Diabetic neuropathy: the future is promising. Reply to Uusitupa M, Niskanen L, Laitinen T [letter] and Coppini DV [letter]

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Abbreviation

MNSI Michigan Neuropathy Screening Instrument

To the Editor: We appreciate the comments by Uusitupa et al [1] and David Coppini [2] pertaining to our recent article in *Diabetologia*: ‘Diabetic neuropathy: what does the future hold?’ [3]. We agree that hyperglycaemia is important in individuals with type 2 diabetes. Hyperglycaemia is the number one risk factor for diabetic complications, including diabetic neuropathy [4]. However, we were emphasising the surprising lack of a large effect of more aggressive control of hyperglycaemia in the prevention of neuropathy in populations with type 2 diabetes. Despite including multiple large clinical trials involving a large number of participants that were followed for long periods of time, a meta-analysis did not demonstrate a statistically significant reduction in the incidence of neuropathy in those with enhanced glycaemic control [5]. The effect was minor and consistent across studies, with an approximately 5% reduction in neuropathy incidence. Therefore, better glycaemic control is likely to be important for the prevention of diabetic neuropathy, but the effect is small, and other factors are also likely important. We hypothesise that obesity and other metabolic risk factors are likely to play an important role in the pathogenesis of diabetic neuropathy and need to be addressed to prevent neuropathy in this population. Obesity has emerged as the second most

important risk factor for neuropathy and interventions to target this risk factor should be further pursued [4, 6–10].

We also agree that cardiovascular autonomic neuropathy is an important complication of diabetes, but this topic was beyond the scope of our recent review [3]. We have demonstrated that central obesity, but not general obesity, is associated with somatic and cardiovascular autonomic neuropathy [11]. This implies that central obesity is important in the pathogenesis of both conditions. Whether this finding is replicated in other populations will be important to guide future interventions.

Moreover, we concur with Uusitupa et al [1] that diet and exercise are promising therapies for the prevention and treatment of somatic and cardiovascular autonomic neuropathy. In the Action for Health and Diabetes (Look AHEAD) study, an obese population with type 2 diabetes ($N = 5145$) was randomised to a lifestyle weight-loss intervention or usual care. The intervention resulted in improvements on the Michigan Neuropathy Screening Instrument (MNSI) questionnaire after 9–11 years of the intervention [12]. We are currently conducting a randomised clinical trial to compare high intensity interval training with routine care in those with and without bariatric surgery. The goal is to determine the effects of exercise, weight-loss surgery and their combination on somatic and cardiovascular autonomic neuropathy outcomes. Dr Coppini argues that weight loss and exercise should be instituted in individuals with diabetes regardless of their effect on neuropathy outcomes [2]. While true, weight loss and exercise are both life-altering lifestyle changes; therefore, understanding which is more important for the health of peripheral nerves is essential. Furthermore, the amount of resources dedicated towards weight loss and exercise needs to be determined given the costs associated with certain implementations of these interventions.

Dr Coppini makes the point that the diagnosis of neuropathy is not straightforward in the clinical setting [2]. We agree that the myriad of diagnostic tests available for neuropathy can be confusing. Currently, the best confirmatory tests for

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neuropathy are nerve conduction studies and skin biopsies for intraepidermal nerve-fibre density. However, most individuals only require a detailed history and neurological examination, especially given the expense and discomfort of the two ‘confirmatory’ options. Therefore, confirmatory tests should be reserved for those with atypical features, such as asymmetry, acute/subacute onset, non-length dependence and/or motor predominance. Dr Coppini provides evidence supporting artificial-intelligence systems utilising corneal confocal microscopy [2]. This diagnostic test shows promise, but much more work is needed before this approach becomes ready for routine clinical use. Corneal confocal microscopy has been shown in a multi-centre study to have only decent diagnostic characteristics [13]. Artificial-intelligence systems are an interesting approach, but will only be as good as the information available for statistical analysis. The AUC for this approach (AUC = 0.83) is comparable with that of the MNSI questionnaire (AUC = 0.75) and examination (AUC = 0.81) [14], which are both much easier and cheaper to administer. The American Diabetes Association currently states that diagnostic testing for diabetic neuropathy should usually stop after a detailed clinical history, neurological examination and routine laboratory tests [15]. Confirmatory tests that are superior to nerve conduction studies and skin biopsies are needed, but require vigorous testing prior to clinical implementation.

Dr Coppini also describes multiple negative clinical trials in neuropathy treatments [2]. These negative results only further emphasise the need for novel disease-modifying therapies for the prevention and treatment of neuropathy. We provide data to support further efforts to target dyslipidaemia and sphingolipids [3]. Hopefully, these pathways will provide the desperately needed new neuropathy medications but, if not, this should not discourage researchers from pursuing other potential mechanisms given the high prevalence and morbidity of neuropathy. Dr Coppini also recommends focusing efforts on prediabetes (impaired fasting glucose and impaired glucose tolerance) and prevention of neuropathy, rather than on treatment of already established neuropathy [2]. Given that prevention of nerve injury has been easier than its reversal, this suggestion has merit and we wholeheartedly agree. Hopefully, the future will lead to treatments that can both prevent and reverse nerve injury. Until that time, researchers should focus on both possibilities with an emphasis on prevention.

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