Shedding Light on Idiopathic Peripheral Neuropathy: Recent Advances in Understanding

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May 2026

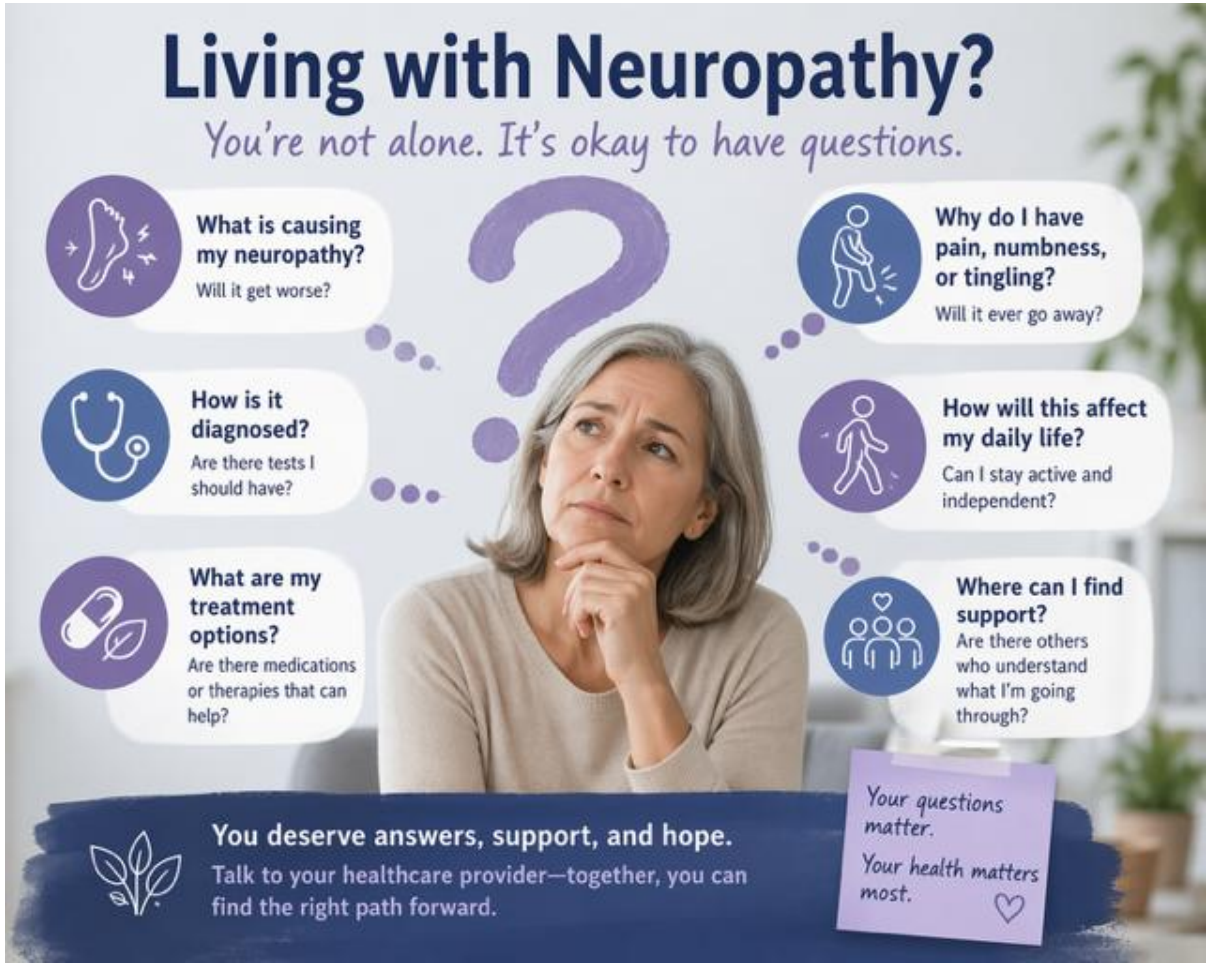
Foundation for Peripheral Neuropathy

Questions to Tackle

Why is diagnosing neuropathy (not just neuropathy symptoms) important?

What does a comprehensive work-up for peripheral neuropathy entail?

What are possible relatively *common* causes for idiopathic neuropathy - and what does this imply about new directions in treatment?



**No financial disclosures*

Image: Chat GPT

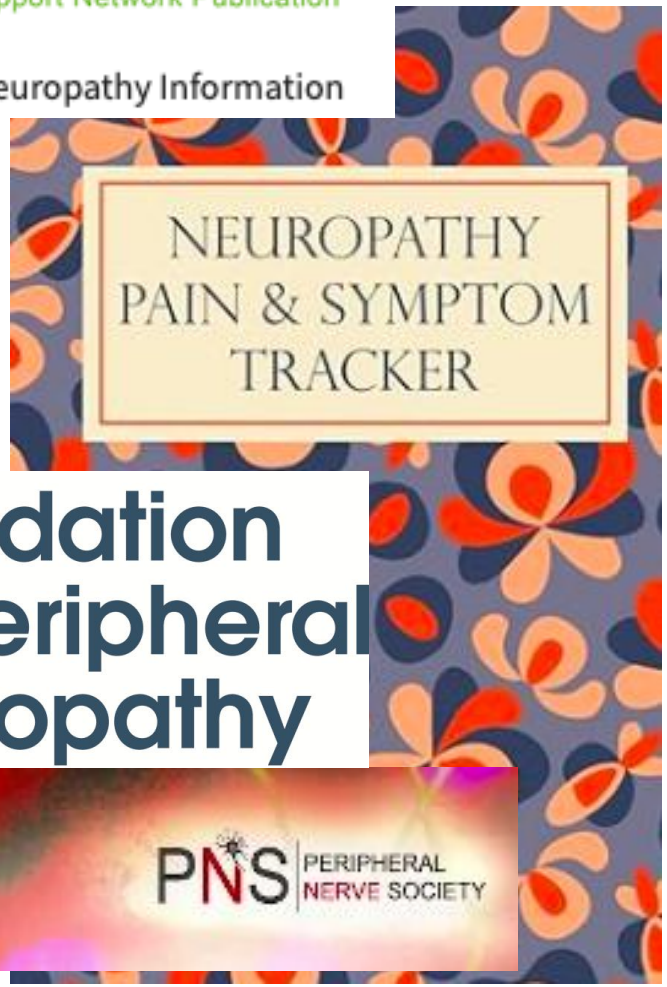
Neuropathy

One of the most prevalent neurologic conditions encountered by physicians of all specialties

Prevalence:

- 2.4% in the general population
- 8% over age 55

The Neuropathy Journal™
A Neuropathy Support Network Publication
Your Trusted Resource for Neuropathy Information



Foundation for Peripheral Neuropathy

JPNS JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM
THE OFFICIAL JOURNAL OF THE PERIPHERAL NERVE SOCIETY

PNS PERIPHERAL NERVE SOCIETY

Mayo Clin Proc. 2015;90(7):940-951

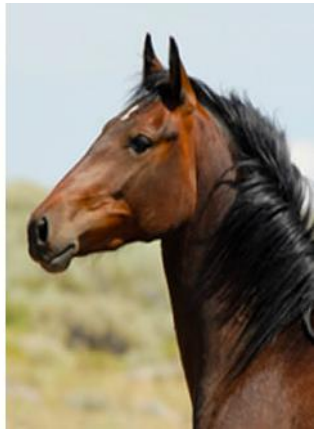
https://www.amazon.com/Neuropathy-Pain-Symptom-Tracker-Management/dp/B097SRZGSB

Causes of Neuropathy

- Neuropathy cause identified in majority of cases
- *Idiopathic* diagnosis for 25% to 46% of cases

Mayo Clin Proc. 2015;90(7):940-951
Am Fam Physician 2020;102(12):732-739

When Zebras are Really Horses… Refocusing in the Forest



- **Other common conditions mimic neuropathy**
  - *This is why diagnosis via EMG/NCS or punch skin biopsy is important*

- **Some patients may have an alternate diagnosis, or multiple diagnoses**

https://www.dallasequestriancenter.com/zebra-and-horse-a-bit-similar/

Serologic Evaluation

TABLE 2. Recommended Evaluation of Chronic, Length-Dependent Peripheral Neuropathy

- Complete blood cell count
- Renal function
- Liver function tests
- Erythrocyte sedimentation rate (extractable nuclear antigen if dry eyes/mouth and sensory neuropathy are present)
- Fasting glucose[a] (11%) or hemoglobin A_{1c}[a] (26%)
- Thyroid stimulating hormone
- Monoclonal protein[a] (serum protein immunofixation electrophoresis) (10%)
- Vitamin B_{12} (2%) (with methylmalonic acid 9%)[a]
- Infectious (if risk factors or endemic region): Lyme disease, human immunodeficiency virus
- Family history of peripheral neuropathy, pes cavus, hammertoes[a]

[a]Indicates highest-yield serologic tests with percentage of cases identified.

- Celiac disease serum studies
- Copper, vitamin E, B1, B6 deficiency
- Vitamin B6 toxicity

Mayo Clin Proc. 2015;90(7):940-951

Autoimmune Neuropathy Testing

Syndrome Panels	Antibody Panels: Individual
[ ] **Motor Neuropathy** IgM vs: GA1, NP-9, GD1b, NS6S, MAG, HH3, GD1a IgM & IgG vs: GM1, GalNAc-GD1a	**Motor** [ ] **GM1 - IgM** (vs GM1, HH3 & GD1a) [ ] **GM1 - IgG** (vs GM1 & Sulfatide) [ ] **GD1b - IgM** (vs GD1b & HH3) [ ] **GalNAc-GD1a - IgM** (vs GalNAc-GD1a, HH3 & GD1a) [ ] **GalNAc-GD1a - IgG** (vs GalNAc-GD1a & Sulfatide) [ ] **NS-6S - IgM** (vs NS-6S, HH3 & GD1a) [ ] **GD1a - IgM** (vs GD1a & HH3) [ ] **NP9 - IgM** (vs GM1 + GalC & GD1a) [ ] **GA1 - IgM** (vs GA1 & HH3) [ ] **Lysoganglioside-GM1 - IgG** (vs Lys-GM1 & Sulfatide)
[ ] **Sensory (± Motor) Neuropathy**: IgM vs: MAG, GD1b, HH3, TS-HDS, Sulfatide, GD1a; IgG vs: FGFR3, Sulfatide & GM1	**Sensory** [ ] **TS-HDS - IgM** (vs TS-HDS, HH3 & GD1a) [ ] **Plexin D1 - IgG** (WB) [ ] **FGFR3 - IgG** (vs FGFR3 & Sulfatide) [ ] **GM2 - IgM** (vs GM2 & HH3) [ ] **Sulfatide - IgM & IgG** (vs Sulfatide (IgM & IgG), HH3 (IgM) & GM1 (IgG)) [ ] **GALOP - IgM** (vs GALOP, & NP9) [ ] **MAG - IgM** (vs MAG & HH3 ± WB)
[ ] **Peripheral Neuropathy** Sensory Neuropathy + IgM vs GM1, GA1, GalNAc-GD1a	**Demyelinating** [ ] **MAG - IgM** (vs MAG & HH3 ± WB) [ ] **SGPG - IgM** (vs SGPG, GD1a & HH3 [ ] **β-Tubulin - IgM & IgG** (vs β-Tubulin (IgM & IgG), HH3 (IgM) & GM1 (IgG)) [ ] **Neurofascins 155** (IgG & IgM); **140** (IgG) (WB ± IgG_4) [ ] **Contactin-1** (IgG) (WB ± IgG_4)
[ ] **Sensory Neuropathy/Neuronopathy** IgM vs: MAG, GD1b, TS-HDS, HH3, GD1a; IgG vs: Hu, FGFR3, GM1 & CRMP-5; IgG & IgM vs: Sulfatide	**Acute** [ ] **GD1b - IgG** (vs GD1b & Sulfatide) [ ] **GQ1b - IgG** (vs GQ1b & Sulfatide) [ ] **GT1a - IgG** (vs GT1a & Sulfatide) [ ] **GM1 - IgG** (vs GM1 & Sulfatide) [ ] **Heparan-SO_4 - IgM** (vs HepSO_4, HH3 & GD1a)
[ ] **Demyelinating Neuropathy**: IgM & IgG vs: β-Tubulin IgM vs: MAG, GM1, GalNAc-GD1a, Hep-SO_4, NF-155, HH3, GD1a IgG vs Neurofascins (140 & 155), Contactin-1; IgG vs GM1	**Myopathy** [ ] **HMGCR - IgG** (vs HMGCR & Sulfatide) [ ] **NT5C1A - IgG** (WB)
[ ] **Acute Neuropathy**: IgM vs Heparan-SO4, GD1a, HH3 IgG vs: GQ1b, Sulfatide, Neurfascin 140, Contactin-1 IgM & IgG vs: GM1, β-Tubulin, GD1b, GalNAc-GD1a, NF-155	

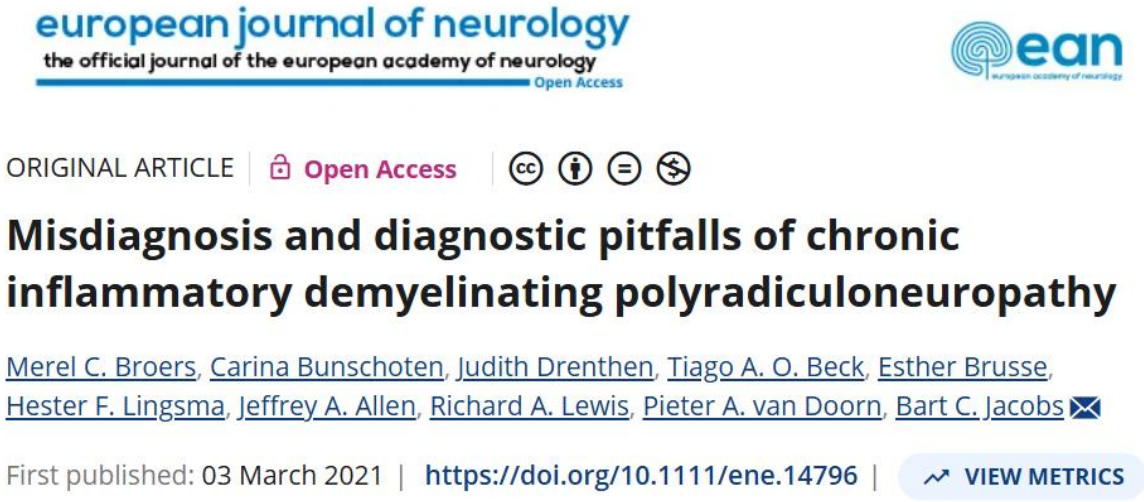
https://neuromuscular.wustl.edu/lab/reqs/SerumRequisition.pdf

Misdiagnosis: Autoimmune Demyelinating Neuropathies

Two studies showed between 20%-68% of patients receive an initial alternative diagnosis before ultimately being correctly identified as having CIDP

Reasons?

- Complex EMG criteria
- Missed/misinterpreted physical exam findings/symptoms (proximal weakness)
- Lack of specific/uniform biomarkers



Neuropathy Genetic Testing

INVITAE

Test catalog > Invitae Comprehensive Neuropathies Panel

Invitae Comprehensive Neuropathies Panel

Test code: 03200 • Up to 111 genes

Primary Panel (102 genes)

AARS, AIFM1, APOA1, ASAH1, ATL1, ATL3, ATP1A1, ATP7A, BAG3, BICD2, BSCL2, CHCHD10, COX6A1, CYP27A1, CYP7B1, DCTN1, DHTKD1, DNAJB2, DNM2, DNMT1, DRP2, DST, DYNC1H1, EGR2, ELP1, EXOSC9, FBLN5, FBXO38, FGD4, FIG4, GAN, GARS, GDAP1, GJB1, GLA, GNB4, GSN, HARS, HEXA, HINT1, HMBS, HSPB1, HSPB8, IGHMBP2, INF2, KIF1A, KIF5A, LITAF, LMNA, LRSAM1, MARS, MCM3AP, MED25, MFN2, MME, MORC2, MPZ, MTMR2, NDRG1, NEFH, NEFL, NGF, NTRK1, PDK3, PLEKHG5, PMP2, PMP22, POLG, POLG2, PRDM12, PRPS1, PRX, RAB7A, REEP1, RETREG1, SBF1, SBF2, SCN11A, SCN9A, SEPT9, SH3TC2, SIGMAR1, SLC12A6, SLC25A46, SLC52A2, SLC52A3, SLC5A7, SMN1, SMN2, SPG11, SPTLC1, SPTLC2, SURF1, TFG, TRIM2, TRPV4, TTR, UBA1, VAPB, VRK1, WNK1, YARS

Add-on Preliminary-evidence Genes for Neuropathies (9 genes)

ARHGEF10, CCT5, HSPB3, LAS1L, MICAL1, SCN10A, SGPL1, SLC25A21, SLC52A1

- Cost can be prohibitive
- Access can be a moving target
- Sponsored programs are helpful
  - partnerships with biopharma companies
  - patients meet eligibility criteria

BURLINGTON, N.C. , Aug. 5, 2024 /PRNewswire/ -- Labcorp (NYSE: LH), a global leader of innovative and comprehensive laboratory services, announced today the completion of its acquisition of select assets of Invitae (OTC:NVTAQ), a leading medical genetics company. Aug 5, 2024

Labcorp
https://ir.labcorp.com › news-release-details › labcorp-fi...

Labcorp Finalizes Acquisition of Select Assets of Invitae

Post-Viral Neuropathy

Virus may trigger an autoimmune response that leads to neuropathy – rather than the virus itself directly causing neuropathy.

Can be challenging to prove as a cause.

Small Fiber Neuropathy

Viral infections can cause small fiber neuropathy presenting with burning pain, dysesthesias, and autonomic dysfunction. Documented viral causes include: Lancet

- Hepatitis C virus
- HIV
- Influenza
- Epstein-Barr virus
- Herpes simplex virus
- Varicella-zoster virus
- Hepatitis B virus
- Rubella

Reference See All (10)

3. The Diagnostic Challenge of Small Fibre Neuropathy: Clinical Presentations, Evaluations, and Causes.
The Lancet. Neurology. 2017. Terkelsen AJ, Karlsson P, Lauria G, et al.

Received: 1 June 2021 | Revised: 2 November 2021 | Accepted: 7 November 2021
DOI: 10.1002/mus.27458

CLINICAL RESEARCH SHORT REPORTS

See Editorial on pages 369-370 in this issue

MUSCLE&NERVE WILEY

Small fiber neuropathy associated with SARS-CoV-2 infection

Rory M. C. Abrams MD[1] | David M. Simpson MD[1] | Allison Navis MD[1] | Nathalie Jette MD MSc, FRCPC[1] | Lan Zhou MD, PhD[2] | Susan C. Shin MD[1]

Idiopathic Neuropathy: What are we Missing?

…. In 25-46% of cases

Idiopathic Neuropathy: What else are we Missing?

Are we missing things we can't test for? (medication/environmental toxicities/prior exposure/prior infection)

Are we missing things we can't test for *yet*? (hereditary, complex immune)

Is there something common causing neuropathy that may be challenging to prove as a cause on an individual level?

Metabolic Syndrome and Neuropathy

Published in final edited form as:
J Neurol Sci. 2008 October 15; 273(1-2): 25–28. doi:10.1016/j.jns.2008.06.005.

Idiopathic Neuropathy Patients are at High Risk for Metabolic Syndrome

A. Gordon Smith, MD[1,2], **Kristi Rose, MD**[3], and **J. Robinson Singleton, MD**[1]

1*University of Utah Department of Neurology*

2*University of Utah Department of Pathology*

3*University of Utah School of Medicine*

Results—Contrary to our hypothesis, neuropathy patients with normoglycemia and IGT shared a similarly elevated prevalence of metabolic syndrome features compared to published normal populations. Compared to diabetic subjects without neuropathy, the normoglycemic neuropathy patients had significantly higher total and LDL cholesterol, and a higher prevalence of abnormal HDL and triglycerides. The prevalence of obesity and hypertension were similar among patient groups. Normoglycemic neuropathy subjects had significantly more features of metabolic syndrome (other than hyperglycemia) than diabetics.

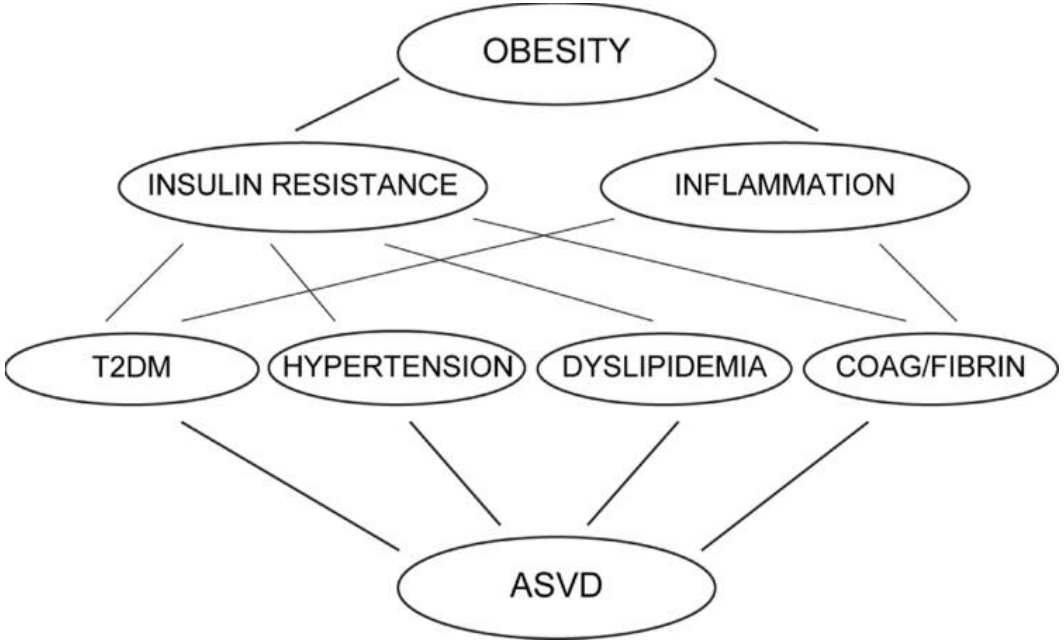
Metabolic Syndrome and Neuropathy

- **Metabolic Syndrome**, WHO (1999)
  - Impaired glucose tolerance, diabetes and/or insulin resistance + 2 or more of the following:
    - High BP
    - Elevated triglycerides (or on treatment)
    - Low HDL
    - Central obesity
    - Microalbuminuria
  - *Abdominal fat cells raise levels of free fatty acids, which contribute to insulin resistance, inflammation*

Endocrinol Metab Clin North Am. 2008 September ; 37(3): 635–ix. doi:10.1016/j.ecl.2008.06.007.

Obesity and Free Fatty Acids (FFA)

Guenther Boden, M.D.
Laura H. Carnell Professor of Medicine and Chief, Division of Endocrinology/Diabetes/Metabolism, Temple University School of Medicine, Philadelphia, PA



Metabolic Syndrome and Neuropathy

Studies have shown a higher risk of neuropathy in the setting of obesity, even in the absence of diabetes or pre-diabetes.

Original Investigation

December 2016

Association Between Metabolic Syndrome Components and Polyneuropathy in an Obese Population

Brian C. Callaghan, MD, MS[1]; Rong Xia, MS[2]; Evan Reynolds, MS[2]; et al

» Author Affiliations | Article Information

JAMA Neurol. 2016;73(12):1468-1476. doi:10.1001/jamaneurol.2016.3745

Polyneuropathy Prevalence Stratified by Glycemic Status

The prevalence of polyneuropathy was 3.8% (2 of 53) in the lean control group, 11.1% (5 of 45) in the obese participants with normoglycemia, 29% (9 of 31) in the obese participants with prediabetes, and 34.6% (9 of 26) in the obese participants with diabetes ($P < .01$ for trend).

In obese and lean control populations who received comprehensive metabolic and neuropathy phenotyping, we found a higher prevalence of neuropathy in obese patients with normoglycemia compared with lean controls. The prevalence of neuropathy continued to increase in obese patients with prediabetes and diabetes. Diabetes, waist circumference, and likely prediabetes were the main metabolic factors associated with neuropathy. In contrast, systolic blood pressure, triglyceride levels, and HDL cholesterol levels were not associated with neuropathy. Future intervention studies are needed to confirm a causal association between these metabolic factors and neuropathy.

Received: 22 June 2020 | Revised: 2 September 2020 | Accepted: 4 October 2020

DOI: 10.1002/mus.27086

INVITED REVIEW

Answer questions and earn CME https://education.aanem.org/URL/JR80.

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Metabolic syndrome and peripheral neuropathy

Mohamed Kazamel MD[1] | Amro Maher Stino MD[2] | Albert Gordon Smith MD[3]

CI, 1.15-1.75) 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 to −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 showed general and abdominal obesity to be associated with the development of CSPN.[44]

4.2 | CSPN is associated with dyslipidemia

Elevated triglycerides and reduced HDL are components of MetS. Robust literature links hypertriglyceridemia to the development of CSPN. Hughes et al reported significantly higher triglyceride levels in CSPN when compared with healthy control patients, with triglyceride levels being higher in patients with painful CSPN.[45] In a separate longitudinal study, hypertriglyceridemia was associated with reduced sural nerve myelin fiber density in DPN patients.[46] Hyper-

Metabolic Syndrome and Neuropathy

2019 and 2023 studies show - Bariatric surgery demonstrates significant benefits for neuropathy in patients with obesity, including those with idiopathic neuropathy, though the evidence comes primarily from observational studies rather than randomized controlled trials. (cannot do placebo-controlled studies)

Outcomes included corneal nerve fiber recovery, symptom and sensory improvement

Improvements occurred in patients with diabetes and those with morbid obesity without diabetes

Metabolic Syndrome and Neuropathy

GLP-1 (glucagon-like peptide-1) receptor agonists work by mimicking the natural GLP-1 hormone which is released in the gut in response to eating.

Medications currently on the market include:

Semaglutide (Ozempic)

Liraglutide (Victoza)

Tirzepatide (Mounjaro)

Metabolic Syndrome and Neuropathy

New directional shift toward finding treatments for idiopathic neuropathy

GLP-1 receptor agonists significantly improved nerve conduction velocity (NCV) compared to controls independent of glucose lowering suggestive of direct neuroprotective effect (anti-oxidant, anti-inflammatory, neurotrophic effects)

SYSTEMATIC REVIEW | Free Access

Effect of the glucagon-like peptide-1 receptor agonists on diabetic peripheral neuropathy: A meta-analysis

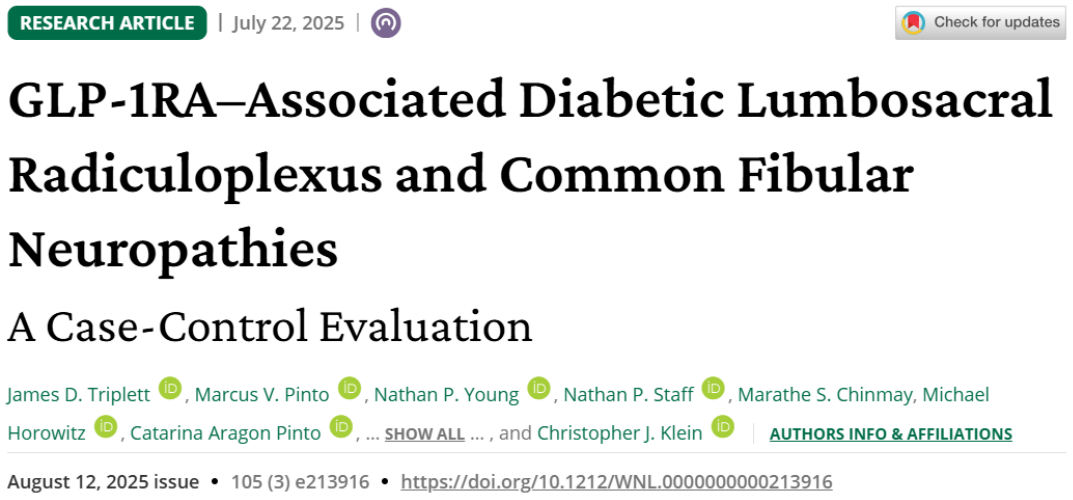
Shujin Fan, Yue Qiu, Jing Liu, Tianxin Zhu, Chuan Wang, Dan Liu, Li Yan, Meng Ren

First published: 25 October 2024 | https://doi.org/10.1111/jnc.16242 |

Metabolic Syndrome and Neuropathy

Caveats with GLP-1 receptor agonist medications, in diabetic patients can trigger inflammatory nerve complications if HgbA1c drops too quickly, nerve compression risk if weight loss is too significant

Overall clinical evidence is limited and mixed currently – reinforces importance of diet and lifestyle interventions



RESEARCH ARTICLE | July 22, 2025 | Check for updates

GLP-1RA–Associated Diabetic Lumbosacral Radiculoplexus and Common Fibular Neuropathies

A Case-Control Evaluation

James D. Triplett, Marcus V. Pinto, Nathan P. Young, Nathan P. Staff, Marathe S. Chinmay, Michael Horowitz, Catarina Aragon Pinto, ... SHOW ALL ... , and Christopher J. Klein | AUTHORS INFO & AFFILIATIONS

August 12, 2025 issue • 105 (3) e213916 • https://doi.org/10.1212/WNL.0000000000213916

Final Comments:

Talking about Idiopathic Neuropathy – Removing Blame

Katie Willard Virant MSW, JD, LCSW

Chronically Me

CHRONIC ILLNESS

Self-Blame and Chronic Illness

Understanding and letting go of a painful narrative.

Posted November 15, 2021 | Reviewed by Jessica Schrader

- Society values concept of having explanations for events in life… asking “why”
- Research has identified that self-blame for illness is associated with emotional distress
- Emphasis of importance for providers to be mindful of how they communicate with patients about neuropathy, the cause of their neuropathy

https://centerforspineandortho.com/news/symptoms-of-diabetic-peripheral-neuropathy/

https://www.psychologytoday.com/us/blog/chronically-me/202111/self-blame-and-chronic-illness

A Few Closing Thoughts

- Desire for a “cure” or external treatment

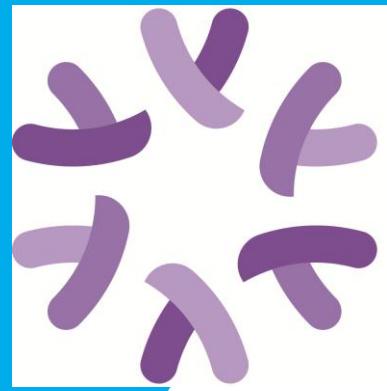
- *Caution* regarding marketing of potentially expensive, ineffective, unproven interventions

HOPE

- Path to findings treatments may be stepwise, incremental – not “one size fits all”

Image: Chat GPT

Thank You!



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