



VIII CONGRESSO
NAZIONALE
PIEDE DIABETICO
INTERASSOCIATIVO SID-AMD

*Focus sul piede nella
gestione del diabete*

ROMA, 18-20 GIUGNO 2026
HOTEL NH VILLA CARPEGNA

Roma 19 Giugno 2026

Sessione III
Strategie multidisciplinari nel piede diabetico

Polineuropatia diabetica: le sfide della terapia patogenetica

Vincenza Spallone



Endocrinologia - Dipartimento di Medicina dei Sistemi
Università di Roma Tor Vergata

Disclosure

Vincenza Spallone dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Novo Nordisk
- Procter & Gamble
- Theras Lifetech S.r.l., Italy
- Uriach
- Wörwag Pharma GmbH & Co, Germany

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).



Polineuropatia diabetica: le sfide della terapia patogenetica

Agenda

- Criticità traslazionali dal laboratorio alla clinica
 - Definizione, diagnosi, outcome, storia naturale, complessità patogenetica
- Proposte per un cambiamento
- Terapia patogenetica
 - Evidenze attuali
 - Prospettive



Polineuropatia diabetica: le sfide della terapia patogenetica

Agenda

- Criticità traslazionali dal laboratorio alla clinica
 - Definizione, diagnosi, outcome, storia naturale, complessità patogenetica
- Proposte per un cambiamento
- Terapia patogenetica
 - Evidenze attuali
 - Prospettive



Epidemiologia della Polineuropatia Diabetica

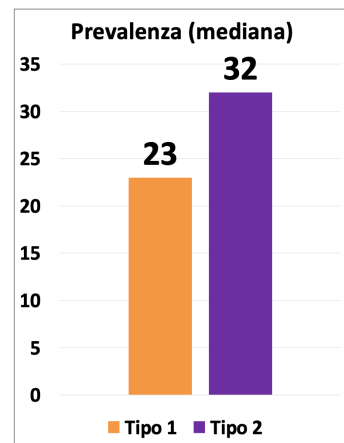
Le malattie del sistema nervoso sono la prima causa di disabilità, la neuropatia diabetica è la 5a condizione neurologica causa di di disabilità cronica nel mondo.

GBD 2021 Nervous System Disorders Collaborators. *Lancet Neurol.* 2024 Apr;23(4):344-381.

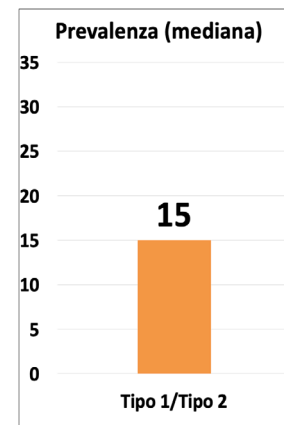
Il diabete è la causa più comune di neuropatia periferica (32%–53% dei casi).

Price R et al *Neurology* 2022;98:31-43

Polineuropatia diabetica



Polineuropatia diabetica dolorosa



Range: 9 - 21%

Prevalenza

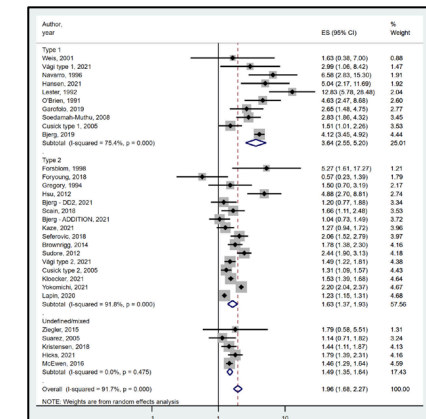
PND 30%

PNDD 15% (9-21%)

PNDD e mortalità per tutte le cause

Association between DSPN and all-cause mortality

PND associata a ↑ rischio:
HR (corretto) 1.60



PNDD associata a ↑ rischio Vs PND:
HR (corretto) 1.42

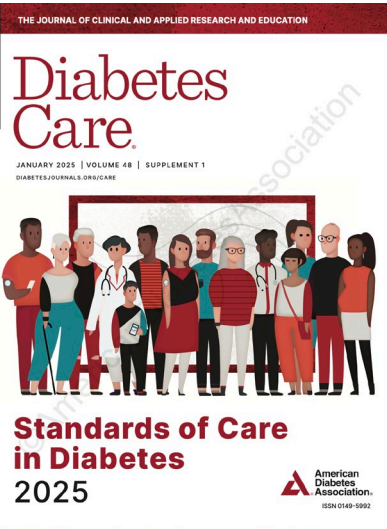
Ziegler D et al *Handb Clin Neurol.* 2014;126:3-22

Spallone V, Vermigli C. Ediz. Bononia University Press 2016, p.233-253

Spallone V. Diabetic neuropathy: current issues in diagnosis and prevention. In Mauricio D and Alonso N. *Chronic Complications of Diabetes Mellitus*, Academic Press 2024, p. 117-163.

Vági OE et al *Front Endocrinol (Lausanne).* 2023;14:1079009.

Lapin BR et al *J Clin Endocrinol Metab* 2020; 105: 3005–3014



12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes - 2026

American Diabetes Association Professional Practice Committee for Diabetes

Diabetes Care 2026;49(Suppl. 1):S261–S276

Specific treatment to reverse the underlying nerve damage in diabetes is currently not available.

Recommendations on Treatment of neuropathy

12.20 Optimize glucose management to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of neuropathy in people with type 2 diabetes. **C**

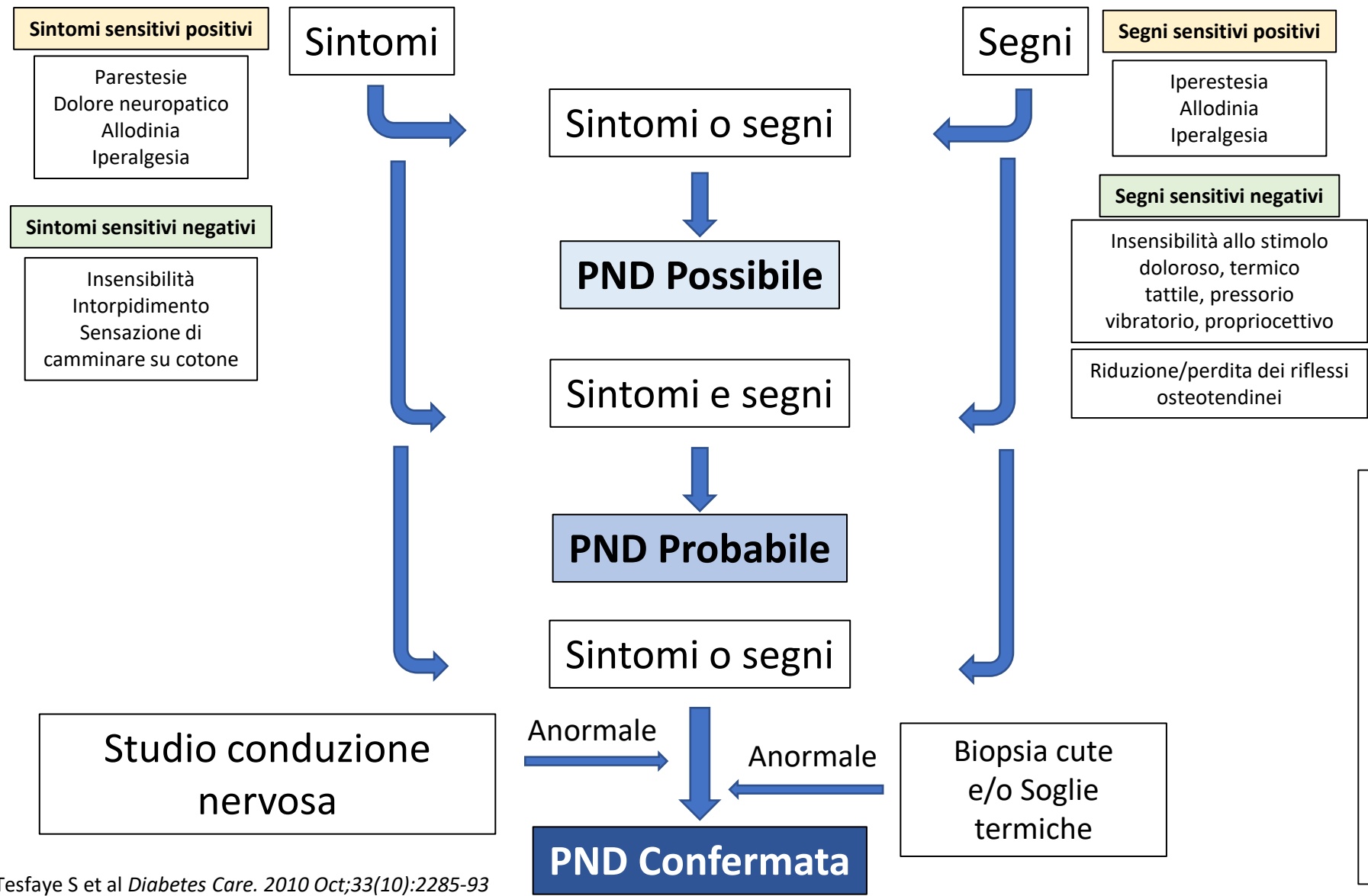
Optimize weight, blood pressure, and lipid management to reduce the risk or slow the progression of diabetic neuropathy. **B**

Possibili responsabilità nella “stagnazione” o “ blocco” traslazionale per la PND

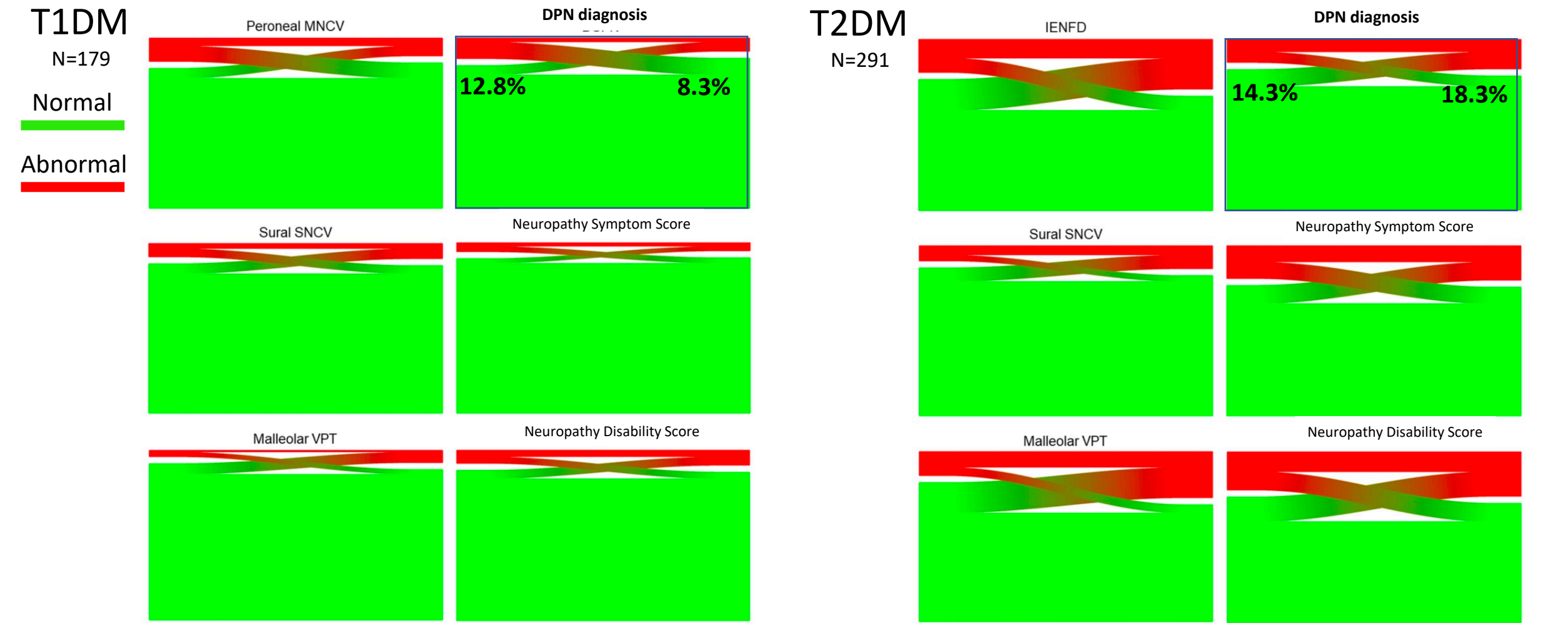
- Disuniformità nei metodi e criteri diagnostici
- Disomogeneità negli *outcome*: sintomi, segni, misure morfometriche e funzionali, dolore neuropatico
- Storia naturale (regressione possibile?)
- Lenta progressione delle alterazioni misurabili
- Patogenesi con multipli meccanismi e multifattoriale



Criteri diagnostici per Polineuropatia Diabetica



Course of small and large fibre function in recently diagnosed type 1 and 2 diabetes over 5 years



Early parallel damage to both small and large nerve fibres in well-controlled recent-onset type 2 and (to a lesser extent) type 1 diabetes. After 5 years nerve morphology and function measures progress to the abnormal range in type 2 diabetes, **but alterations are also reversible.**

Heterogeneous course of diabetic polyneuropathy in type 1 diabetes over 5 years: is regression possible?

Pertile P, D'Ippolito I, Mascambroni S, D'Amato C, Andreadi A, Lauro D, Spallone V
Endocrine. 2026 Apr 27;91(1):147.

In a retrospective analysis on 43 participants with T1D (age 38.9, duration 23 years), **natural course of DPN over 5 years was heterogeneous** with 37% of progressors, 16% regressors and 46.5% unchanged in DPN stage.

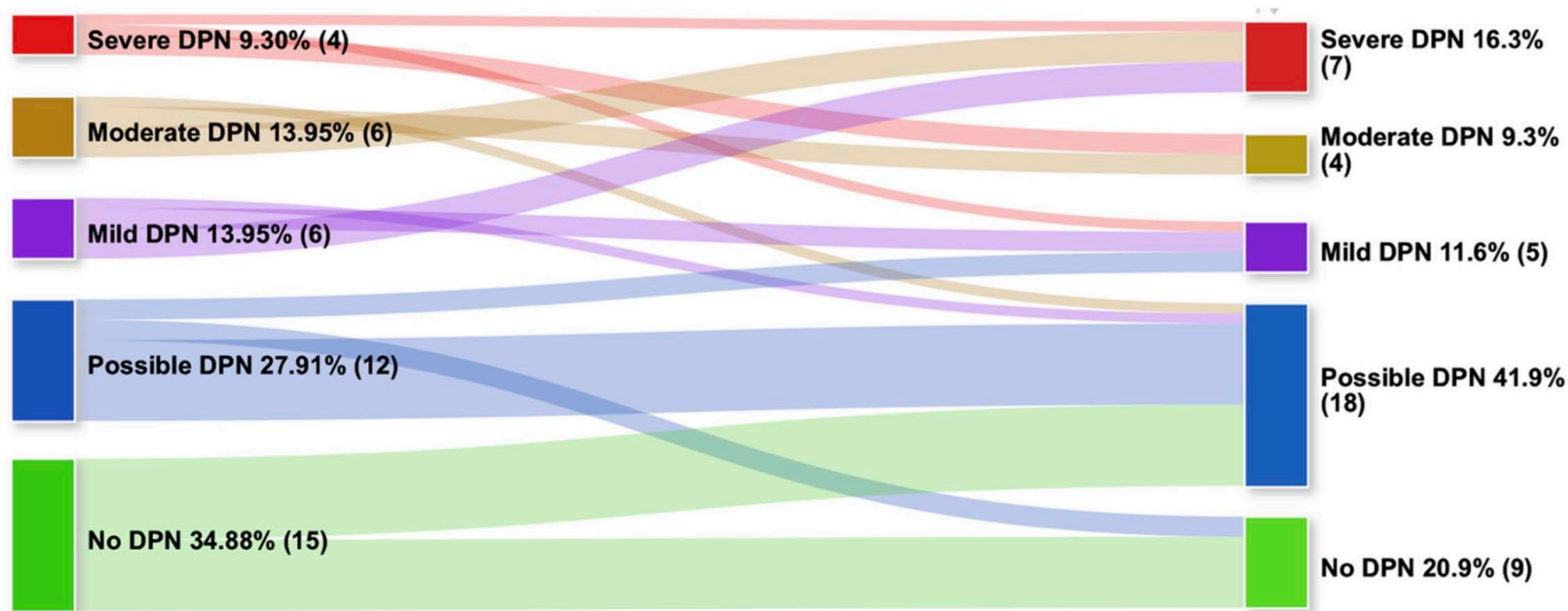
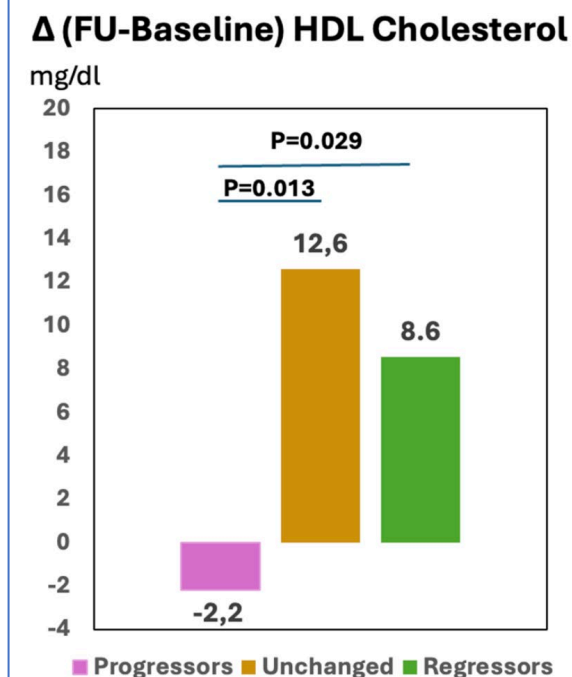


Fig. 1 Sankey diagram with the changes in DPN status from baseline to follow-up



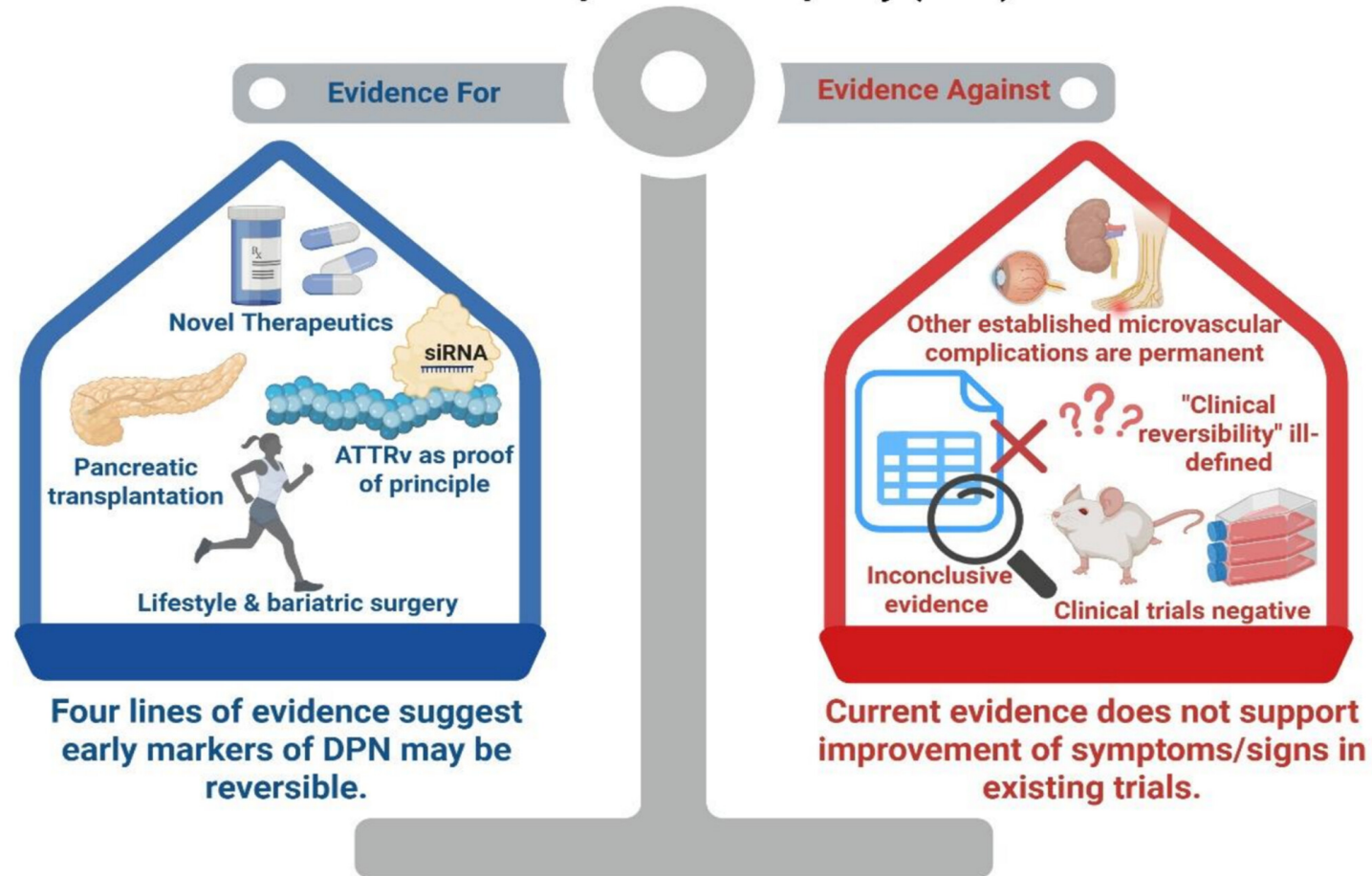
Δ in HDL Cholesterol from follow-up to baseline according to DPN course.

Over 5 years the overall prevalence of DPN increased; however, **regression to less severe DPN or complete absence of DPN occurred**, indicating that regression of DPN is still possible even in longstanding T1D.

Changes in lipids and HbA1c may predict DPN course, suggesting that **continued intervention remains beneficial well after a DPN diagnosis**.

Clinical Diabetic Peripheral Neuropathy: Can It Be Reversed? Arguments for and against from a NEUROdiab debate

Can Clinical Diabetic Peripheral Neuropathy (DPN) Be Reversed?



Key considerations: Late diagnosis and limited treatments lead to established DPN; rigorous trials with standardized endpoints are needed to determine if clinical DPN is reversible.

Predictors of incident diabetic peripheral neuropathy: a systematic review of longitudinal studies in patients with diabetes mellitus

Chew SM, Dua Avinashi S, Venkataraman K.

Rev Endocr Metab Disord. 2025 Aug;26(4):659-677



Redefining distal symmetrical polyneuropathy features in type 1 diabetes: a systematic review

Galosi E, Hu X, Michael N, Nyengaard JR, Truini A, Karlsson P.

Acta Diabetol. 2022 Jan;59(1):1-19.

Longitudinal studies on DPN (until March 2024) in T1D and T2D investigating clinical predictors of DPN.

27 studies analysing 21 predictors were included (sample size of 985 and follow-up of 72 months).

Age, HbA1c, BMI, diabetes duration, and systolic blood pressure were strong positive predictors of incident DPN.

Modest associations for *fasting BG, smoking, height, weight, waist circumference, sex, anti-hyperlipidemia drugs, and retinopathy.*

Incident Vs non incident DPN

Age	+3.04 years
HbA1c	+0.36 %
BMI	+0.89 kg/m ²
Duration	+2.67 years
SBP	+0.03 mmHg

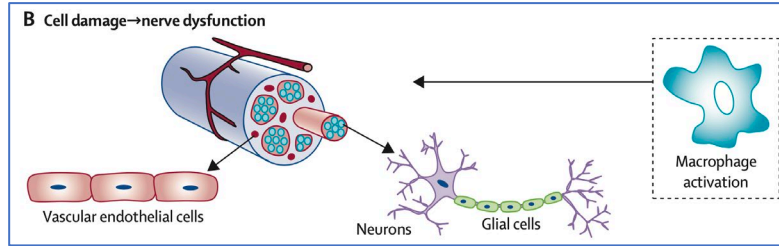
A subgroup analysis demonstrated that these findings were relevant to both Type 1 and Type 2 diabetes.

Review of 182 clinical and preclinical studies in T1D.

Risk markers/factors for DPN in T1D:

- **diabetes duration** (11 studies)
- **HbA1c** (8 studies)
- **age** (6 studies)
- **hypertension** (5 studies)
- **smoking** (4 studies)
- *retinopathy (3 studies)*
- *nephropathy (3 studies)*
- *dyslipidemia (3 studies)*

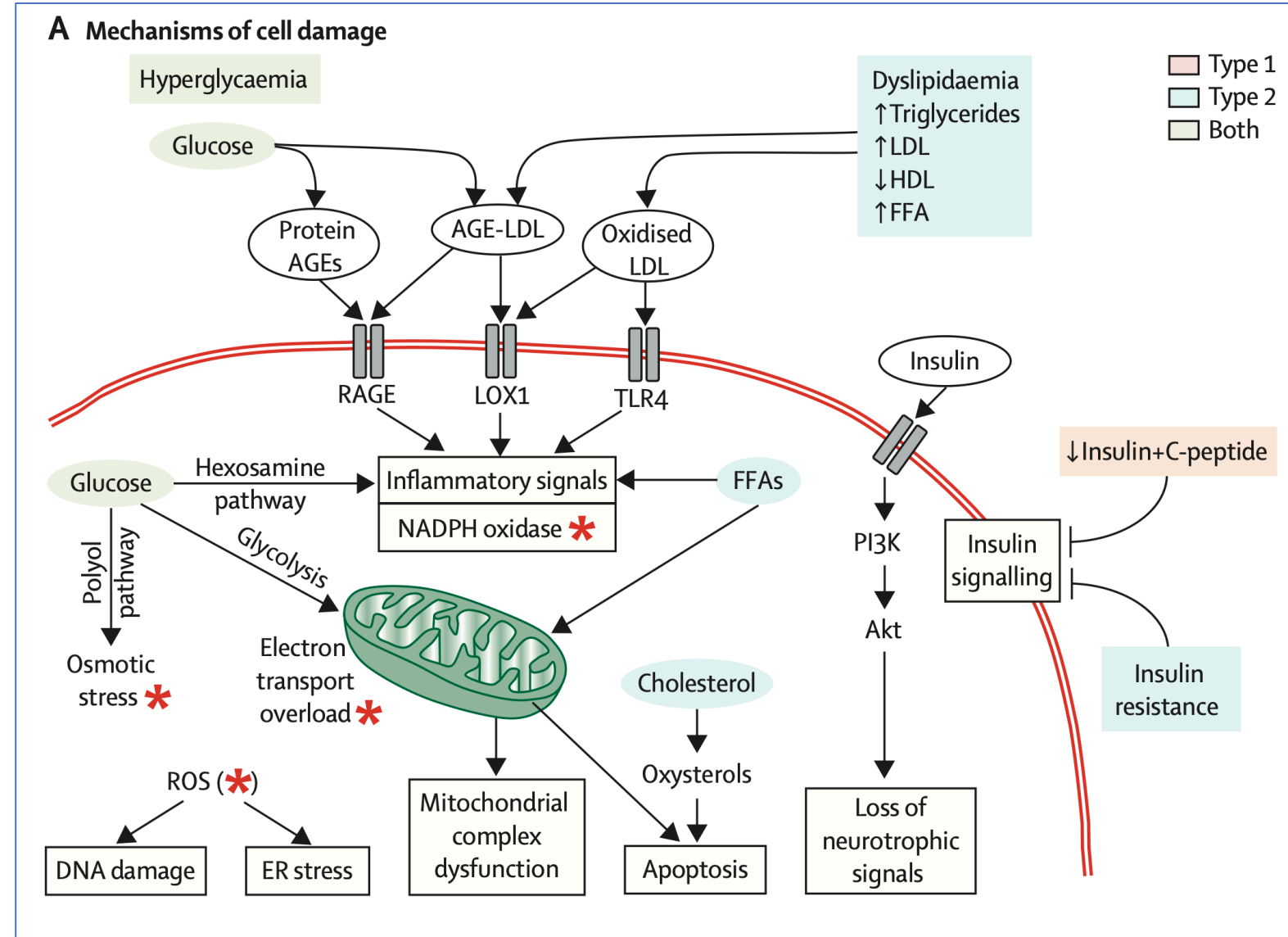
Meccanismi patogenetici della polineuropatia diabetica



**Iperglicemia
Dislipidemia
Deficit insulina**

**↑ AGE
↑ stress ossidativo (ROS)
Infiammazione**

**Danno DNA
Stress Reticolo Endoplasmico
Disfunzione mitocondriale
Apoptosi
Perdita di segnali neurotrofici**

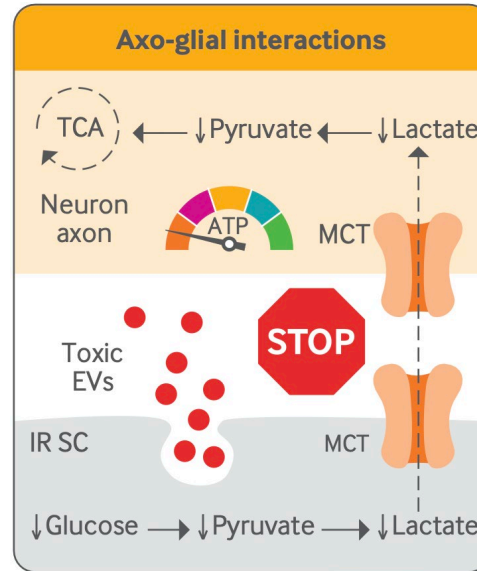


Meccanismi patogenetici emergenti: interazioni asso-gliali

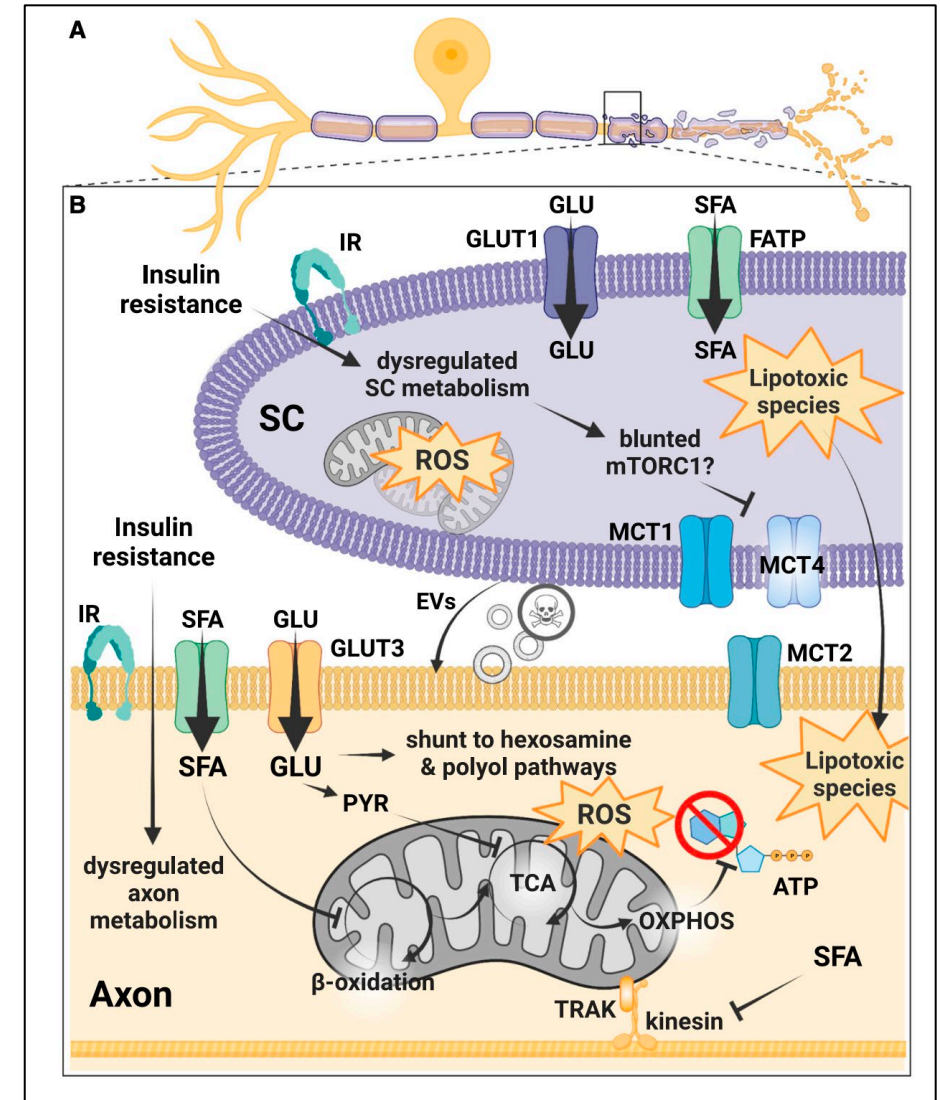
Cellule di Schwann insulino-resistenti

Nella PND, le interazioni assogliai di supporto strutturale e metabolico agli assoni sono compromesse, con **ridotto trasporto di lattato e carenza di ATP e rilascio di vescicole extracellulari tossiche (EV)** da cellule di Schwann insulino-resistenti (IR SC).

Fridman V et al *BMJ*. 2026 Mar 26;392:e081217.



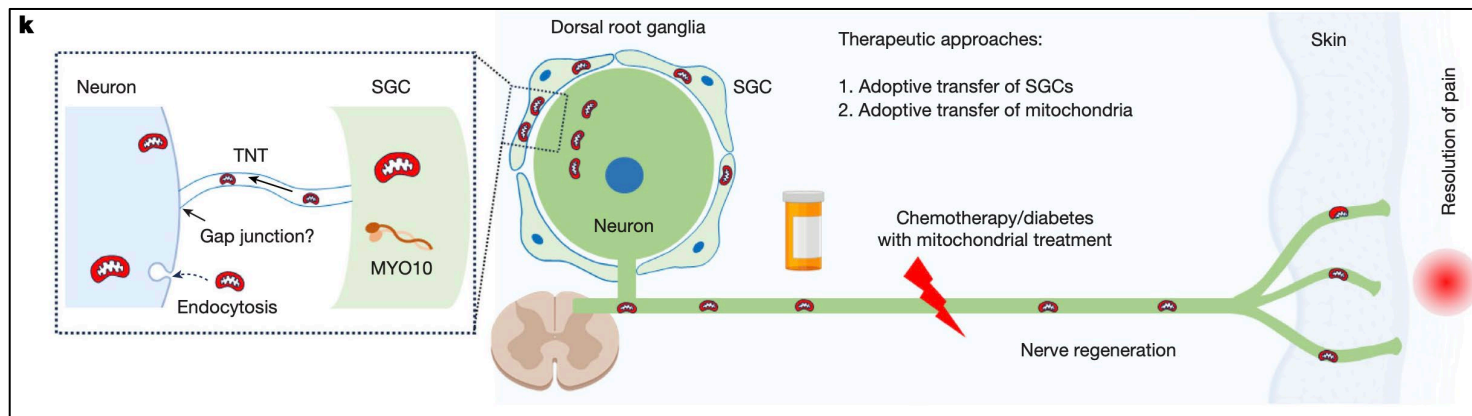
Difetto bioenergetico



DPN pathophysiology and bioenergetics failure

Eid SA et al *Neuron*. 2023 Sep 6;111(17):2623-2641.

Le **cellule gliali satellite (SGC)** nei DRG **trasferiscono mitocondri** ai neuroni formando nanotubi tunnel con miosina 10 (MYO10) proteggendo da degenerazione assonale e dolore neuropatico

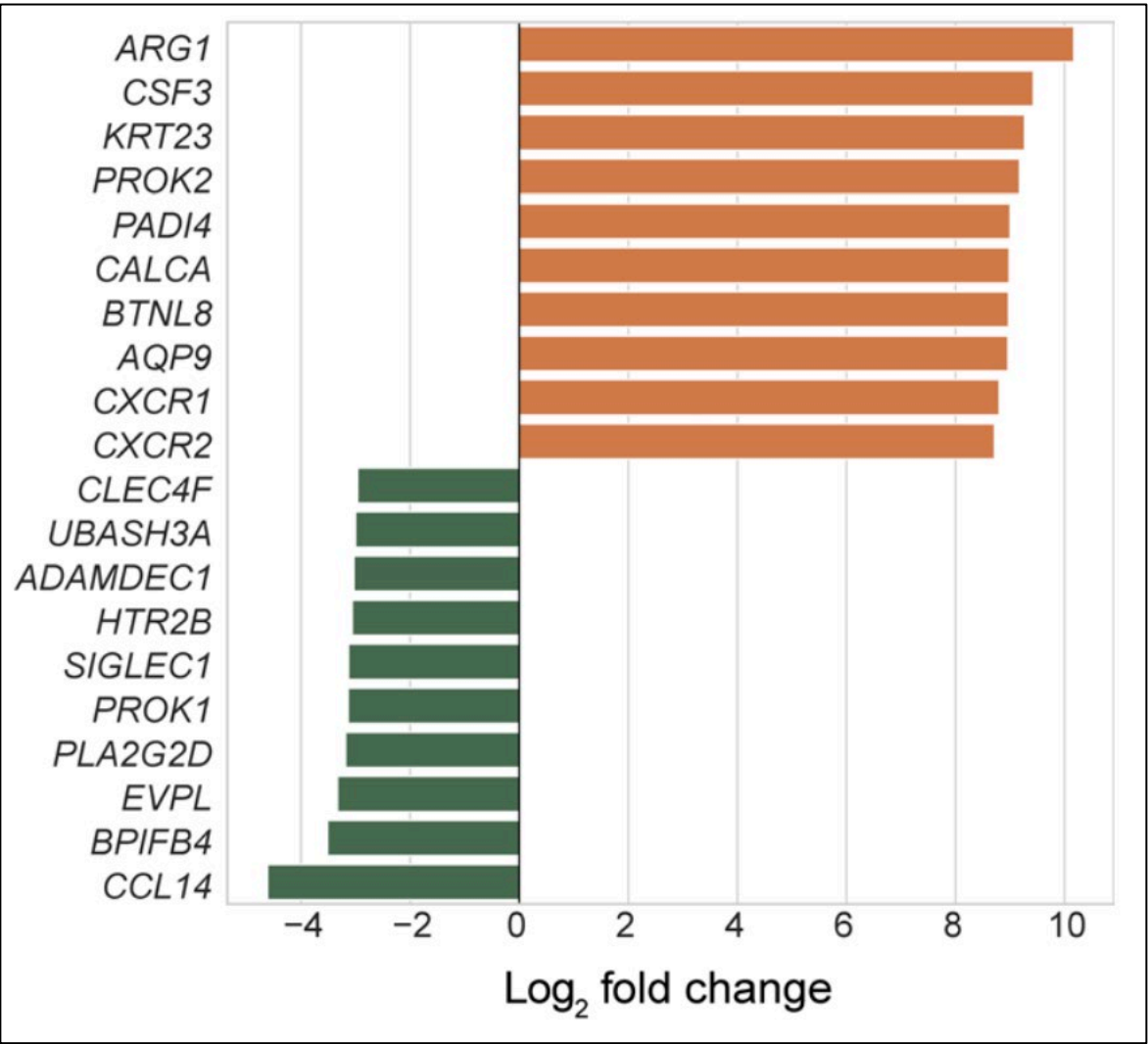


Potential therapeutic strategies for neuropathic pain: (1) adoptive transfer of SGCs; and (2) transfer of isolated SGC mitochondria into the DRG

Xu J et al *Nature*. 2026 Feb;650(8103):951-960

Meccanismi patogenetici emergenti: omica

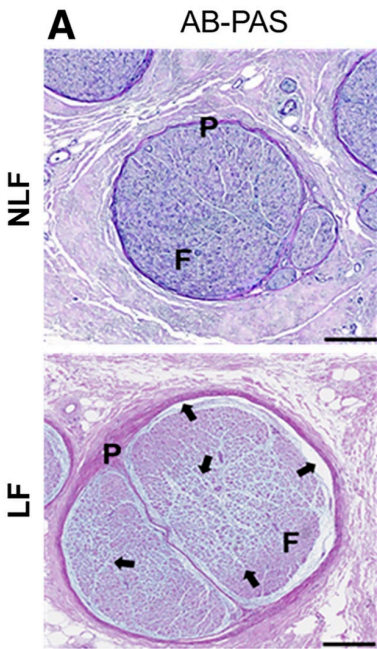
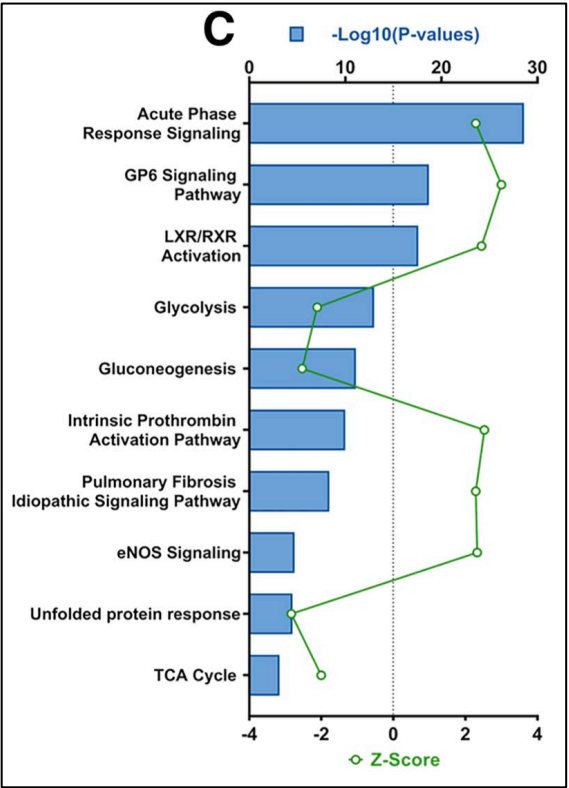
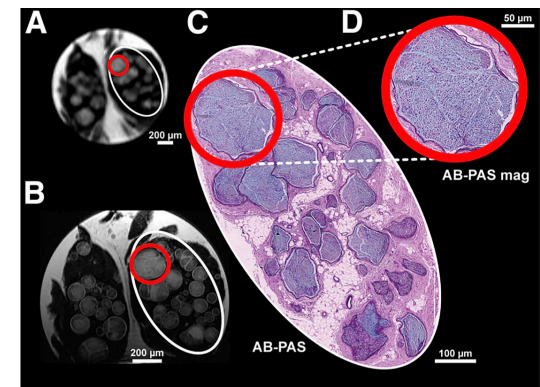
Trascrittomica del n. surale : ↑ infiammazione e ↓ trasporto mRNA



Top 10 upregulated (orange) and downregulated (green) genes in DPN

Tavares-Ferreira D et al *J Clin Invest.* 2025;135(20):e184075

RMN e proteomica del n. surale



- Nei fascicoli lesionati**
- Risposta infiammatoria
 - ↓ barriera emato-nervosa
 - Attivazione complemento
 - ↓ neuroprotezione
 - Infiltrazione di proteine epatiche

Schwarz D et al *Diabetes.* 2025 Jan 1;74(1):65-74

Polineuropatia diabetica: le sfide della terapia patogenetica

Agenda

- Criticità traslazionali dal laboratorio alla clinica
 - Definizione, diagnosi, outcome, storia naturale, complessità patogenetica
- **Proposte per un cambiamento**
- Terapia patogenetica
 - Evidenze attuali
 - Prospettive



Possibili risposte e opportunità per una terapia patogenetica della PND

- **Collaborazione** tra ricercatori preclinici e clinici
- Collegare prove epidemiologiche ai risultati di laboratorio per generare **nuove ipotesi**
- Considerare sottogruppi e fenotipi diversi e migliorare **fenotipizzazione**
- Mappare la fisiopatologia per sviluppare trattamenti mirati
- Possibili **disegni pragmatici** nella *real life* ma RCT per nuovi farmaci
- Misure di **outcome**: definirne caratteristiche diagnostiche, clinicamente significative, espressione delle fasi di malattia, **sensibili** (IENFD, CCM?)
- Migliorare validazione e accuratezza di misure bedside
- Inserire misure PRO
- **Biomarker per nuovi meccanismi e nuovi fattori di rischio**

Polineuropatia diabetica: le sfide della terapia patogenetica

Agenda

- Criticità traslazionali dal laboratorio alla clinica
 - Definizione, diagnosi, outcome, storia naturale, complessità patogenetica
- Proposte per un cambiamento
- **Terapia patogenetica**
 - **Evidenze attuali**
 - Prospettive



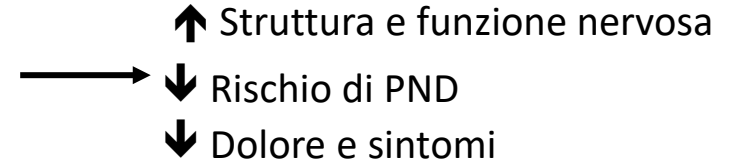
Trattamento patogenetico per la polineuropatia diabetica

Trattamenti patogenetici

- **Controllo glicemico efficace nel T1D** (DCCT and EDIC), di limitata efficacia nel T2D

Intervento sullo stile di vita

- **Esercizio fisico:** 8 studi di piccole dimensioni o non controllati (n. 2), da solo o parte di intervento sullo stile di vita, in pazienti con e senza PND, con diverse modalità di intervento, ed alti dropout



Maggior numero di studi e maggiore numerosità per il T2D (Look AHEAD research group 2017)

Calo ponderale: effetto modesto

- Supplementi con **ω -3 PUFA** efficaci in 2 small open studies in T1D and T2D e efficaci solo su innervazione corneale in 1 RCT nel **T1D**.
Analisi Cochrane inconclusiva.

Britten-Jones AC et al *Diabetes* 2021;70:1794–1806; Britten-Jones AC et al *Cochrane Database Syst Rev.* 2025 Sep 24;9(9):CD014623

- **Acetil-carnitina** moderatamente efficace sul dolore neuropatico in 4 studi in T1D+T2D. Analisi Cochrane inconclusiva.

Rolim LC et al *Cochrane Database Syst Rev.* 2019 Jun 15;6(6):CD011265)

- Vitamina D efficace su sintomi e dolore in 5 studi non controllati

- **Manidipine/delapril** e delapril efficace su incidenza e progressione DPN in 1 RCT nel **T2D**



Nel RCT **DEMAND** (*Delapril and Manidipine for Nephroprotection in Diabetes*), in 200 T2D a 3 anni la combinazione riduceva il rischio di PND Vs delapril o placebo (OR 0.45 e 0.52, P=0017 e P=0.048).

Ruggenenti P et al *Hypertension.* 2011;58:776-783

Impact of Exercise Training in Patients with Diabetic Peripheral Neuropathy: An Umbrella Review

Gracia-Sánchez A, López-Pineda A, Nouni-García R, Zúñica-García S, Chicharro-Luna E, Gil-Guillén VF.

Sports Med Open. 2025 Jun 15;11(1):75

We included **14 systematic reviews and meta-analyses** assessing exercise interventions in adults with type 1 or type 2 diabetes and DPN.

Results

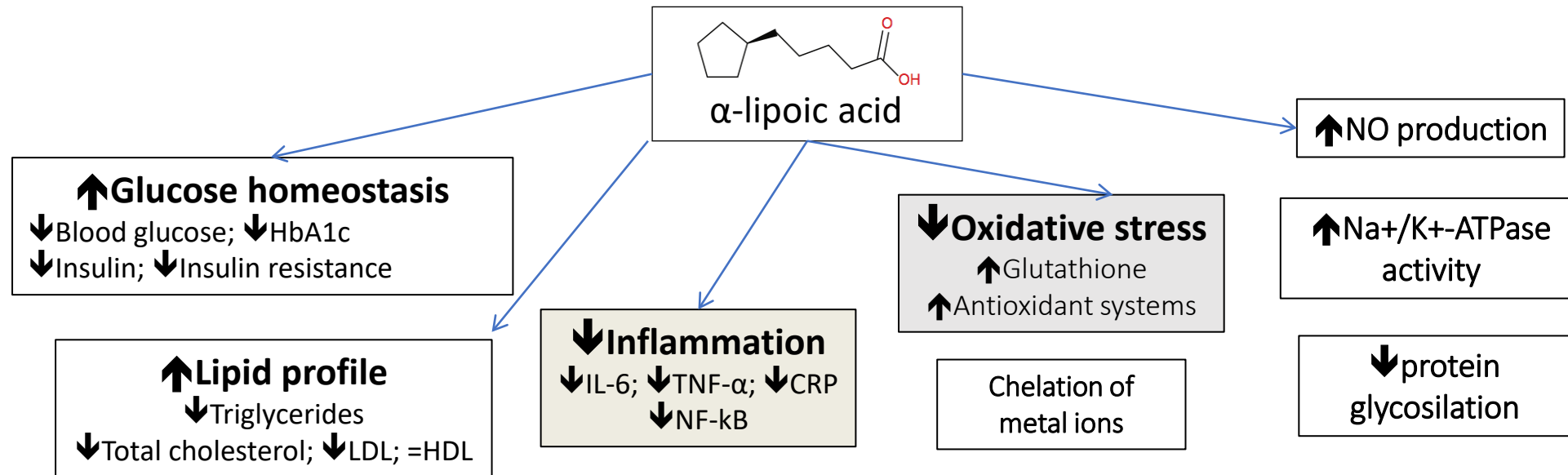
Exercise, particularly when combining **aerobic, strength, and balance training**, can

- improve glycemic control,
- **reduce neuropathic symptoms**,
- enhance joint mobility, and
- support physical function.

However, the effects on other outcomes, such as fall risk and ulcer prevention, remain inconclusive.

The substantial **heterogeneity** in study designs and exercise protocols underscores the need for standardized, evidence-based exercise guidelines tailored to this population

Effects of α -lipoic acid on pathogenetic mechanisms of diabetic neuropathy



Akbari M et al *Metabolism* 2018;87:56-69; Akbari M et al *Nutr Metab (Lond)* 2018;15:39.; Saboori S et al *Nutr Metab Cardiovasc Dis* 2018 Apr 17.; Golbidi S et al *Front Pharmacol.* 2011;2:69.



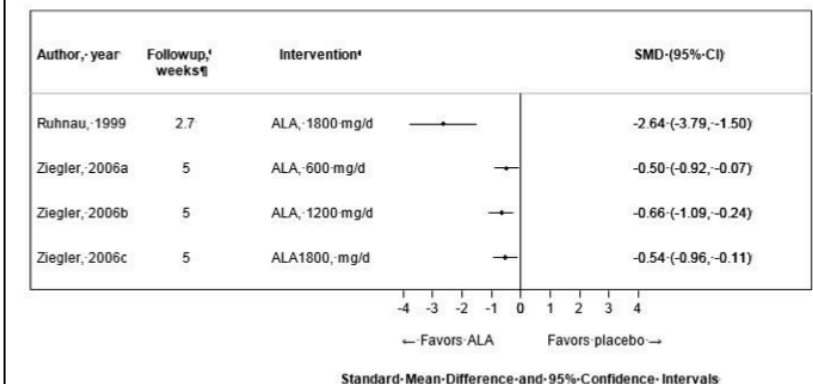
Agency for Healthcare Research and Quality Publication No. 17-EHC005-EF. March 2017

Benefits and Harms of Non-pharmacologic Treatment Options (Alpha-Lipoic Acid) To Improve Symptoms of Diabetic Peripheral Neuropathy

Agent	RCTs (patients)	Findings (SMD, CI)	Conclusion	Evidence strength
Alpha-lipoic acid	5 (984)	-2.64 to - 0.54	Effective short-term	Low

Alpha-lipoic acid was more effective than placebo for reducing pain, although studies were short-term (<3 months) (low strength of evidence). There were few adverse effects

Figure 10. Calculated standardized mean difference between alpha-lipoic acid (ALA) and placebo on change in the total symptom score (TSS) pain subscale



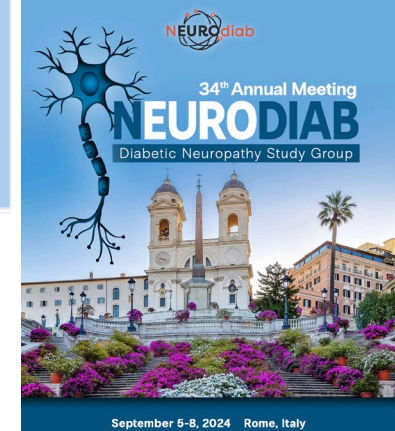
Main results: Our analysis incorporated **three trials involving 816 participants**. Two studies included people with type 1 or type 2 diabetes, while one study included only people with type 2 diabetes. The duration of treatment was **between six months and 48 months**. We judged all studies at high risk of overall bias due to attrition. ALA compared with placebo probably has little or no effect on neuropathy symptoms measured by TSS (lower score is better) after six months (mean difference (MD) -0.16 points, 95% confidence interval (CI) -0.83 to 0.51; 1 study, 330 participants; moderate-certainty evidence). The CI of this effect estimate did not contain the minimal clinically important difference (MCID) of 0.97 points. ALA compared with placebo may have little or no effect on impairment measured by the Neuropathy Impairment Score-Lower Limbs (NIS-LL; lower score is better) after six months (MD -1.02 points, 95% CI -2.93 to 0.89; 1 study, 245 participants; low-certainty evidence). However, we cannot rule out a significant benefit, because the lower limit of the CI surpassed the MCID of 2 points. There is probably little or no difference between ALA and placebo in terms of adverse events leading to cessation of treatment within six months (risk ratio (RR) 1.48, 95% CI 0.50 to 4.35; 3 studies, 1090 participants; moderate-certainty evidence). No studies reported quality of life or complications associated with DPN.

Authors' conclusions: Our analysis suggests that **ALA probably has little or no effect on neuropathy symptoms or adverse events at six months**, and **may have little or no effect on impairment at six months**. All the studies were at high risk of attrition bias. Therefore, future RCTs should ensure complete follow-up and transparent reporting of any participants missing from the analyses.



1. Pathogenetic and symptomatic treatments for diabetic polyneuropathy: current evidence and novel approaches

Dan Ziegler
(Düsseldorf, Germany)



 **Cochrane Library**
Cochrane Database of Systematic Reviews

Comment on Alpha-lipoic acid (ALA) for diabetic peripheral neuropathy (DPN)
Published : 9 May 2024

Dan Ziegler | Institute for Clinical Diabetology, German Diabetes Center, Düsseldorf, DE
| 0000-0001-8956-3552

➤ The claim was to focus on “disease-modifying treatment”, for which a time frame of 6 months is simply too short.

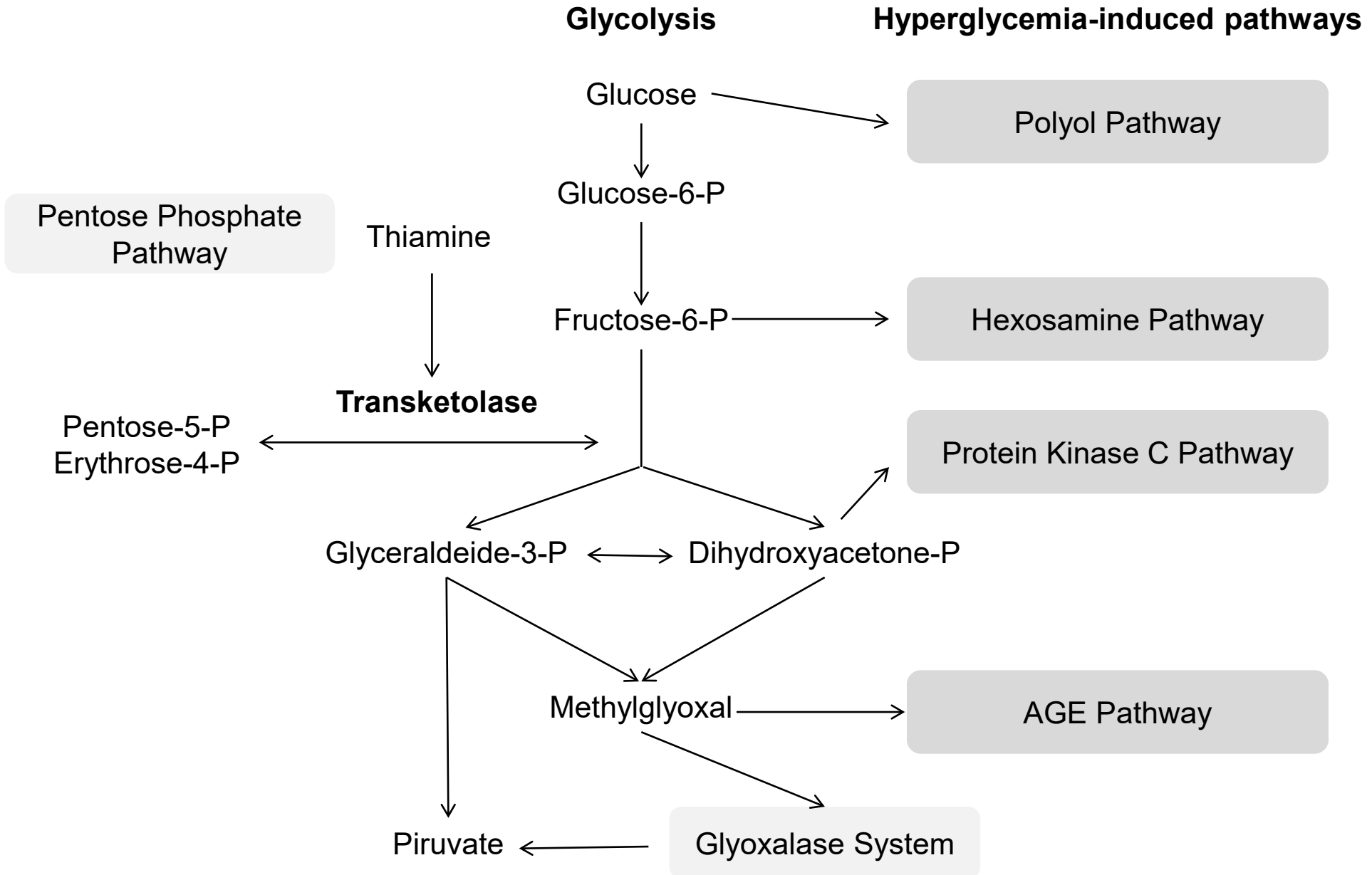
- The claim was to focus on “disease-modifying treatment, for which **6 months is simply too short.**
- DSPN progression is very slow, only the NATHAN 1 study qualifies “**to assess the effects of ALA as a disease-modifying agent** in people with DPN”, but no to assess symptoms.
- By **excluding RCTs shorter than 6 months** this Cochrane review contrasts with the clear evidence supporting **the efficacy of ALA on symptoms** available by several meta-analyses.

➤ In conclusion, due to fundamental flaws and bias, this Cochrane Review is not suitable to adequately assess the efficacy of ALA as a disease modifying pharmacotherapy in DSPN.

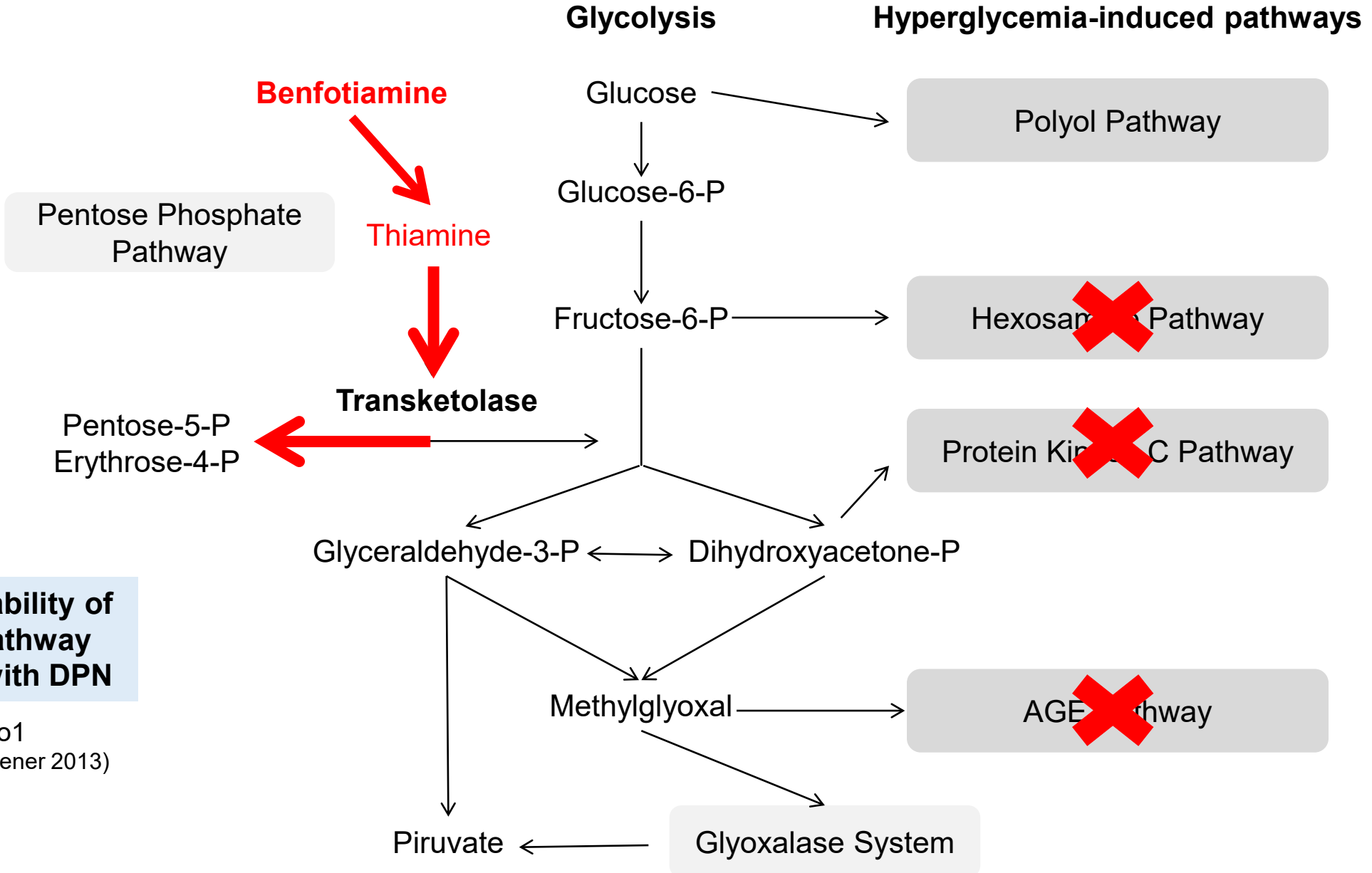
 **DDZ**
German Diabetes Center

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012967.pub2/detailed-comment/id?messageId=433433537>

Biochemical pathways during hyperglycaemia: the role of transketolase



Thiamine Benfotiamine inhibits the pathways of hexosamine, AGE's formation, and protein kinase C through transketolase activation



12 months on morphometric, neurophysiological and clinical measures in type 2 diabetes patients with symptomatic polyneuropathy: a randomized, placebo-controlled, double-blind clinical trial (BOND study)

Ziegler D, Sipola G, Strom A, Strassburger K, Jander L, Herder C, Knebel B, Reule C, Jaghutriz BA, Moreira Tupac Yupanqui AC, Icks A, Al-Hasani H, Roden M, Kuss O, Bönhof GJ.

BMJ Open Diabetes Res Care. 2026 Jan 22;14(1):e005773

In a phase II mono-center, double-blinded, placebo-controlled RCT, in **57 T2D with mild-to-moderate symptomatic DSPN** (24 in active, 27 in placebo arm), **benfotiamine** (300 mg orally x 2 day) **over 12 months did not have a favourable effect on morphometric, functional and clinical neuropathic endpoints, and quality of life compared with placebo.**

Primary endpoint: **Δ in corneal nerve fiber length (CNFL) on CCM from baseline to 12 months.**

Secondary endpoints

- **morphometric:** three other CCM parameters, **skin biopsy**
- **functional:** **NCS, QST, CARTs**, sudomotor function tests
- **clinical:** scores and scales for **neuropathic symptoms and signs**, and QoL and depression instruments
- **pharmacokinetics:** six thiamine blood analytes

Table 4 Clinical scores for neuropathic symptoms and signs

Endpoint	Treatment groups (n)	Baseline (BL)	Month 6	Month 12	Difference BL vs month 12	Treatment effect (95% CI)	P value
NSS	Benfotiamine (24)	7.958 (1.268)	7.333 (2.140)	7.273 (2.511)	−0.565 (2.483)	−0.982 (−2.145 to 0.181)	0.098
	Placebo (27)	7.667 (1.177)	7.667 (1.240)	7.958 (1.398)	0.333 (1.494)		

Only the Neuropathy Symptom Score tended to improve (p=0.098).

These findings do **not contradict the use of benfotiamine for neuropathies due to vitamin B1 deficiency.**
Larger scale RCTs conducted over **several years**, arguably in individuals **selected for low thiamine levels** are needed.

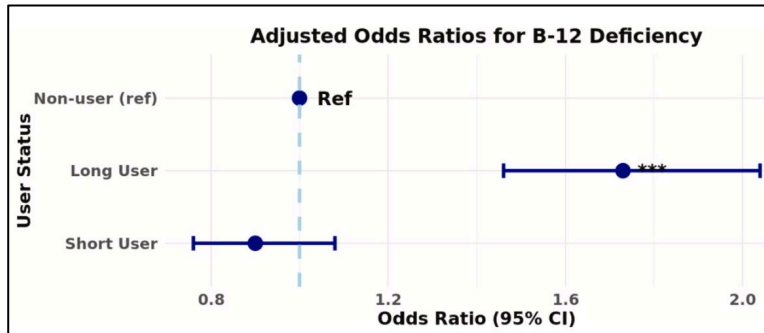
Vitamina B12 e polineuropatia diabetica

Da una meta-analisi di 31 studi (5500 soggetti) evidenza di **associazione tra uso di metformina e**

- **carenza di vitamina B12** (RR 2.09, IC 1.49, 2.93, $P < 0.0001$)
 - livelli più bassi di vitamina B12 (MD -63.70, $P < 0.00001$) in maniera dipendente da dose e durata del trattamento
- No evidenza di associazione tra metformina e prevalenza di anemia e neuropatia.

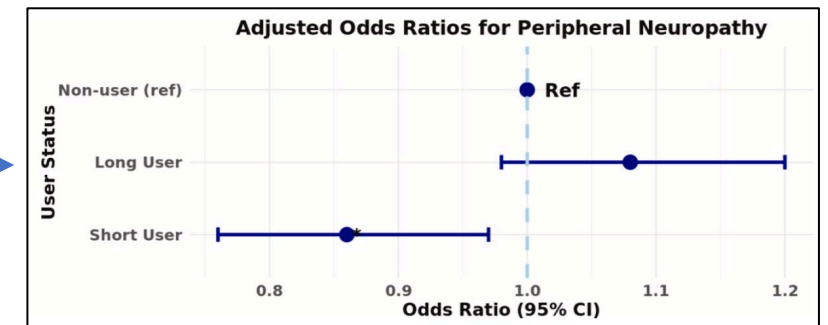
Yang W et al *J Diabetes*. 2019 Sep;11(9):729-743

Analisi retrospettiva in ampio database (NIH's All of Us) in 14808 soggetti con T2D: uso da ≥ 4 anni di metformina associato a $\uparrow$ rischio di carenza di vitamina B12 (< 200 pg/ml) (significativo) e di PND (**non significativo**).



Carenza vitamina B12

Neuropatia periferica



Sepassi A et al *Diabetes Res Clin Pract*. 2025 Oct;228:112424

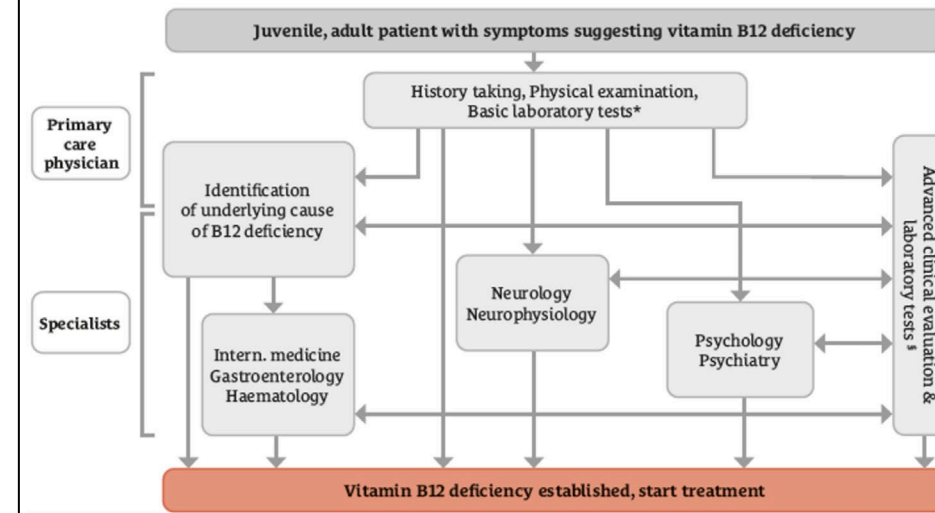
La carenza di vitamina B12 non rappresenta tutto il rischio di PND

In un RCT in doppio cieco su 90 pazienti con T2D, metformina per ≥ 4 anni, **livelli di vitamina B12 < 400 pmol/L** e DPN e CAN, la metilcobalamina 1000 g/die per 1 anno normalizzava i livelli di B12 (da 232 ± 72 a 777 ± 24 pmol/L) e **migliorava** NCV e ampiezza del nervo surale, VPT, sintomi neuropatici, intensità del dolore e sudorazione, ma non i CART e i segni, a fronte di un peggioramento delle misure DPN nel gruppo di controllo.

Didangelos T et al *Nutrients*. 2021 Jan 27;13(2):395.

The Panellists of Delphi Expert Consensus on Vit B12 deficiency agreed on

- the need for changes in the current medical practices for diagnosing and treating B12 deficiency
- **clinical symptoms** (haematological, muscular, epithelial, gastrointestinal, neurologic, mental) should receive the highest priority in establishing the diagnosis;
- **serum B12 concentration** is useful as a screening marker and methylmalonic acid or homocysteine can support the diagnosis;
- **patient lifestyle, disease history** (elderly, vegetarian diet, autoimmunity, gastrointestinal diseases), **and medications** (metformin) can provide clues to the cause of B12 deficiency;
- initial treatment with **parenteral** B12 was regarded as the first choice for patients with acute and severe manifestations of B12 deficiency; **high-dose oral** B12 may be considered for long-term treatment;
- **prophylactic B12 supplementation** should be considered for specific high-risk groups.



ADA Standard of Care 2026

- For people taking metformin (especially with ≥ 1500 mg/day or for ≥ 4 years or CKD) monitor annually B12
- In all people with diabetes and DPN, **causes of neuropathy other than diabetes should be considered, including B12**
- **Periodic testing of B12 in those under metformin** especially with anemia or neuropathy.

3.10 Consider periodic assessment of vitamin **B12** levels in individuals receiving long-term metformin therapy, especially in those with anemia or peripheral neuropathy. **B**

Polineuropatia diabetica: le sfide della terapia patogenetica

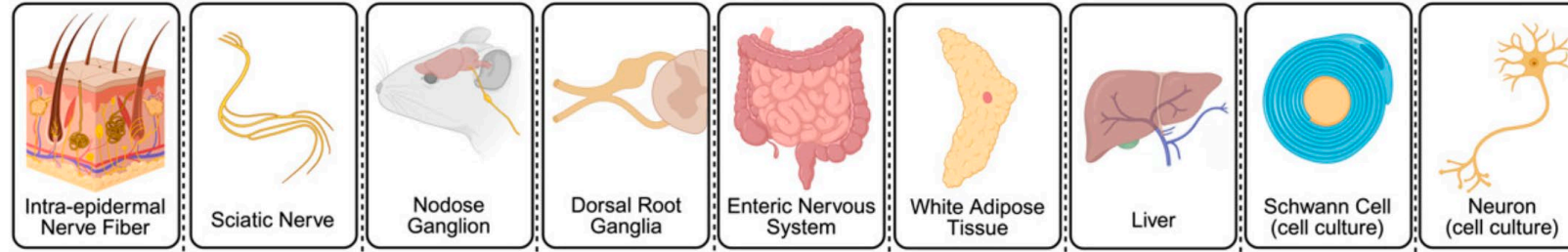
Agenda

- Rilevanza della polineuropatia diabetica
- Criticità traslazionali dal laboratorio alla clinica
 - Definizione, diagnosi, outcome, storia naturale, complessità patogenetica
- Proposte per un cambiamento
- **Terapia patogenetica**
 - Evidenze attuali
 - **Prospettive**



Incretine e polineuropatia diabetica

GLP-1 RAs and diabetic neuropathy: receptors expressed on PNS and preclinical studies



Neuroprotective effects of GLP1-RAs

GLP1-RAs provide a multimodal neuroprotection by

- ↓ inflammation (via inhibition of NF-κB and MAPK pathways and ↓ pro-inflammatory cytokines)
- ↓ oxidative stress
- ↓ mitochondrial dysfunction
- ↑ Schwann cell survival and neurite growth
- ↓ astrocyte and microglial activity

Analgesic effects of GLP1-RAs

- Activation of μ -opioid receptors via ↑ IL-10 and β -endorphin in microglia
- Suppression of pain-related synaptic transmission in the spinal dorsal horn.

De Sousa E et al *Diabetes* 2025;74:1313–1319

Human studies

↑ Na /K –ATPase pump function

Dhanapalaratnam R et al *J Neurophysiol.* 2025;133(1):14-21

Trials with GLP1-RA and DPN measures as outcome

Author (year)	Design	Population	GLP1-RA	Follow-up	DPN measures	Autonomic measures
Jaiswal (2015)	Open-label RCT	46 T2DM (32 with confirmed DPN)	Exenatide (Vs. glargine)	18 months	Symptoms, signs, NCS, VPT, IIEF	No difference in prevalence of confirmed DPN, and in any measure Vs glargine. Borderline higher post-capsaicin regeneration with insulin (p=0.06).
Brock (2019)	Double-blind RCT	48 T1DM with confirmed DPN	Liraglutide (Vs. placebo)	26 weeeeks	NCS, Thermal and pressure sensation	No change in DPN measures, ↓ IL-6 Vs placebo.
Ponirakis (2020)	Open-label RCT (Qatar Study)	38 with poorly controlled T2DM	Exenatide + pioglitazone Vs basal bolus insulin	1 year	CCM, DN4, VPT, ESC	Similar increase in CCM branch density (regeneration) but VPT impairment Vs insulin.
Issar (2021)	Observational	10 T2DM	Exenatide	3 months	NCS	No change in SNAP and CMAP but better nerve excitability
Dhanapalaratnam (2024)	Observational	22 T2DM (1 month) 14 (3 months)	Dulaglutide or semaglutide	1 month 3 months	mTCNS, TNS, tibial nerve size, NCS	↓ nerve size, ↓ TNS, no change at 1 month but improvement at 3 months in mTCNS and sural amplitude
The GRADE Study Research Group (2022)	RCT	5047 T2DM	Liraglutide Vs. glargine, glimepiride, sitagliptin	5 years	MNSI-Q, MNSI-E	No difference in incidence of DPN (based on symptoms or signs)
Deng (2022)	Emulation GRADE Trial (based on OLDW US database)	8252 T2DM	Liraglutide Vs. glargine, glimepiride, sitagliptin	7 years	Diagnosis code	No difference in incidence of DPN (based on symptoms or signs)

Jaiswal M et al *J Diabetes Complications*. 2015;29(8):1287-94

Brock C et al *Br J Clin Pharmacol*. 2019; 85:2512-2523

Ponirakis G et al *BMJ Open Diab Res Care* 2020;8:e001420

Issar T et al *Clin Neurophysiol*. 2021;132(10):2532-2539.

Dhanapalaratnam R et al *Diabetologia*. 2024 Mar;67(3):561-566.

GRADE Study Research Group et al *N Engl J Med*. 2022 Sep 22;387(12):1075-1088

Glucagon-like peptide-1 receptor agonists reverse nerve morphological abnormalities in diabetic peripheral neuropathy

Dhanapalaratnam R, Issar T, Lee ATK, Poynten AM, Milner KL, Kwai NCG, Krishnan AV.

Diabetologia. 2024 Mar;67(3):561-566

This study investigated in **22 participants with T2D** whether GLP-1 RAs can improve nerve structure, assessed using peripheral nerve ultrasonography and measurement of tibial nerve cross-sectional area, in conjunction with validated neuropathy symptom scores and nerve conduction studies before and 1 month after **semaglutide or dulaglutide**.

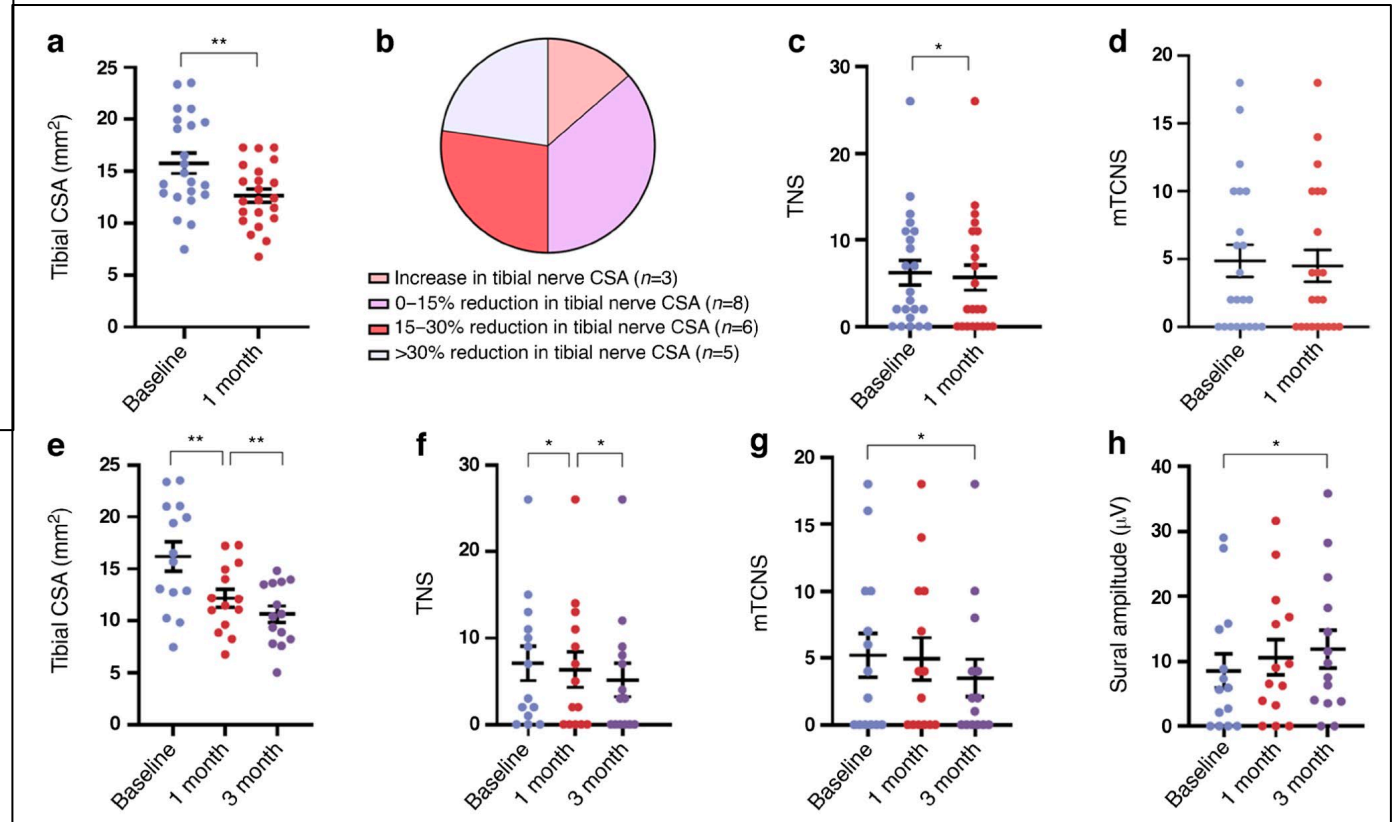
Results. At baseline, pathological $\uparrow$ in nerve size in 81.8%. At 1 month, **improvement in nerve size** in 86% ($p < 0.05$), with normalization in 32%. A 3 months ($n = 14$), further improvement in nerve size in 93% of participants, with $\downarrow$ severity of neuropathy ($p < 0.05$) and $\uparrow$ **sural amplitude** ($p < 0.05$).

Conclusions. **Efficacy of GLP-1 RAs in improving neuropathy outcomes.** Future studies to investigate the benefits for small fibre function and structure.

Proposed mechanisms (experimental findings):

- Antiinflammatory pathways
- Remyelination, reduction in Schwann cell apoptosis
- PI3K/Akt pathway and restoration of cAMP
- **Augmentation of sodium–potassium pump activity** and normalisation of the sodium electrochemical gradient *

Clinical, morphological and electrophysiological neuropathy outcomes



*improvements in Na /K –ATPase pump function documented by axonal excitability recordings (Dhanapalaratnam R et al *J Neurophysiol*. 2025;133(1):14-21)

Analisi sistematiche, review e meta-analisi: GLP1-RA e PND

Diabetologia
<https://doi.org/10.1007/s00125-023-05988-3>

REVIEW

Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy

Jonathan Goldney^{1,2}  · Jack A. Sargeant^{2,3}  · Melanie J. Davies^{1,2,3} 

Diabetes Ther (2025) 16:1077–1105
<https://doi.org/10.1007/s13300-025-01712-z>

REVIEW

The Therapeutic Potential of Dipeptidyl Peptidase 4 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists in Diabetic Peripheral Neuropathy

Theodoros Panou · Evanthia Gouveri · Djordje S. Popovic · Dimitrios Papazoglou · Nikolaos Papanas 

SYSTEMATIC REVIEW

 WILEY

Journal of Neurochemistry. 2025;169:e16242

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

Shujin Fan^{1,2,3,4} | Yue Qiu^{1,4} | Jing Liu^{1,4} | Tianxin Zhu^{1,4} | Chuan Wang^{1,4} | Dan Liu^{1,4} | Li Yan^{1,4} | Meng Ren^{1,4} 

Diabetes Ther
<https://doi.org/10.1007/s13300-025-01828-2>

REVIEW

Innovative Diabetes Therapies and Impact on Peripheral and Autonomic Diabetic Neuropathies: A State-of-the-Art Review

Jelena Vekic · Aleksandra Zeljkovic · Viviana Maggio · Manfredi Rizzo · Sanja Medenica 

 Korean J Pain 2025;38(3):219-221
<https://doi.org/10.3344/kjp.25214>
pISSN 2005-9159, eISSN 2093-0569 

Editorial

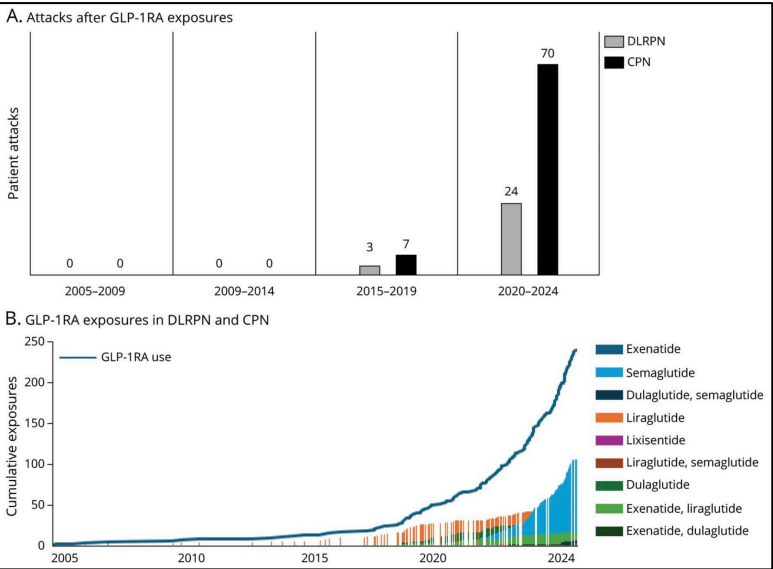
Glucagon-like peptide-1 receptor agonists in neuropathic pain: hype or hope?

Jeong Il Choi

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

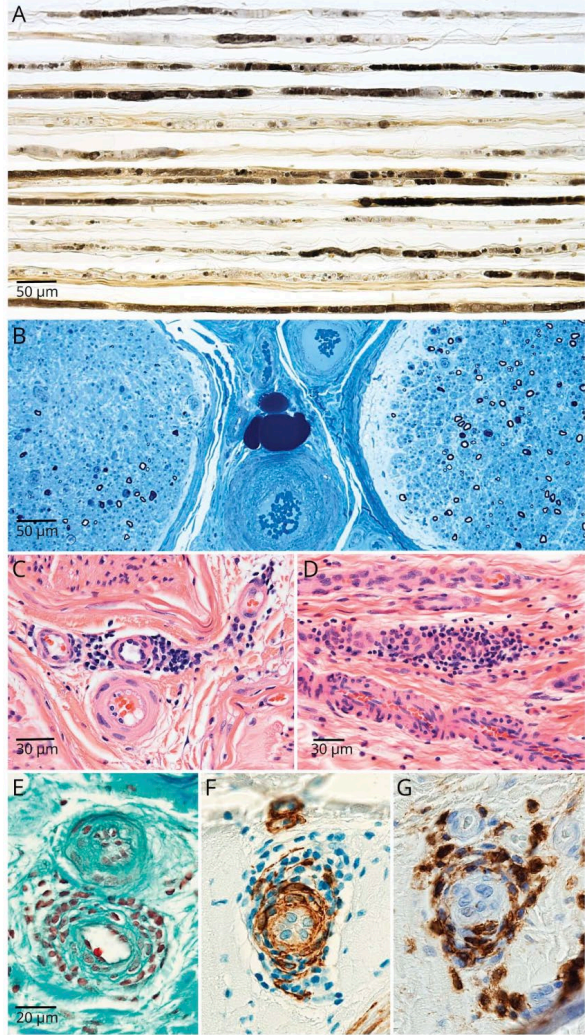
Retrospective case-control study 2005-2024. 26 cases of DLRPN and 77 of CFN were analysed for GLP-1RA exposure and matched with a control group.

	DLRPN	CFN
Cases	26	77
HbA1c	↓ 2.4%	↓ 1.2%
BMI	↓ 4 Kg/m2	↓ 4 Kg/m2
Microvasculitis	4/5 biopsies	4/5 biopsies
OR Vs. controls	1.5	1.4



Episodes most common >2020 with semaglutide and dulaglutide (increasing prescriptions).

Sural nerve biopsy in GLP-1RA (dulaglutide)–induced DLRPN



Axonal degeneration

Subperineurial edema and intrafascicular fiber loss

Mononuclear collections around epineurial microvessels

Vessel wall infiltration and destruction with inflammatory cells (mostly leukocytes)

Mechanisms: overlapping features with treatment-induced neuropathy of diabetes (TIND). For DLRPN more relevant ↓ HbA1c for CFN ↓ weight.

Incretins and diabetic neuropathy: developments

GIP receptor expression has been found in the DRG and sciatic nerve, indicating that GIP receptor activity is essential for peripheral neuron health.

Buhren BA et al *J Neurosci Res.* 2009 Jun;87(8):1858-70

A-094

IMPACT OF TIRZEPATIDE, A DUAL GIP AND GLP1 RECEPTOR AGONIST, REDUCES THE RELATIVE RISK OF NEW ONSET DIABETIC NEUROPATHY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A LARGE-SCALE OBSERVATIONAL STUDY



J. Russell^{*1}, B. Ara¹, S. Dunlap¹

¹CAMC Department of Neurology and Center for Academic Medicine

Data from TrinetX global health research network. The only medication that progressively reduced the RR of neuropathy over 2 years was Tirzepatide (n=41,893) at 1 year (5.4% vs. 3.8%) and 2 years (**6.5% vs. 3.9%**).

Amylin is a calcitonin gene-related peptide family member expressed by nociceptors. Amylin's expression is down-regulated following nerve damage, and studies suggested it affects nociception.

Almeida LS et al *Eur J Pain.* 2019;23:784–799.

Cagrilintide and Semaglutide in painful DPN

- A Research Study to Investigate the Effects of Cagrilintide and Semaglutide Compared to Placebo in People With Type 2 Diabetes and Painful Diabetic Peripheral Neuropathy
- ClinicalTrials.gov ID NCT06797869

Conclusioni su GLP1-RA/incretine e polineuropatia diabetica

- I dati preclinici suggeriscono un'azione neuro protettiva anche periferica
- I dati clinici da piccoli studi non documentano efficacia su misure neurologiche
- Idem per i dati di *real world*, ma valutazioni in corso con *outcome* meglio definiti possono fornire dati più affidabili
- Possibili differenze tra farmaci della classe (breve Vs lunga durata)
- Alcune rare segnalazioni di neuropatie atipiche associate all'uso di GLP1-RA suggeriscono un approccio personalizzato ai target di controllo glicemico e peso in casi particolari
- I dati preclinici di altre incretine (GIP, amilina) incoraggiano ad esplorarne le potenzialità.

SGLT2i e polineuropatia diabetica

Canagliflozin e rischio di neuropatia: analisi post-hoc del trial CREDENCE

Il canagliflozin non ha un impatto significativo sul rischio di neuropatia in persone con diabete di tipo 2 e nefropatia diabetica

Disegno

Studio clinico CREDENCE: 4401 partecipanti con diabete di tipo 2 e malattia renale (eGFR: 30-90 ml/min/1.73m², ACR: 300-5000 mg/g) randomizzati a canagliflozin 100 mg/die o placebo.

Analisi post-hoc degli eventi neuropatia (da codici amministrativi, classificati come polineuropatia sensitivomotoria, neuropatia diabetica ed neuropatia non autonoma).

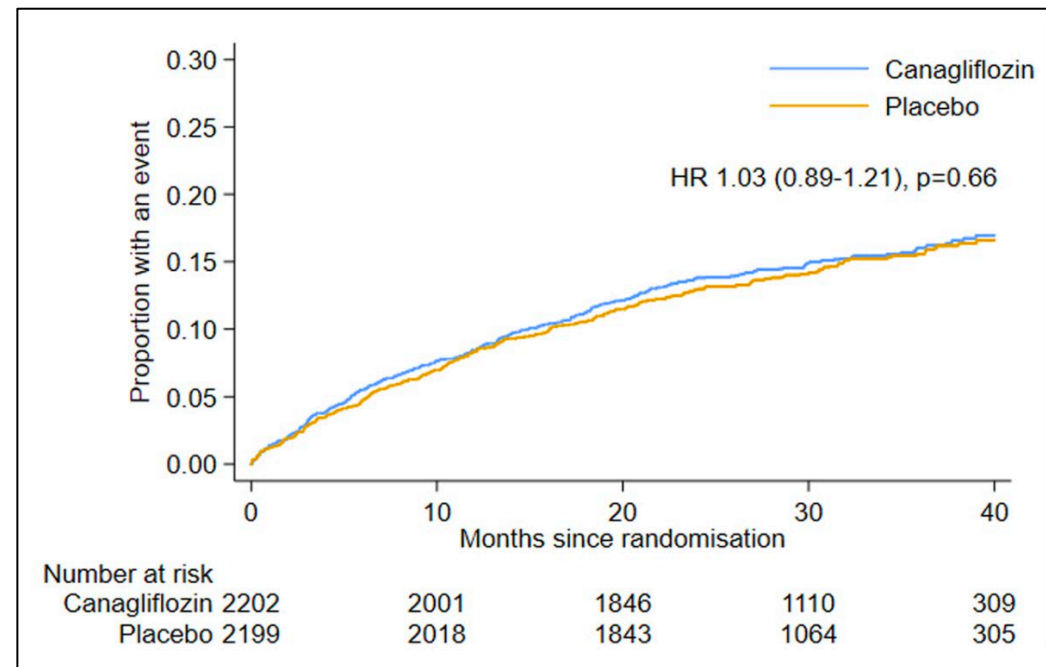
Risultati

Nel follow-up di 2.45 anni, 63.2 per 1000 pazienti anno sviluppavano un evento neuropatia senza differenze tra canagliflozin e placebo.

Canagliflozin e rischio di eventi neuropatia

Eventi	HR	95% IC	P
Polineuropatia sensitivomotoria	0.93	0.69-1.25	0.63
Neuropatia diabetica	0.91	0.68-1.22	0.52
Neuropatia non autonoma	1.03	0.87-1.21	0.77

Curva di Kaplan-Meier per eventi neuropatia



Predittori indipendenti di eventi neuropatia

Variabile	HR	95% IC	P
Età (5 anni)	0.87	0.81-0.93	<0.0001
Razza asiatica	1.45	1.18-1.79	<0.0001
HbA1c (%)	1.10	1.03-1.17	0.002
eGFR (ml/min/1.73m ²)	0.986	0.979-0.994	<0.0001

Effect of Empagliflozin, a Selective Sodium-Glucose Cotransporter 2 Inhibitor, on Kidney and Peripheral Nerves in Streptozotocin-Induced Diabetic Rats

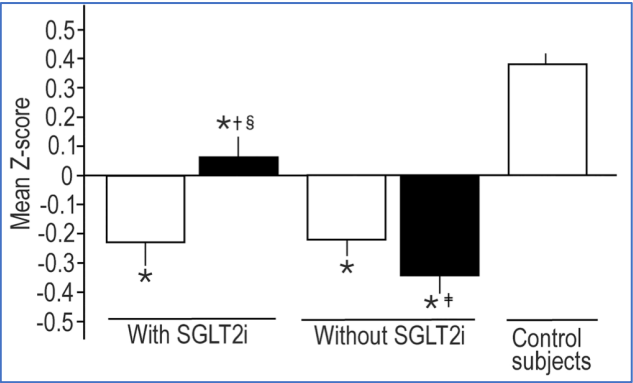
Lee KA, Jin HY, Lee NY, Kim YJ, Park TS
Diabetes Metab J. 2018 Aug;42(4):338-342.

In rats with streptozotocin-induced diabetes, 24-week empagliflozin treatment **prevented** hypersensitivity and the **loss of skin intraepidermal nerve fibers**.

Sodium Glucose Cotransporter-2 Inhibitor Protects Against Diabetic Neuropathy and Nephropathy in Modestly Controlled Type 2 Diabetes: Follow-Up Study

Ishibashi F, Kosaka A, Tavakoli M.
Front Endocrinol (Lausanne). 2022 Jun 17;13:864332

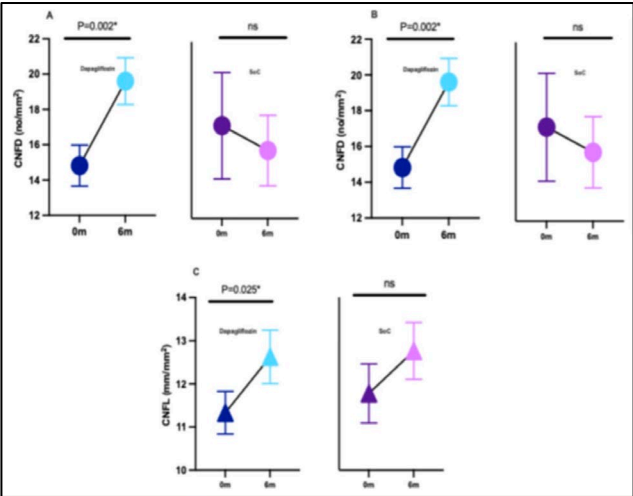
Longitudinal observational study in 113 T2D: Over 3 years, **SGLT2i improved** some neuropathy outcome measures and **mean Z-score of 8 neurophysiological tests** , attenuated nephropathy in modestly controlled T2D by reducing glycemic variability and mean nonglycemic factors of diabetic microvascular complication (BP, HDL, uric acid).



Dapagliflozin for Small Nerve Fibre Regeneration in Diabetic Peripheral Neuropathy: A Randomised Controlled Study (DINE)

Adhikari U, Gad H, Chatterjee D, Malhotra C, Bhadada SK, Malik RA, Rastogi A
J Peripher Nerv Syst. 2025 Mar;30(1):e70011

In a prospective, **open-label, RCT**, 40 DPN were randomised to add-on 10 mg dapagliflozin to existing oral antidiabetic drugs or continue standard of care. Dapagliflozin was associated with **reduced oxidative stress and ↑ small nerve fibre regeneration (CCM)** in patients with DPN.



Agenti emergenti e inaspettati

A muscarinic receptor antagonist reverses multiple indices of diabetic peripheral neuropathy: preclinical and clinical studies using oxybutynin

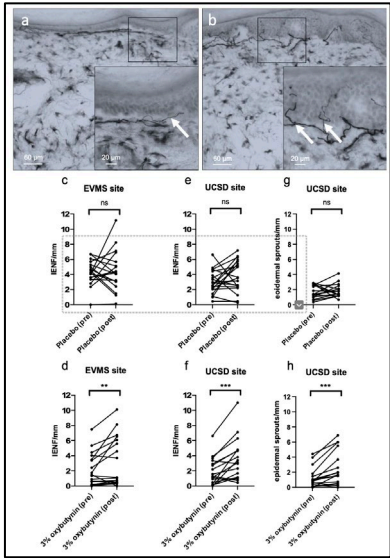
Casselini CM, Parson HK, Frizzi KE, Marquez A, Smith DR, Guernsey L, Nemmani R, Tayarani A, Jolivalt CG, Weaver J, Fernyhough P, Vinik AI, Calcutt NA. *Acta Neuropathol.* 2024 Mar 25;147(1):60

In a randomized, double-blind, placebo-controlled interventional trial 46 T2D and established DPN, daily topical treatment with 3% oxybutynin gel or placebo for 6 months was administered.

Oxybutynin promotes neurite outgrowth in human sensory neuron cultures.

Topical 3% oxybutynin increases sensory innervation (IENFD in skin biopsies) in diabetic subjects at 5 months (no effect of topical placebo)

Secondary endpoints showed significant improvement with oxybutynin treatment included scores on clinical neuropathy, pain and quality of life scales.

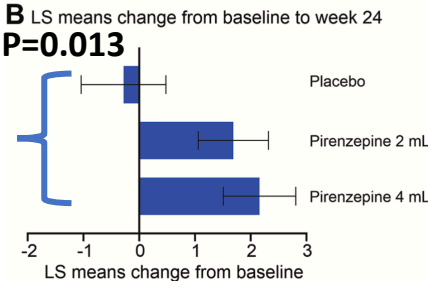
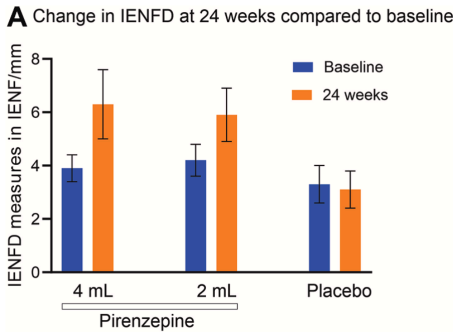


Topical application of the antimuscarinic pirenzepine increased lower limb nerve fibre density in a phase 2a study in type 2 patients with diabetes with peripheral neuropathy

Sivadasan A, Fernyhough P, Calcutt NA, Frizzi KE, Gardner K, Hansen A, Breiner A, Zochodne DW, McInnes N, Punthakee Z, Gosselin S, Perkins BA, Bril V. *EBioMedicine.* 2026 Jan;123:106055

A proof-of-concept randomised Phase 2a, double-blind, placebo-controlled, clinical multicenter trial with pirenzepine (M1R subtype antimuscarinic agent with **removal of tonic cholinergic suppression of mitochondrial respiratory capacity and neurite outgrowth**).

Topical pirenzepine once daily for 24 weeks in 58 patients with definite DPN, resulted in a **significant increase in IENFD** at the ankle not accompanied by a statistically significant change in the clinical measures.



Disease-modifying treatment: SCS 10 Hz

Improvement in Protective Sensation: Clinical Evidence From a Randomized Controlled Trial for Treatment of Painful Diabetic Neuropathy With 10 kHz Spinal Cord Stimulation

Argoff CE, Armstrong DG, Kagan ZB, Jaasma MJ, Bharara M, Bradley K, Caraway DL, Petersen EA; for Investigators.
J Diabetes Sci Technol. 2025 Jul;19(4):992-998

In SENZA-PDN clinical study (RCT with 10 kHz SCS), significant **improvements in protective sensation** (10g monofilament) from preimplantation to 24 months post-implantation for the 10 kHz SCS.

Evaluating pain and neurological function with high frequency 10 kHz spinal cord stimulation in the treatment of painful diabetic neuropathy: design of a multicentre, randomised controlled trial (PDN-Sensory)

Pop-Busui R, Petersen EA, Levy BL, Tesfaye S, Armstrong DG, Grunberger G, Boulton AJ, Bharara M, Edgar D, Azalde RP, Caraway D.
BMJ Open. 2025 Nov 27;15(11):e101647.

The design of the PDN-Sensory study to evaluate changes in pain and neurological function with 10 kHz SCS in the treatment of PDN. The study will include **objective measures of neurological function**, including the modified Toronto Clinical Neuropathy Score (mTCNS) and intraepidermal nerve fibre density (IENFD).

Disease-modifying treatment: Capsaicin 8%

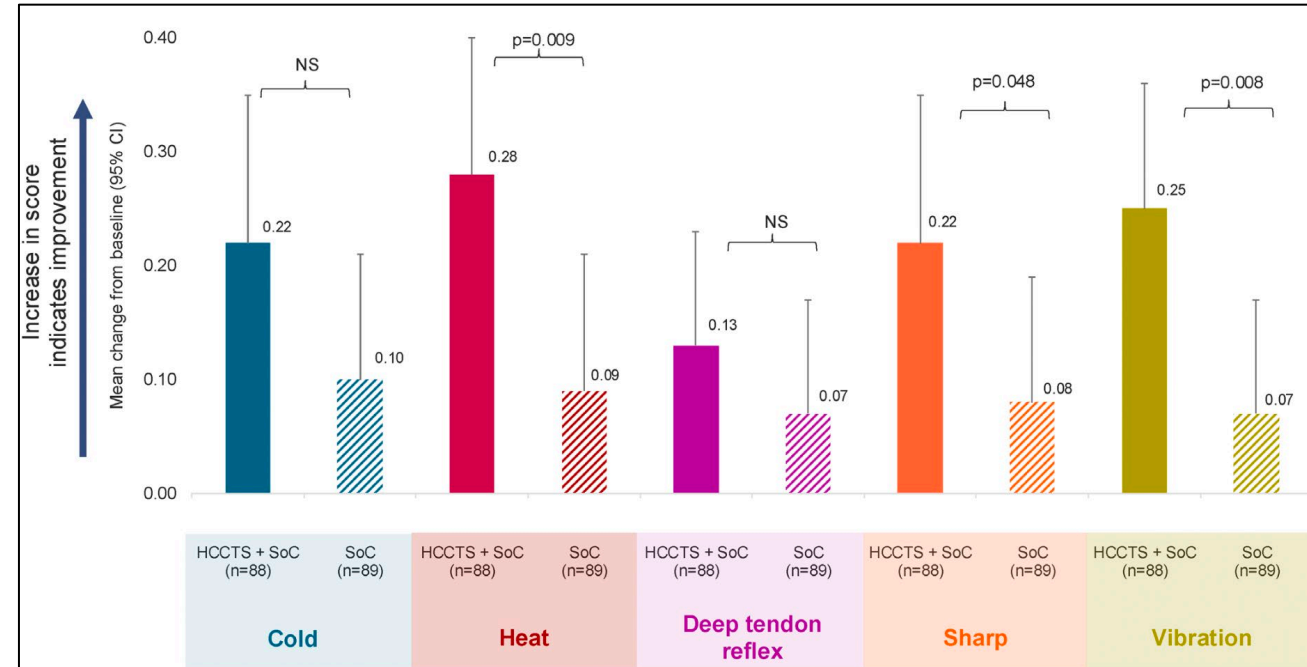
Improvement in Protective Sensation: Clinical Evidence From a Randomized Controlled Trial for Treatment of Painful Diabetic Neuropathy With 10 kHz Spinal Cord Stimulation

Argoff CE, Armstrong DG, Kagan ZB, Jaasma MJ, Bharara M, Bradley K,
Caraway DL, Petersen EA; for Investigators.

J Diabetes Sci Technol. 2025 Jul;19(4):992-998



In a PACE study's post hoc analysis in 301 PDPN repeated 30-min 8% capsaicin topical system (HCCTS) treatments + standard of care (SOC) lead to improvement in sensory function in the feet over 12 months compared with SOC alone.



Capsaicin

Neurolysis of TRPV1-expressive fibers

↑ Regeneration of small fibers (IENFD)

↑ Axon-reflex vasodilation (↑ CGRP)

Repeated treatments

↑ Fiber response

↑↑ Axon-reflex vasodilation

Regeneration of all sensory fibers

Disease-modifying treatment: where we are

Novel biomarkers, risk markers/factors and mechanisms in the spotlight

- Genetics
 - Omics
 - Animal models
- Dyslipidaemia
 - Inflammation
 - Mitochondrial failure
 - Changes in glia cells (oligodendrocytes, Schwann cells)

Pathogenetic intervention

Glycaemic control Lifestyle intervention

- Physical exercise

More knowledge on few disease-modifying agents

- α -lipoic acid for symptoms
- ACEi, **ARBs (+ manidipine)**
- Vitamin B12 for deficiency
- Acetyl-L-carnitine for pain
- Benfotiamine (?)

New candidates on the horizon (1)

- ω -3 PUFA
- Muscarinic receptor antagonists**
 - Oxybutinin (RCT in T2D)
 - Pirenzepine (RCT in T2D)
- NFkB blocker (salsalate) (unpublished)
- Spinal Cord Stimulation (10kHz)
- Capsaicin 8%
- Fecal microbiota transplantation

Diabetes drugs (2)

- GLP1-RAs
- Thiazolidinediones
- SGLT2i for CAN

NEUROdiab Symposium: From present challenges to future opportunities in diabetic neuropathy

Sat13

SESSION INFORMATION

- 60th EASD Annual Meeting
- Retiro Hall
- 12-09-2024 09:00 - 11:00
- 588 views

CHAIRPERSONS



Vincenza Spallone



Niels Ejbjerg

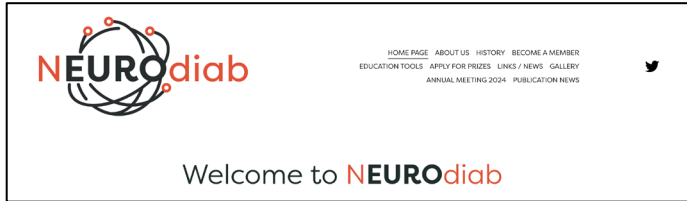
[Write comment →](#)

[Add favourite →](#)

1. Britten-Jones AC et al *Diabetes*. 2021;70:1794-1806; Casellini CM et al *Acta Neuropathol*. 2024;147(1):60; Calcutt NA et al *J Clin Invest*. 2017;127(2):608-622; 2024; Ang L et al *NEUROdiab Annual Meeting Rome 2024*; Petersen et al., *Diabetes Res Clin Pract* 2023; 203: 110865; Argoff et al *J Diabetes Sci Technol* 2024, Jan 9: 19322968231222271; Yang et al *Cell Metab* 2023; 35: 1548-1562

2. Dhanapalaratnam R et al *Diabetologia*. 2024 Mar;67(3):561-566; Pop-Busui R et al *Diabetes Care* 2013;36(10):3208-3215; Spallone V and Valensi P *Diabetes Metab* 2021;47(4):101224

WEBSITE



<https://www.neurodiab.eu/>

PUBLICATION NEWS

Publication News 230 - 08 June 2026 by Gidon J Bönhof

Improved sensory function after treatment with high-concentration capsaicin patches over 12 months

[Click here](#) to read the Publication News

HALLMARK PAPERS

Hallmark Papers in Diabetic Neuropathy

This commentary series, published by the Youth Committee, called Hallmark Papers in Diabetic Neuropathy, will highlight seminal articles that are historically significant and essential reading for early-career researchers in diabetic neuropathy.

Each instalment will feature a concise summary of the chosen article, reflections from one of the paper's authors on its impact and a complementary graphical summary of the paper's key findings

Hallmark Papers in Diabetic Neuropathyn. 1

Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severity, and Treatments. Tesfaye S et al Diabetes Care 2010;33(10):2285- 2293

[Click here](#) to read the commentary

Hallmark Papers in Diabetic Neuropathy n. 2

The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. Dyck PJ et al Neurology 1993;43(4):817-824

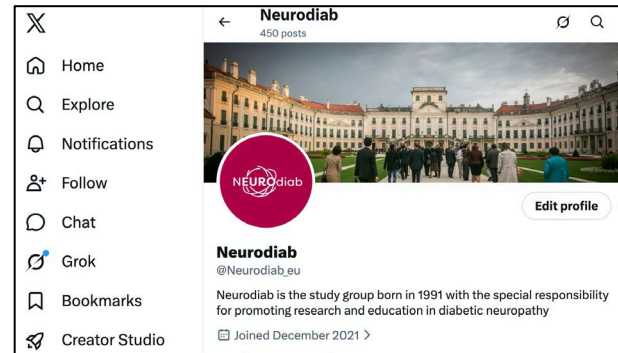
[Click here](#) to read the commentary

Hallmark Papers in Diabetic Neuropathy n. 3

Enhanced glucose control for preventing and treating diabetic neuropathy. Callaghan BC et al Cochrane Database Syst Rev. 2012 Jun 13;2012(6):CD007543

[Click here](#) to read the commentary

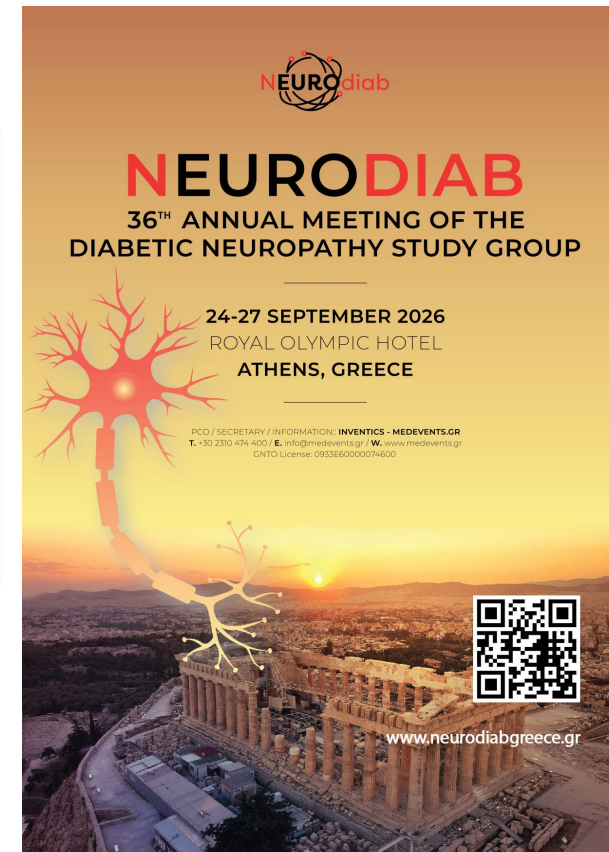
X



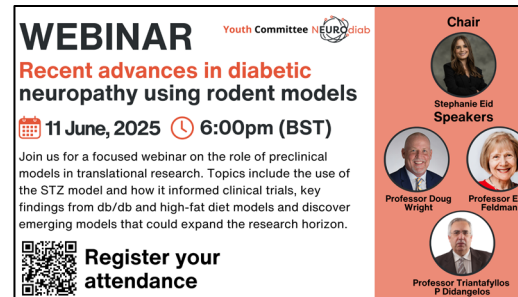
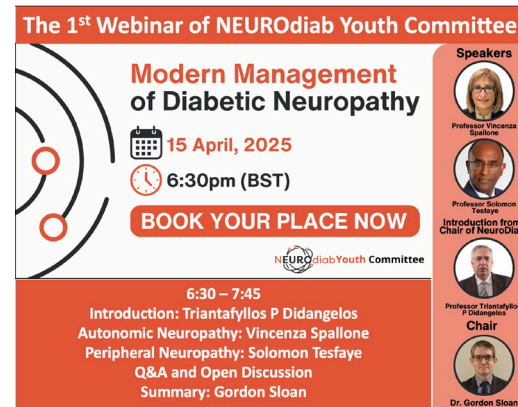
NEWSLETTER



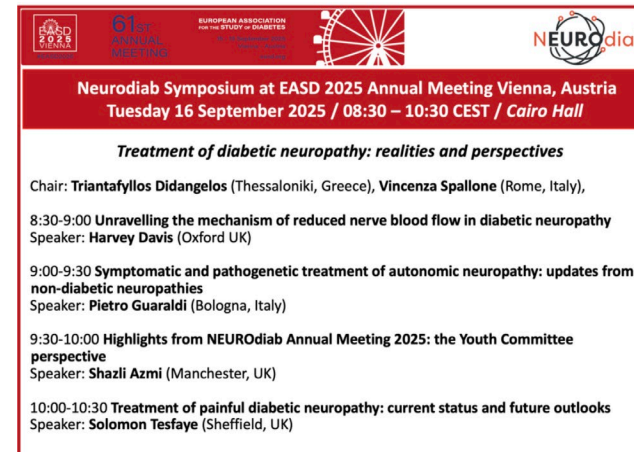
ANNUAL MEETING



WEBINAR



SYMPOSIUM at EASD



Grazie x l'attenzione