Small Fiber Neuropathy in Patients With Latent Autoimmune Diabetes in Adults

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The prevalence of latent autoimmune diabetes in adults (LADA) in patients diagnosed with type 2 diabetes mellitus (T2DM) ranges from 7 to 10% (1). They present at a younger age and have a lower BMI but poorer glycemic control, which may increase the risk of complications (2). However, a recent analysis of the Collaborative Atorvastatin Diabetes Study (CARDS) has demonstrated no difference in macrovascular or microvascular events between patients with LADA and T2DM, but neuropathy was not assessed (3). Previous studies quantifying neuropathy in patients with LADA are limited. In this study, we aimed to accurately quantify neuropathy in subjects with LADA compared with matched patients with T2DM.

This study was approved by the local research ethics committee, and after informed consent, we studied 19 subjects with LADA (diagnosis age >30 years, no insulin initiation for 6 months after the diagnosis of diabetes, and antiglutamic acid decarboxylase antibody positive), 17 subjects with T2DM, and 20 age- and sex-matched control subjects.

Patients underwent an assessment of symptoms and clinical neurologic deficits: quantitative sensory testing for vibration perception threshold (VPT), cold sensation threshold (CST), warm sensation threshold (WST), lower limb electrophysiology, corneal confocal microscopy with the Heidelberg Retina Tomography III, and intraepidermal nerve fiber density (IENFD) from the dorsum of the foot (in a smaller subset).

Clinical data and neuropathy evaluation are presented in Table 1 and show differences in both LADA and T2DM compared with control subjects. Patients with LADA and T2DM were matched for age, duration of diabetes, and blood pressure. Patients with LADA had a higher HbA_{1c} ($P < 0.0001$) and HDL ($P = 0.03$) but a lower BMI ($P = 0.001$) compared with T2DM. There was no significant difference in the neuropathy symptom profile, McGill visual analog score, neuropathy disability score, and measures of large fiber neuropathy, specifically VPT and sural and peroneal nerve electrophysiology, between patients with LADA and T2DM. However, detailed measures of small fiber neuropathy including CST ($P = 0.03$), WST ($P = 0.02$), and IENFD ($P = 0.03$) were significantly abnormal in patients with LADA compared with T2DM. Furthermore, there was a significant reduction in corneal fiber density ($P = 0.03$) and corneal nerve fiber length ($P = 0.01$) in LADA compared with T2DM.

Previous studies have focused on crude measures of large fiber neuropathy and, perhaps misleadingly, have concluded no evidence of an increased prevalence of neuropathy in patients with LADA (4). However, in the current study we have demonstrated evidence of small fiber neuropathy in patients with LADA and poor glycemic control compared with patients with T2DM with good glycemic control. This emphasizes the need to include measures of small fiber neuropathy when assessing neuropathy, especially as small fibers mediate pain, sweating, and tissue blood flow and are the earliest to be damaged and may indeed repair following intervention (5). These data also provide a means of risk stratifying neuropathy in patients with LADA; evidence of a small fiber neuropathy should alert treating clinicians to limit the progression of neuropathy in optimizing risk factors, such as glycemia, blood pressure, and lipids.

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Table 1—Participant demographics and metabolic and neuropathy parameters in control subjects and patients with T2DM and LADA

	Control (n = 20)	T2DM (n = 17)	LADA (n = 19)	T2DM vs. LADA (P value)
Age (years)	53.3 ± 9.8	54.9 ± 6.8	50.6 ± 11.9	NS
Sex (male), %	65	76	58	NS
Duration of diabetes (years)	—	9.8 ± 5.4	11.4 ± 10.2	NS
Neuropathy disability score (-/10) Median (IQR)	0.5 ± 1.0 0 (0–1)	2.1 ± 1.9 1 (0–4)	3.9 ± 3.6 3 (1–6)	NS
Neuropathy symptom profile (-/38) Median (IQR)	0.1 ± 0.3 0 (0–0)	4.5 ± 5.6 2 (1–4)	4.4 ± 6.0 2.5 (0–6)	NS
McGill VAS (-/10) Median (IQR)	0.6 ± 1.8 0 (0–0)	1.9 ± 2.5 0.5 (0–4)	0.5 ± 1.2 0 (0–0)	NS
HbA_{1c} (%)	**5.7 ± 0.4**	**7.0 ± 0.7**	**9.8 ± 2.3**	**<0.0001**
HbA_{1c} (mmol/mol)	**38.4 ± 4.2**	**52.8 ± 7.4**	**83.4 ± 24.7**	**<0.0001**
BMI (kg/m^2)	**27.5 ± 4.5**	**32.8 ± 4.6**	**27.1 ± 4.0**	**0.001**
Total cholesterol (mmol/L)	5.5 ± 0.7	4.1 ± 1.3	4.5 ± 1.3	NS
HDL (mmol/L)	**1.6 ± 0.4**	**1.1 ± 0.4**	**1.4 ± 0.4**	**0.03**
Triglycerides (mmol/L)	1.5 ± 0.6	2.0 ± 1.3	1.6 ± 1.2	NS
Systolic BP (mmHg)	133 ± 16	137 ± 25	137 ± 22	NS
Diastolic BP (mmHg)	76 ± 10	79 ± 11	76 ± 11	NS
eGFR (mL/min/1.73 m^2)	80 ± 9	79 ± 16	82 ± 13	NS
Corneal nerve fiber density (n/mm^2)	**36.7 ± 5.1**	**30.5 ± 11.25**	**24.2 ± 5.3**	**0.03**
Corneal nerve branch density (n/mm^2)	**93.4 ± 37.1**	**70.1 ± 29.4**	**60.4 ± 29.3**	**NS**
Corneal nerve fiber length (mm/mm^2)	**26.1 ± 5.3**	**24.7 ± 6.9**	**19.9 ± 4.8**	**0.01**
Corneal nerve fiber tortuosity	16.0 ± 3.7	19.7 ± 4.9	19.5 ± 5.3	NS
IENFD (n/mm)	**9.9 ± 3.2 (n = 9)**	**7.4 ± 4.4 (n = 8)**	**3.6 ± 3.0 (n = 8)**	**0.03**
CST (°C)	**28.6 ± 2.0**	**26.0 ± 3.1**	**22.6 ± 6.9**	**0.03**
WST (°C)	**36.8 ± 2.6**	**41.3 ± 3.4**	**43.9 ± 3.6**	**0.02**
VPT (V)	6.0 ± 3.5	10.5 ± 6.9	13.5 ± 11.8	NS
Sural sensory nerve conduction velocity (m/s)	49.6 ± 4.0	46.6 ± 5.7	45.2 ± 6.4	NS
Sural sensory nerve amplitude (μV)	17.8 ± 8.2	12.6 ± 8.2	10.8 ± 6.0	NS
Peroneal motor nerve conduction velocity (m/s)	47.8 ± 3.6	42.5 ± 7.4	40.9 ± 7.2	NS
Peroneal motor nerve amplitude (mV)	6.1 ± 1.9	4.2 ± 2.1	3.8 ± 2.8	NS

BP, blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; McGill VAS, McGill visual analog score. Boldface type indicates significance.

sensory testing. I.N.P. researched data and analyzed the corneal confocal microscopy images. G.P. was the study coordinator. M.J. undertook the IENFD analysis. A.M. undertook the neurophysiology. M.T. undertook the corneal confocal microscopy. A.J.M.B. and N.E. conceived and devised the study, supervised the project, and reviewed and revised the manuscript. R.A.M. conceived and devised the study, supervised the project, undertook the IENFD assessment, and reviewed and revised the manuscript. R.A.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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