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Obesity and Hyperlipidemia are Risk Factors for Early Diabetic Neuropathy

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Abstract

The Utah Diabetic Neuropathy Study (UDNS) examined 218 type 2 diabetic subjects without neuropathy symptoms, or with symptoms of < 5 years, in order to evaluate risk factors for neuropathy development. Each subject completed symptom questionnaires, the Utah Early Neuropathy Scale (UENS), nerve conduction studies (NCS), quantitative sensory testing (QST) for vibration and cold detection, quantitative sudomotor axon reflex testing (QSART), and skin biopsy with measurement of intraepidermal nerve fiber density (IENFD). Those with abnormalities of 3 were classified as having probable, and those with 1–2 as possible neuropathy. The relationship between glycemic control, lipid parameters (high density lipoprotein and triglyceride levels), blood pressure, and obesity, and neuropathy risk was examined. There was a significant relationship between the number of abnormalities among these features and neuropathy status ($p < 0.01$). Hypertriglyceridemia, obesity and 3 or more abnormalities increased neuropathy risk (risk ratios 2.1 $p < 0.03$, 2.9 $p > 0.02$ and 3.0 $p < 0.004$ respectively). Multivariate analysis found obesity and triglycerides were related to loss of small unmyelinated axons based on IENFD whereas elevated hemoglobin A1c was related to large myelinated fiber loss (motor conduction velocity). These findings indicate obesity and hypertriglyceridemia significantly increase risk for peripheral neuropathy, independent of glucose control. Obesity/hypertriglyceridemia and hyperglycemia may have differential effects on small versus large fibers.

Keywords

peripheral neuropathy; diabetes; obesity; hyperlipidemia

Introduction

Over 20 million Americans have diabetes and this number increases by 5% annually. Peripheral neuropathy is the most common microvascular complication, affecting 50%. (Tesfaye, Boulton et al. 2010) Neuropathy is a major cause for disability due to pain, loss of protective sensation, foot ulceration and amputation, and fall risk. In 2003 diabetic

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neuropathy accounted for over \$13 billion in direct health care costs.(Gordois, Scuffham et al. 2003) Despite promising data from preclinical models, treatment trials have failed. The only recognized therapy is aggressive glycemic control. However, while there is convincing data supporting efficacy of intensive glycemic control for neuropathy prevention in type 1 diabetes,(Diabetes Control and Complications Trial Research Group 1995) several studies suggest this strategy may not meaningfully reduce neuropathy risk in type 2 diabetes. (Ismail-Beigi, Craven et al. 2010) A fuller understanding of factors predicting neuropathy risk is essential to better define disease pathogenesis and develop effective prevention or treatment strategies.

The Utah Diabetic Neuropathy Study (UDNS) prospectively follows a community based cohort of over 200 subjects with type 2 diabetes either without neuropathy symptoms at baseline or with recent onset symptoms, in order to better understand risk factors for early neuropathy and to develop and validate potential surrogate measures for future use in prevention or therapeutic trials. We report here the relationship between obesity, dyslipidemia and hypertension and neuropathy risk at study entry for 218 UDNS subjects. The results suggest obesity and dyslipidemia are potent neuropathy risk factors, challenging traditional belief that hyperglycemia is the dominant risk factor in type 2 diabetes, and suggest that different nerve fiber classes may be preferentially vulnerable to hyperglycemic versus dyslipidemic injury.

Materials and Methods

Subjects 18–65 years old with type 2 diabetes (Tesfaye, Boulton et al. 2010, 2011) were recruited from the University of Utah Health Care Network, which includes 10 primary care clinics in the Salt Lake City metropolitan area. Potential subjects were identified by searching discharge codes for type 2 diabetes. A randomly selected sample was sent letters describing the study. Interested subjects underwent a telephone screen. Those fulfilling inclusion and exclusion criteria were scheduled for a screening visit. The University of Utah Institutional Review Board approved the study and all participants provided informed consent.

Subjects with diabetes who had no neuropathy symptoms, or symptoms consistent with distal symmetric polyneuropathy in the opinion of the investigators (AGS, JRS), of < 5 years duration were recruited. Those with > 5 years of symptoms were excluded, as were those with findings on a complete neurologic examination suggesting a potentially confounding disorder (e.g. polyradiculopathy, myelopathy). Those who had a history of medical conditions associated with neuropathy (including heavy alcohol use) and those with a first-degree family member with a non-diabetic neuropathy were excluded. Each subject completed a questionnaire regarding exposure to potentially neurotoxic medications. Those responding affirmatively to any were excluded. Vitamin B12 level, thyroid stimulating hormone (TSH), antinuclear antibody, and serum protein electrophoresis were measured in each subject and those with abnormalities excluded. Subjects with conditions that might interfere with electrophysiologic testing or skin biopsy (severe edema, Coumadin use, dermatologic disorder) were also excluded.

Hemoglobin A1c (HgbA1c) and fasting lipid panel including total, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglycerides (TRG) were measured. Weight and height were measured and body mass index (BMI) calculated. Systolic and diastolic blood pressures were recorded. (The Expert Panel on Detection 2001) Hypertension was defined as SPB > 130 or DBP >85), abnormal HDL as < 40 mg/dl for men or 50 mg/dl for women, and abnormal TRG as > 149 mg/dl (The Expert Panel on Detection 2001). Subjects taking a blood pressure medication for hypertension were considered to have fulfilled the

hypertension criterion even if blood pressure was normal. Those with a normal lipid panel were considered to fulfill one criterion if they were taking a lipid-lowering agent. Obesity was defined as a BMI of $>30 \text{ kg/m}^2$ (Grundey, Brewer et al. 2004). (2011)The duration of diabetes and neuropathy symptoms was recorded. Each subject underwent validated quantitative neuropathy examinations including the Michigan Diabetic Neuropathy Score (MDNS)(Feldman, Stevens et al. 1994) and the Utah Early Neuropathy Scale (UENS) (Singleton, Bixby et al. 2008) as well as a visual analog pain scale.

Nerve conduction studies (NCS) included Sural sensory amplitude and conduction velocity, and Peroneal motor amplitude, distal latency and conduction velocity in the leg. Studies were performed by one of the investigators (AGS, JRS) or an AAET certified technician (CD) using an Oxford Synergy nerve conduction machine. A temperature of at least 31 degrees Celsius was maintained. Quantitative sensory testing (QST) for cold and vibration detection and heat pain threshold was performed using a Case IV device (WR Medical, Stillwater MN) and a 4-2-1 stepping algorithm Quantitative sudomotor reflex testing (QSART) of the foot, distal leg, thigh and forearm was performed (QSweat, WR Medical, Stillwater MN).

Three millimeter punch skin biopsies taken from the distal leg, distal thigh, and proximal thigh were stained with PGP 9.5 using established methods.(Lauria, Hsieh et al. 2010) Intraepidermal nerve fiber density (IENFD) was assessed by counting the number of fibers traversing the dermal-epidermal junction. Epidermal length was measured using image analysis software (Image Pro Plus) and the linear IENFD calculated.

Peripheral neuropathy was defined based on six criteria: symptoms, signs (defined as a UENS >4)(Singleton, Bixby et al. 2008), abnormal NCS (defined as abnormal Sural or Peroneal motor amplitude or motor conduction velocity using age adjusted normative data), abnormal QST (CDT or VDT greater than the age-specific 95th percentile), abnormal QSART using age- and gender-adjusted normal values, and abnormal ankle IENFD using published age and sex normative data (to which the University of Utah contributed control IENFD data).(Lauria, Bakkers et al. 2010) UDNS subjects who fulfilled 0 criteria were classified as having no neuropathy, those fulfilling 1–2 criteria as possible neuropathy, and those fulfilling three or more (e.g. symptoms and signs in addition to one confirmatory test, symptoms or signs in addition to two confirmatory tests, or “laboratory based” diagnosis based on three confirmatory tests without signs or symptoms) as probable neuropathy.

Analysis of variance with post hoc Bonferonni analysis was used to compare lipid parameters, blood pressure, and BMI and key neuropathy endpoints (sural sensory amplitude, peroneal motor conduction velocity, QSART and IENFD) between neuropathy groups. Because there is decline in IENFD at distal sites early in neuropathy, often resulting in absent IENF at the distal leg, all three were included in the analysis. Correlation coefficients were used to examine the relationship between continuous measures and neuropathy parameters. Correlations were assessed for all variables controlling for age, duration of diabetes and hemoglobin A1c. Chi squared analysis including linear by linear association and risk ratios were used to examine the relationship between potential risk factors and neuropathy risk. The relationship between statin medication use and neuropathy risk was also examined. Multiple linear regression was used to examine the cumulative risk of obesity, hypertension, low HDL and hypertriglyceridemia and small (IENFD) versus large (Peroneal motor conduction velocity) fiber function. In order to further compensate for the effect of subjects with outlying HbA1c values, risk ratios were determined again in those with a hemoglobin A1c of between 6.0–7.9%.

Results

A total of 218 subjects enrolled in UDNS. The mean age was 59.0 $\pm$ 8.8 years and 52% were women. The mean duration of diabetes was 87.7 $\pm$ 80 months. Among those who had neuropathy symptoms, the symptom duration was 16 $\pm$ 32 months. Table 1 summarizes the cohort's clinical and laboratory characteristics. At baseline, 33 (15%) subjects had no neuropathy features, 83 (38%) met the criteria for probable neuropathy, and the remaining 101 (47%) had possible neuropathy. Among those with probable neuropathy, 95% had either symptoms or an abnormal UENS examination. Subjects with probable neuropathy had longer diabetes duration ($p < 0.01$), were taller ($p < 0.03$) and heavier ($p < 0.02$), and had a higher mean HgbA1c ($p < 0.02$) and lower HDL cholesterol ($p < 0.02$) than those without neuropathy features. Chi squared analysis of peripheral neuropathy criteria versus the number of potential risk factors revealed a significant relationship ($p < 0.009$) (Figure 1). Comparison of individual risk factors to neuropathy status (including statin use) found hypertriglyceridemia as the only significant risk determinant ($p < 0.01$). When subjects with no neuropathy were compared to those with probable neuropathy hypertriglyceridemia ($p < 0.02$), obesity ($p < 0.03$) and the presence ≥ 3 risk factors ($p < 0.004$) were significantly related to neuropathy risk. The neuropathy risk ratio was 2.3 (95% confidence interval 1.1–4.7) for those with elevated triglycerides and 2.1 (95% confidence interval 1.1–4.3) for obesity. Those having ≥ 3 risk factors showed 3.0 times the risk of probable neuropathy (95% confidence interval 1.4–5.8) (Figure 2).). Statin use did not influence neuropathy risk.

In order to exclude an effect of outlying hemoglobin A1c values, the risk analysis was repeated for the 109 subjects who's HgbA1c was between 6.0 and 8.0%. The risk relationships were similar but stronger in this group (obesity 3.9, hypertriglyceridemia 4.1 and ≥ 3 risk factors 4.0 fold risk (all significant to $p < 0.05$). Further narrowing of the A1c window did not change these results.

The relationship between risk factors and individual neuropathy characteristics was examined for those with possible or probable neuropathy. Table 2 summarizes the correlation coefficients between individual measures. In general, neuropathy severity based on the UENS correlated best with age, diabetes duration, height and hemoglobin A1c. Nerve conduction parameters, particularly conduction velocity, correlated best with HgbA1c and height, whereas IENFD and pain severity correlated best with weight. Distal leg IENFD correlated significantly with serum triglycerides. Figure 3 illustrates scatter plots of BMI and HgbA1c against IENFD, Sural sensory amplitude and Peroneal motor conduction velocity. IENFD, which is a relatively pure measure of small sensory fiber integrity, correlated significantly with BMI but not with HgbA1c, whereas Peroneal motor conduction velocity, which reflects large myelinated fiber integrity, correlated with HgbA1c but not BMI. Sural sensory amplitude, a measure of large sensory fibers correlated significantly with both.

The correlation data suggests there may be differential impact of dyslipidemia and hyperglycemia on individual neuropathy measures. Because the risk and correlation studies indicate HgbA1c, age, BMI and serum triglycerides convey the most neuropathy risk, multiple linear regression was performed to determine their cumulative impact on IENFD and Peroneal motor conduction velocity. This model had an R² of 0.12 for IENFD with age ($p < 0.001$), BMI ($p < 0.01$), and triglycerides ($p < 0.05$) significantly related to reduced IENFD. There was no relationship between HgbA1c and IENFD. The same model had an R² of 0.18 for Peroneal motor conduction velocity. However, in contrast to IENFD, HgbA1c and age were significantly related to Peroneal velocity ($p < 0.001$ for each) but BMI and triglycerides were unrelated.

There were significant differences in key neuropathy severity measures (Sural sensory amplitude, Peroneal motor conduction velocity, QSART and IENFD) between diagnostic groups ($P < 0.001$) (Table 3). There were significant differences between each of the three diagnostic groups for sural sensory amplitude and all IENFD measures. There were also significant differences between those with no vs. probable, and possible vs. probable neuropathy for QSART at the foot and distal leg, and Peroneal motor conduction velocity. These findings suggest sensory axons (both small unmyelinated and large myelinated) are affected early in the course of neuropathy.

Discussion

These results indicate that obesity and hypertriglyceridemia are significant early diabetic neuropathy risk factors, independent of glycemic control. Indeed, the significance of the risk ratios for each was higher among participants with good glycemic control. Moreover, hypertriglyceridemia and obesity significantly correlated with small fiber integrity (IENFD), while glucose control more closely correlated with large myelinated fiber function (NCS conduction velocity). These findings suggest disparate pathogenesis for injury to sensory axons (particularly those with small diameter) versus myelinated motor fibers, and offer additional support to a competing narrative to the traditional understanding of diabetic neuropathy as driven by prolonged sustained hyperglycemia.

Strengths of the UDNS protocol include the use of an unbiased recruitment strategy, which was designed to enroll participants reflective of the general Utah population. Other strengths include an unusually extensive characterization of peripheral nerve function and use of stepped agnostic diagnostic criteria. Because the goal was to evaluate risks for early/developing neuropathy (a stage at which therapeutic intervention would have the highest likelihood of success), criteria needed to be sensitive to early small fiber neuropathy. Application of too rigid criteria assures specificity, but captures only those with advanced disease. In choosing a definition of neuropathy, we sought to give equal weight to small and large fiber features, and to recognize progression from possible to probable neuropathy in an agnostic fashion. While the UDNS recruitment first started in 2005, prior to recent consensus criteria, 95% of probable neuropathy subjects would have been classified as having confirmed or subclinical neuropathy using the Toronto criteria. (Tsfaye, Boulton et al. 2010)

This study also has several limitations. The development and evolution of diabetic neuropathy occurs over years, thus reliance on single measures of HgbA1c and lipid values may not be as valuable as longitudinal assessment. The cohort had generally well controlled blood pressure, which limits the ability to examine the risk of more significant levels of hypertension. Similarly, the predictive validity of baseline risk factors and their change over time for future neuropathy development, or progression, is stronger than the concurrent validity analysis performed in this study. Therefore, the UDNS cohort is being followed prospectively in order to perform such analyses.

It is commonly accepted that aggressive diabetes control is the only effective treatment strategy for diabetic neuropathy. The efficacy of intensive glucose lowering was well established in type 1 diabetes by the Diabetes Complications and Control Trial (DCCT). The DCCT randomized 1441 patients to intensive or standard glucose control. The intensive therapy cohort experienced a 65% reduction in clinical neuropathy risk after 5 years. (DCCT Research Group 1993) This effect is durable. The subsequent Epidemiology of Diabetes Interventions and Complications (EDIC) study found that while the two treatment cohorts had similar glycemic control over 14 years following the DCCT, those in the intensive

treatment group were still significantly less likely to develop neuropathy (25% vs. 35%, $p<0.001$). (Albers, Herman et al. 2010)

By contrast, the benefit of intensive glycemic control on neuropathy risk in type 2 diabetes appears to be much less robust (Callaghan, Little et al. 2012). Several large studies, including the ACCORD study, failed to demonstrate efficacy of intensive glycemic control in type 2 patients. (Azad, Emanuele et al. 1999; Duckworth, Abaira et al. 2009) Thus, it is likely that different risk determinants, and distinct mechanisms, contribute to neuropathy in type 1 and type 2 diabetes populations (Callaghan, Hur et al. 2012). These factors may establish neuropathy risk early in the course of diabetes in affected individuals. For this reason the current study specifically sought out patients with early neuropathy of less than 5 years duration. Identification of risk factors for early neuropathy development is essential in better understanding disease mechanism and developing treatment strategies at a stage when the disease is most likely to respond to therapy.

In the present study, the relationship between glycemic control, HDL, TRG, HTN, height, weight, and diabetes duration and features of neuropathy was examined in a cohort of participants with early type 2 diabetes to better understand risk factors for early neuropathy development. By contrast, most published studies examining neuropathy risk factors include patients with well-established and more advanced neuropathy. UDNS subjects who had probable neuropathy had a longer duration of diabetes, were taller, and had higher mean hemoglobin A1c than those who did not. The likelihood of having neuropathy increased as the number of risk factors present increased. Both hypertriglyceridemia and obesity increased neuropathy risk two fold, whereas having 3 risk factors increased risk 3 fold. These risk relationships became more robust when considering patients with otherwise well controlled diabetes, yielding risk ratios of 4.

Vascular risk factors have been identified as potential neuropathy risk factors in diabetic and non-diabetic populations. The EURODIAB study followed 1172 patients with type 1 diabetes, and found that incident neuropathy risk was increased by both glycemic control and other vascular risk factors including hypertriglyceridemia, hypertension, obesity and tobacco use. (Tefaye, Chaturvedi et al. 2005) Among 28,700 diabetic patients, serum triglyceride level was an independent stepwise risk factor for lower extremity amputation. (Callaghan, Feldman et al. 2011) A series of studies have examined neuropathy risk factors among subjects who underwent sequential sural nerve biopsies as part of diabetic neuropathy clinical trials. Subjects were divided into those who had progressive neuropathy and those who did not. Progressors had significantly higher baseline triglycerides controlling for other relevant variables. (Wiggin, Sullivan et al. 2009) More recently, this same group has taken advantage of the banked biopsies to examine gene expression profiles. A total of 532 genes were differentially expressed between those who progressed and those who did not. These genes were clustered in pathways relevant for inflammation and lipid metabolism. In particular, networks involving apolipoprotein E, jun, leptin, serpin peptidase inhibitor E type 1, and peroxisome proliferator activated receptor gamma appeared most relevant. (Hur, Sullivan et al. 2011)

Idiopathic (non-diabetic) neuropathy patients have a significantly higher risk of dyslipidemia and obesity than the normal population. (Smith, Rose et al. 2008). The only carefully performed idiopathic neuropathy case control study identified hypertriglyceridemia as a neuropathy risk factor. (Hughes, Umapathi et al. 2004) Small studies comparing obese and thin subjects have shown relative abnormalities of both nerve conduction measures and small fiber axonal function in the obese subjects, most of who were asymptomatic. (Herman, Brower et al. 2007) Animal models of diet-induced obesity have demonstrated both microvascular and neural dysfunction in non-hyperglycemic animals (Oltman, Coppey et al.

2005; Obrosova, Ilnytska et al. 2007; Davidson, Coppey et al. 2010). Non-diabetic mice fed a high-fat diet develop increased levels of oxidized low density lipoproteins, free fatty acids and triglycerides, as well as evidence of increased systemic and nerve oxidative stress. These mice develop neuropathy in the absence of hyperglycemia (Vincent, Hinder et al. 2009). Results of the current study adds substantially to this evolving literature suggesting toxic adiposity and dyslipidemia may be more important contributors to diabetic and idiopathic neuropathy risk than has previously been recognized.

Correlation data assess the relationship between potential risk factors and disease severity. Large myelinated nerve fiber measures such as motor conduction velocity or sensory nerve action potential amplitude correlated best with hemoglobin A1c and height, both of which are well-recognized neuropathy risk factors. By contrast, IENFD, which primarily reflects small unmyelinated axons, correlated best with obesity and serum triglycerides. Interestingly, sural sensory amplitude also correlated with BMI and TRG. These findings suggest hyperglycemia, obesity and dyslipidemia may have distinct but overlapping effects on peripheral nerve function. Hyperglycemia appears to cause preferential injury to large myelinated fibers, reflected by motor nerve conduction velocity, whereas dyslipidemia and obesity preferentially affect small nerve fibers, reflected by IENFD. The fact that sural sensory amplitude also correlated with BMI and TRG suggests these risk factors may be particularly important in loss of sensory axons of all sizes, which is the primary pathology underlying patient symptoms and disability. The relationship between obesity and IENFD has not been observed in normal populations, including a large multicenter normative data study in which our laboratory participated. (Lauria, Bakkers et al. 2010), arguing against the concept of skin stretching as a mechanism for reduced IENFD in the obese.

These findings are potentially significant for clinical trial design. The most common surrogate measures employed by diabetic neuropathy clinical trials are nerve conduction studies, in particular motor conduction velocity. Motor conduction velocity is an appealing surrogate measure because it declines early in the course of diabetic neuropathy, is responsive to aggressive glycemic control in type 1 diabetes, and is reproducible. However, nerve conduction parameters do not change meaningfully in diabetic natural history cohorts or the placebo arms of recently completed diabetic neuropathy trials, suggesting they are not sensitive to change early in the disease course. (Dyck, Norell et al. 2007) There is an urgent need for better surrogate markers of early axon loss. The observation that there is differential relationship between small versus large fiber measures and hyperglycemia versus dyslipidemia/obesity supports development of potential small fiber endpoint measures. Small fiber measures may be particularly important in any study examining the effect of a treatment designed to lower lipids or ameliorate the deleterious effects of central adiposity. Longitudinal studies are required to evaluate the extent to which these risk factors predict future neuropathy development, as well as whether IENFD or other potential small fiber endpoints are clinically meaningful, valid surrogate measures.

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Figure 1.

(A) Chi squared analysis revealed a significant relationship between the number of risk factors present and peripheral neuropathy criteria fulfilled ($p < 0.009$). (B) Subjects with probable or possible neuropathy had abnormalities of more risk factors than those without neuropathy ($p < 0.07$).

Figure 2.

Obesity, hypertriglyceridemia and abnormalities of 3 risk factors each significantly increased the risk for peripheral neuropathy, while there was a trend for reduced HDL cholesterol doing so (A). These relationships were more robust when only subjects with well controlled diabetes (HbA1c 6–8%) were considered (B).

Figure 3.

IENFD at each biopsy site was significantly correlated to BMI (proximal thigh $cc -0.23, p < 0.001$), but not HbA1c. Sural sensory amplitude correlated with both BMI ($cc -0.23, p < 0.001$) and HbA1c ($cc -0.24, p < 0.001$), whereas Peroneal motor conduction velocity (a relatively pure large fiber metric) only correlated with HbA1c ($cc -0.35, p < 0.001$).

Table 1

Demographic, clinical, and laboratory features of subjects based on neuropathy status. Analysis of variance with a Bonferonni post hoc analysis revealed a significant relationship between duration of diabetes, height, weight, HDL cholesterol, hemoglobin A1c and peripheral neuropathy risk

	Peripheral Neuropathy Status			p Value
	None	Possible	Probable	
Number	33	101	83	---
Age	57.5 +/- 9.8	58.5 +/- 9.1	60 +/- 7.9	ns
Gender	55%	50%	53%	ns
Duration DM (months)	89.4 +/- 79	72.7 +/- 79	104 +/- 78	p<0.01 [*] , ^{**}
BMI (kg/m²)	33.3 +/- 8.7	32.7 +/- 6.8	34.6 +/- 8.5	ns
Height (inches)	66.7 +/- 3.9	67.0 +/- 3/6	68.4 +/- 3.5	p<0.03 ^{**}
Weight (pounds)	216 +/- 62	209 +/- 44	230 +/- 52	p<0.02 ^{**}
Chol (total) (mg/dl)	172 +/- 48	175 +/- 51	172 +/- 34	ns
LDL (mg/dl)	97.4 +/- 44	88.6 +/- 33	86.0 +/- 27	ns
HDL(mg/dl)	48.3 +/- 13	50.0 +/- 13	46.5 +/- 11	P<0.02 [*]
TRG(mg/dl)	275 +/- 751	189 +/- 204	200 +/- 123	ns
A1c (%)	6.6 +/- 1.2	6.6 +/- 1.2	7.2 +/- 1.9	p<0.02 ^{**}
Systolic BP (mm Hg)	137 +/- 14	133 +/- 18	134 +/- 17	ns
Diastolic BP (mm Hg)	78 +/- 10	76 +/- 9.8	74 +/- 9.9	ns

* None versus Probable Neuropathy.

** Possible versus Probable Neuropathy.

Table 2

Neuropathy severity by examination correlated with age, diabetes duration, height, weight and HbA1c. IENFD, which directly reflects small fiber integrity, correlated with age BMI and triglycerides but not A1c, whereas peroneal motor conduction velocity, a large fiber surrogate, correlated best with HbA1c, but not BMI or triglycerides. Correlation coefficients and p values are displayed for significant relationships.

Measure	Age	Diabetes duration	Height	Weight	BMI	HbA1c	HDL	TRG
UENS	.209, p<0.002	.221, p<0.001	.189, p<0.007	.153, p<0.028		.161, p<0.022		
VAS				.175, p<0.012	.163, p<0.019			
IENFDI	-.220, p<0.002		-.194, p<0.008	-.256, p<0.000	-.164, p<0.024			-.184, p<0.011
Samp	-.247, p<0.001	-.237, p<0.001	-.325, p<0.000	-.433, p<0.000	-.293, p<0.001	.243, p<0.001	.164, p<0.019	
PMCV	-.153, p<0.034	-.184, p<0.011	-.405, p<0.000	-.236, p<0.001		-.355, p<0.000		

UENS – Utah Early Neuropathy Scale, VAS – Visual analog pain scale, IENFDI – Intraepidermal nerve fiber density at the distal leg, Samp – Sural sensory amplitude, PMCV – Peroneal motor conduction velocity

Table 3

Physiological and structural measures of neuropathy severity were significantly reduced in those with possible and probable peripheral neuropathy. One way ANOVA with a post hoc Bonferroni analysis revealed a significant relationship between neuropathy status and each measure except for QSART sweat volume at the proximal leg and forearm sites ($p<0.001$). P values for statistically significant comparisons between those with no and possible, no and probable, and possible and probable neuropathy are provided. The only measures with significant differences between each group were Sural sensory amplitude and IENFD at each site.

Neuropathy Measure		None	Possible	Probable	No-Pos	No-Prob	Poss-Prob
Nerve Conduction Studies	<i>Sural Amplitude (uV)</i>	14.4 +/- 6.1	11.1 +/- 5.4	4.9 +/- 6.3	p<0.02	p<0.000	p<0.000
	<i>Peroneal Motor Conduction Velocity (m/sec)</i>	46.5 +/- 4.9	45.0 +/- 4.1	40.6 +/- 5.4	ns	p<0.000	p<0.000
	<i>Foot</i>	1.29 +/- 0.68	1.09 +/- 0.76	0.74 +/- 0.72	ns	p<0.002	p<0.006
QSART Sweat Volume (uL)	<i>Distal Leg</i>	1.15 +/- 0.68	0.88 +/- 0.70	0.68 +/- 0.74	ns	p<0.007	ns
	<i>Proximal Leg</i>	0.98 +/- 0.67	0.88 +/- 0.73	0.70 +/- 0.68	ns	ns	ns
	<i>Forearm</i>	1.21 +/- 0.79	1.07 +/- 0.90	0.99 +/- 0.87	ns	ns	ns
	<i>DL</i>	5.71 +/- 2.1	3.66 +/- 2.8	1.47 +/- 1.7	p<0.000	p<0.000	p<0.000
IENFD (fibers/mm)	<i>DT</i>	7.61 +/- 2.7	5.84 +/- 3.7	4.02 +/- 2.6	p<0.009	p<0.000	p<0.001
	<i>PT</i>	7.94 +/- 2.5	6.39 +/- 3.5	4.83 +/- 3.2	p<0.022	p<0.005	p<0.005