al. [19] have investigated the relationship between DPN and myocardial ischaemia (MI) in patients with type 2 diabetes mellitus (T2DM) and no history of cardiovascular events. Overall, 82 patients with DPN ($n = 41$) or without DPN ($n = 41$) were included. Among those with DPN, 15 had active ulcers. MI was estimated through Technetium-99 m Sestamibi Single-Photon Emission Computed Tomographic imaging expressed as Summed Stress Score (SSS): SSS $\geq$4 was considered abnormal. Furthermore, two well-known indices of CAN (abnormal RR ratio and orthostatic hypotension) were used to detect this condition [1, 2, 8]. DPN was diagnosed clinically by the established examination system Neuropathy Disability Score (NDS) and defined as NDS $\geq$5 [1, 2]. A negative 10-g monofilament test served to exclude DPN [1, 2].

In this study [19], patients with DPN had a higher risk of abnormal SSS than those without DPN (46.3% vs. 9.8%, $p < 0.001$). Multivariate

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analysis identified NDS as the strongest predictor of SSS ($\beta = 0.32$, $p = 0.003$), among other significant predictors, namely, waist circumference and gender. This association was not affected by the exclusion of patients with abnormal RR ratio or with ulcers ($\beta = 0.32$, $p = 0.003$, and $\beta = 0.24$, $p = 0.04$, respectively). This is important for two reasons. First, the RR ratio was also significantly associated with SSS in univariate ($\beta = -0.30$, $p = 0.005$) and multiple regression ($\beta = 0.24$, $p = 0.02$) [19] and CAN has an established relationship with both cardiovascular mortality [6–8] and silent MI [20]. Secondly, MI was significantly higher in patients with DPN and foot ulcers (60% in patients with DPN and ulcer vs. 26.9% in those with DPN but without ulcer, $p < 0.05$) [19]. In a recent meta-analysis, diabetic foot ulceration was also associated with an increased risk of fatal myocardial infarction [risk ratio (RR): 2.22, 95% confidence interval (CI) 1.09, 4.53] [21]. It has also been identified as a significant predictor of silent MI in T2DM women [22]. Thus, it is suggested that the association between DPN and MI exceeds autonomic neuropathy and foot ulceration. Finally, in the present study [19], the area under the curve (AUC) of the receiver operator characteristics (ROC) curve (0.76, 95% CI 0.65–0.86; $p < 0.001$) showed a fair to good performance of the NDS to discriminate patients with ischaemia.

The limitations of this interesting study may be summarised as follows. The first relates to the relatively limited number of patients with ulcers and the possibility of objective bias. Moreover, data on the timing of ulceration would be very useful to evaluate the relationship between active ulceration and abnormal SSS. A third limitation is inherent in the cross-sectional analysis which precludes the duration of follow-up. Moreover, average T2DM duration was 14.8 years, which may have influenced mortality as a confounding factor, given that the long T2DM duration is associated with a greater burden of silent MI [23]. However, this confounding effect is probably reduced by the virtue of excluding patients with a history of cardiovascular events. Finally, data on microalbuminuria and insulin usage would be highly welcome, because both these features [23, 24] are more prevalent among T2DM patients with vascular complications.

The clinical implication of the study by Baltzis et al. [19] is that DPN should not be underestimated as an index of asymptomatic MI in T2DM patients without known cardiovascular events. This is important irrespective of the exact causality. Indeed, the putative mechanism may relate to a common pathophysiological pathway, such as oxidative stress [25]. The authors have also proposed that NDS may prove useful to identify T2DM patients at risk of cardiovascular disease. Interestingly, there is evidence that asymptomatic high-risk T2DM patients, whose cardiovascular risk is controlled by an optimal medical treatment, should not be expected to improve hard outcomes (including cardiac death or non-fatal myocardial infarction) through the systematic detection of silent MI [26, 27]. The COURAGE (Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation) [28] and BARI 2D (Bypass Angioplasty Revascularisation Investigation 2 Diabetes) [29] trials have demonstrated that the revascularisation of asymptomatic diabetic patients through the detection of silent MI may not provide an additive survival benefit with respect to the rates of death or major cardiovascular events, including myocardial infarction. Nonetheless, such lack of improvement contrasts with the favourable results in life expectancy (reduction in 5-year mortality from 58% to 36%; relative reduction

38% for neuroischaemic and from 36% reduction to 19%; relative reduction 47% for neuropathic patients, all $p < 0.001$) via aggressive cardiovascular risk management policy in a less selected population with diabetic foot ulcers [30]. Granted these conflicting results, NDS as a quick, relatively simple and widely used clinical tool of DPN [31, 32] may be taken to serve as a useful tool to evaluate the risk of cardiovascular complications of an early stage in T2DM. Indeed, NDS is cheaper and more practical than other costly techniques, such as stress-myocardial perfusion imaging, which cannot be widely implemented [33, 34]. However, both a cost-utility analysis (which was beyond the scope of the study by Baltzis et al. [19]) and larger randomised trials are vital to confirm its potential utility.

In conclusion, the new data point to a significant and clinically important association between DPN and myocardial infarction [19]. This study enriches the evidence on the association of DPN with coronary ischaemia, indicating that the former may serve as an indication of the latter. Given the association of MI with mortality [35], DPN may be taken to predict cardiovascular mortality as well. Accordingly, the efforts to improve early and reliable detection of DPN with new easy-to-use diagnostic tools [36–39] acquire an additional meaning in the context of improved screening for coronary ischaemia. In clinical practice, then, patients with DPN should receive even more zealous therapeutic attention.

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