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Does Prediabetes Cause Small Fiber Sensory Polyneuropathy? Does it Matter?

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Abstract

Background and Objectives—The association between prediabetes and distal polyneuropathy (DPN) remains controversial. Here we test whether the prevalence of small fiber sensory distal polyneuropathy is increased in prediabetes.

Methods—Prospectively recruited cohorts of healthy subjects and those with prediabetes from Olmsted County, Minnesota, were assessed for positive neuropathic sensory symptoms, or pain symptoms characteristic of small fiber sensory DPN. Hyperalgesia and hypoalgesia were assessed by “smart” quantitative sensation testing (QST). The prevalence of symptoms and QST abnormalities were compared among the groups.

Results—There was no significant increase in the prevalence of positive neuropathic sensory or pain symptoms, nor of hyper- or hypoalgesia in the prediabetes group. There was an increased prevalence of hypoalgesia of the foot only in newly diagnosed diabetes.

Conclusions—Based on positive sensory and pain symptoms and QSTs, we did not find an increase in small fiber sensory DPN in prediabetes. Recognizing that obesity and diabetes mellitus are implicated in macro- and microvessel complications, physicians should encourage healthy living and weight loss in patients with prediabetes. In medical practice, alternate causes should be excluded before concluding that small fiber sensory distal neuropathy is secondary to prediabetes.

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Conflict of Interest

Dr. Charles Kassardjian reports no disclosures. Dr. P. James B. Dyck reports no disclosures. Jenny Davies reports no disclosures.

Author Contributions:

C.D.K. and R.E.C. contributed to the review, statistical analysis and drafting of the manuscript. P.J.B.D. contributed to the study design and critical editing of the manuscript.

J.L.D. performed the statistical analysis.

P.J.D. contributed to the overall design and execution of the OC IG Trial and the drafting of the manuscript. He 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.

Keywords

Prediabetes; diabetes mellitus (DM); distal polyneuropathy (DPN); small fiber sensory DPN

1. Introduction

Obesity, prediabetes and type 2 diabetes mellitus (DM) are increasing to epidemic frequencies, and their increased prevalence is associated with burdensome health and economic outcomes [1–6]. Prevention and pharmacologic treatment of DM may decrease or prevent these poor outcomes [5, 6] and are major objectives of modern health care [6–9].

Previous studies using historic controls reported that prediabetes occurred with increased frequency in subjects with painful small fiber distal polyneuropathy [10–12]. Using nerve conduction study abnormality to define sensorimotor distal polyneuropathy (DPN), the Olmsted County Impaired Glycemia Trial (OC IG Trial) found no increased prevalence of DPN in prediabetes (termed impaired glycemia in that publication) [13]. There was also no increase in retinopathy or nephropathy in prediabetes. Other studies have supported our conclusions [14–17], while some have not [18–20]. Thus, the relationship between peripheral neuropathy and prediabetes remains controversial, but scientifically and medically important.

Prediabetes is one feature of the metabolic syndrome, a constellation of metabolic abnormalities that often co-occur. Recent work has highlighted that obesity and hypertriglyceridemia are independent risk factors for developing polyneuropathy, regardless of glycemic status [27]. The early diagnosis of prediabetes provides an opportunity for intervention to prevent the development of frank DM and DPN. Ascribing peripheral polyneuropathy to prediabetes without considering other acquired or hereditary causes may result in missed diagnosis and treatment.

By focusing on nerve conduction abnormalities (a test of large myelinated nerve fiber function) as the criterion for DPN, small fiber sensory DPN may have been underestimated in our previously published OC IG Trial. The present study tests the hypothesis that small fiber sensory DPN is more common in prediabetes than in healthy subjects [21, 22]. We assessed positive neuropathic sensory symptoms (PNSS) and neuropathy pain symptoms (NPS) as contained in the Neuropathy Symptoms and Change (NSC) score. Hyper- and hypoalgesia were assessed by quantitative sensation testing (QST) of the foot. These data were collected at the time of the OC IG Trial but not previously analyzed. The analysis is limited to subjects without nerve conduction abnormality.

2. Methods

The conduct and results of the OC IG Trial were described in previous publications [13, 23]. Briefly, healthy and prediabetic subjects were recruited from the Mayo Clinic's medical and laboratory records of patients in Olmsted County, MN, USA. All subjects signed informed consent to participate. Subjects with known DM, and with diagnosed neurologic diseases unrelated to DM were excluded. A representative sampling of Olmsted County patients is

possible since more than one-half of them were evaluated at Mayo Clinic in a three year time period [24]. Subjects were then restudied for their glycemia status and for the occurrence of polyneuropathy, retinopathy and nephropathy using masked assessments (examiners unaware of subject's diagnoses or test results). Healthy subjects were defined as having fasting plasma glucose (FPG) < 100 mg/dL or a 2-hour 75 gram oral glucose tolerance test (OGTT) plasma glucose (PG) < 140 mg/dL. Prediabetes had values of FPG 100 – < 126 mg/dL or 2-hour OGTT PG of 140 – < 200 mg/dL. New DM subjects had FPG ≥ 126, 2-hour OGTT PG ≥ 200 mg/dL, or an A1c ≥ 6.5%, or were classified as new DM if they had previously been diagnosed or treated as DM.

We assessed the frequency of PNSS, NPS, hyperalgesia and hypoalgesia. Questions 23 to 29 of the NSC were analyzed (containing positive sensory symptoms such as “asleep numbness” or “prickling”), and varieties of pain (e.g. “lancinating,” “burning,” “deep aching” or “other pain” in the feet or legs). All patients underwent a neurological examination at the time of assessment, but this information was not included in the analysis. Thermoelectric heat stimuli were used to estimate 0.5, 5, and 5-0.5 pain intensity (of a 1–10 ordinal scale) using CASE IVc (WR Medical Electronics, Inc., Maplewood, MN, USA). Hyperalgesia was defined as a HP-5 value ≥ 5th percentile, and hypoalgesia as a HP-5 value ≤ 95th percentile – each of which can be a finding associated with small sensory fiber DPN. The Fisher's exact test was used to compare each group, with significance set at $p < 0.05$.

3. Results

The demographic characteristics of the trial subjects are given in our previous publication [13]. A total of 498 subjects were recruited to the study, and most had QSTs: 138 healthy subjects, 165 prediabetes and 195 new DM. PNSS and NPS were not significantly increased in prediabetes or in new DM compared to healthy subjects (Table 1). Similarly, there was no significant statistical difference in the prevalence of hyper- or hypoalgesia in prediabetes compared to healthy subjects. There was a trend towards increasing frequency of hyper- and hypoalgesia going from healthy subjects to prediabetes to new DM. Hypoalgesia, but not hyperalgesia was significantly increased at a low frequency in new DM compared to healthy subjects. Using clinical signs and symptoms, no increased prevalence of DPN was found in prediabetes (Table 1).

4. Discussion

In this study we assessed whether small fiber sensory DPN is more prevalent in prediabetes than in a prospective cohort of healthy subjects. Positive symptoms of small fiber sensory dysfunction (PNSS), neuropathic pain symptoms (NPS), or QST measurements of hyper- or hypoalgesia were not significantly more prevalent in prediabetes. Only hypoalgesia was increased at a low frequency in new DM compared to healthy subjects. There was a non-significant trend towards increased hyper- or hypoalgesia comparing healthy subjects, prediabetes and new DM groups.

Our results are consistent with a recent study that did not find decreased epidermal nerve fibers in subjects with impaired glucose tolerance [14]. Also, in the population-based

Rochester Diabetic Neuropathy Study (RDNS), pain was not a manifestation of early or mild DPN, whereas nerve conduction abnormality, decrease in touch-pressure or vibration sensation, and decreased muscle stretch reflexes were early manifestations [9, 25]. Two recent prospective studies examining the etiology of chronic idiopathic axonal polyneuropathy (CIAP) found associations with hypertriglyceridemia [17, 26], or abdominal obesity and hypertension [17], but not prediabetes. Similarly, Smith and Singleton found that obesity and elevated triglycerides increase the risk of peripheral neuropathy independent of glucose control [27]. Prediabetes may be a marker of broader metabolic derangements (grouped together as the metabolic syndrome), with multiple pathological mechanisms, including toxic deoxysphingolipids [28].

There are several possible explanations for the conflicting conclusions of published studies regarding prediabetes and polyneuropathy. These include: 1) different criteria for the diagnosis of prediabetes; 2) different diagnostic criteria for DPN; 3) different degrees of surveillance; 4) no or different reference values for polyneuropathy endpoints; and 5) no use epidermal nerve fiber density measurements to diagnose small fiber sensory DPN. Our rigorously-defined glycemia criteria, as well as assessing for polyneuropathy within days of determining the glycemia status, may account for a lower prevalence of small fiber sensory DPN in prediabetes than reported by others. In this study, quantitative and masked assessment of subjects was performed, and reference values were drawn from the same population. Although we believe the sample to be representative of the Olmsted county population, inherent bias could have been introduced in population attributes by including only patients seen at Mayo Clinic. Given the conflicting results, further clarity may be obtained from long-term prospective studies following prediabetic patients over years, and utilizing multiple different markers of neuropathy (including objective clinical assessments, QSTs and skin biopsy). Alternatively, a randomized trial of aggressive treatment of prediabetes versus standard of care would be of interest.

Our findings have important implications, but do not indicate that prediabetes is irrelevant to the cause or management of peripheral neuropathy. Indeed, the non-significant trend towards a higher frequency of hyper and hypo-algesia going from healthy subjects, to prediabetics and to new DM may suggest a relationship between prediabetes and small fiber sensory DPN. A large proportion of prediabetic patients develop type 2 DM (up to 50% lifetime risk), which is a known risk factor for DPN [29]. Therefore, interventions aimed at preventing the conversion from prediabetes to frank DM should be expected to lead to fewer microvascular complications, including DPN. Examples of such interventions include changes in diet, exercise and pharmacotherapy [29]. Exercise in particular has recently been demonstrated to be associated with increased epidermal nerve fiber density in diabetic patients without neuropathy, compared to controls [30]. Our results also highlight the importance of a thorough evaluation for other causes of peripheral neuropathy in patients with painful small fiber sensory polyneuropathy and prediabetes.

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Abbreviations

DM	diabetes mellitus
DPN	distal polyneuropathy
FPG	fasting plasma glucose
NC	nerve conduction
NSC Score	Neuropathy Symptoms and Change Score
OC IG Trial	Olmsted County Impaired Glycemia Trial
OGTT	oral glucose tolerance test
PG	plasma glucose
PNSS	positive neuropathic sensory symptoms
NPS	neuropathy pain symptoms
QST	quantitative sensation test
RDNS	Rochester Diabetic Neuropathy Study

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Highlights

- Positive neuropathic or pain symptoms were not increased in prediabetes.
- Hyper- and hypoalgesia was not increased in prediabetes versus controls.
- A search for alternate neuropathy causes is needed in patients with prediabetes.

Table 1

Comparison of Positive Neuropathic Sensory Symptoms (PNSS), Neuropathy Pain Symptoms (NPS), Hypoalgesia (HP-5 95th) and Hyperalgesia (HP-5 5th) in Healthy Subjects, Prediabetes and New Diabetes

	HS		Prediabetes		New DM		Prediabetes vs. HS		New DM vs. HS		New DM vs. Prediabetes	
	n	n (%) Abnormal	n	n (%) Abnormal	n	n (%) Abnormal	OR	95% Exact CI	OR	95% Exact CI	OR	95% Exact CI
PNSS score [†] > 1	138	7 (5.1)	165	9 (5.5)	195	12 (6.2)	1.08	(0.35, 3.51)	1.23	(0.43, 3.78)	1.14	(0.43, 3.14)
NPS score [§] > 1	138	3 (2.2)	165	4 (2.4)	195	4 (2.1)	1.12	(0.19, 7.76)	0.94	(0.16, 6.54)	0.84	(0.15, 4.60)
HP-5 95th [¶]	134	18 (13.4)	161	33 (20.5)	184	42 (22.8)	1.66	(0.85, 3.31)	1.91	(1.01, 3.71)	1.15	(0.66, 1.99)
HP-5 5th ^{**}	134	10 (7.5)	161	15 (9.3)	184	18 (9.8)	1.27	(0.51, 3.29)	1.34	(0.56, 3.38)	1.06	(0.48, 2.34)

* Fisher's exact test

[†] PNSS = positive neuropathic sensory symptoms, from evaluation of items in Neuropathy Symptom and Change score described in Materials and Methods.

[§] NPS = neuropathy pain symptoms as described in Materials and Methods.

[¶] HP-5 95th = hypoalgesia (HP-5 95th percentile) of the foot as assessed by CASE IVc described in Materials and Methods.

^{**} HP-5 5th = hyperalgesia (HP-5 5th percentile) of the foot as assessed by CASE IVc described in Materials and Methods.