Treatment-induced neuropathy of diabetes: an update

Juan Eduardo Quiroz-Aldave[1]
MD

Marcio José Concepción-Zavaleta[2]
MD

María del Carmen Durand-Vásquez[3]
MD

Elman Rolando Gamarra-Osorio[4]
MD

Rosa María Alcalá-Mendoza[5]
MD

Susan Luciana Puelles-León[6]
MD

Sofía Ildefonso-Najarro[7]
MD

Luis Alberto Concepción-Urteaga[8]
PhD

Jorge Estanislao Gonzáles-Mendoza[9]
MD

José Paz-Ibarra[10]
MSc

(See Appendix 1 for authors' affiliations)

Correspondence to:
Dr Marcio José Concepción-Zavaleta, 2150 Simon Bolivar Avenue, 15175, Lima, Perú;
email: mconcepcion@cientifica.edu.pe

Received: 24 March 2023
Accepted in revised form: 5 April 2023

Abstract

Background and aims: Treatment-induced neuropathy of diabetes is an acute small-fibre neuropathy associated with rapid glycaemia improvement.

Methods: This study is a narrative review carried out based on a bibliographic review, using articles indexed in PubMed/Medline and Scielo.

Results: This entity is more frequent in adult patients with poor previous glycaemic control. Its precise pathophysiology is unknown, but it is likely related to unrestored microcirculation changes that occurred during the hyperglycaemic period. It presents with intense, sudden neuropathic pain and autonomic dysfunction after a rapid glycaemic correction and a poorer analgesic response than in diabetic neuropathy.

Conclusions: Since rapid glycaemia correction is the cause of this problem, clinical practice guidelines that can help physicians to prevent, diagnose and manage this entity should be developed.

Practical Diabetes 2023; 40(6): 28–35

Key words

diabetic neuropathies; small fibre neuropathy; diabetes mellitus; treatment

Background

Diabetic neuropathy (DN) is one of the main complications of diabetes mellitus (DM), and it is related to poor glycaemic control.[1] Its prevalence in persons with DM is approximately 50%, being similar for type 1 and type 2 DM.[2] The most common form is distal symmetric polyneuropathy, which accounts for almost 75% of all cases; however, there are some less frequent forms.[3–5] One of them is the treatment-induced neuropathy of diabetes (TIND), which is an acute and painful small-fibre neuropathy associated with rapid glycaemic control, and mainly observed in patients with poor previous glycaemic control.[6] This condition was first described in 1933, in a female with diabetes who developed severe burning pain after starting insulin therapy. The condition remitted after suspending insulin, and it reappeared after restarting insulin. Back then, it was thought that it was an allergic reaction to insulin, and it was named 'insulin neuritis'.[7] Many similar cases have been reported since then, with the same naming, and others have been classified as 'acute painful neuropathy' or 'diabetic neuropathic cachexia'.[8,9]

It was in 2010 that 'treatment-induced neuropathy of diabetes' was suggested as a more adequate denomination for this condition since it affects DM patients treated with insulin and oral hypoglycaemic agents and even with a severely restrictive diet; moreover, some of these affected patients developed not only painful peripheral neuropathy but also autonomic neuropathy.[10]

The objective of this updated review is to describe the epidemiology, pathophysiology, diagnosis, therapy, and perspectives of TIND, aiming to remind our colleagues about this condition and limit the quality-of-life deterioration it brings.

Methodology

Search strategy

A narrative review was performed, so we started searching papers published in PubMed/Medline and Scielo databases for the period between 2005 and 2022. Papers should be written in Spanish or English. MeSH (Medical Subject Heading) term used was 'diabetic neuropathies'. We also used 'insulin neuritis' as a search term because this is not included as a MeSH term.

The search was restricted to studies undertaken in humans.

Screening

A total of 12,887 citations were identified. Most of them discussed diabetic neuropathy broadly but did not refer specifically to TIND. Sixty-five papers complied with the inclusion criteria. This process is shown in Figure 1.

Data extraction and synthesis

The results of included papers were carefully assessed including topics regarding epidemiology, pathophysiology, diagnosis, and therapy.

Quality assessment

The quality of our narrative review was assessed using the SANRA scale, which comprises the following items: an explanation of the importance of this review and a description of the literature search, references, scientific reasoning, and appropriate data presentation. The score was 12 points, corresponding to all the required items.[11]

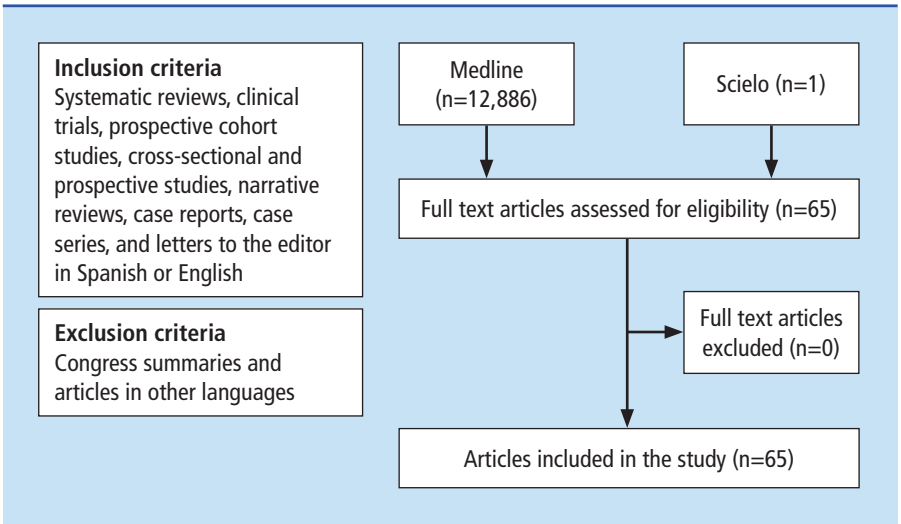

Figure 1. Flowchart of the narrative review process

Epidemiology

During the years after its first description, few TIND cases were reported; however, its presence in the medical literature has increased in the last decades[12] (Appendix 2), indicating that this condition would be more frequent than it was initially thought.[13] Its prevalence in subjects with diabetes in a third-level reference centre was reported to be 10.9%.[13]

Cases reported in the literature[4,14–31] show that the mean age of those affected by TIND is 36.55 years (95% CI 30.99–42.11), and that there is a slight male predominance (57.14% vs 42.86%). Type 1 DM was more frequent than type 2 DM (64.29% vs 35.71%), and patients had the disease for a mean of 4.9 years (95% CI 3.17–6.64). Four-fifths of all patients (81%) used insulin for treating their DM and 14.3% used oral hypoglycaemic agents only. One case associated with pancreatic islet transplantation was reported. In patients with TIND, HbA_{1c} reduction was on average 7.22% (95% CI 6.11–8.33%) [55mmol/mol (95% CI 43–68)] in a 5.4-week period (95% CI 4.4–6.4 weeks), during which time painful neuropathic symptoms and autonomic manifestations occurred. Some patients used a single drug for alleviating their symptoms, and others used drug combinations: 50% of patients used anticonvulsant drugs (gabapentin and pregabalin) for their therapy, almost 40% used antidepressant agents, and nearly 25% used analgesics. Total or nearly total remission was achieved in 60% of all the cases, 38% had partial remission, and one patient did not achieve symptom remission.

Considering the frequency of type 1 and 2 DM in patients with TIND, and that the prevalence of type 2 DM is approximately 15 times that of type 1 DM,[32] we may estimate the risk for the occurrence of TIND to be nearly 30 times higher in individuals with type 1 DM than in those with type 2 DM.

Pathophysiology

Until recently it was thought that TIND was an allergic reaction to insulin.[7] TIND pathophysiology has not been completely elucidated, but some hypotheses are trying to explain this issue.[5,33,34] One of these is related to changes in microcirculation that occur during hyperglycaemia periods and that do not restore as fast as glycaemia level corrections. This proposed mechanism involves the formation of arteriovenous shunts that may lead to relative hypoxia or ischaemia within the endoneurium.[26,33–35] Changes in the retina and the kidneys that may simultaneously occur support this microvascular mechanism.[26] Other hypotheses include cell apoptosis as a result of relative glucose deprivation,[18,29,36] and areas with axonal regeneration that are formed once normoglycaemia is reached, and these may lead to ectopic depolarisation and pain.[16,35] One less robust hypothesis contemplates an immune reaction against insulin, considering that type 1 DM is likely to be an autoimmune condition and that the frequency of TIND is higher in this form of DM.[13,19] Figure 2 summarises the hypotheses regarding the origin of TIND.

TIND must be differentiated from hypoglycaemic neuropathy, another form of neuropathy described in patients with diabetes who use hypoglycaemic agents, in which hypoglycaemic state leads to distal axonopathy including both degenerative and regenerative events, the motor axons being more vulnerable than sensory ones. The cellular mechanisms behind the development of hypoglycaemic disorders of the peripheral nervous system are unknown, hence more

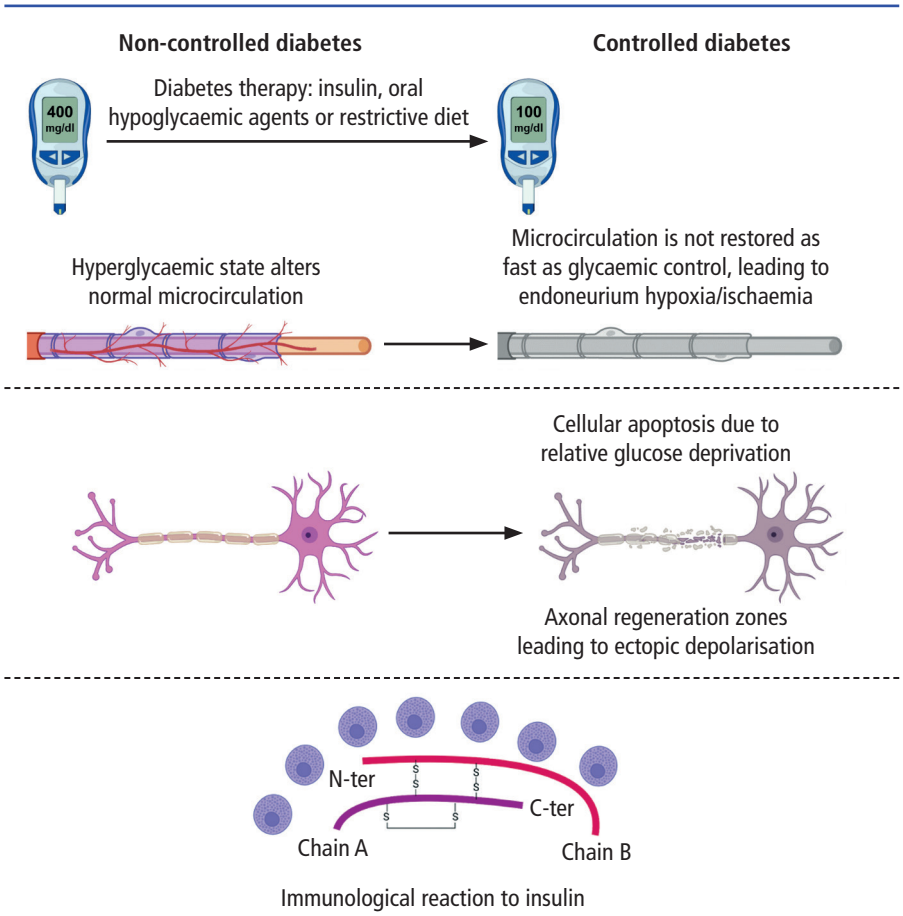

Figure 2. Proposed pathophysiological mechanisms for treatment-induced neuropathy of diabetes

studies are needed to elucidate the pathophysiology of hypoglycaemic neuropathy.[37]

Diagnosis

Clinical manifestations of TIND include burning and stinging neuropathic pain, depending on length, that suddenly occurs two to six weeks after the improvement of glycaemic control. Should there be a large reduction of mean glucose levels, proximal and distal neuropathic pain may ensue; if the reduction is not that marked, neuropathic pain may only be distally located.[38] Most patients present with autonomic dysfunction (orthostatic hypotension, syncope, early satiety, excess or reduced sweating, and sexual dysfunction) that may occur simultaneously or shortly thereafter, but this may be unnoticed because of the severity of neuropathic pain.[13,21,38] The severity of autonomic dysfunction is also correlated with the extent of the reduction of mean glucose levels.[13]

Neurologic examination usually is normal, except for allodynia and hyperalgesia. Nerve conduction studies are usually normal. Some elderly patients with diabetes may present with mild features of pre-existing neuropathy, with absent patellar reflex, and reduced distal vibrating sensitivity.[10]

Besides neuropathy, many patients with TIND may show rapid progression of other microvascular complications (retinopathy and nephropathy), with the occurrence of neuropathic pain.[10,39] There may likely be a common pathophysiologic pathway involving microcirculation.

In 2015, three criteria for diagnosing TIND were proposed:[13]

- ≥2% HbA_{1c} reduction over three months (or a proportional equivalent in time).
- Occurrence of neuropathic pain and/or autonomic dysfunction within eight weeks after HbA_{1c} reduction.
- Acute onset of neuropathic pain (more than a three-point increase in the 11-point Likert scale) and/or autonomic dysfunction lasting for more than two weeks, and severely enough for seeking medical care.

Two other important characteristics associated with TIND are the presence of very high HbA_{1c} levels (>10% [86mmol/mol]) before starting therapy and very fast glycaemic control (in a few weeks) after having started therapy.[13] A reduction greater than 2% compared to baseline HbA_{1c} values is a strong functional predictor for TIND.[40]

At the beginning in its natural history, TIND may occur as an acute small-fibre sensitive neuropathy;[41] therefore, the main differential diagnoses include variants of Guillain–Barré syndrome,[42] steroid-susceptible small-fibre sensorial neuropathy,[43] and non-systemic vasculitic neuropathy.[44]

Electroneuromyography can be used as a complementary tool in the diagnostic evaluation of patients with suspected TIND; sometimes being able to find evidence of sensorimotor polyneuropathy, but at other times obtaining normal results which do not exclude the diagnosis of TIND, because this technique is not totally appropriate to establish a diagnosis of small-fibre neuropathy.[45] Skin biopsy with determination of intraepidermic nervous fibre density remains the gold standard method to diagnose small-fibre neuropathy.[45] Moreover, corneal confocal microscopy has been proposed as an alternative, non-invasive method; however, its use is not widely available and is restricted to specialised centres.[46]

Treatment

A few studies showed that reduction in the insulin doses allowing a permissive hyperglycaemic metabolic state could reduce pain;[13] however, the long-term complications remain because of the chronic hyperglycaemia.[47]

Since the main reason for visiting a physician is neuropathic pain, the main objective of the therapy is pain management; therefore, the same drugs prescribed for DN may be used.[33] Although the evidence does not point toward relaxing glycaemic control aiming to accelerate pain resolution, the current consensus states that good glycaemic control must not be relaxed.[12,16,42,43]

Neuropathic pain in patients with TIND may progressively alleviate in a few weeks or in up to 36 months;[30,41] however, it is necessary to start analgesic therapy to reduce pain.[10,48–50]

In some cases, TIND pain is much more severe than that of DN, so single-agent therapy may be maximised, or a second or a third drug may be added to analgesic therapy.[47,51]

A poor response to opioids has been observed;[13] however, should pain persist, these drugs could be used additionally to other compounds.[29]

Tricyclic antidepressants may be included in drug therapy, but these should be used with caution, since their anticholinergic adverse effects may worsen TIND-associated orthostatic hypotension.[33]

Table 1 shows the drugs used in TIND.[6,20,24,32,48–50,52] Use cautiously in kidney disease and adjust for renal function as needed.

Drug	Class	Objective	Dose (mg/day)	Effect (weeks)
Pregabalin	First-line anticonvulsant	α2-δ ligand	300–600	8–12
Gabapentin	Second-line anticonvulsant	GABA	900–3600	4–6
Duloxetine	First-line antidepressant	SNRI	40–60	10–12
Amitriptyline	Second-line antidepressant	SNRI	25–100	2–4

GABA = gamma-aminobutyric acid; SNRI = serotonin and norepinephrine reuptake inhibitors.

Table 1. Drugs used for managing pain in treatment-induced neuropathy of diabetes, and general dosing

KEY POINTS

- Treatment-induced neuropathy of diabetes (TIND) is associated with rapid glycaemic improvement in patients with poor previous glycaemic control
- TIND pathophysiology is not completely clear, but may be related to changes in microcirculation that occur during hyperglycaemia periods
- TIND diagnosis is clinical but skin biopsy remains the gold standard method to diagnose small-fibre neuropathy
- Treatment of TIND includes the use of the same drugs prescribed for painful diabetic neuropathy and the maintenance of adequate glycaemic control

Perspectives

The ACCORD trial showed that intensive management of DM, aiming to reach HbA1c normal level, increased mortality and did not significantly reduce major cardiovascular events;[53] therefore, the benefit of aggressive therapy for DM may be smaller than its associated risks, and TIND is an excellent reminder of this situation.[4] Not all persons with DM get benefit from rapid glycaemia correction, so clinical practice guidelines should pay greater attention to this condition, establishing therapy goals limiting an excessive HbA1c reduction in a determined time period (2% as maximum in three months) and then allowing a safer approach.[54] More studies are needed to identify the most adequate way for achieving glycaemic control without increasing the risk of the occurrence of TIND and worsening retinopathy and nephropathy.[55,56]

There is still some doubt regarding this issue, such as how long should hyperglycaemia last for reaching the risk of occurrence of TIND and whether there may be other comorbidities that may increase or reduce the risk of developing TIND. Another point to be considered is whether a vegetarian diet may be a therapeutic option for those who are at risk for developing TIND since the improvement in glycaemia is gradual and not abrupt.[57]

Limitations

All authors recognise that despite describing the methodology used for the development of this narrative review, a research question is not answered; therefore, the scientific evidence is less than a systematic review. Additionally, minor limitations include the absence of clinical practice guidelines related to the diagnosis and management of TIND and the lack of epidemiological studies that describe its current prevalence worldwide.

Conclusions

TIND is a complication of intensive control of diabetes, in which, despite its prevalence, there is still not enough scientific evidence for guiding its management; therefore, it is necessary to look for the most adequate way of reaching a good glycaemic control without increasing the risk for the occurrence of TIND and, anticipating this, preventing

poor diabetes control, which is the primary cause of TIND.

Declaration of interests

There are no conflicts of interest declared.

References

1. American Diabetes Association Professional Practice Committee. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Medical Care in Diabetes – 2022. *Diabetes Care* 2021;45(Suppl 1):S185–94.
2. Feldman EL, *et al.* Diabetic neuropathy. *Nat Rev Dis Primer* 2019;5(1):1–18.
3. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Curr Diab Rep* 2019;19(10):86.
4. Tran C, *et al.* Acute painful diabetic neuropathy: an uncommon, remittent type of acute distal small fibre neuropathy. *Swiss Med Wkly* 2015;145:w14131.
5. Oh J. Clinical spectrum and diagnosis of diabetic neuropathies. *Korean J Intern Med* 2020;35(5): 1059–69.
6. Ferreira M, *et al.* Treatment-induced diabetes neuropathy: reminder of an important clinical lesson. *BMJ Case Rep* 2021;14(5):e241849.
7. Caravati C. Insulin neuritis: A case report. *Va Med Monthly* 1933;59:745–6.
8. Ellenberg M. Diabetic neuropathic cachexia. *Diabetes* 1974;23(5):418–23.
9. Archer AG, *et al.* The natural history of acute painful neuropathy in diabetes mellitus. *J Neurol Neurosurg Psychiatry* 1983;46(6):491–9.
10. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. *Ann Neurol* 2010;67(4):534–41.
11. Baethge C, *et al.* SANRA – a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev* 2019;4(1):5.
12. Quiroz-Aldave JE, *et al.* Treatment-induced neuropathy of diabetes: an underdiagnosed entity. *Lancet Neurol* 2023;22(3):201–2.
13. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain J Neurol* 2015;138(Pt 1):43–52.
14. Cuenca Hernández R, *et al.* Neuropatía inducida por el tratamiento de la diabetes o neuritis insulínica. *Neurología* 2018;33(9):616–8.
15. Duarte JM, *et al.* Polineuropatía desmielinizante inflamatoria crónica en paciente diabética con sífilis. *Med B Aires* 2018;78(4):286–9.
16. Hwang YT, Davies G. 'Insulin neuritis' to 'treatment-induced neuropathy of diabetes': new name, same mystery. *Pract Neurol* 2016;16(1):53–5.
17. Yuan J, *et al.* Treatment-induced neuropathy in diabetes: A report of 2 cases and literature review. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2020; 45(3):349–53.
18. Dabby R, *et al.* Acute painful neuropathy induced by rapid correction of serum glucose levels in diabetic patients. *Biomed Pharmacother Biomedecine Pharmacother* 2009;63(10):707–9.
19. Wilson JL, *et al.* Acute painful neuropathy (insulin neuritis) in a boy following rapid glycemic control for type 1 diabetes mellitus. *J Child Neurol* 2003; 18(5):365–7.
20. Aladdin Y, *et al.* Insulin neuritis and effect of pregabalin. *J Clin Neuromuscul Dis* 2017;19(1):1–4.
21. Gibbons CH. Small fiber neuropathies. *Contin Minneap Minn* 2014;20(5 Peripheral Nervous System Disorders):1398–412.
22. Chandler E, *et al.* Treatment-induced neuropathy of diabetes (TIND) in pediatrics: A case report and review of the literature. *J Clin Endocrinol Metab* 2020;105(2):dgz067.
23. Stainforth-Dubois M, McDonald EG. Treatment-induced neuropathy of diabetes related to abrupt glycemic control. *CMAJ* 2021;193(28):E1085–8.
24. Alexandrou EG, *et al.* Treatment-induced neuropathy of diabetes in youth: Case series of a heterogeneous and challenging complication. *J Endocr Soc* 2020; 4(12):bvaa154.
25. Smith AG, Singleton JR. Diabetic neuropathy. *Contin Minneap Minn* 2012;18(1):60–84.
26. Tesfaye S, *et al.* Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glycaemic control (insulin neuritis). *Diabetologia* 1996;39(3):329–35.
27. Meillet L, *et al.*, TRIMECO trial and the GRAGIL Network. First case of insulin neuritis after islet transplantation. *Acta Diabetol* 2019;56(6):713–5.
28. Song KB, *et al.* A case of insulin neuritis that developed in a patient under regular insulin treatment on increasing the insulin dose. Insulin neuritis: is it a misnomer? *J Neurol* 2009;256(2):274–5.
29. Varadharaju N, *et al.* A case of treatment-induced neuropathy in an adolescent with type 1 diabetes. *Ann Pediatr Endocrinol Metab* 2019;24(3):203–6.
30. Siddique N, *et al.* Acute diabetic neuropathy following improved glycaemic control: a case series and review. *Endocrinol Diabetes Metab Case Rep* 2020; 2020:EDM190140.
31. Broadhead DY, Devenport SB. Sensorimotor polyneuropathy in a diabetic patient after rapid overcorrection of chronic hyperglycemia. *J Investig Med High Impact Case Rep* 2021;9:23247096211051930.
32. Bullard KM, *et al.* Prevalence of diagnosed diabetes in adults by diabetes type – United States, 2016. *MMWR Morb Mortal Wkly Rep* 2018;67(12):359–61.
33. Gibbons CH. Treatment induced neuropathy of diabetes. *Auton Neurosci Basic Clin* 2020;226:102668.
34. Rasmussen VF, *et al.* Treatment-induced neuropathy of diabetes in an adolescent with rapid reduction in HbA_{1c} and weight loss: Persistent neuropathic findings at follow-up after 1.5 years. *Clin Case Rep* 2022;10(2):e05415.
35. Asbury AK, Fields HL. Pain due to peripheral nerve damage: an hypothesis. *Neurology* 1984;34(12): 1587–90.
36. Honma H, *et al.* Acute glucose deprivation leads to apoptosis in a cell model of acute diabetic neuropathy. *J Peripher Nerv Syst* 2003;8(2):65–74.
37. Mohseni S. Hypoglycaemic neuropathy. *Acta Neuropathol (Berl)* 2001;102(5):413–21.
38. Gibbons CH. Treatment-Induced Neuropathy of Diabetes. *Curr Diab Rep* 2017;17(12):127.
39. Bain SC, *et al.* Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. *Diabetes Obes Metab* 2019;21(3):454–66.
40. Hoffmann Y, *et al.* Functional predictors of treatment induced diabetic neuropathy (TIND): a prospective pilot study using clinical and neurophysiological functional tests. *Diabetol Metab Syndr* 2022; 14(1):35.
41. Gibbons CH, Goebel-Fabbri A. Microvascular complications associated with rapid improvements in glycemic control in diabetes. *Curr Diab Rep* 2017;17(7):48.
42. Seneviratne U, Gunasekera S. Acute small fibre sensory neuropathy: another variant of Guillain-Barré syndrome? *J Neurol Neurosurg Psychiatry* 2002; 72(4):540–2.
43. Dabby R, *et al.* Acute steroid responsive small-fiber sensory neuropathy: a new entity? *J Peripher Nerv Syst* 2006;11(1):47–52.
44. Naddaf E, Dyck PJB. Vasculitic neuropathies. *Curr Treat Options Neurol* 2015;17(10):374.
45. Samakidou G, *et al.* Rare diabetic neuropathies: It is not only distal symmetrical polyneuropathy. *Diabetes Res Clin Pract* 2021;177:108932.
46. Papanas N, Ziegler D. Corneal confocal microscopy: Recent progress in the evaluation of diabetic neuropathy. *J Diabetes Investig* 2015;6(4):381–9.
47. Campos C. Chronic hyperglycemia and glucose toxicity: Pathology and clinical sequelae. *Postgrad Med* 2012;124(6):90–7.
48. Alam U. Diabetic Neuropathy collection: Treatment of diabetic neuropathy. *Diabetes Ther* 2020;11(4):765–72.
49. Rolim LC, *et al.* A Systematic review of treatment of painful diabetic neuropathy by pain phenotype versus treatment based on medical comorbidities. *Front Neurol* 2017;8:285.
50. Bouhassira D, *et al.* Neuropathic pain phenotyping as a predictor of treatment response in painful diabetic neuropathy: data from the randomized, double-blind, COMBO-DN study. *Pain* 2014; 155(10):2171–9.
51. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352(9131):837–53.
52. Price R, *et al.* Oral and topical treatment of painful diabetic polyneuropathy: Practice guideline update summary: Report of the AAN Guideline Subcommittee. *Neurology* 2022;98(1):31–43.
53. Action to Control Cardiovascular Risk in Diabetes Study Group; Gerstein HC, *et al.* Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358(24):2545–59.
54. Storz MA. Treatment-induced neuropathy of diabetes: a call for acknowledgement. *Diabet Med* 2020; 37(2):369–70.
55. Arezzo JC, *et al.* Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *BMC Neurol* 2008;8:33.
56. Hossain SM, *et al.* Duloxetine in painful diabetic neuropathy: A systematic review. *Clin J Pain* 2016; 32(11):1005–10.
57. Storz MA. No common denominator: Plant-based diets and treatment-induced neuropathy of diabetes. *Med Hypotheses* 2019;129:109250.

Appendix 1. Author affiliations. (Superscript numbers correspond to those shown in the author details panel on the first page of this paper)

[1]Division of Medicine, Hospital de Apoyo Chepén, Chepén, Perú
[2]Carrera de Medicina Humana, Universidad Científica del Sur, Lima, Perú
[3]Division of Family Medicine, Hospital de Apoyo Chepén, Chepén, Perú
[4]Division of Endocrinology, Hospital Víctor Lazarte Echegaray, Trujillo, Perú
[5]Division of Physical Medicine and Rehabilitation, Hospital Víctor Lazarte Echegaray, Trujillo, Perú
[6]Division of Internal Medicine, Hospital de Apoyo Chepén, Chepén, Perú
[7]Division of Endocrinology. Hospital Nacional Guillermo Almenara Irigoyén, Lima, Perú
[8]School of Medicine, National University of Trujillo, Trujillo, Perú
[9]Alexander von Humboldt Institute of Tropical Medicine, Peruvian University Cayetano Heredia, Lima, Perú
[10]School of Medicine, National University of San Marcos, Lima, Perú

Case	Age (years)	Sex	Years of DM	Type of DM	DM treatment	HbA_{1c} reduction % (mmol/mol)	Time (weeks) to develop neuropathy	Reversion	Neuropathy treatment	Authors
1	54	F	2.00	2	Insulin	9.60 (81)	8	Partial	Acetaminophen, imipramine	Tesfaye S, *et al.* (1996)[26]
2	52	M	5.00	2	Insulin	3.90 (19)	6	Complete	Acetaminophen, codeine	Tesfaye S, *et al.* (1996)[26]
3	62	M	5.00	2	Insulin	8.50 (69)	4	Partial	Imipramine	Tesfaye S, *et al.* (1996)[26]
4	34	M	0.17	1	Insulin	Not specified	4	Complete	Acetaminophen, codeine	Tesfaye S, *et al.* (1996)[26]
5	35	F	0.17	1	Insulin	9.60 (81)	8	Complete	Not specified	Tesfaye S, *et al.* (1996)[26]
6	14	M	1.08	1	Insulin	6.50 (48)	6	Partial	Gabapentin, acetaminophen	Wilson JL, *et al.* (2003)[19]
7	30	M	15.00	1	Insulin	2.20 (1)	3	Complete	Amitriptyline	Song KB, *et al.* (2009)[28]
8	29	M	3.00	1	Insulin	13.90 (128)	4	Complete	Carbamazepin, tramadol	Dabby R, *et al.* (2009)[18]
9	30	F	4.00	1	Insulin	11.80 (105)	2	Complete	Gabapentin, duloxetine	Dabby R, *et al.* (2009)[18]
10	27	M	4.00	1	Insulin	6.20 (44)	3	Complete	Duloxetine, pregabalin	Dabby R, *et al.* (2009)[18]
11	56	M	5.00	2	OADs	4.60 (27)	2	Complete	Amitriptyline, gabapentin, pregabalin, duloxetine	Dabby R, *et al.* (2009)[18]
12	58	M	5.00	2	Glibenclamide	6.70 (50)	4	Complete	Carbamazepine, amitriptyline, duloxetine	Dabby R, *et al.* (2009)[18]
13	52	M	5.00	2	OADs	9.10 (76)	2	Complete	Duloxetine, gabapentine, oxycodone	Dabby R, *et al.* (2009)[18]

DM = diabetes mellitus; M = male; F = female; OADs = oral antidiabetic drugs; NSAIDs = non-steroidal anti-inflammatory drugs.

Appendix 2. Case reports of treatment-induced neuropathy of diabetes.[4,14–31] *(Continued on the next 2 pages)*

Case	Age (years)	Sex	Years of DM	Type of DM	DM treatment	HbA_{1c} reduction % (mmol/mol)	Time (weeks) to develop neuropathy	Reversion	Neuropathy treatment	Authors
14	22	F	Many years (not specified)	1	Insulin	Not specified	4	Complete	Gabapentin, opioids	Smith AG, *et al.* (2012)[25]
15	23	F	Not specified	1	Insulin	Not specified	5	Partial	Not specified	Gibbons CH. (2014)[21]
16	57	M	5.00	2	Not specified	4.00 (20)	4	Complete	Diet	Tran C, *et al.* (2015)[4]
17	44	M	0.50	1	Insulin	7.90 (63)	6	Partial	Pregabalin, gabapentin, duloxetine, opioids	Tran C, *et al.* (2015)[4]
18	49	M	0.33	2	Insulin	9.00 (75)	Not specified	Complete	Duloxetine	Tran C, *et al.* (2015)[4]
19	41	F	0.08	1	Insulin	9.10 (76)	4	Partial	Pregabalin, amitriptyline	Tran C, *et al.* (2015)[4]
20	22	F	16.00	1	Insulin	1.10 (-)	16	Partial	Gabapentin	Hwang YT, *et al.* (2016)[16]
21	24	F	16.00	1	Insulin	5.20 (33)	2	Complete	Pregabalin	Hwang YT, *et al.* (2016)[16]
22	43	F	16.00	1	Insulin	8.40 (68)	4	Complete	Pregabalin	Aladdin Y, *et al.* (2017)[20]
23	46	M	14.00	2	Metformin, glibenclamide	12.10 (109)	4	Partial	Gabapentin	Aladdin Y, *et al.* (2017)[20]
24	54	F	2.00	2	Insulin	2.70 (6)	8	Complete	Human immunoglobulin	Duarte JM, *et al.* (2018)[15]
25	25	M	0.25	1	Insulin	6.20 (44)	6	Partial	NSAIDs, tramadol, duloxetine	Cuenca Hernández R, *et al.* (2018)[14]
26	35	F	23.00	1	Pancreatic islet transplant	9.10 (76)	1.5	Non-remission	Pregabalin, duloxetine, venlafaxine, amitriptyline	Meillet L, *et al.* (2019)[27]
27	16	F	1.50	1	Insulin	10.40 (90)	4	Complete	Amitriptyline, pregabalin and gabapentin	Varadharaju N, *et al.* (2019)[29]
28	56	M	0.67	2	Insulin	8.10 (65)	6	Complete	Pregabalin	Siddique N, *et al.* (2020)[30]
29	67	M	1.00	2	Insulin, metformin, glicazide	9.40 (79)	8	Partial	Pregabalin	Siddique N, *et al.* (2020)[30]
30	58	M	2.00	2	Dapagliflozin	Not specified	2	Complete	None	Siddique N, *et al.* (2020)[30]

DM = diabetes mellitus; M = male; F = female; OADs = oral antidiabetic drugs; NSAIDs = non-steroidal anti-inflammatory drugs.

Appendix 2. Case reports of treatment-induced neuropathy of diabetes.[4,14–31] *(Continued on the next page)*

Case	Age (years)	Sex	Years of DM	Type of DM	DM treatment	HbA_{1c} reduction % (mmol/mol)	Time (weeks) to develop neuropathy	Reversion	Neuropathy treatment	Authors
31	19	F	5.00	1	Insulin	8.80 (73)	6	Partial	Not specified	Yuan J, *et al.* (2020)[17]
32	81	F	12.00	2	Metformin	Not specified	0.5	Complete	Not specified	Yuan J, *et al.* (2020)[17]
33	18	M	1.00	1	Insulin	7.30 (56)	5	Partial	Pregabalin	Chandler E, *et al.* (2020)[22]
34	14	M	0.25	1	Insulin	8.40 (68)	12	Complete	Gabapentin	Alexandrou EG, *et al.* (2020)[24]
35	16	F	0.08	1	Insulin	4.10 (21)	4	Partial	Gabapentin	Alexandrou EG, *et al.* (2020)[24]
36	19	M	5.00	1	Insulin	3.50 (15)	4	Complete	Gabapentin	Alexandrou EG, *et al.* (2020)[24]
37	22	M	3.00	1	Insulin	3.50 (15)	8	Complete	Duloxetin	Alexandrou EG, *et al.* (2020)[24]
38	19	M	3.00	1	Insulin	5.70 (39)	8	Partial	Not specified	Alexandrou EG, *et al.* (2020)[24]
39	9	F	0.17	1	Insulin	8.00 (64)	4	Complete	Not specified	Alexandrou EG, *et al.* (2020)[24]
40	17	M	0.08	1	Insulin	3.30 (13)	4	Complete	Gabapentin and cannabis	Alexandrou EG, *et al.* (2020)[24]
41	20	F	New onset	1	Insulin	10.30 (89)	12	Partial	Venlafaxine	Stainforth-Dubois M, *et al.* (2021)[23]
42	66	F	9	2	Insulin, metformin	8.90 (74)	12	Partial	Not specified	Broadhead DY, *et al.* (2021)[31]

DM = diabetes mellitus; M = male; F = female; OADs = oral antidiabetic drugs; NSAIDs = non-steroidal anti-inflammatory drugs.

Appendix 2. Case reports of treatment-induced neuropathy of diabetes.[4,14–31] *(Continued on from the previous 2 pages)*