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ORIGINAL ARTICLE

Epidemiology/Genetics

Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology

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Abstract

Objective: The aim of this study was to determine the effect of dietary weight loss on neuropathy outcomes in people with severe obesity.

Methods: A prospective cohort study of participants attending a medical weight-management program was followed. Weight loss was achieved with meal replacement of 800 kcal/d for 12 weeks and then transitioning to 1,200 to 1,500 kcal/d. The co-primary outcomes were changes in intraepidermal nerve fiber density (IENFD) at the distal leg and proximal thigh. Secondary outcomes included nerve conduction studies, Michigan Neuropathy Screening Instrument questionnaire and exam, Quality of Life in Neurological Disorders, and quantitative sensory testing.

Results: Among 131 baseline participants, 72 (mean [SD] age: 50.1 [10.5] years, 51.4% female) completed 2 years of follow-up. Participants lost 12.4 (11.8) kg. All metabolic syndrome components improved with the exception of blood pressure. IENFD in the distal leg (0.4 [3.3], $p = 0.29$), and proximal thigh (0.3 [6.3], $p = 0.74$) did not significantly change. Improvements were observed on the Michigan Neuropathy Screening Instrument questionnaire, two Quality of Life in Neurological Disorders subdomains, and quantitative sensory testing cold threshold.

Conclusions: Dietary weight loss was associated with improvements in all metabolic parameters except blood pressure, and both IENFD outcomes remained stable after 2 years. Given that natural history studies reveal decreases in IENFD over time, dietary weight loss may halt this progression, but randomized controlled trials are needed.

INTRODUCTION

Neuropathy is a highly prevalent condition that results in pain, falls, and lower quality of life (1). Although diabetes has long been known to be the leading cause of neuropathy (2–4), obesity has recently emerged as an important risk factor (5–14). Furthermore, obesity is likely sufficient to cause neuropathy even in those with normal glucose control (7,9). In addition to hyperglycemia and obesity, other individual components of metabolic syndrome (hypertension, hypertriglyceridemia, and low high-density lipoprotein [HDL]

See Commentary, pg. 1990 (Dietary management of obesity-associated neuropathy: implications for clinical practice and trial design).

cholesterol) have also been shown to be associated with neuropathy (13). Unfortunately, despite multiple potentially modifiable risk factors, the only established disease-modifying therapy for neuropathy is glycemic control, which prevents neuropathy to a much larger degree in type 1 than in type 2 diabetes (14). We contend that newer interventions are needed to treat and prevent neuropathy.

Few studies, to our knowledge, have evaluated the effects of weight loss on neuropathy. Two uncontrolled studies have shown the potential for lifestyle interventions to improve neuropathy, but both primarily focused on exercise with only minimal weight loss (15,16). The most rigorous investigation to date, the Action for Health in Diabetes (Look AHEAD) study, randomized 5,145 participants with diabetes to 9 to 11 years of a lifestyle intervention designed to achieve and maintain weight loss compared with a diabetes support group (17). They found that the Michigan Neuropathy Screening Instrument (MNSI) questionnaire, but not the examination score, improved in those in the lifestyle intervention group, and that changes in weight, hemoglobin A_{1c} (HbA_{1c}), HDL cholesterol, and triglycerides were associated with changes in the MNSI questionnaire. No studies, to our knowledge, have investigated the effects of significant dietary weight loss on neuropathy outcomes in populations without diabetes or used the best quantitative measure of small fiber nerve injury, intraepidermal nerve fiber density (IENFD), as the primary outcome.

In a population with obesity with and without diabetes, we aimed to determine the effects of 2 years of a dietary weight-loss intervention on extensive neuropathy outcomes with the coprimary outcomes defined as IENFD at the distal leg and proximal thigh.

Study Importance

What is already known?

- ► Obesity is a consistent risk factor for neuropathy across many studies in different populations around the world.
- ► Metabolic syndrome and its individual components are also associated with neuropathy.
- ► Dietary weight loss has been demonstrated to improve questionnaire assessments of neuropathy in patients with diabetes but not in patients without diabetes, and no studies, to our knowledge, have used more comprehensive neuropathy phenotyping.

What does this study add?

- ► After 2 years, successful dietary weight loss in those with severe obesity leads to stable neuropathy as measured by our primary outcome (intraepidermal nerve fiber density).
- ► Successful dietary weight loss leads to improvements in secondary outcomes such as the Michigan Neuropathy Screening Instrument questionnaire, two Quality of Life in Neurological Disorders subdomains, and quantitative sensory testing cold threshold.
- ► Dietary weight loss also leads to stable cardiovascular autonomic neuropathy.

How might these results change the direction of research or the focus of clinical practice?

- ► Future randomized clinical trials are needed to confirm that dietary weight loss can stabilize neuropathy.
- ► If successful, dietary weight loss would become the second disease-modifying therapy for neuropathy along with glycemic control.
- ► Furthermore, studies are needed to compare the effectiveness of dietary weight loss, surgical weight loss, and exercise to allow clinicians to focus on the best intervention to prevent neuropathy.

METHODS

Population

From November 2010 to December 2014, we recruited participants with obesity attending the University of Michigan Weight Management Program and followed them for 2 years after starting a dietary weight-loss intervention. Inclusion criteria included being aged 18 years or older and having BMI ≥ 35 kg/m^2 or ≥ 32 kg/m^2 if they had one or more comorbidities (18). The intervention consisted of a very low-energy diet in the form of liquid meal replacement plus 2 cups of nonstarchy vegetables (~800 kcal/d) for approximately 12 weeks to promote a 15% weight reduction from the pre-dietary intervention weight. Participants were then slowly transitioned to a 1,000- to 1,200-kcal/d partial meal replacement diet until their desired weight loss was achieved. This consisted of three replacement products and 400 kcal of conventional food, consisting of half a plate of nonstarchy vegetables, 3 to 4 oz of lean protein, and half a cup of whole grain or fruit. Participants were counseled to perform 40 min/d of moderate activity including cardio and light strength training during the initial intensive dietary phase and then 60 min/d during the weight-loss maintenance phase.

This study was approved by the University of Michigan Institutional Review Board and registered on ClinicalTrials.gov (NCT02043457), and all participants signed informed consent documents.

Metabolic phenotyping

Participants underwent glucose tolerance testing (except those with a previous diagnosis of diabetes) and a fasting lipid panel at baseline and after 2 years. Participants also had blood pressure, height, weight, waist circumference, and BMI measurements taken monthly

throughout the study. Participants with diabetes also had a HbA_{1c} test. Diabetes and prediabetes were defined at baseline and after 2 years using HbA_{1c} and glucose tolerance testing, according to the American Diabetes Association (19).

Polyneuropathy definition (primary outcome)

Our coprimary outcome measures were the IENFD measured at the distal leg and proximal thigh. IENFD was evaluated using bright-field immunohistochemistry using an established protocol (20).

Secondary neuropathy outcomes

Our secondary outcome measures included 17 nerve conduction study (NCS) parameters from six different nerves (sural sensory, median sensory, ulnar sensory, peroneal motor, tibial motor, and median motor). NCS was performed using Viking on the Nicolet EDX electrodiagnostic system (CareFusion, San Diego, California). The MNSI questionnaire and examination (performed by a neuromuscular specialist) were completed as previously described (21). Quantitative sensory testing (QST) measurements of vibration and cold detection thresholds were performed using the Computer Aided Sensory Evaluator (CASE) IV (WR Medical Electronics Co., Maplewood, Minnesota). Quantitative sudomotor axon reflex testing (QSART) measurements were performed at the foot, distal leg, proximal leg, and arm using the Q-Sweat quantitative sweat measurement system (WR Medical Electronics). Monofilament testing was performed with a Semmes-Weinstein 5.07/10-g monofilament on the dorsum of the dominant great toe. Monofilament testing was normal if the participant felt eight or more out of ten responses, reduced for one to seven responses, and absent for zero responses. Clinical neuropathy was defined using the Toronto Consensus definition of probable polyneuropathy, which requires two or more of the following: neuropathy symptoms, abnormal sensory examination, and abnormal reflexes as determined by one of four neuromuscular specialists (22).

Patient-oriented neuropathy outcomes

The validated Quality of Life in Neurological Disorders (Neuro-QoL) instrument was used to measure neuropathy-specific quality of life, with higher numbers reflecting a worse quality of life (23). The validated short-form McGill Pain Questionnaire was employed to measure pain with a visual analog scale, a six-point rating scale of present pain intensity (PPI) score, and a four-point rating scale of 15 different neuropathic pain descriptors (McGill Pain score) (24).

Cardiovascular autonomic neuropathy outcomes

All cardiovascular autonomic neuropathy (CAN) tests were performed using the ANX 3.0 device (The Ansar Group, Inc., Philadelphia, Pennsylvania). Outcomes included three cardiovascular reflex tests (expiration to inspiration [E:I] ratio, 30:15 ratio, and the average of two Valsalva ratios), which are associated with mortality (25) and are considered the gold standard tests for autonomic neuropathy (26). Other measurements that were recorded included the resting median heart rate, frequency-domain measures (low-frequency area [LFA, measure of sympathetic activity], respiratory frequency area [RFA, measure of parasympathetic activity], and LFA/RFA [measure of sympathovagal balance]), time-domain measures (standard deviation [SD] of the normal-to-normal interval [sdNN]), and root mean square of successive differences of the normal-to-normal interval (rmsSD).

Statistical analysis

Descriptive statistics were used to characterize participants in terms of demographics, metabolic phenotyping, and neuropathy outcomes at baseline and after 2 years of follow-up. For continuous measurements, we determined the within-participant change during the study by subtracting baseline measurements from measurements taken after 2 years of follow-up.

We compared demographic information between participants who completed follow-up and those who did not using two-sample *t* tests for continuous covariates and Pearson χ^2 tests or Fisher exact tests for categorical covariates. Paired *t* tests were used to compare within-patient differences in continuous metabolic factors and all outcomes during follow-up. For ordinal outcomes, the Wilcoxon signed rank test was used to determine within-patient change during follow-up.

All analyses were completed using R version 3.4.2 (R Foundation, Vienna, Austria).

RESULTS

Population

During recruitment, the University of Michigan Weight Management Program enrolled 532 participants, including 394 who consented to be contacted about research studies and 131 who consented to our study. Of the 131 participants who completed baseline assessments, 72 completed assessments at 2 years. Reasons for attrition included the following: 16 participants decided to opt out of the study, 2 moved out of state, 1 died, 30 did not respond to multiple contacts, and 10 stopped participation for unclear reasons. Of the 59 who did not complete the neuropathy outcomes, 12 completed 2 years of follow-up with the weight-management program but did not want to complete the neuropathy outcomes. Of the remaining patients, median (interquartile range) follow-up in the weight-management clinic was 370 days (179-528 days).

Several outcome variables had missing information at baseline (V1) or at 2 years (V2): IENFD leg (V1:1,V2:6); IENFD thigh (V1:1,V2:8);

TABLE 1 Demographics of primary cohort and those lost during follow-up

	All participants ($n = 131$)	Completed follow-up ($n = 72$)	Lost to follow-up ($n = 59$)	p value
Age, mean (SD)	49.1 (10.6)	50.2 (10.2)	47.8 (11.0)	0.19
Sex, *n* (%) female	72 (55.0%)	37 (51.4%)	35 (59.3%)	0.47
Race, *n* (%)				0.59
Asian	1 (0.8%)	0 (0.0%)	1 (1.7%)	
Black	10 (7.6%)	7 (9.7%)	3 (5.1%)	
White	118 (90.1%)	64 (88.9%)	54 (91.5%)	
Unknown	2 (1.5%)	1 (1.4%)	1 (1.7%)	
Ethnicity, *n* (%)				
Hispanic/Latino	2 (1.5%)	1 (1.4%)	1 (1.7%)	1
Smoking status, *n* (%)				0.39
Current smoker	3 (2.3%)	3 (4.2%)	0 (0.0%)	
Ex-smoker	42 (32.6%)	22 (31.0%)	20 (34.5%)	
Never smoker	84 (65.1%)	46 (64.8%)	38 (65.5%)	
Marital status, *n* (%)				0.52
Divorced	7 (5.6%)	4 (5.9%)	3 (5.3%)	
Married	94 (75.2%)	53 (77.9%)	41 (71.9%)	
Single	21 (16.8%)	11 (16.2%)	10 (17.5%)	
Separated	2 (1.6%)	0 (0.0%)	2 (3.5%)	
Widowed	1 (0.8%)	0 (0.0%)	1 (1.8%)	
Education, *n* (%)				0.09
Professional or graduate degree	51 (39.2%)	33 (45.8%)	18 (31.0%)	
College degree	54 (41.5%)	25 (34.7%)	29 (50.0%)	
Some college or vocational college	23 (17.7%)	14 (19.4%)	9 (15.5%)	
High school or less	2 (1.5%)	0 (0.0%)	2 (3.4%)	
Employment status, *n* (%)				0.03
Employed	101 (77.7%)	50 (69.4%)	51 (87.9%)	
Retired	19 (14.6%)	16 (22.2%)	3 (5.2%)	
Seeking work	2 (1.5%)	1 (1.4%)	1 (1.7%)	
Keeping house	4 (3.1%)	2 (2.8%)	2 (3.5%)	
Other	4 (3.1%)	3 (4.2%)	1 (1.7%)	
Insurance, *n* (%)				0.59
Blue Care Network (HMO)	77 (59.7%)	41 (56.9%)	36 (63.2%)	
Other	52 (40.3%)	31 (43.1%)	21 (36.8%)	

Abbreviation: HMO, health maintenance organization.

NCS parameters, including sural (V1:1), peroneal F wave (V2:1), median motor F wave (V2:2), and median motor conduction velocity (V2:1); QST cold threshold (V1:2, V2:2); QST vibration threshold (V1:1,V2:1); QSART parameters, including arm (V1:2,V2:3), proximal leg (V1:1,V2:7), distal leg (V1:1,V2:2), and proximal foot (V1:3,V2:4); MNSI questionnaire (V2:1); monofilament (V2:1); Neuro-QoL parameters, including social (V2:1), emotional (V2:1), and total (V2:2); CAN measures including E:I ratio (V2:2), 30:15 ratio (V1:1,V2:4), Valsalva ratio (V1:1,V2:3), RFA (V2:2), LFA (V2:2), sdNN (V2:2), rmsSD (V2:2), and resting median heart rate (V2:2); waist circumference (V2:7); triglycerides (V1:1,V2:7); HDL cholesterol (V1:1, V2:7); low-density lipoprotein (LDL) cholesterol (V1:2,V2:7); and fasting glucose (V1:12,V2:8). All patients had at least one measure of glycemic status at baseline, but three patients had no measure of glycemic status at 2 years.

Among those with complete follow-up, 19 (26.4%) had clinical neuropathy at baseline, and 14 (19.4%) had clinical neuropathy after 2 years. No difference in the dropout rate between those with and without neuropathy at baseline was observed ($p = 0.4$).

Demographics

At baseline, the mean (SD) age was 49.1 (10.6) years, and 55.0% of participants were female (Table 1). No significant demographic

TABLE 2 Change in metabolic factors after dietary weight-loss intervention

	Baseline	2-year follow-up	Change	*p* value (paired *t* test)
Weight (kg)	120.7 (23.0)	108.3 (22.3)	−12.4 (11.8)	<0.01
Height (cm)	171.7 (10.3)	171.8 (10.4)	0.1 (3.1)	0.86
BMI	40.8 (6.0)	36.5 (5.8)	−4.3 (3.8)	<0.01
Waist circumference (cm)	123.1 (15.0)	114.7 (15.7)	−9.0 (9.7)	<0.01
Systolic blood pressure (mmHg)	126.4 (11.0)	126.9 (13.9)	0.5 (12.5)	0.74
Diastolic blood pressure (mmHg)	64.4 (7.3)	68.2 (9.0)	3.8 (9.0)	<0.01
Triglycerides (mg/dL)	153.4 (78.3)	127.8 (65.1)	−27.1 (55.6)	<0.01
HDL (mg/dL)	45.3 (11.1)	51.0 (11.5)	5.2 (7.9)	<0.01
LDL (mg/dL)	97.5 (23.6)	98.1 (28.0)	1.1 (18.4)	0.64
Cholesterol (mg/dL)	172.2 (30.0)	174.6 (33.9)	0.7 (25.1)	0.83
Fasting glucose (mg/dL)	101.7 (23.9)	99.3 (23.6)	−7.5 (22.9)	0.02
2-hour glucose (mg/dL)	134.8 (57.3)	110.9 (34.4)	−21.8 (43.5)	<0.01
HbA_{1c} (%)	6.0 (0.9)	5.8 (0.7)	−0.3 (0.6)	0.01

Data given as mean (SD).

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

differences were observed between those who completed follow-up compared with those who did not, with the exception of employment status (69.4% vs. 87.9%, $p = 0.03$).

Change in metabolic risk factors

With the exception of systolic blood pressure and LDL cholesterol, all metabolic parameters significantly changed after 2 years (Table 2). Among those with complete follow-up, 22.2% had diabetes, 37.5% had prediabetes, and 40.3% had normoglycemia at baseline. After 2 years, 14.7% had diabetes, 27.9% had prediabetes, and 57.4% had normoglycemia ($p < 0.01$). The median (interquartile range) weight loss comparing baseline with the end of the study was 5.5% (5.0%-14.7%) (Figure 1). At maximum weight loss, participants had lost 16.4% (13.0%-22.4%) of their weight. Comparing minimum weight to the end of the study, participants regained 8.5% (5.4%-13.9%) of their weight.

Change in coprimary outcomes

IENFD did not change significantly in the distal leg (0.4 [3.3] fibers/mm, $p = 0.29$) or proximal thigh (0.3 [6.3] fibers/mm, $p = 0.74$) after 2 years (Figure 2).

Change in secondary neuropathy outcomes

Of the 17 NCS parameters, significant changes were observed only in the ulnar sensory peak latency (0.1 [0.4] milliseconds, $p < 0.01$) and median sensory peak latency (0.2 [0.4] milliseconds, $p < 0.01$), which both worsened after 2 years (Table 3). The MNSI questionnaire (−0.6 [1.4], $p < 0.01$) improved, but there were no significant changes in the MNSI examination (0.04 [1.2], $p = 0.76$). The QST cold threshold (−2.0 [4.9] just noticeable difference, $p < 0.01$) improved, but there was no change in the QST vibration threshold (0.2 [4.2] just noticeable difference, $p = 0.77$). Monofilament and QSART measures were unchanged.

Change in patient-oriented neuropathy outcomes

The Neuro-QoL (−0.3 [1.4], $p = 0.06$), visual analog scale pain scores (−1.8 [29.3] mm, $p = 0.60$), McGill Pain scores (−0.8 [4.7], $p = 0.15$), and PPI (17.1% worsened, 12.9% improved, $p = 0.75$) were unchanged after 2 years (Table 3). However, the Neuro-QoL subdomains of pain (−0.4 [1.1], $p = 0.01$) and emotion (−0.7 [2.2], $p = 0.01$) were improved.

Change in CAN outcomes

No significant changes were seen in any of the CAN outcomes, including E:I ratio, 30:15 ratio, Valsalva ratio, RFA, LFA, RFA/LFA ratio, sdNN, rmsSD, or resting median heart rate (Table 3).

DISCUSSION

A successful dietary weight-loss intervention in those with severe obesity was associated with no change in our coprimary neuropathy outcomes (IENFD of the distal leg and proximal thigh). This sharply contrasts with the natural history of IENFD decline in those with small fiber neuropathy of any cause, including prediabetes

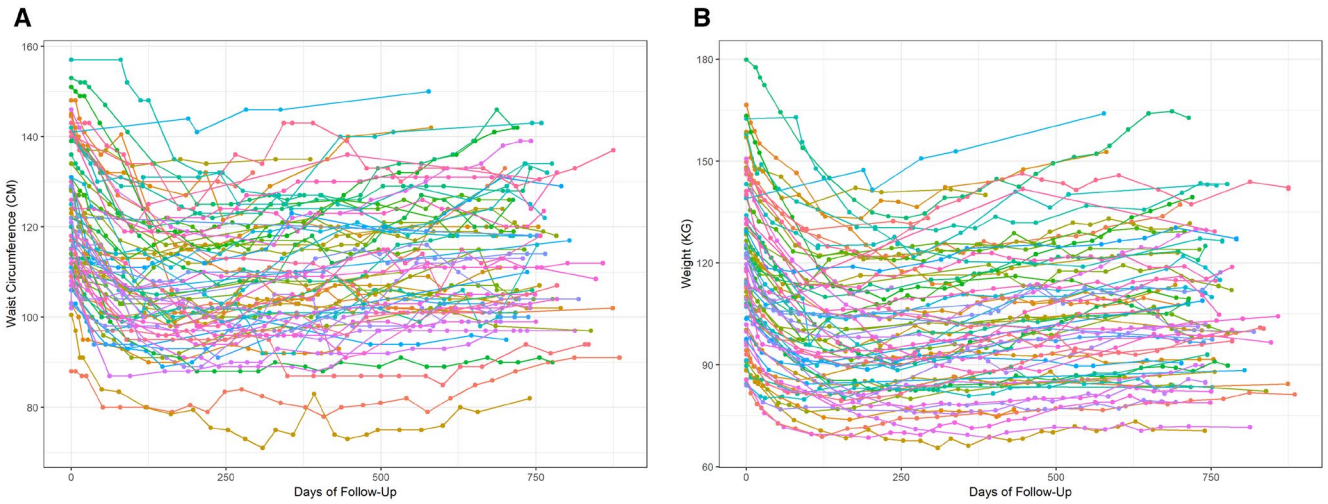

FIGURE 1 Change in obesity measures over 2 years. Longitudinal measures of waist circumference (A) and weight (B) during 2 years of follow-up after a dietary weight-loss intervention [Color figure can be viewed at wileyonlinelibrary.com]

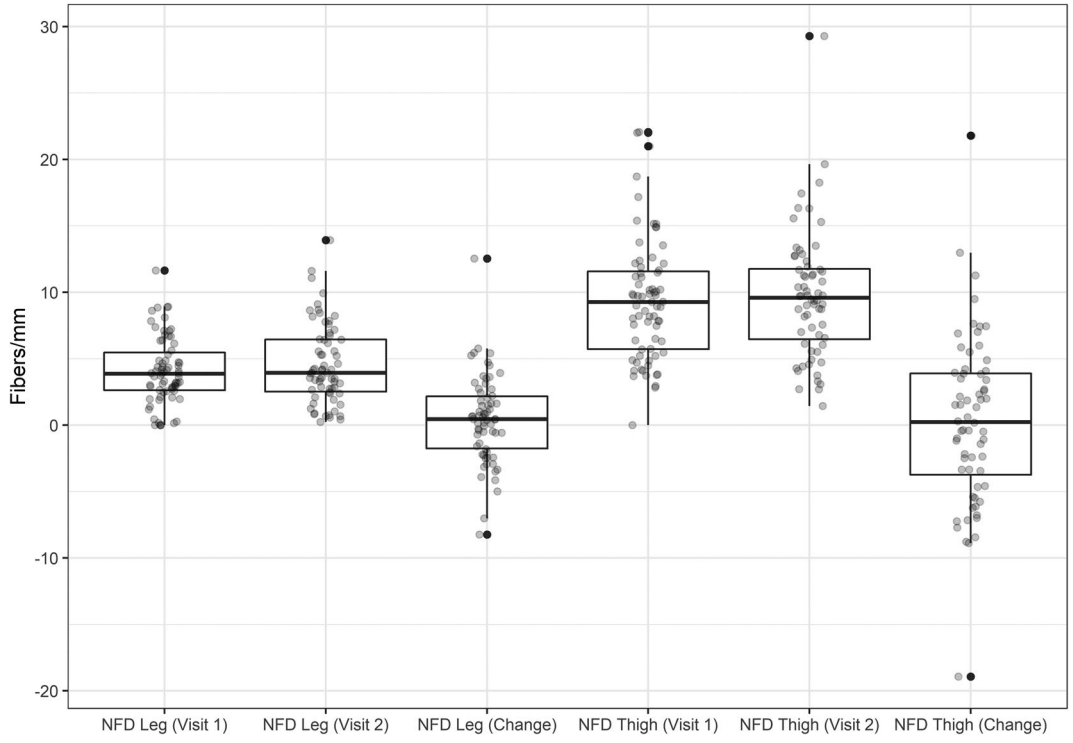

FIGURE 2 Change in IENFD (primary outcome) of the distal leg and proximal thigh after 2 years of a dietary weight-loss intervention. IENFD, intraepidermal nerve fiber density

and diabetes (27), but it is not as impressive as the improvements that have been reported with exercise intervention studies (15,16,28,29). Importantly, the natural history of IENFD decline in populations with obesity is unknown. Some secondary outcomes revealed improvements, specifically the MNSI questionnaire, QST cold threshold, and two subdomains of the Neuro-QoL, but NCS parameters and other secondary outcomes remained unchanged. Similar to neuropathy outcomes, CAN measures were also stable after 2 years.

This study is the second, to our knowledge, to evaluate the effects of a lifestyle intervention that was focused on dietary weight loss on neuropathy outcomes. The Look AHEAD study randomized more than 5,000 participants who had type 2 diabetes and overweight or obesity to a dietary weight-loss intervention for 9 to 11 years (17). Our study is complementary in that we were able to study a population with obesity that included those with normoglycemia and prediabetes in addition to those with diabetes. We also performed much more detailed neuropathy phenotyping.

TABLE 3 Changes in outcomes following weight loss

	Baseline	2-year follow-up	Change	*p* value (paired *t* test)
Neuropathy outcomes				
IENFD leg (fibers/mm)	4.1 (2.5)	4.6 (3.0)	0.4 (3.3)	0.29
IENFD thigh (fibers/mm)	9.4 (4.6)	9.7 (4.8)	0.3 (6.3)	0.74
NCS outcomes				
Ulnar peak latency (ms)	3.4 (0.4)	3.5 (0.4)	0.1 (0.4)	<0.01
Ulnar amplitude (μV)	28.0 (13.9)	25.0 (12.7)	−3.0 (12.5)	0.05
Peroneal distal motor latency (ms)	4.9 (0.9)	5.0 (0.7)	0.1 (0.8)	0.41
Peroneal amplitude (μV)	5.4 (2.6)	5.2 (2.9)	−0.2 (2.2)	0.38
Peroneal F (ms)	50.6 (5.8)	50.9 (5.7)	0.1 (5.9)	0.85
Peroneal CV (m/s)	44.7 (5.2)	44.0 (5.3)	−0.9 (5.7)	0.21
Sural peak latency (ms)	3.8 (0.4)	3.9 (0.4)	0.1 (0.4)	0.08
Sural amplitude (μV)	12.3 (6.9)	13.1 (8.8)	0.9 (7.9)	0.38
Tibial distal motor latency (ms)	4.8 (0.9)	5.1 (0.8)	0.2 (1.0)	0.08
Tibial amplitude (μV)	9.1 (5.3)	8.5 (4.5)	−0.5 (4.2)	0.30
Tibial F (ms)	53.1 (6.5)	52.3 (6.0)	−0.4 (6.6)	0.65
Median distal motor latency (ms)	3.9 (0.7)	3.9 (0.8)	0.001 (0.5)	0.98
Median motor amplitude (μV)	7.7 (3.3)	7.9 (3.3)	0.2 (3.6)	0.60
Median motor F (ms)	29.0 (2.7)	29.0 (3.6)	0.2 (2.8)	0.56
Median motor CV (m/s)	52.6 (5.2)	53.2 (6.3)	0.5 (6.2)	0.47
Median sensory peak latency (ms)	3.8 (0.6)	3.9 (0.6)	0.2 (0.4)	<0.01
Median sensory amplitude (μV)	28.8 (15.4)	28.0 (16.1)	−0.7 (5.8)	0.29
QST				
QST cold threshold	13.1 (4.8)	10.8 (4.4)	−2.0 (4.9)	<0.01
QST vibration threshold	17.8 (3.7)	17.9 (4.2)	0.2 (4.2)	0.77
QSART				
QSART arm	1.2 (1.1)	1.9 (6.7)	0.7 (6.9)	0.43
QSART proximal leg	0.5 (0.5)	1.4 (9.3)	1.0 (9.4)	0.41
QSART distal leg	0.5 (0.4)	1.3 (6.9)	0.9 (7.0)	0.31
QSART proximal foot	0.5 (0.5)	0.9 (4.7)	0.5 (4.8)	0.45
MNSI				
MNSI questionnaire	2.8 (2.5)	2.2 (2.2)	−0.6 (1.4)	<0.01
MNSI exam	1.0 (1.5)	1.1 (1.6)	0.04 (1.2)	0.76
Monofilament				
Normal	65 (90.3%)	66 (93.0%)	Worsened: 2 (2.8%)	1.00[#]
Reduced	5 (6.9%)	2 (2.8%)	Stable: 65 (91.6%)	
Absent	2 (2.8%)	3 (4.2%)	Improved: 4 (5.6%)	
Patient-oriented outcomes				
McGill Pain score				
McGill total	4.7 (6.0)	3.9 (5.7)	−0.8 (4.7)	0.15
McGill sensory	4.0 (5.0)	3.3 (4.6)	−0.7 (4.0)	0.12
McGill affective	0.6 (1.3)	0.5 (1.4)	−0.1 (1.3)	0.58
VAS total	19.6 (24.6)	17.8 (22.8)	−1.8 (29.3)	0.60
PPI				
No pain	54 (77.1%)	52 (72.2%)	Worsened: 12 (17.1%)	0.75[#]
Mild	9 (12.9%)	14 (19.4%)	Stable: 49 (70.0%)	

(Continues)

TABLE 3 (Continued)

	Baseline	2-year follow-up	Change	*p* value (paired *t* test)
Discomforting	7 (10.0%)	6 (8.3%)	Improved: 9 (12.9%)	
Neuro-QoL				
Neuro-QoL total	2.3 (1.8)	2.0 (1.1)	−0.3 (1.4)	0.06
Neuro-QoL pain	2.3 (1.8)	2.0 (1.5)	−0.4 (1.1)	0.01
Neuro-QoL reduced sensation	2.1 (2.3)	2.0 (2.4)	−0.1 (1.9)	0.65
Neuro-QoL sensory motor	1.9 (1.6)	2.0 (1.8)	0.04 (1.3)	0.80
Neuro-QoL social	2.1 (1.6)	2.0 (1.0)	−0.03 (1.9)	0.90
Neuro-QoL emotional	2.4 (2.6)	1.7 (1.0)	−0.7 (2.2)	0.01
Neuro-QoL activities of daily living	3.2 (3.0)	2.9 (2.1)	−0.3 (2.7)	0.34
CAN outcomes				
E:I ratio	1.13 (0.08)	1.19 (0.40)	0.07 (0.41)	0.17
30:15 ratio	1.40 (0.64)	1.38 (0.53)	−0.02 (0.46)	0.71
Valsalva ratio	1.48 (0.34)	1.54 (0.51)	0.07 (0.60)	0.35
RFA	10.5 (65.5)	26.5 (196.2)	15.8 (208.4)	0.53
LFA	7.5 (45.1)	57.9 (446.0)	50.2 (449.2)	0.35
LFA/RFA	3.1 (4.1)	5.4 (17.5)	2.2 (18.0)	0.31
sdNN	53.9 (31.1)	54.1 (40.2)	0.5 (48.7)	0.93
rmsSD	35.3 (32.7)	38.7 (49.4)	3.9 (59.5)	0.58
Median heart rate	66.8 (11.9)	67.6 (13.9)	0.5 (16.6)	0.80

Data given as mean (SD) unless otherwise indicated.

Abbreviations: CAN, cardiovascular autonomic neuropathy; CV, conduction velocity; E:I, expiration to inspiration; IENFD, intraepidermal nerve fiber density; LFA, low-frequency area, measure of sympathetic activity; LFA/RFA, low-frequency area/respiratory frequency area, measure of sympathovagal balance; MNSI, Michigan Neuropathy Screening Instrument; PPI, present pain intensity; NCS, nerve conduction study; Neuro-QoL, Quality of Life in Neurological Disorders, neuropathy-specific quality of life instrument; QSART, quantitative sudomotor axon reflex testing; QST, quantitative sensory testing; RFA, respiratory frequency area, measure of parasympathetic activity; rmdSD, root mean square of successive differences of the normal-to-normal interval; sdNN, SD of the normal-to-normal interval.

#*p* value represents results from Wilcoxon signed rank test.

Both Look AHEAD and our study found that dietary weight loss was associated with improvements on the MNSI questionnaire but not the MNSI examination. The consistency of these results provides more evidence for the benefits of dietary weight loss for peripheral nerves, but it also highlights the limitations of this intervention. Subjective measures such as the MNSI questionnaire improved, which we also observed for two Neuro-QoL subdomains. In contrast, objective measures of neuropathy, such as the MNSI examination, were largely stable. Our study included IENFD and NCS parameters that also demonstrated stability. Taken together, these studies indicate that dietary weight loss can halt the progression of neuropathy, if not lead to mild improvements, but that different interventions are likely needed if more dramatic improvement is the goal. Importantly, the natural history of small fiber neuropathy, regardless of cause, is to decline at a predictable rate (27); therefore, any intervention that leads to stability should be considered a success.

Other potential interventions to improve multiple metabolic risk factors and neuropathy outcomes include surgical weight loss, medication-induced weight loss, and exercise. To our knowledge, surgical weight loss was evaluated only in one small study of 12 participants before and after Roux-en-Y gastric bypass with a hint of efficacy (30). Medication-induced weight loss has not been studied, to our knowledge. In contrast, exercise has been the most studied of these interventions, including three uncontrolled studies and one randomized study (15,16,28,29). Two of these studies also had a dietary component, but weight loss was minimal: 0.1 and 1.1 decrease in BMI compared with 4.3 decrease in our study (15,16). Three of these exercise studies demonstrated improvements in IENFD outcomes, and the randomized trial revealed improvements in NCS and vibration thresholds. Taken together, the previous exercise studies indicate an improvement in neuropathy outcomes, whereas dietary weight loss demonstrates stability or mild improvement in subjective outcomes. However, more definitive studies comparing the effects of exercise and different weight-loss strategies (dietary, surgical, and medication induced) are needed before strong clinical recommendations can be made favoring one of these interventions. Given the modest effect size and adherence issues with dietary weight loss, future interventions may need to combine exercise and dietary weight loss or include dietary adjustments designed to improve adherence and/or to improve neuropathy through limiting certain metabolites that may lead to nerve injury.

Although IENFD and NCS parameters did not change after dietary weight loss, the MNSI questionnaire, two Neuro-QoL subdomains, and the QST cold threshold all demonstrated improvement after 2 years. This is an important finding because using more sensitive measures of neuropathy improvement has the potential to lead to more efficient clinical trials. We looked at several secondary outcome measures; therefore, these results should be considered hypothesis generating rather than definitive. On the other hand, the Look AHEAD study also demonstrated improvement in the MNSI questionnaire over the first couple of years as well as after 9 to 11 years of dietary weight loss (17). These results provide stronger justification for using the MNSI questionnaire as a sensitive measure of neuropathy improvement. Interestingly, the Neuro-QoL may also be a sensitive indicator of improvement, which could be important as this is also a patient-oriented outcome. Future studies are needed to determine whether the Neuro-QoL demonstrates sensitivity to neuropathy improvement. Despite these encouraging results, more sensitive biomarkers are needed to detect earlier changes in patients with neuropathy, which would enable more efficient clinical trials. Furthermore, the MNSI questionnaire and Neuro-QoL are more subjective neuropathy measures compared with IENFD and NCS, which may account for the differences observed with these outcomes.

Similar to neuropathy, CAN also demonstrated stability 2 years after dietary weight loss on all nine measures. Only one randomized trial, to our knowledge, investigated the effects of dietary weight loss in combination with exercise on CAN outcomes, and this was in a population of individuals with type 2 diabetes (31). The investigators found no improvement on the E:I ratio in the overall population, although diet and exercise did lead to improvement in women. Analogously to neuropathy, the natural history of CAN is to worsen over a 2-year period in those with diabetes (32). Therefore, the stability in CAN measures after dietary weight loss in both this study and our current study provides supporting evidence for a positive effect, but future randomized studies are needed especially because the natural history of CAN in populations with obesity is unknown. Comparable to neuropathy, most of the intervention studies have focused on the effects of exercise on CAN (33). These studies have generally showed improvement in CAN outcomes, but they are uniformly small, with varying outcomes and exercise regimens, which limits interpretability (28,34–38). Just like with neuropathy, studies that compare the effects of exercise with different weight-loss strategies are needed to guide clinical recommendations.

Interestingly, the improvement in neuropathy outcomes that we observed in humans with obesity after a dietary intervention has also been observed in obese mice. Mice on a high-fat diet developed neuropathy that was completely normalized after dietary reversal (39). Although we did not observe such robust results in humans, the dietary reversal was not nearly as complete as in the murine models, and the metabolic impairments were present for far longer in humans. Importantly, lipidomic analyses have shed light on potential biologic mechanisms of obesity-related neuropathy. Nerves from high-fat-fed mice with neuropathy contained an increase in triglycerides containing saturated fatty acids compared with nerves from control mice (40). Mice fed a high-fat diet consisting of saturated fatty acids developed neuropathy that was completely reversed by switching to a high-fat diet consisting of monounsaturated fatty acids (41). The monounsaturated fatty acid oleate also prevented defects in axonal mitochondrial transport and membrane potential that were present in sensory neurons treated with the saturated fatty acid palmitate. These results indicate that nerve-lipid signaling is an important factor in peripheral nerve injury (42).

Limitations of this study include the small sample size, which limits our power to detect small changes. However, we did observe significant changes in multiple secondary outcomes. We also had significant loss to follow-up, but only employment status was significantly different between the whole cohort and those who followed up after 2 years. We were unable to investigate longer-term effects of dietary weight loss on outcomes after 2 years, but our results are consistent with the Look AHEAD study, which followed participants for 9 to 11 years (17). Our pre-post intervention design does not allow for causal inferences. Generalizability to other populations, particularly those with different race/ethnicity and educational status, is unclear. Strengths of this study include the comprehensive metabolic and neuropathy phenotyping before and after a successful dietary weight-loss intervention.

After a dietary weight-loss intervention, participants with severe obesity had large improvements in multiple metabolic risk factors. Neuropathy, as measured by IENFD, and CAN were stable after 2 years, which is an improvement from the known natural history of decline in those with small fiber neuropathy from any cause (28). Randomized trials are needed to definitively address the effects of dietary weight loss on neuropathy and compare and contrast with other weight-loss measures and/or exercise.

CONFLICT OF INTEREST

BCC consults for DynaMed, performs medical legal consultations, including consultations for the Vaccine Injury Compensation Program, and receives research support from the American Academy of Neurology. AER consults for Nestle S.A., Rhythm Pharmaceuticals, and REWIND Inc. The other authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT02043457.

AUTHOR CONTRIBUTIONS

BCC was involved in the study design and interpretation of the statistical analysis and wrote the manuscript. ELR, MB, AER, CFB, and ELF were integrally involved in the study design, interpretation of the data, and critical revisions of the manuscript. ELR performed the statistical analyses. GA was involved in interpretation of the data and critical revisions of the manuscript. EVU and EC were involved in the study design and critical revisions of the manuscript.

DATA AVAILABILITY STATEMENT

Individual patient-level data will be available upon request.

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