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Central obesity is associated with neuropathy in the severely obese

Brian C. Callaghan, MD, MS[1], **Evan Reynolds, PhD**[1], **Mousumi Banerjee, PhD.**[1], **Ericka Chant, MPH**[1], **Emily Villegas-Umana, BSN, RN**[1], **Eva L. Feldman, MD, PhD**[1]

[(1)]University of Michigan, Ann Arbor, MI

Abstract

Objective: To determine the prevalence of neuropathy stratified by glycemic status and the association between extensive anthropometric measurements and neuropathy.

Patients and Methods: We performed a cross sectional, observational study in obese individuals, prior to surgery, with body mass index >35. Lean controls were recruited from a research website. Neuropathy was defined by the Toronto consensus definition of probable neuropathy. We compared nine anthropometric measurements between obese participants with and without neuropathy. We used multivariable logistic regression to explore associations between these measures, and other metabolic risk factors, and neuropathy.

Results: We recruited 138 obese individuals and 46 lean controls. The mean age (SD) was 45.1 (11.3) in the obese population (76% female) and 43.8 (12.1) in the lean controls (82% female). The prevalence of neuropathy was 2.2% in lean controls, 12.1% in obese participants with normoglycemia, 7.1% in obese participants with pre-diabetes, and 40.8% in obese participants with diabetes (p=<0.01). Waist circumference was the only anthropometric measure that was larger in those with neuropathy (139.3cm vs. 129.1cm, p=0.01). Hip-thigh (71.1cm vs. 76.6cm, p<0.01) and mid-thigh (62.2cm vs. 66.3cm, p=0.03) circumferences were smaller in those with neuropathy. The BMI was comparable between obese with and without neuropathy (p=0.86). Waist circumference (OR=1.39, 95%CI 1.10–1.75), systolic blood pressure (OR=2.89, 95%CI 1.49–5.61), and triglycerides (OR=1.31, 95%CI 1.00–1.70) were significantly associated with neuropathy.

Corresponding author: Brian Callaghan, 109 Zina Pitcher Place, 4021 BSRB, Ann Arbor, MI 48104, 734-764-7205 office, 734-615-7300 fax bcallagh@med.umich.edu.

Author contributions:

Brian Callaghan was involved in the study design, interpretation of the statistical analysis, and wrote the manuscript. Evan Reynolds, Mousumi Banerjee, and Eva Feldman were integrally involved in the study design, interpretation of the data, and critical revisions of the manuscript. Evan Reynolds performed the statistical analyses. Emily Villegas-Umana and Ericka Chant were involved in the study design and critical revisions of the manuscript.

Disclosures:

Dr. Callaghan consults for a PCORI grant, DynaMed, the Immune Tolerance Network, and performs medical legal consultations including consultations for the Vaccine Injury Compensation Program. Drs. Reynolds, Banerjee, and Feldman report no disclosures. Mrs. Villegas-Umana and Ms. Chant report no disclosures.

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Conclusions: Normoglycemic obese patients have a high prevalence of neuropathy indicating that obesity alone may be sufficient to cause neuropathy. Waist circumference, but not general obesity, is significantly associated with neuropathy.

Introduction

Neuropathy is a highly prevalent condition that is especially common in those with diabetes (834%).[1–6] We previously reported that neuropathy is also common in individuals with obesity (23%) even in the absence of hyperglycemia (14%).[7] Neuropathy leads to increased pain, falls, and lower quality of life.[8] Unfortunately, no disease modifying treatments exist for neuropathy other than control of diabetes. To inform future treatments, we need a better understanding of the metabolic factors that contribute to neuropathy.

Multiple studies show that diabetes and obesity are the most consistent metabolic factors associated with neuropathy.[7, 9–15] What is less studied is the effect of obesity, in the absence of hyperglycemia (pre-diabetes including impaired fasting glucose and impaired glucose tolerance and diabetes), and neuropathy. This is particularly critical because over 2 billion individuals are either overweight or obese, making the obesity epidemic one of the most important health problems in the world.[16] Essential questions include whether obesity alone is sufficient to cause neuropathy, and whether the distribution of obesity or general obesity is the main driver of neuropathy. A single study in Germany found associations between waist circumference, waist-to-hip ratio, waist-to-height ratios, and body mass index (BMI) with neuropathy.[15] However, the influence of the distribution of obesity in other parts of the body on neuropathy status was not examined.

The goal of the current study was to confirm, in a second patient cohort, if obesity without hyperglycemia is associated with neuropathy. Furthermore, we aimed to understand the importance of obesity distribution as a neuropathy risk factor by utilizing nine anthropometric measurements to assess their independent associations with neuropathy.

Methods

Population

From March 2015 to June 2018, we recruited patients attending the University of Michigan bariatric surgery clinic (prior to surgical intervention). Inclusion criteria were age 18 years or older and body mass index (BMI) > 35. Exclusion criteria were BMI >70 (bariatric surgery clinic criterion), anticoagulant therapy, current tobacco, marijuana, or nicotine use, active cancer within the last year, suicide attempt in the last year or multiple suicide attempts, reliance on a wheelchair or scooter, high dose steroids, cardiac stent within the last year, history of open Nissen surgery or esophagectomy, and cirrhosis of the liver. We recruited lean controls with no metabolic syndrome components (National Cholesterol Education Program/ Adult Treatment Panel III (NCEP) criteria) through a University website.

This study was approved by the University of Michigan Institutional Review Board.

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Anthropometric measurements

Anthropometric measurements collected included arm (midway between the acromion and olecranon process), forearm (maximal circumference), high waist (narrowest part of torso, above umbilicus and below xiphoid process), abdomen (greatest anterior extension of the abdomen), NCEP waist (top of the iliac crest), buttocks/hips (maximal circumference of the buttocks), hips/thigh (maximal circumference of the hip/proximal thigh just below the gluteal fold), mid-thigh (midway between the inguinal crease and the proximal border of the patella), and calf (maximal circumference between the knee and ankle). Measurements were taken without compressing the subcutaneous adipose tissue. Two measurements were collected and averaged for each location.

Other metabolic phenotyping

Obese and lean participants underwent glucose tolerance testing (except for obese patients with a previous diagnosis of diabetes) and a fasting lipid panel. HbA1c was obtained on obese participants only. Patients also had blood pressure, height, weight, and BMI measurements at the time of study entry.

Metabolic Syndrome components

Diabetes and pre-diabetes were defined according to the Expert Committee on the diagnosis and classification of diabetes mellitus.[17] The updated NCEP criteria were used to define the metabolic syndrome and its individual components.[18]

Polyneuropathy Definition (primary outcome)

Our primary outcome measure was the Toronto consensus definition of probable polyneuropathy, which requires 2 or more of the following: neuropathy symptoms, abnormal sensory examination, and abnormal reflexes as determined by one of 4 neuromuscular specialists.[19]

Secondary neuropathy outcomes

Our secondary outcome measures were intraepidermal nerve fiber density (IEIENFD) measured at the distal leg and four nerve conduction study (NCS) parameters (the sural sensory and tibial motor amplitudes, the peroneal distal motor latency (DML), and the tibial F response). The sural amplitude was chosen based on a previous study demonstrating good diagnostic characteristics.[20] The other three nerve conduction studies were chosen based on our previous work that revealed that they had the best diagnostic test characteristics in an obese population.[21] Nerve fiber density was evaluated using an established protocol.[22] Nerve conduction studies were performed using the CareFusion’s Viking on Nicolet EDX electrodiagnostic system.

Additional neuropathy measures

To further characterize peripheral nerve function, we obtained the IENFD at the proximal thigh, and other nerve conduction study parameters including the sural sensory (peak latency), peroneal motor (amplitude, conduction velocity, and F response), tibial motor (distal motor latency). The Utah Early Neuropathy Scale (UENS) and the Michigan

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Neuropathy Screening Instrument (MNSI) questionnaire and examination (performed by a neuromuscular specialist) were completed as previously described.[23, 24] Neurothesiometer testing was performed on the plantar surface of the dominant great toe, and the average of three trials was recorded. Quantitative sensory testing (QST) measurements of vibration and cold detection thresholds were performed using the WR Medical Electronics Co. CASE IV (Computer Aided Sensory Evaluator).

Pain and quality of life measures

The validated Neuro-QOL instrument was utilized to measure neuropathy specific quality of life.[25] The short form McGill Pain questionnaire was employed to measure pain with a visual analogue scale (0–100), and 4-point rating scale of 15 different neuropathic pain descriptors (McGill pain score).[26] The Inventory of Depressive Symptomatology Self Report (IDS-SR) was used to measure depression.[27] The Impact of Weight on Quality of Life (IWQOL-Lite) questionnaire was utilized as a measure of obesity related quality of life.[28] A EuroQol visual analogue scale was also given to ascertain current health state with 100 representing the best imaginable health state.[29]

Statistical Analysis

Descriptive statistics were used to describe the demographics, metabolic phenotyping, anthropometric measurements, and neuropathic outcome measures of the obese and lean participants. Chi square or Fisher's Exact tests were used to compare the two groups in terms of categorical variables and t-tests were used for continuous variables. We determined the prevalence of neuropathy stratified by glycemic status. We then applied a Cochran-Armitage test to investigate for a trend in the neuropathy prevalence in the four groups (lean controls, obese with normoglycemia, obese with pre-diabetes, and obese with diabetes). Anthropometric measurements were also stratified by sex, and t-tests were used to determine if there were significant differences in the average measures between those with and without neuropathy within each gender stratum.

We performed regression analyses to evaluate the associations between neuropathy outcomes and metabolic syndrome components, restricted to the obese population (complete-case analysis). For the primary analysis, multivariable logistic regression was used to model neuropathy as a function of the metabolic syndrome components (NCEP waist circumference, pre-diabetes, diabetes, HDL, triglycerides, systolic blood pressure), after adjusting for demographic factors (age, sex, height) for a total of nine variables. We performed nine additional models with each of the other eight anthropometric measurements and weight replacing waist circumference. For the secondary neuropathy outcomes including IENFD at leg, sural amplitude, tibial F response, peroneal DML, and tibial amplitude, we fitted multivariable linear regression models to analyze each as a function of the metabolic syndrome components, adjusting for the same demographic factors. To address departures from normality and homoscedasticity assumptions, we transformed the outcomes peroneal DML and IENFD leg using logarithmic and square root transformations, respectively, and fitted regression models on the transformed outcomes.

All analyses were completed using R v.3.4.2.

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Results

From March 2015 to June 2018, 1,021 potential bariatric surgery candidates were contacted. Of those contacted, 163 (16%) consented (657 did not respond, 87 not interested, 48 did not pursue surgery, 33 could not schedule before surgery, 22 later determined ineligible, and 11 not surgical candidates). Of those consented into the study, 138 (85%) completed all three baseline visits (12 withdrew/lost to follow-up, 6 had surgery greater than 6 months after completing outcomes, 4 did not have surgery, and 3 were excluded (1 each for anticoagulant therapy, unable to draw blood, and mental health concerns). We also recruited 46 lean controls.

Several outcome variables had missing information: IENFD leg (3), IENFD thigh (2), NCS parameters including sural (2), peroneal (1), tibial (1), Neurothesiometer (1), QST cold (3), IDS-SR (1), IWQOL-lite (8), EuroQol (1), and waist and buttocks/hips measurements (1).

The prevalence of neuropathy was 2.2% in lean controls (N=1) and 20.3% in obese participants (N=28). Among the obese, the neuropathy prevalence was 12.1% in those with normoglycemia, 7.1% in pre-diabetes, and 40.8% in diabetes (test of trend: p=<0.01). Demographics and metabolic phenotyping of the population is presented in Table 1. The BMI was comparable between obese with and without neuropathy (46.4kg/m^2 (7.5) vs. 46.6 kg/m^2 (7.3), p=0.86).

Anthropometric measurements revealed that only NCEP waist circumference was larger on obese participants with neuropathy compared to those without neuropathy (139.3cm (18.2) vs. 129.1cm (18.7), p=0.01) (Table 2). Measurements of the hips/thighs (71.1cm (8.5) vs. 76.6cm (10.2), p=<0.01) and mid thighs (62.2cm (8.8) vs. 66.3cm (9.3), p=0.03) were smaller in those with neuropathy compared to those without. No differences were seen with other anthropometric measures. When stratified by sex, the estimates were comparable but statistical significance was not retained for most comparisons.

Restricted to obese participants, multivariable logistic regression revealed that NCEP waist circumference was the only anthropometric variable significantly associated with neuropathy (1.39, 95%CI 1.10–1.75) (Table 3). The model including NCEP waist circumference had an AUC of 0.94 compared with 0.92 for the other nine models including weight and the other anthropometric measures. In our primary model including waist circumference, age (1.19, 95%CI 1.08–1.30), female sex (19.81, 95%CI 1.73–226.52), height (2.08, 95%CI 1.22–3.56), systolic blood pressure (2.89, 95%CI 1.49–5.61), and triglycerides (1.31, 95%CI 1.00–1.70) were significantly associated with neuropathy. Higher age, height, and systolic blood pressure were significantly associated with neuropathy in all 10 models, and higher triglyceride levels in 8 out of the 10 models. Multivariable linear regression revealed that the only demographic and metabolic variables significantly associated with more than one secondary neuropathy outcome were age (5 of 5), height (3 of 5), and NCEP waist circumference (2 of 5) (Table 4).

Obese participants with neuropathy had significantly lower IENFD of the leg (3.0 fibers/mm (3.3) vs 9.3 fibers/mm (6.9), p<0.01) and borderline lower IENFD of the thigh (12.2 fibers/mm (6.6) vs 15.1 fibers/mm (8.2), p=0.06) (Table 5). All nine nerve conduction study

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parameters were significantly worse in those neuropathy with the exception of peroneal conduction velocity. However, an absent peroneal response was more common in those with neuropathy (14.3% vs. 1.8%), which would preclude peroneal conduction velocity measurements in these patients. All secondary neuropathy measures were significantly worse in obese patients with neuropathy compared to those without with the exception of the neurothesiometer and QST cold. Both pain outcomes, neuropathic specific quality of life (3.2 (0.9) vs 2.6 (1.0), $p<0.01$) and general quality of life (54.0 (19.9) vs 66.3 (20.6), $p=0.01$) were worse in those with neuropathy. Depression (20.1 (14.6) vs 17.1 (11.2), $p=0.34$) and weight specific quality of life (88.7 (25.1) vs 82.6 (24.2), $p=0.29$) were not different based on neuropathy status.

Comparing obese participants without neuropathy and lean controls, obese participants without neuropathy had significantly lower IENFD of the leg (9.3 fibers/mm (6.9) vs 13.7 fibers/mm (6.3), $p<0.01$) and thigh (15.1 fibers/mm (8.2) vs 26.4 fibers/mm (7.6), $p<0.01$). However, nerve conduction study parameters were not consistently different between these two groups. All secondary neuropathy measures were significantly worse in obese participants without neuropathy compared to lean controls with the exception of QST cold and vibration. Similarly, all pain, quality of life and depression scores were also significantly worse in obese participants without neuropathy compared to lean controls.

Discussion

In a bariatric surgery population, prior to surgery, we demonstrated that the prevalence of neuropathy is high even in those with normoglycemia. In conjunction with our previous report in an obese, medical weight loss population, the current study provides evidence for obesity as a potential cause of neuropathy, which has important diagnostic and potentially therapeutic ramifications.[7, 9, 11–15] We also found that obese participants with neuropathy had larger NCEP waist circumference measurements, but not other anthropometric measures or BMI, compared with those without neuropathy. Furthermore, NCEP waist circumference was the only anthropometric measure with a significant association with neuropathy in fully adjusted models. Therefore, utilizing extensive anthropometric measurements, we demonstrate that central obesity, and not general obesity, is likely the key risk factor for the development of neuropathy.

Our study adds to the growing literature that supports central obesity as a risk factor and potential cause of neuropathy.[7, 9, 11–15] While diabetes is the most consistently observed risk factor for neuropathy and likely has the largest effect size, obesity is emerging as the next most important risk factor as evidenced by many recent studies. Previous studies in the United States, Denmark, the Netherlands, and Germany have shown an independent relationship between waist circumference and neuropathy, but they did not investigate other anthropometric measures.[7, 9, 11, 13, 15] Studies in Denmark, Germany, and China have also demonstrated differences in general obesity between individuals with and without neuropathy.[9, 10, 15] However, our investigation reveals no differences in general obesity between participants with and without neuropathy. In fact, the BMI in both groups was 46. Our results suggest that it is the type and distribution of fat that is more important than general obesity in mediating nerve injury. These findings are also congruent with

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epidemiologic studies detailing the associations between obesity and mortality. Specifically, investigators demonstrated that waist-to-hip and waist-to-thigh ratios are more highly associated with mortality than BMI.[30] Future studies using more advanced measure of body fat distribution, such as DEXA scans, are needed to further investigate influence of body fat distribution on neuropathy. Similarly, investigators should define the precise mechanisms by which fat causes neuropathy. Inflammatory cascades resulting from visceral fat is one possibility but requires further study, but other mechanisms are also plausible.[31]

In addition to central obesity, we revealed associations between high systolic blood pressure and triglycerides with neuropathy. While previous studies have shown consistent associations between hyperglycemia and obesity with neuropathy, the associations with other metabolic factors have been less consistent.[32] Possible reasons for these inconsistent findings may be the magnitude of the true associations and the relative treatability of each risk factor. For example, diabetes likely has the strongest association with neuropathy; therefore, the most consistent results. On the other hand, pre-diabetes likely has a smaller effect size, and we did not see an association with neuropathy in this study. Importantly, most previous studies support an association of pre-diabetes with neuropathy, but there are a few notable exceptions. In regards to treatability of metabolic risk factors, hypertension and dyslipidemia are the easiest to treat; therefore, less consistent associations with neuropathy have been seen. In contrast, obesity is much harder to treat. Diet, exercise and surgery are all efficacious but are either difficult to initiate and/or maintain or require a surgical intervention. Our work adds to the current literature supporting hypertriglyceridemia and hypertension as metabolic risk factors for neuropathy, but our results should be interpreted with caution given the potential for overfitting in our models.[13, 33, 34] All of the metabolic syndrome components likely play a role in the development of neuropathy as evidenced by multiple studies demonstrating an association with the number of metabolic syndrome components with neuropathy[12, 13] even after exclusion of hyperglycemia.[10, 11] Given the above, perhaps it should not be surprising that diabetes and obesity are the most consistent metabolic factors associated with neuropathy, but that all metabolic risk factors likely play a role.

Similar to our previous study in obese patients in a medical weight loss clinic, we have demonstrated that obese patients that do not meet the formal criteria for neuropathy also have evidence of incipient nerve injury.[7] In both studies, obese patients without neuropathy had higher levels of pain, and worse neuropathy specific quality of life than lean controls. In this study, we also found differences in neuropathy questionnaire and outcome scores, providing further evidence of early nerve injury. While the lower IENFD could be explained by a larger surface area in obese individuals and not nerve injury, the changes in pain and quality of life would argue that the decrease in IENFD has functional relevance and is likely secondary to nerve injury. Since nerve injury is often irreversible, the importance of this finding is that obese individuals without neuropathy may be the ideal group to study interventions to prevent nerve injury before it has become too severe. Many disease modifying clinical trials have failed to reverse nerve injury in those with well-established neuropathy. Perhaps future clinical trials should focus on the obese population with evidence of nerve injury but not meeting formal neuropathy criteria.

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In conjunction with our previous study of patients with obesity in a medical weight loss clinic, we have also characterized the magnitude and type of neuropathy in the obese population. The prevalence of neuropathy was 20.3% in this study and 22.5% in the medical weight loss clinic population.[7] Both studies revealed a much high prevalence of neuropathy in obese with normoglycemia (12.1% and 13.5%) than in lean controls (2.2% and 3.8%). Both groups meeting formal criteria for neuropathy had changes in nerve conduction studies and nerve fiber density. Similarly, both studies revealed decreased nerve fiber density without changes in nerve conduction study parameters when comparing the obese participants without neuropathy to lean controls. These results provide more evidence that small fiber nerve injury pre-dates large fiber nerve injury in obesity related neuropathy. Finally, both results revealed that neuropathy is associated with higher pain and worse quality of life, demonstrating once again the impact of this condition on patients.

Limitations include a small sample size, which limits the power to detect small associations between metabolic factors and neuropathy and increases the likelihood of overfitting our models. Despite this limitation, we were able to demonstrate multiple significant associations. We were unable to study the differential effects of impaired fasting glucose and impaired glucose tolerance because of our low sample size. The generalizability of these results to other populations, including to those with less extreme obesity, is unclear. Moreover, neuropathy risk factors may differ depending on the population studied. However, many of our results are congruent with those from studies performed in other populations.[7, 9–15] While we had detailed anthropometric measurements, we were unable to measure body fat percentage; these more refined measures should be the focus of future studies. Furthermore, the cross sectional design of our study limits our ability to infer causal relationships. Cohort studies of non-diabetic participants with and without obesity are needed to provide stronger epidemiologic evidence.

Obesity is an emerging risk factor for neuropathy independent of hyperglycemia. Whether neuropathy should be considered cryptogenic in an obese individual is unclear and deserves further study, but our current work supports obesity as a potential cause. Furthermore, obesity distribution is likely more important than general obesity in the development of neuropathy. While diabetes and central obesity are the most consistent metabolic factors associated with neuropathy, we also demonstrate significant associations with hypertension and hypertriglyceridemia. Finally, our results detail why obese patients prior to meeting formal neuropathy criteria may be the ideal target population for future disease modifying therapies to prevent and/or reverse nerve injury.

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Table 1:

Demographic and metabolic variables of the lean controls and the obese group with and without neuropathy

Variable	Lean Controls without neuropathy* (n=45)	Obese without Neuropathy (n=110)	P-Value*	Obese with Neuropathy (n=28)	P-Value**
Age, mean (SD)	43.8 (12.1)	43.5 (11.2)	0.90	51.4 (9.6)	<0.01
Male, N (%)	8 (17.8%)	23 (20.9%)	0.83	10 (35.7%)	0.16
Race, N (%)					
White	39 (86.7%)	84 (76.4%)		24 (85.7%)	
Black	1 (2.2%)	22 (20.0%)	<0.01	3 (10.7%)	<0.01
Asian	3 (6.7%)	1 (0.1%)		1 (3.6%)	
Other	2 (4.4%)	3 (2.7%)		0 (0.0%)	
Hispanic, N (%)	2 (4.4%)	2 (1.8%)	0.58	0 (0.0%)	1.00
Marital status					
Single	12 (26.7%)	32 (29.1%)		8 (28.6%)	
Married	27 (60.0%)	60 (54.6%)	0.46	17 (60.7%)	0.97
Divorced	6 (13.3%)	16 (14.5%)		3 (10.7%)	
Widowed	0 (0.0%)	2 (1.8%)		0 (0.0%)	
Smoking status					
Current	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Never	37 (82.2%)	78 (70.9%)	0.16	18 (64.3%)	0.50
Former	8 (17.8%)	32 (29.1%)		10 (35.7%)	
Education level					
High school	0 (0.0%)	12 (10.9%)		4 (14.3%)	
Some college	4 (8.9%)	29 (26.4%)	<0.01	14 (50.0%)	0.19
College degree	26 (57.8%) 14 (31.1%)	52 (47.3%) 17 (15.5%)		8 (28.6%) 4 (14.3%)	
Graduate degree	14 (31.1%)	17 (15.5%)		4 (14.3%)	
Alcohol (Drinks per week during past 12 months), mean (SD)	1.9 (2.2)	0.9 (1.5)	<0.01	0.6 (2.8)	0.60
Height (cm), mean (SD)	167.4 (9.8)	167.6 (9.1)	0.91	171.3 (12.4)	0.16
Weight (kg), mean (SD)	64.5 (9.9)	131.6 (26.7)	<0.01	137.4 (34.5)	0.41
BMI kg/m^2, mean (SD)	22.9 (2.0)	46.6 (7.3)	<0.01	46.4 (7.5)	0.86
HDL mg/dL, mean (SD)	68.1 (16.7)	45 (10.7)	<0.01	41.8 (13.5)	0.26
SBP (mm Hg), mean (SD)	108.6 (10.3)	128.2 (14.3)	<0.01	137.7 (14.6)	<0.01
DBP (mm Hg), mean (SD)	66.1 (9.6)	73.5 (11.7)	<0.01	73.0 (11.3)	0.85

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Variable	Lean Controls without neuropathy* (n=45)	Obese without Neuropathy (n=110)	P-Value*	Obese with Neuropathy (n=28)	P-Value**
Triglycerides mg/dL, mean (SD)	71.8 (22.5)	122.9 (68.9)	<0.01	166.5 (136.9)	0.11
Fasting glucose mg/dL, mean (SD)	84.9 (6.4)	102.8 (28.8)	<0.01	123.9 (37.1)	<0.01
2-hour glucose mg/dL, mean (SD) **	88.7 (19.6)	119.6 (36.0)	<0.01	106.5 (41.2)	0.48
Fasting insulin mg/dL, mean (SD)	6.2 (5.0)	26.2 (18.1)	<0.01	29.4 (16.9)	0.40
2-hour insulin mg/dL, mean (SD) **	41.3 (26.8)	93.6 (70.1)	<0.01	101.4 (44.2)	0.71
HbA1c ***	NA	6.02 (1.27)	NA	6.85 (1.09)	<0.01
NCEP Waist circumference (cm), mean (SD)	80.4 (7.1)	129.1 (18.7)	<0.01	139.3 (18.2)	0.01
Metabolic syndrome, N (%)	0 (0.0%)	74 (67.3%)	<0.01	26 (92.9%)	0.01

BMI=body mass index, HDL=high density lipoprotein, SBP=systolic blood pressure,

DBP=diastolic blood pressure, HbA1c=hemoglobin A1c, NCEP=National Cholesterol Education Program

* Excluded the one lean patient with neuropathy

** Only reported for those without diabetes

*** HbA1c was not measured for lean control patients

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Table 2:

Comparing anthropometric measures between those with and without neuropathy

	Lean controls without Neuropathy*		Obese without Neuropathy		Obese with Neuropathy		P-Value**	
Arm (cm), mean (SD)	27.5 (3.2)		41.6 (5.1)		41.4 (5.7)		0.86	
Forearm (cm), mean (SD)	24.2 (2.6)		30.2 (2.9)		30.6 (2.2)		0.54	
High waist (cm) mean (SD)	79.3 (7.9)		123.1 (14.8)		129.0 (15.4)		0.08	
Abdomen (cm) mean (SD)	84.8 (9.1)		135.4 (18.1)		137.4 (18.7)		0.61	
NCEP Waist (cm), mean (SD)	80.4 (7.1)		129.1 (18.7)		139.3 (18.2)		0.01	
Buttocks/Hips (cm), mean (SD)	97.3 (11.2)		142.6 (15.8)		140.9 (17.4)		0.65	
Hips/Thighs (cm), mean (SD)	57.4 (9.1)		76.6 (10.2)		71.1 (8.5)		<0.01	
Mid Thighs (cm), mean (SD)	50.4 (8.5)		66.3 (9.3)		62.2 (8.8)		0.03	
Calf (cm), mean (SD)	35.9 (2.9)		46.3 (4.8)		46.1 (5.3)		0.91	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
Arm (cm), mean (SD)	30.2 (3.0)	26.9 (2.9)	42.6 (5.1)	41.3 (5.1)	43.4 (6.4)	40.2 (5.2)	0.71	0.42
Forearm (cm), mean (SD)	27.0 (2.4)	23.6 (2.3)	33.0 (2.2)	29.5 (2.6)	32.4 (2.0)	29.5 (1.7)	0.42	0.95
High waist (cm) mean (SD)	86.3 (9.6)	77.8 (6.7)	138.1 (14.1)	119.2 (12.3)	141.2 (14.4)	122.2 (11.4)	0.58	0.33
Abdomen (cm) mean (SD)	87.8 (12.6)	84.1 (8.3)	147.9 (19.1)	132.1 (16.4)	147.8 (19.3)	131.6 (16.1)	0.99	0.91
NCEP Waist (cm), mean (SD)	86.6 (8.3)	78.9 (6.2)	140.6 (16.7)	126.1 (18.1)	148.3 (20.4)	134.1 (15.1)	0.31	0.06
Buttocks/Hips (cm), mean (SD)	96.6 (18.3)	97.4 (9.3)	141.6 (19.9)	142.8 (14.6)	141.9 (22.6)	140.4 (14.5)	0.97	0.52
Hips/Thighs (cm), mean (SD)	62.8 (16.3)	56.2 (6.5)	76.0 (11.5)	76.7 (9.9)	71.8 (10.6)	70.8 (7.4)	0.32	<0.01
Mid Thighs (cm), mean (SD)	50.2 (3.2)	50.5 (9.3)	64.1 (10.4)	66.9 (9.0)	63.5 (12.4)	61.4 (6.4)	0.88	<0.01
Calf (cm), mean (SD)	37.2 (2.8)	35.6 (2.9)	46.6 (4.8)	46.2 (4.9)	47.3 (7.0)	45.5 (4.2)	0.79	0.55

NCEP=National Cholesterol Education Program

*Measurements for lean controls exclude the lean patient with neuropathy

**Comparison between obese with and obese without neuropathy

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Table 3:

Associations between metabolic variables, including different anthropometric measures, and neuropathy

Variable	NCEP Waist unit=5 cm	Arm unit=5 cm	Forearm unit=5 cm	Buttocks/ Hips unit=5 cm	High Waist unit=5 cm	Abdomen unit=5 cm	Hips/Thigh unit=5 cm	Mid-Thigh unit=5 cm	Calf unit=5 cm
Age	1.19 (1.08,1.30) *	1.15 (1.06,1.25) *	1.17 (1.07,1.27) *	1.16 (1.06,1.26) *	1.16 (1.07,1.26) *	1.18 (1.08,1.29) *	1.15 (1.06,1.24) *	1.15 (1.05,1.25) *	1.16 (1.07,1.27) *
Female (reference male)	19.81 (1.73,226.52) *	9.09 (0.88,93.71)	10.99 (1.05,114.65) *	6.63 (0.70,62.43)	10.67 (1.15,98.93) *	13.70 (1.36,137.86) *	12.47 (1.11,140.4) *	10.45 (0.95,114.78)	6.62 (0.67,65.71)
Height unit=5 cm	2.08 (1.22,3.56) *	1.97 (1.17,3.31) *	1.81 (1.10,2.99) *	1.87 (1.15,3.04) *	1.83 (1.13,2.97) *	1.96 (1.20,3.21)*	2.10 (1.24,3.58) *	1.99 (1.20,3.32) *	1.85 (1.12,3.04) *
Glycemic status Pre-diabetes (reference normal)	0.14 (0.01,1.48)	0.10 (0.01,0.81) *	0.10 (0.01,0.92) *	0.11 (0.01,0.92) *	0.13 (0.01,1.17)	0.08 (0.01,0.71) *	0.07 (0.01,0.67) *	0.09 (0.01,0.77) *	0.12 (0.01,1.10)
Diabetes (reference normal)	7.17 (0.78,65.63)	2.85 (0.49,16.57)	3.37 (0.51,22.34)	3.24 (0.53,19.83)	3.54 (0.53,23.62)	3.19 (0.51,20.04)	2.19 (0.36,13.51)	2.60 (0.43,15.61)	3.16 (0.52,19.21)
SBP unit=10 mm Hg	2.89 (1.49,5.61) *	3.09 (1.64,5.84) *	2.90 (1.59,5.30) *	2.89 (1.57,5.32) *	2.75 (1.50,5.07) *	3.15 (1.64,6.02) *	3.45 (1.75,6.81) *	3.14 (1.67,5.90) *	2.89 (1.56,5.36) *
Triglycerides unit=50 mg/dL	1.31 (1.00,1.70) *	1.30 (1.00,1.69) *	1.36 (1.05,1.75) *	1.33 (1.03,1.72) *	1.30 (1.01,1.68) *	1.32 (1.02,1.70) *	1.26 (0.97,1.63)	1.28 (0.99,1.67)	1.36 (1.04,1.79) *
HDL unit=10 mg/dL	0.67 (0.38,1.16)	0.59 (0.36,0.99) *	0.67 (0.40,1.14)	0.62 (0.37,1.02)	0.62 (0.37,1.03)	0.62 (0.37,1.03)	0.60 (0.36,1.00) *	0.60 (0.36,0.99)	0.63 (0.38,1.05)
Anthropometric Measure	1.39 (1.10,1.75) *	0.89 (0.43,1.83)	2.65 (0.50,14.13)	1.07 (0.88,1.30)	1.18 (0.92,1.51)	1.21 (0.98,1.49)	0.78 (0.50,1.21)	0.89 (0.58,1.36)	1.34 (0.60,2.95)
AUC	**0.94**	**0.92**	**0.92**	**0.92**	**0.92**	**0.92**	**0.92**	**0.92**	**0.92**

NCEP=National Cholesterol Education Program, SBP=systolic blood pressure, HDL=high density lipoprotein, AUC=area under the ROC curve

* =p<0.05

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Table 4:

Multivariable linear regression evaluating the association of metabolic variables and secondary neuropathy outcome measures

Variable	Sqrt(IENFD leg) Parameter estimate (m/s) (95%CI)	Sural amplitude Parameter estimate (uV) (95%CI)	Tibial F Parameter estimate (uV) (95%CI)	Log(Peroneal DML) Parameter estimate (uV) (95%CI)	Tibial amplitude Parameter estimate (mV) (95%CI)
Age	−0.05 (−0.06,−0.03) *	−0.17 (−0.27,−0.07) *	0.17 (0.10,0.24) *	0.00 (0.00,0.01) *	−0.08 (−0.16,0.00) *
Female (reference male)	−0.29 (−0.82,0.24)	−0.98 (−4.37,2.42)	−0.78 (−3.21,1.66)	−0.02 (−0.12,0.09)	1.12 (−1.50,3.75)
Height unit=5 cm	−0.25 (−0.36,−0.14) *	−0.69 (−1.40,0.02)	1.94 (1.43,2.46) *	0.04 (0.02,0.06) *	−0.40 (−0.95,0.15)
Glycemic status Pre-diabetes (reference normal)	0.05 (−0.37,0.47)	2.90 (0.25,5.55) *	0.50 (−1.44,2.43)	0.00 (−0.08,0.09)	−0.26 (−2.35,1.83)
Diabetes (reference normal)	−0.27 (−0.73,0.19)	0.41 (−2.51,3.33)	2.09 (−0.09,4.27)	0.10 (0.01,0.19) *	−2.17 (−4.48,0.14)
SBP unit=10 mm Hg	−0.18 (−0.29,−0.06) *	−1.10 (−1.81,−0.39) *	0.09 (−0.44,0.63)	−0.01 (−0.03,0.02)	−0.44 (−1.00,0.12)
Triglycerides unit=50 mg/dL	−0.14 (−0.23,−0.05) *	0.01 (−0.58,0.60)	0.32 (−0.12,0.75)	0.01 (−0.01,0.03)	0.19 (−0.28,0.66)
HDL unit=10 mg/dL	0.11 (−0.05,0.26)	−0.09 (−1.08,0.90)	0.39 (−0.34,1.11)	0.00 (−0.03,0.03)	−0.14 (−0.91,0.64)
NCEP Waist Circumference unit=5 cm	−0.08 (−0.12,−0.03) *	−0.39 (−0.69,−0.10) *	0.08 (−0.14,0.30)	−0.01 (−0.02,0.00)	−0.19 (−0.42,0.04)

* =p<0.05

Sqrt=square root, IENFD=intraepidermal nerve fiber density, DML=distal motor latency, SBP=systolic blood pressure, HDL=high density lipoprotein

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Table 5:

A comparison of neuropathy outcome measurements between lean controls and obese patients with and without neuropathy

Variable	Lean* (n=45)	Obese without neuropathy (n=110)	P-Value	Obese with neuropathy (n=28)	P-Value
IENFD leg (fibers/mm)	13.7 (6.3)	9.3 (6.9)	<0.01	3.0 (3.3)	<0.01
IENFD thigh (fibers/mm)	26.4 (7.6)	15.1 (8.2)	<0.01	12.2 (6.6)	0.06
Sural amplitude (uV)	20.7 (9.0)	11.3 (6.7)	<0.01	5.8 (4.7)	<0.01
Sural PL (ms)	4.0 (0.4)	3.8 (0.5)	0.01	4.1 (0.5)	0.03
Sural NR	0 (0.0%)	5 (4.6%)		5 (17.9%)	
Peroneal amplitude (mV)	5.6 (2.3)	5.4 (2.7)	0.76	2.9 (2.3)	<0.01
Peroneal DML (ms)	5.0 (1.0)	4.5 (0.8)	<0.01	5.0 (1.0)	0.05
Peroneal CV (m/s)	46.1 (4.8)	46.6 (5.2)	0.61	40.5 (4.2)	<0.01
Peroneal NR	0 (0.0%)	2 (1.8%)		4 (14.3%)	
Peroneal F response (ms)	49.4 (5.4)	48.6 (5.3)	0.44	52.8 (7.4)	0.02
Peroneal F NR	1 (2.2%)	7 (6.4%)		4 (14.3%)	
Tibial amplitude (mV)	12.9 (5.4)	9.6 (4.8)	<0.01	4.9 (4)	<0.01
Tibial DML (ms)	4.9 (0.8)	4.7 (0.9)	0.36	5.3 (0.9)	0.01
Tibial NR	0 (0.0%)	1 (1.0%)		3 (10.7%)	
Tibial F response (ms)	49.7 (4.8)	50.4 (5.4)	0.43	55.7 (7.1)	<0.01
Tibial F NR	1 (2.2%)	1 (1.0%)		3 (10.7%)	
UENS	0.7 (1.8)	1.6 (2.9)	0.02	11.9 (6.7)	<0.01
MNSI Questionnaire	0.5 (0.9)	2.5 (2.3)	<0.01	6.5 (2.6)	<0.01
MNSI Examination	0.2 (0.7)	0.7 (1.0)	<0.01	2.4 (1.7)	<0.01
Neurothesiometer (um)	14.0 (19.0)	46.0 (65.9)	<0.01	52.7 (57.5)	0.6
QST Cold (JND)	9.1 (3.1)	9.8 (3.8)	0.25	11.4 (3.8)	0.06
QST Vibration (JND)	14.9 (3.0)	15.5 (2.9)	0.29	19.1 (2.9)	<0.01
Pain and QOL Outcomes					
Neuro-QOL	1.8 (0.9)	2.6 (1.0)	<0.01	3.2 (0.9)	<0.01
McGill Pain score	1.4 (3.8)	4.4 (5.8)	<0.01	12.0 (7.9)	<0.01
VAS Pain score	7.2 (19.2)	24 (26.4)	<0.01	46.3 (31.6)	<0.01
IDS-SR	10.4 (8.1)	17.1 (11.1)	<0.01	20.3 (14.1)	0.28
IWQOL-Lite	36.2 (8.9)	82.6 (24.2)	<0.01	88.7 (25.1)	0.29
EuroQol Health state (VAS)	84.2 (12.9)	66.3 (20.6)	<0.01	54.0 (19.9)	0.01

IENFD=intraepidermal nerve fiber density, PL=peak latency, NR=no response, DML=distal motor latency, CV=conduction velocity, UENS=Utah Early Neuropathy Scale, MNSI=Michigan Neuropathy Screening Instrument, QST=quantitative sensory testing, JND=just normal distance, QOL=quality of life, VAS=visual analog scale, IDS-SR=Inventory of Depressive Symptomatology Self Report, IWQOL-Lite= Impact of Weight on Quality of Life-Lite

*Measurements for lean controls exclude the lean patient with neuropathy