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Title: Metabolic Syndrome and peripheral neuropathy

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Abstract:

Diabetic peripheral neuropathy (DPN) and metabolic syndrome (MetS) are both global health challenges with well-established diagnostic criteria and significant impacts on quality of life. Clinical observations, epidemiological evidence and animal models of disease have strongly suggested MetS is associated with an elevated risk for cryptogenic sensory peripheral neuropathy (CSPN). MetS neuropathy preferentially affects small unmyelinated axons early in its course, and it may also affect autonomic and large fibers. CSPN risk is linked to MetS and several of its components including obesity, dyslipidemia, and prediabetes. MetS also increases neuropathy risk in patients with established type 1 and type 2 diabetes. Animal data regarding the role of inflammation and dyslipidemia in MetS neuropathy pathogenesis is presented. Several studies suggest exercise-based lifestyle modification is a promising treatment approach for MetS neuropathy.

Keywords: Cryptogenic sensory polyneuropathy; Diabetic peripheral neuropathy; Hypertriglyceridemia; Dyslipidemia; Metabolic syndrome; Prediabetes; and Small fiber neuropathy

Introduction

Diabetic peripheral neuropathy (DPN) affects half of all diabetic patients [1-3] and a significant portion of peripheral neuropathy cases (18-49%) can be attributable to diabetes.[4] DPN is a major cause of disability due to pain, foot ulcers and amputations and it is associated with significant healthcare costs. DPN costs $10 billion annually in the United States [5] and adds at least 20-30% to annual health care expenses.[6] We now know that type 1 DPN (T1DPN) and type 2 DPN (T2DPN) are separate disease entities and respond differently to glycemic control.[7] While aggressive glycemic control significantly reduces DPN risk and rate of progression in T1D, this approach is only modestly beneficial in T2D.[8] In addition, emerging evidence now supports the role of metabolic syndrome (MetS) as a major cause of cryptogenic sensory peripheral neuropathy (CSPN), although MetS often overlaps with DPN. Due to the significant

overlap between MetS neuropathy and T2DPN, validated research tools developed to study DPN also apply to patients with MetS-associated peripheral neuropathy. MetS affects nearly 34.2% of all adults in the US, with 58.4% of those affected being less than 50 year of age.[9]

MetS and some of its individual components (see below) are significant risk factors for both T1DPN and T2DPN. This risk is particularly relevant in T2DPN, which shares clinical and pathophysiological features with MetS. In this review, we highlight the strong body of evidence that associates MetS with CSPN as well as its role in T2DPN pathogenesis and treatment response. Animal model data is presented, highlighting the toxic effects of dyslipidemia and inflammation in particular, as well as concordant potential therapeutic targets. Finally, we conclude with a review of completed and ongoing human clinical trials, as well as practical clinical considerations.

Diagnostic criteria: MetS, prediabetes, and diabetes

MetS is the combination of hyperlipidemia (elevated serum triglycerides and/or reduced high-density lipoprotein - HDL), central obesity, insulin resistance (diabetes or prediabetes), and hypertension. The diagnostic criteria of MetS have evolved over the years to give more weight to central obesity **(Table 1)**. The American Heart Association and National Heart, Lung, Blood Institute (AHA/NHLBI) criteria for MetS require three out of five specific criteria to be fulfilled.[10] The International Diabetes Federation (IDF) definition requires central obesity in

addition to two or more additional criteria. Central obesity is defined on the basis of waist circumference, measured midway between the costal margin and the apex of the iliac crest, and varies by ethnic background.[11]

Glucose dysregulation encompasses a spectrum ranging from impaired fasting glucose (IFG) to impaired glucose tolerance (IGT) to frank diabetes. IFG and IGT constitute prediabetes and are distinguished by fasting plasma glucose and 2 h oral glucose tolerance testing (OGTT), respectively. The American Diabetes Association diagnoses prediabetes based on a hemoglobin A1C of 5.7– 6.4% **(Table 2).**[12] Given the centrality of the OGTT in the clinical and research evaluation of MetS, prediabetes, and diabetes, a brief review of the test is warranted. When undergoing an OGTT, patients are instructed to complete an overnight fast and then have their fasting blood glucose measured early the next morning (ideally before 09:00 AM). A 75 g dose of oral anhydrous dextrose is then given, and a blood glucose check is completed two hours later. A fasting blood glucose value of 100–125 mg/dl (5.6–6.9 mmol/L) indicates IFG. A 2-hour oral glucose tolerance value of 140–199 mg/dl (7.8–11.0 mmol/L) defines IGT. A fasting glucose level of 126 mg/dl or greater and/or a 2-hour glucose tolerance of 200 mg/dl or greater establish a diagnosis of diabetes. The OGTT is not without its limitations, however. It has low reproducibility in diagnosing patients with IGT (73% for diabetics and 93% for normoglycemics).[13] Repeat testing is not unreasonable in cases where, for example, the fasting test is normal, but the 2-hour glucose tolerance is abnormal.

Clinical evaluation and diagnostic testing

MetS neuropathy and early DPN are associated with preferential injury to small nerve fibers.[14] Both classically manifest with length-dependent ‘stocking ‘or ‘stocking glove ‘pattern sensory loss. The epidemiological data linking MetS to both T2DPN and CSPN and the clinical similarities suggest a common underlying pathophysiology. Neuropathic pain is common, described as burning, stinging, electrical, or pins and needles-like. Early on, there is usually relative sparing of vibration and proprioceptive sensation. It is clear that epidermal C fibers (free nerve endings) are particularly prone to injury. Although disproportionately prone to metabolic, vascular and mechanical injury, epidermal fibers are still uniquely capable of regeneration and sprouting,[15] allowing such fibers to survive in the treacherous distal epidermal environment.[16] In addition, data suggest that small unmyelinated axons may be disproportionately prone to injury from obesity and hypertriglyceridemia, while large myelinated fibers are more susceptible to injury in the setting of hyperglycemia.[17]

Autonomic neuropathy can also occur, manifesting with cardiac vagal (reduced heart rate variability (HRV), cardiac adrenergic (reduced chronotropy and inotropy), vasomotor (orthostatic hypotension), gastrointestinal (gastroparesis), genitourinary (erectile dysfunction), and secretomotor (anhidrosis) dysfunction. In 268 individuals with IGT enrolled in the Finnish Diabetes Prevention Study, the prevalence of parasympathetic or sympathetic dysfunction was 25% and 6%, respectively. Subjects with parasympathetic dysfunction were older, more obese [with increased weight, waist circumference, and body mass index (BMI)], and had higher

triglyceride levels as compared to those with normal parasympathetic function.[18] In particular, the presence of two or more components of MetS in IFG patients was shown to be associated with cardiac vagal impairment (reduced HRV), as compared to control subjects or those with only one MetS component.[19] Cardiac vagal impairment in early T2DM (<5 years diagnosed) also portends increased cardiac mortality.[20,21] Of note, sudomotor abnormalities are a common manifestation of IGT neuropathy [14] and coincide with histologic evidence of small fiber neuropathy (SFN) as shown via reduced IENFD. Although the timing of autonomic neuropathy relative to the onset of SFN in MetS is unknown, it is likely that cardiac vagal autonomic dysfunction occurs early in disease course, as obesity leads to reduction in indices of heart rate variability.[22]

Per the Toronto Consensus Criteria, the diagnosis of confirmed DPN is based on the recognition of neuropathic symptoms and signs with abnormality of either nerve conduction studies or a validated measure of small fiber function, such as skin biopsy evaluation for assessment of IENFD.[23] In addition to a thorough history, examination, and proper lab testing, a number of validated instruments have been developed to capture the diagnosis and monitor DPN severity and progression, such as the Michigan Neuropathy Symptom Inventory (MNSI)[24] and the Utah Early Neuropathy Scale (UENS),[25] which are equally applicable to MetS neuropathy. Nerve conduction studies (NCS), while helpful for large fiber neuropathy, are not sensitive to diagnose SFN, and thus cannot be solely used to confirm or exclude MetS-related neuropathy.[26]

Skin punch biopsy evaluation for IENFD assessment (**Figure 1**) is the gold standard for objectively diagnosing SFN.[27] Punch biopsies, 3mm in diameter, are performed at the lateral distal leg 10 cm proximal to the lateral malleolus and at the proximal thigh 10 cm distal to the greater trochanter. Unmyelinated axons are immunohistochemically stained with an antibody toward a common axonal antigen, protein gene product 9.5 (PGP 9.5). Age- and sex- adjusted normative values for the number of axons crossing the dermal-epidermal junction per millimeter are available [28] and the reproducibility of IENFD is well-established (although it is very important that labs maintain a high degree of quality control such as inter-institutional test retest reliability assessments for qualitative interpretation and IENFD assessment).[29] IENFD was found have a sensitivity of 81-88% for the diagnosis of SFN.[30] In addition to its clinical utility, IENFD is a valuable outcome measure in clinical trials and natural history studies as it is sensitive, reproducible and responsive to disease progression or improvement.

Automated assessment of heat pain perception as a function of the small nerve fibers can be performed via quantitative sensory testing (QST).[27] Heat pain hyper-or hypo-algesia are diagnosed when the detection threshold of graded standardized stimulus intensities is lower than the 5^{th} or higher than 95^{th} percentiles, respectively.[31] One retrospective study did not show a significant increase in the prevalence of heat pain hyper- or hypo-algesia in prediabetics when compared to healthy controls.[32] In the previously-cited study exploring the association between MetS components and peripheral neuropathy in an obese population, however, QST vibration

and cold perception thresholds differed between obese patients with and without neuropathy, but not between obese and lean patients who did not have neuropathy.[33]

For autonomic evaluation, the autonomic reflex screen is used to assess cardiac vagal, cardiac adrenergic, vascular adrenergic, and sympathetic sudomotor post-ganglionic function in such patients. The quantitative sudomotor axon reflex test (QSART) component of the autonomic reflex screen evaluates sympathetic cholinergic postganglionic sudomotor activity (C autonomic fibers). QSART may be used to document small fiber neuropathy when IENFD cannot be obtained, although its sensitivity is lower at 74% and there are concerns regarding test-retest reliability.[34-36] Other measures of sudomotor function like the thermoregulatory sweat test (TST) might also be helpful in confirming SFN, yet this is only available in a few major tertiary centers in the United States and Europe. A distal pattern of anhidrosis/hypohidrosis was reported in 93% of cases of SFN using QSART and TST combined.[34]

All patients should have a thorough history and neurological examination to assess for other potential causes of neuropathy. Evidence-based laboratory tests for patients with distal symmetric polyneuropathy should be performed, including testing for diabetes and prediabetes and a fasting lipid profile. It is reasonable to start with a hemoglobin A1c, although a 2-hour OGTT is more sensitive for prediabetes. Other testing should include a vitamin B12 level and serum protein electrophoresis and immunofixation.[37] Other components of MetS including blood pressure and BMI and/or waist circumference should be documented, in addition to whether the

patient meets syndromic criteria. Patients should also be queried regarding diet, the amount and nature of their exercise, and the level of sedentary behavior.

Epidemiology linking MetS, CSPN, and DPN

Through numerous cross-sectional, observational, and case-control studies completed over the last four decades, and spanning Europe, the United States, and Asia, a clear pattern emerges linking MetS to CSPN. Individual components of MetS, particularly obesity, prediabetes and diabetes, and dyslipidemia have been associated with an elevated risk of CSPN. MetS has also been shown to increase the risk of neuropathy in both type 1 and type 2 diabetics.[38,17]

1. CSPN is associated with MetS:

The association between CSPN and prediabetes was first observed by clinicians caring for patients with neuropathy who did not have overt diabetes. Subsequent observations broadened the association to MetS and its other components. [39,40] Since then, numerous cross-sectional and longitudinal international, population-based studies have corroborated those initial findings, in addition to smaller trials. The association between MetS and CSPN is independent of prediabetes, diabetes, or glycemic status, supporting a role for these other constituent components of MetS that is of equal or greater value than glycemic index, especially in T2DPN.

One US cross sectional study, which focused on obese patients, and which defined probable neuropathy on the basis of the Toronto Clinical Neuropathy Score, identified waist circumference as being significantly associated with neuropathy. The association between obesity and neuropathy held even in the setting of normoglycemia. [33] In a separate case-control study, normoglycemic CSPN subjects were compared to diabetic non-neuropathy subjects. Compared to their diabetic counterparts, the normoglycemic CSPN patients had significantly more features of MetS (other than hyperglycemia) [40] and dyslipidemia. In a separate similarly-sized study, nearly 55% of the CSPN cohort fulfilled MetS criteria as compared to only 34% of the control group. Hypertension and abdominal obesity were also more prevalent in the CSPN group. [41] To reiterate, such findings were independent of glycemic control.

Pivotal among such trials was the Health ABC study, which combined cross-sectional and longitudinal data, and focused on the relationship between MetS and distal symmetric polyneuropathy (DSP). In this study, DSP was defined as (a) fulfillment of neuropathy criteria via self-reported symptoms on at least one of two questionnaires *and* (b) at least one of three confirmatory objective tests: (1) the inability to feel heavy monofilament on the dorsum of the great toe, (2) peroneal nerve conduction study changes, and/or (3) elevated vibration detection threshold on QST. DSP prevalence increased as the number of MetS components increased. Diabetes (OR=1.65, 95% CI= 1.18-2.31, cross-sectional model) and baseline hemoglobin A1C (OR=1.42, 95% CI=1.15–1.75, longitudinal model) were significantly associated with DSP. In addition, waist circumference was significantly associated with multiple secondary neuropathy

outcomes, including the presence of any neuropathic symptoms (OR=1.07, 95% CI=1.03-1.11), the inability to feel heavy monofilament (OR=1.10, 95% CI=1.03-1.17), peroneal compound muscle action potential amplitude (OR= -0.05, 95% CI= -0.09, -0.01), and vibration detection threshold (OR=0.58, 95% CI=0.01-1.14), independent of glycemic status. Low HDL was significantly associated with a few secondary outcomes, including the presence of any neuropathic symptoms (OR=0.091, 95% CI=0.85-0.97) and the inability to feel light monofilament (OR=0.92, 95% CI=0.86-0.98). All associations were independent of glycemic status.[42] A Dutch study similarly found CSPN to be more prevalent as more components of MetS were fulfilled. The association with CSPN was particularly strong for waist circumference and hypertriglyceridemia and was independent of glycemic status.[43] A longitudinal German study also found general and abdominal obesity to be associated with the development of CSPN.[44]

2. CSPN is associated with dyslipidemia

Elevated triglycerides or reduced HDL are components of MetS. Robust literature links hypertriglyceridemia to the development of CSPN. Hughes el al. reported significantly higher triglyceride levels in CSPN as compared to healthy control patients, with triglyceride levels being higher in patients with painful CSPN.[45] In a separate longitudinal study, hypertriglyceridemia associated with reduced sural nerve myelin fiber density in DPN patients.[46] Hypertriglyceridemia also associates with reduced IENFD independent of glycemic control.[17]

HDL was found to correlate inversely with mean dendrite length, itself reduced in MetS, when compared with healthy controls.[47] Hypertriglyceridemia is an independent risk factor for non-traumatic lower limb amputation in diabetic patients.[48]

Furthermore, lipid-lowering therapy reduces the likelihood of the long-term (six-year) development of DPN in T2DM. Fenofibrate [hazard ratio (HR)=0.52, 95% CI=0.27-0.98] and statin use (HR=0.65, 95% CI=0.46-0.93) significantly reduced the incidence of neuropathy as defined by the clinical portion of MNSI,[49] although there is insufficient data to suggest optimal dosing of lipid-lowering agents or its effect on neuropathy risk or incidence.

3. The association between prediabetes and CSPN

Numerous studies suggest patients with CSPN are more likely to have prediabetes, and that individuals with prediabetes are conversely more likely to have neuropathy, although other data suggests no association. The classic San Luis Valley study of 1984–1986 defined patients as having either definite or possible neuropathy based on history, deep tendon reflexes, vibration, and temperature sensation assessments, while OGTT was used to discern glycemic status. The results showed a 25.8% age-adjusted prevalence of neuropathy in diabetic patients, 11.2% in the IGT group, and 3.9% in control participants.[1] The MONICA/KORA study identified a painful neuropathy prevalence of 13.3% in people with diabetes, 8.7% in those with IGT, 4.2% in those with IFG, and 1.2% in normoglycemic individuals.[50] Longitudinal data through the PROMISE

study also confirmed the robustness of prediabetes as a cause of neuropathy, on par with diabetes. Patients who progressed to diabetes and prediabetes at 3-year follow up had a neuropathy prevalence of 50% and 49%, respectively. When progression status was excluded, the neuropathy prevalence was identical at 49% for both groups. Prediabetics also had higher MNSI scores and vibration detection thresholds than normoglycemic subjects.[51] Conversely, patients with preexisting CSPN are at higher risk of having IFG and/or IGT. Of a cohort of 73 patients who underwent OGTT, 56% were found to have IFG, while 36% had IGT, with the IGT group showing preferential small fiber involvement.[52]

While there is compelling evidence linking prediabetes to neuropathy risk, other studies have questioned the association, although they suggested other metabolic syndrome components are neuropathy risk factors. A recent study of 208 patients at a single center suggested that obesity, high triglycerides, and low HDL (and not prediabetes) impacted small fiber structure (reduced IENFD) but not function (QSART, QST).[53] A 2015 study at the Mayo Clinic compared healthy and prediabetic cohorts and found no difference in the prevalence of neuropathy symptoms as measured by QST, suggesting no increased prevalence of SFN among patients with prediabetes.[32] Another previous 2012 Mayo Clinic study of Olmsted County, MN found that impaired glycaemia (without frank diabetes) did not confer an increased risk of peripheral neuropathy.[54] A 2004 study from England did not find glucose intolerance to confer an increased risk of CSPN, although there was a trend towards more impairment of glycemic control in the CSPN group, especially in the presence of hypertriglyceridemia.[45]

4. MetS accelerates DPN progression

MetS also accelerates the progression of DPN in patients with established diabetes. The Utah Diabetic Neuropathy Study assessed the prevalence of MetS and its component features in patients with T2DM (without neuropathy symptoms) as well as those with DPN symptoms of less than five years' duration. All participants completed the UENS, NCS, QST for vibration and cold detection, QSART, and IENFD. Those with abnormalities in three or more tests were deemed to have probable neuropathy, while those with one or two were classified as having possible neuropathy. Hypertriglyceridemia, obesity, and MetS were found to be independent risk factors for early DPN, irrespective of glycemic status. Interestingly, hemoglobin A1c was inversely correlated with the motor nerve conduction velocity, while obesity and triglycerides correlated with IENFD,[17] suggesting hyperglycemia may impair large fiber function whereas obesity and dyslipidemia may differentially impact small unmyelinated axons. A national Italian study found MetS to be independently associated with the likelihood of DPN for both T1DM and T2DM, and likely contributory to the pathogenic microvascular complications of diabetes.[38] This finding has been reproduced in other countries, including China, where a population-based study showed that obesity and hypertriglyceridemia accelerated DPN progression in established DPN patients, with neuropathy prevalence increasing as glycemic status worsened.[55]

DPN pathophysiologic mechanisms

Due to the clear clinical and epidemiologic association between MetS and CSPN, this relationship was further investigated in murine models, with the goal of understanding pathomechanisms and developing targeted therapies. Multiple murine models emerged including the high-fat chow diet (HFD) mouse (C57BL/6J),[56,57] the juvenile genetic T2DM model of prediabetes and diabetes,[58,59] the leptin (*ob/ob*) and leptin receptor (*db/db*) knockout dyslipidemic models,[60] and the streptozocin-exposed HFD-C57BL/6J T2DM models.[59] These models have facilitated a better understanding of the underlying mechanisms leading to axonal injury in MetS neuropathy. Obesity appears to be the main driver in MetS and introduces an increased pool of long chain fatty acids that penetrate the blood-nerve barrier resulting in neuro-inflammation. Neuronal oxidative stress triggers a cascade of downstream pro-inflammatory cytokines and chemokines, [61] which generate oxidized cholesterol. Central to the harmful downstream effects of MetS inflammation is NF-κB, a redox-sensitive transcriptional factor protein that is activated by oxidative stress, pro-inflammatory cytokines, and hyperglycemia.[62] It modulates multiple downstream pro-inflammatory genes, notably cyclooxygenase-2 directly or indirectly through modulating tumor necrosis factor-alpha.[63]

In addition, the impact of dyslipidemia on mitochondrial function and bioenergetics has become a major focus of research. By impacting mitochondrial morphology, motility, fission, and fusion, dyslipidemia contributes to neuronal and Schwann cell injury that ultimately

contributes to MetS neuropathy. High concentrations of long chain fatty acids have been shown to alter axonal mitochondrial transport. For example, palmitate, a saturated long chain fatty acid, lowers the number and velocity of motile mitochondria, and additionally, hyperpolarizes the mitochondrial outer membrane,[64] which leads to impaired electron transport. In the setting of substrate overload, mitochondrial oxidative phosphorylation is impaired, ATP production is reduced, reactive oxygen species are generated, and more low density lipoproteins are oxidized, leading to further mitochondrial membrane damage.[65,66]

Reversal of MetS neuropathy

To reverse MetS neuropathy, timing is of great importance as injury becomes difficult to reverse once it extends to large fibers. Furthermore, glycemic control alone is insufficient in T2DPN and MetS neuropathy (and overcorrection of hemoglobin A1C to less than 6.0% in T2DM patients has been shown to increase mortality).[67] In light of pathomechanistic data from murine models, investigators have naturally researched the role of dietary reversal as well as the impact of mono- and poly-unsaturated fatty acids on CSPN. In a study on HFD and HFD-STZ mice, dietary reversal from a HFD to a standard chow for four weeks reduced the levels of harmful palmitate and stearate in sciatic nerves. These mice demonstrated resolution of neuropathy based on both NCS and IENFD assessment, improved insulin sensitivity, enhanced weight loss, and lower levels of LDL and other oxidative lipoproteins.[57] Mono- and polyunsaturated fatty acids were also found to prevent the development of peripheral neuropathy

in mice pre-exposed to long chain fatty acids.[68] A 2:1 mixture of oleate, a mono-unsaturated fatty acid, and palmitate has also been shown to prevent palmitate-induced impairment of mitochondrial transport.[64] In humans, increasing the ratio of *n-3* to *n-6* polyunsaturated fatty acids appears to decrease diabetic renal[69] and retinal[70] complications in T2DM adults.

In humans, a strong body of evidence now supports the role of exercise and lifestyle modification. Using IENFD as the primary outcome, three studies show the impact of exercise on cutaneous nerve regeneration in DPN and MetS neuropathy patients. The Impaired Glucose Tolerance Neuropathy Study showed improvement in 32 IGT patients as measured at 12 months.[14] In addition, patients showed statistically significant improvements in two pain sub-scores, namely the 100-mm visual analog scale and the Gracely pain scale. The intervention consisted of quarterly dietary counseling and 150 minutes of weekly exercise for 1 year, with a target weight loss of 7%. The second study, the Utah Diabetic Neuropathy Study, randomized T2D patients without neuropathy to standard of care counseling or an intervention consisting of 30-90 minutes of supervised mixed aerobic and resistance exercise weekly and personalized dietary counseling. After one year, there was a significant increase in the proximal thigh IENFD in the treatment group while there was no change in those in the standard of care arm.[17] The study did not assess for changes in neuropathy quality of life metrics. Small fiber regenerative capacity was the focus of a third study of 67 patients with MetS neuropathy or DPN using a capsaicin axotomy technique.[71] This technique takes advantage of chemical axotomy using topical capsaicin, which causes degeneration of cutaneous TRPV1 expressing unmyelinated

axons. Baseline IENFD is measured at the distal thigh prior to placement of a capsaicin patch for 48 hours, after which a repeat skin biopsy is performed to document decline in IENFD. Repeat skin biopsies are then performed at 1 and 3 months to assess the rate of axonal regeneration. In this study, 32 patients with MetS without diabetes and 35 with MetS and T2D (both without neuropathy) underwent baseline assessment of regenerative capacity. Those without T2D subsequently completed a 6-month course of twice-per-week supervised exercise and lifestyle counseling, followed by a repeat assessment of axonal regenerative capacity in the opposite leg. Nerve regeneration rate was no different between those with and without T2D. Following exercise, nerve regeneration rate significantly improved from 0.051 +/- 0.027 fibers/mm/day to 0.072 +/- 0.030 fibers/mm/day (p=0.002). Those with improvement in more MetS criteria showed greater improvement in the rate of axonal regeneration.[71] Furthermore, the benefit of lifestyle intervention may occur after only a brief period of treatment. IENFD improved as soon as only 10 weeks after intervention among 17 patients with T2D and neuropathy.[72] Also, improvement in IENFD occurs even in the absence of significant weight reduction. Exercise-based lifestyle interventions, however, are limited by poor sustainability. The study did not assess for changes in pain intensity or neuropathy quality of life metrics. Of note, the ongoing Activity for Diabetic Polyneuropathy (ADAPT) trial (NCT02341261) is exploring the impact of actigraphy-based counseling (aimed at reducing sedentary behavior) and moderate-intensity supervised exercise on the Norfolk Quality of Life-Diabetic Neuropathy score and IENFD.[73]

The Topiramate as a Disease Altering Therapy for Cryptogenic Neuropathy (TopCSPN) study is a multi-center, double-blinded, placebo-controlled, randomized trial in the United States that has just completed enrollment. It aims to determine if topiramate can alter the natural history of MetS related neuropathy by weight reduction, improved insulin sensitivity, and voltage gated sodium channel antagonism (NCT02878798). TopCSPN is employing a novel approach of using IEFND and a validated neuropathy specific quality of life scale (the Norfolk Quality of Life – Diabetic Neuropathy scale) as co-primary outcome measures. Secondary outcome measures include NCS, UENS and a variety of measures assessing physical functioning and balance. Other interventions being evaluated include bariatric surgery, either alone or in combination with high intensive interval training (NCT03617185).

Conclusion

We now know that MetS is a substantial and important contributor to global neuropathy disease burden, as shown initially through clinical then epidemiologic and now animal data. Patients with CSPN should be evaluated for MetS. MetS also accelerates neuropathy progression in patients with established T1DPN and T2DPN, although the association is particularly strong for T2DPN, with which MetS shares many features. Therapeutic data from animal models is promising, although no disease modifying therapies are currently approved for humans. Human

data points to the role of exercise as a promising intervention. Ongoing and future studies aim to address the potential impact of drug and other disease modifying interventions on MetS neuropathy.

FIGURE LEGENDS:

Figure 1: Skin punch biopsy (PGP 9.5 stained section) obtained from a patient with metabolic syndrome (MetS) and small fiber neuropathy showing reduced intra-epidermal nerve fiber density at the ankle (A) site (mean = 0.3 fiber/millimeter, 5^{th} percentile normative value for age

and sex is 2.1 fiber/millimeter [28]), arrow pointing to surviving axonal showing signs of degeneration (axonal bulbing) when compared to the thigh (B) site (mean = 3.2 fiber/millimeter). Patient was diagnosed with MetS based on a body mass index of 40.9 kg/m², elevated fasting blood glucose (111mg/dl), and use of antihypertensive treatment. Courtesy of the Shin J. Oh Muscle and Nerve Histopathology Laboratory at the University of Alabama at Birmingham.

LIST of ABBREVIATIONS

ADAPT, the Activity for Diabetic Polyneuropathy trial; AHA/NHLBI, The American Heart Association and National Heart, Lung, Blood Institute; BMI, body mass index; CSPN, cryptogenic sensory polyneuropathy; DPN, Diabetic peripheral neuropathy; DSP, distal symmetric polyneuropathy; EGIR, The European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; HFD, high fat diet; HR, hazard ratio; HRV, heart rate variability; IDF, The International Diabetes Federation; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IEFND, intra-epidermal nerve fiber density; LDL, low-density lipoprotein; MetS, metabolic syndrome; MNSI, Michigan Neuropathy Screening Instrument; NCEP ATP III, The National Cholesterol Education Program-Third Adult Treatment Panel; NCS, nerve conduction studies; OGTT, oral glucose tolerance test; OR, odds ratio; PGP 9.5, protein gene product 9.5; PROMISE, the Prospective Metabolism and Islet Cell Evaluation study; QSART, quantitative sudomotor axon reflex testing; QST, quantitative sensory testing; SFN, small fiber neuropathy; STZ, streptozocin; TopCSPN, The Topiramate as a Disease Altering Therapy for Cryptogenic Neuropathy study; T1D, type 1 diabetes; T2D, type 2 diabetes; TST, thermoregulatory sweat test; UENS, Utah Early Neuropathy Scale.

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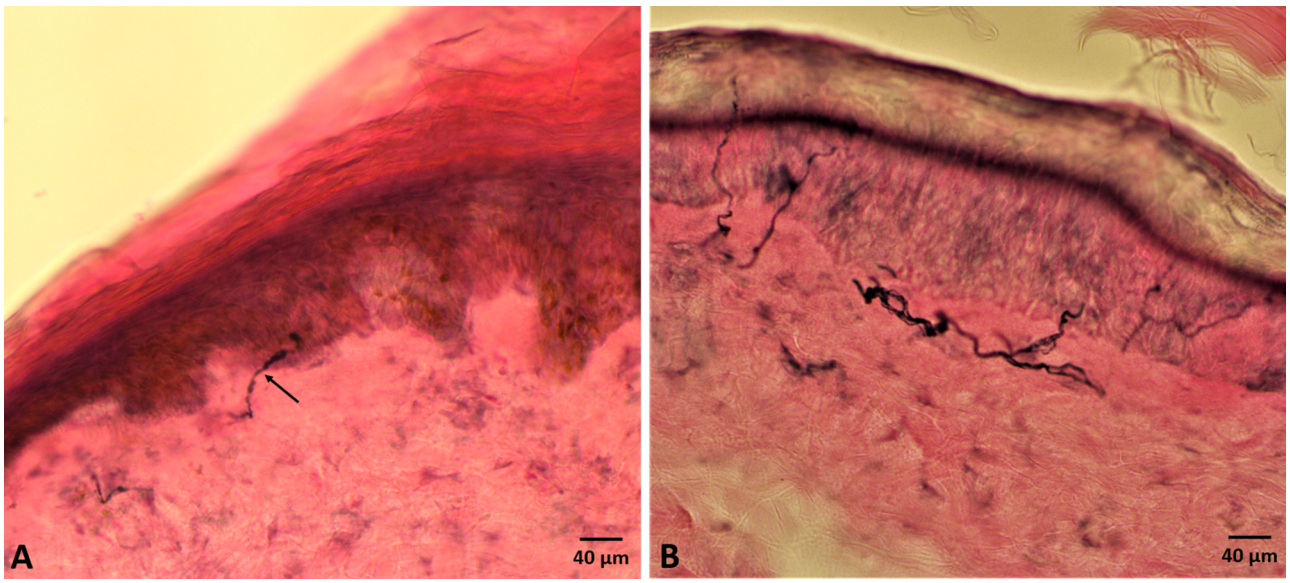

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Table 1: Commonly used different sets of criteria for diagnosis of metabolic syndrome:

	WHO (1999) [74]	EGIR (1999) [75]	NCEP ATP III [76]	AHA/NHLBI [10]	IDF [11]
Frame/core criterion	IGT or diabetes and/or insulin resistance* Plus ≥2 other criteria	Insulin resistance (defined as Hyperinsulinaemia: top 25% of fasting insulin values among the non-diabetics) plus ≥ 2 other criteria	≥3 of the 5 criteria below	≥3 of the 5 criteria below	Ethnicity specific waist circumference† as below or BMI > 30 kg/m² plus ≥2 other criteria
Fasting plasma glucose		≥ 6.1 mmol/l (110 mg/ dl) but non-diabetic	≥ 5.6 mmol/l (100 mg/dl)	≥100 mg/dL‡ or specific treatment for elevated glucose	≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed T2DM OGTT is strongly recommended but not necessary
Blood pressure	≥ 140/90 mmHg	≥ 140/90 mmHg or treatment	≥ 130/85 mmHg	≥130/85 mmHg or treatment of previously diagnosed hypertension	≥ 130/80 mmHg or treatment of previously diagnosed hypertension
Plasma triglycerides	≥ 1.7 mmol/l (150 mg/dl) or treatment	≥ 2.0 mmol/l (178 mg/dl) or treatment	≥ 1.7 mmol/l (150 mg/dl)	≥150 mg/dL (1.7 mmol/L) or specific treatment for hypertriglyceridemia	≥ 1.7 mmol/l (150 mg/dl) or specific treatment for hypertriglyceridemia
HDL-cholesterol	M: < 0.9 mmol/l (35 mg/dl)	< 1.0 mmol/l (39 mg/dl) or	M: < 1.03 mmol/l (40 mg/dl)	M: <40 mg/dL (1.03 mmol/L)	M: < 1.03 mmol/l (40 mg/dl)

	F: < 1.0 mmol/l (39 mg/dl)	treatment	F: < 1.29 mmol/l (50 mg/dl)	F: <50 mg/dL (1.3 mmol/L) or specific treatment for low HDL	F: < 1.29 mmol/l (50 mg/dl) or specific treatment for low HDL
Central obesity	M: waist–hip ratio > 0.90 F: waist–hip ratio > 0.85 or BMI > 30 kg/m²	Waist circumference: M: ≥ 94 cm F: ≥ 80 cm	Waist circumference: M: > 102 cm F: > 88 cm	Waist circumference: M ≥102 cm (40 inches) F ≥88 cm (35 inches)	Waist circumference: Europids§ M ≥ 94 cm F≥ 80 cm South Asians‖ M ≥ 90 cm F ≥ 80 cm Chinese M ≥ 90 cm F ≥ 80 cm Japanese M ≥ 85 cm F ≥ 90 cm
Microalbuminuria	Excretion rate ≥ 20 µg/min or Albumin/creatinine ≥ 30 mg/g				

AHA/NHLBI, American Heart Association and National Heart, Lung, and Blood Institute; BMI, body mass index; EGIR, The European Group for the Study of Insulin Resistance; IDF; International Diabetes Federation; IGT, impaired glucose tolerance; HDL, high-density lipoprotein; NCEP ATP III, The National Cholesterol Education Program-Third Adult Treatment Panel; OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

*Insulin sensitivity measured under hyperinsulinaemic normoglycaemic conditions.

†Waist circumference should be measured horizontally, midway between the costal margin and the superior border of the iliac crest.

‡In clinical practice, IGT is also acceptable. However, all studies on the prevalence of MetS should use only the fasting plasma glucose and presence of previously diagnosed diabetes to be able to include this criterion.

§Clinicians and investigators can use European data for Sub-Saharan Africans, Eastern Mediterranean, and Middle Eastern population.

||Clinicians and investigators can use South Asians data for South and Central Americans population.

Table 2: The American Diabetic Association diagnostic criteria of diabetes and prediabetes.[12]

Diagnosis	Hemoglobin A1C	Fasting plasma glucose	2-hour oral glucose tolerance test
Normal	< 5.7%	< 100 mg/dl (5.6 mmol/L)	< 140 mg/dL (7.8 mmol/L)
Prediabetes	5.7–6.4%	100–125 mg/dL (5.6-6.9 mmol/L) *	140–199 mg/dL (7.8–11 mmol/L) †
Diabetes	≥ 6.5%	≥ 126 mg/dL (7 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)

*Impaired fasting glucose

†Impaired glucose tolerance