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Journal of Diabetes Education

To Dispel Darkness Of Diabetes

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EXERCISE

MEDICATION

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JOURNAL OF DIABETES EDUCATION

To Dispel Darkness of Diabetes

Vol. 13 **Number 3** **July-September, 2025**

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DIABETES REVERSAL: HYPE, HOPE OR HAPPENING?

Purvi Chawla*

INTRODUCTION

Diabetes reversal is a popular topic, especially for those who have just been diagnosed with diabetes, those living with it and health care providers. In 2022, over 828 million adults aged 18 and older had diabetes, up from 630 million in 1990. Most people affected by diabetes, especially those who don't get treatment, are in low-income and middle-income countries. It is the quadrupled prevalence of diabetes that makes it imperative for newer and more aggressive interventions to curb the disease (1).

Most patients expect a "natural" cure or a way to be able to reverse their diabetes and not take any medications for the same. Hence, the real question is, is there a way that can reverse the pathophysiology or biology of diabetes? In order to avoid controversy and unrealistic claims, one must paraphrase and explain it as the process of achieving diabetes remission. Diabetes is considered in remission if a person's HbA1c level drops to 6.5% or lower, either on its own or after treatment and stays there for three months without using any medicine to lower blood glucose (2).

Diabetes remission means having good blood glucose levels without using glucose lowering medications. It is important to think about using drugs like SGLT2 inhibitors and GLP-1 receptor agonists, which are often used for heart failure, obesity and kidney disease, even if a person doesn't have diabetes. Also, metformin, the main oral medicine for diabetes, is often given for pre-diabetes and polycystic ovarian syndrome, not just for diabetes (3).

PATHOGENESIS OF TYPE 2 DIABETES

Type 2 diabetes mellitus (T2DM) is a condition marked by primarily two factors: defective insulin secretion by the beta cells in the pancreas and the inefficient or inappropriate response to insulin from the insulin-sensitive tissues. The insulin secretion from the pancreas, as the disease progresses, is unable to maintain glucose homeostasis, leading to hyperglycemia. With increasing obesity or higher body fat accumulation, especially in the abdominal region, there is enhanced insulin resistance in various tissues via increased free fatty acid release and adipokine dysregulation. Besides obesity, drivers of T2DM are high caloric dietary intake, sedentary lifestyle and an aging population. There are multiple organs involved, like the beta and alpha cells in the pancreas, the liver, heart, skeletal muscle, kidneys, brain, small intestine and adipose tissue and multiple processes involved, like adipokine dysregulation, inflammation, dysfunctional gut microbiota, immune dysregulation and inflammation (4).

PATHOPHYSIOLOGICAL BASIS OF DIABETES AND THE TWIN CYCLE HYPOTHESIS

To understand diabetes remission, it is necessary to understand that T2DM is the result of excessive fat accumulation in the liver and pancreas. In the award-winning lecture by Roy Taylor at Diabetes UK in 2012, he explained the "Twin Cycle Hypothesis" (Figure 1). The hypothesis included the two cycles of fat infiltration in the liver and pancreas. With constant excess caloric intake, carbohydrates undergo de novo lipogenesis in the liver, which simply means conversion to fats, thus accumulating fat in the liver. In those individuals with baseline insulin resistance attributable to a positive family history or lifestyle factors, the fat accumulation in the liver is fast and aided by

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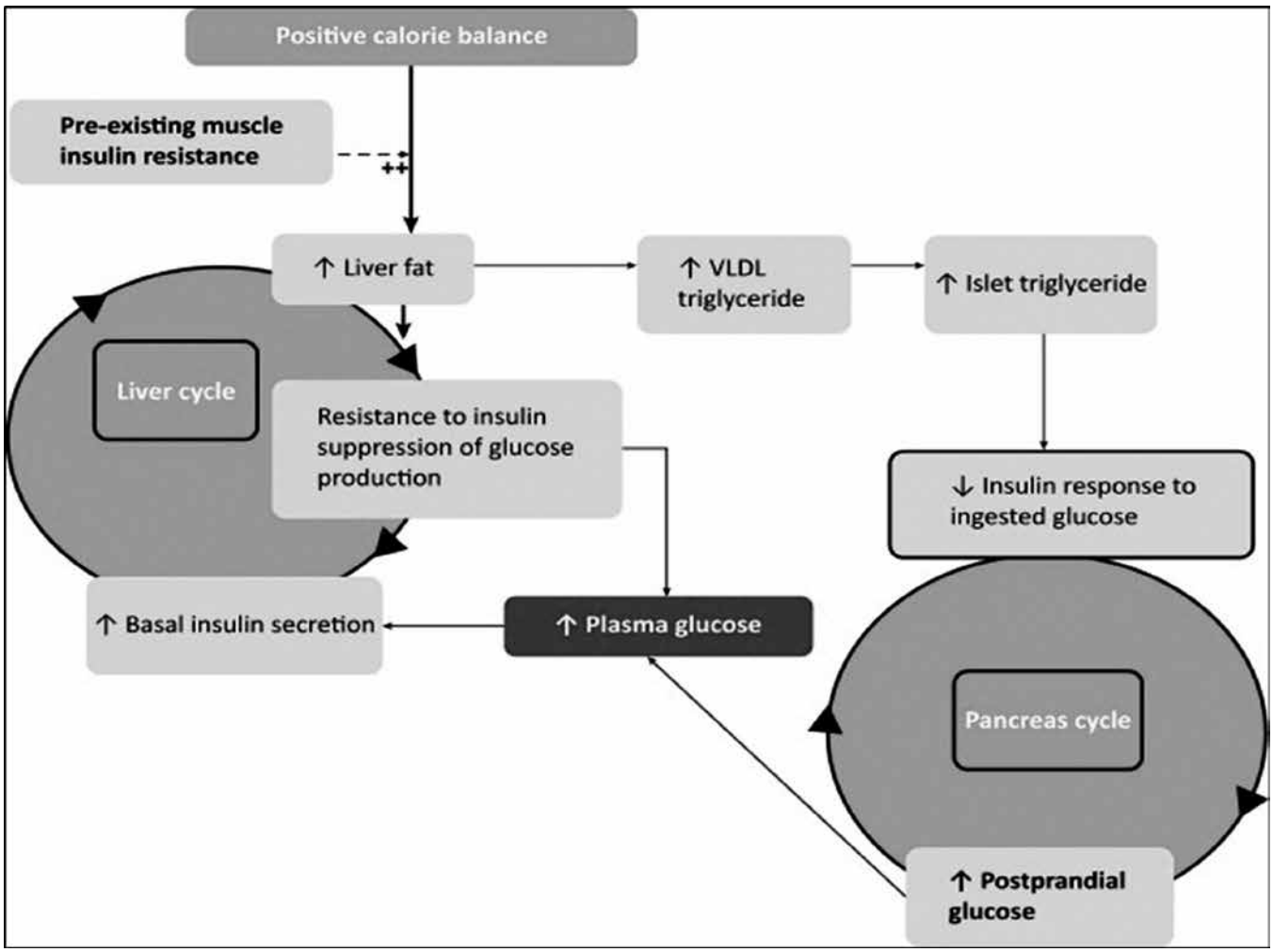
high plasma insulin levels. The increased hepatic fat further accentuates the resistance, in turn causing unrestricted hepatic glucose production. This continued insult with the intake of excessive calories followed by fat accumulation is the first vicious cycle in the liver with hyperinsulinemia and increased liver fat. Once the liver has excessive fat, there is evidence of VLDL triacylglycerol being exported to the pancreas. The increased fatty acid exposure in the pancreas impairs the islet secretion of insulin, especially the first phase of acute insulin release in response to the food eaten. Furthermore, the fatty acids and glucose inhibitory effect on the islets continues as the second vicious cycle, manifesting as clinical diabetes. Due to the immediate and acute negative caloric balance induced by bariatric surgery, there is a reversal of this "twin cycle" observed. This phenomenon was observed in individuals with diabetes of up to 6-year duration. undergoing bariatric surgery. These individuals were able to reverse the abnormalities associated with diabetes in proportion to the weight loss they achieved with surgery. This inspired a series of experiments to find a non-surgical approach to achieve these results (5).

Figure 1

The Twin Cycle Hypothesis (5)



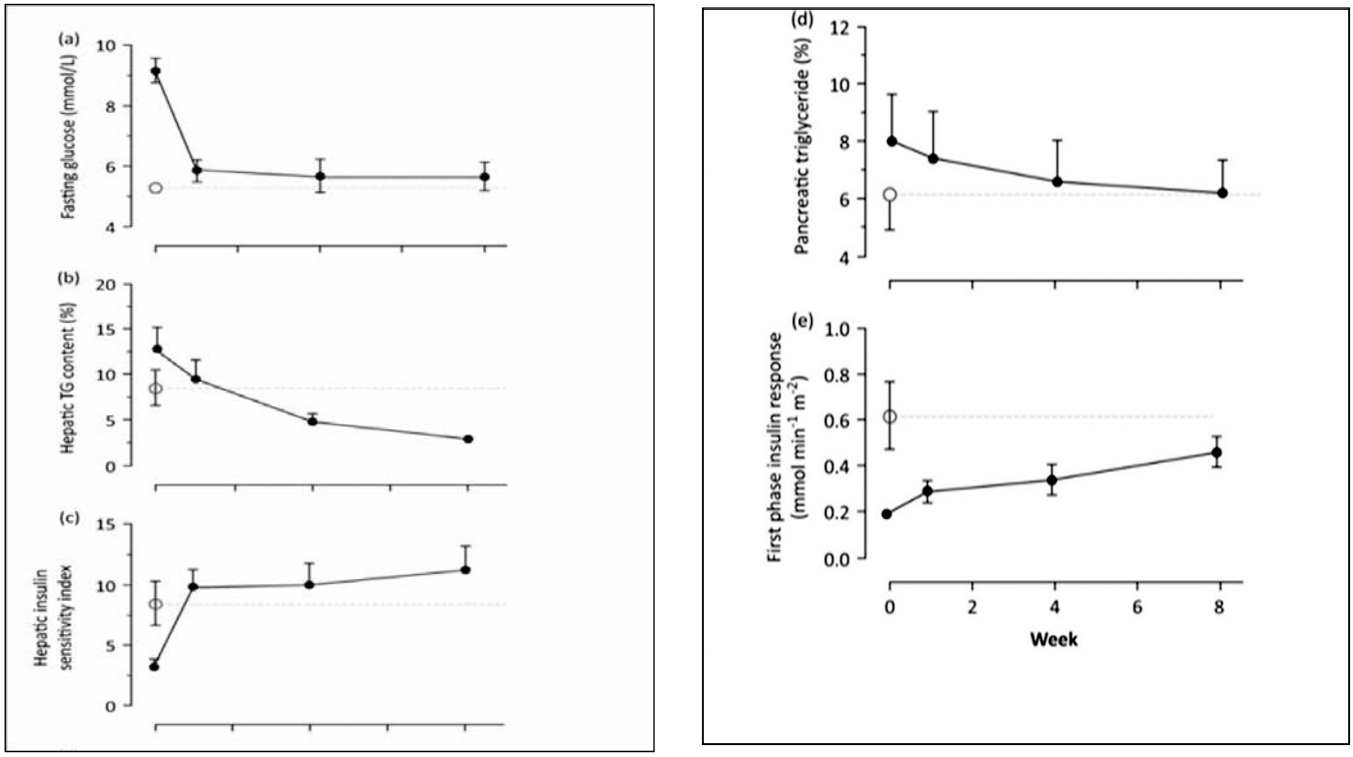
EVIDENCE

Several approaches have been tried to effect diabetes reversal. The most relevant studies have been described here to present the view that "Diabetes Remission" is not just hype or hope; it is indeed happening.

One of the earliest studies to test the Twin Cycle Hypothesis was the Counterpoint study (Counteracting Pancreatic Inhibition by Triglyceride) that evaluated the effect of a very low caloric diet in a group of individuals with T2DM of less than four years' duration. A total of eleven individuals with T2DM (nine male and two female subjects) completed the study (mean age 49.5 ± 2.5 years, mean BMI 33.6 ± 1.2 kg/m² over a duration of 8 weeks. Approximately 600 kilocalories were provided per day by way of three packets of liquid meal replacements (Optifast, Nestle UK Ltd., UK) and non-starch vegetables/salad during the study. Key results included improvement in a number of glycemic parameters following a 15.3kg weight loss over 8 weeks in 33% of these individuals. There was a 30% reduction in the liver fat observed within the first seven days with liver insulin sensitivity reversing to the normal state. Fasting blood glucose also normalised to non-diabetes levels within the first seven days, although the pancreatic fat content decreased and normal insulin secretion was restored only by eight weeks. This study proved that dietary intervention in the form of a very low-calorie diet in the home setting could produce a clinically significant magnitude of weight loss in motivated individuals and help achieve diabetes remission (6).

Figure 2

Results from the Counterpoint study (6)



(a) plasma glucose, (b) hepatic triglyceride content, (c) hepatic insulin sensitivity, (d) pancreas triglyceride content and (e) first phase insulin response. Data are shown as mean ±standard error, for diabetic subjects (filled circles) and measured at a single time point for a weight matched non-diabetic control group

Although the COUNTERPOINT study had small numbers and a short duration, the results were encouraging. The durability of diabetes remission was further tested in the Counterbalance study (COUNTER acting BetA cell failure by Long term Action To Normalize Calorie IntakE), a prospective, longitudinal study in which at least thirty individuals with T2DM of varying duration (0.5-23 years) were recruited to undergo an eight-week phase of very low caloric diet, followed by a two-week stepped reintroduction of normal food and a six-month weight maintenance phase. The pathophysiological factors underlying diabetes remission and the durability of remission were evaluated. Anti-diabetes medications were stopped on the first day of the diet, including any sulfonylureas/insulin. Subjects who lost a significant amount of weight, i.e., 15% weight loss, showed remission of T2DM after the eight-week dietary intervention. In those with diabetes of a short duration (< 4 years), there was a rapid decline in fasting plasma glucose as compared to those with diabetes duration of > 8 years, the group in which fifty percent of individuals had restored normoglycemia. Weight loss normalized both liver fat content and insulin sensitivity, indicating improved liver handling of glucose. A clear relationship between the fasting plasma glucose at the end of the first phase and the duration of diabetes was established ($r=0.50$, $p<0.0006$). Those who did not respond or show remission had a similar liver fat reduction as those who did show remission, clearly indicating that it is also the capacity of the pancreatic beta cells to recover that drives the remission process. Improvement in liver and pancreatic fat content and the first phase of insulin secretion remained constant and normoglycemia was maintained during this period as long as the weight loss was maintained. The concept of the "personal fat threshold" was introduced, suggesting that different individuals have different fat tolerance levels, regardless of their BMI and when that fat threshold within the hepatic and pancreatic tissues is crossed, there is a manifestation of T2DM (7).

The ReTUNE study was undertaken to investigate if people with T2DM who were not overweight/obese could achieve remission through weight loss using a low-calorie diet. Thus, twenty individuals with T2DM (mean age 59.3±7.1 years, BMI 24.8±1.7kg/m^2) who underwent up to three cycles of 5% weight loss, every cycle comprising of two to four weeks of a low-energy diet (800 kcal/day with meal replacements and non-starchy vegetables) followed by 4-6 weeks of weight maintenance. The study subjects were compared to normoglycemic matched controls (n=20) over a one-year period with several evaluations. In this study, seventy percent (n=14) of the individuals achieved remission (HbA1c<6.5%) with an associated reduction in adipose tissue distress, BMI, total body fat, fasting plasma insulin, liver fat, plasma triglycerides, intrapancreatic fat and related parameters. The remission was maintained throughout the study duration on a normal diet, as long as the weight loss was maintained. These results well-demonstrated that weight loss of approximately 10% in those with a normal BMI was responsible for diabetes remission with the same mechanistic changes in the liver and pancreas as seen in the overweight/obese with T2DM. Thus, diabetes manifests when a person gains weight more than the individual threshold, irrespective of the BMI and amount of weight loss; specifically, reduction in liver and pancreatic fat are key to achieving remission in all (8).

A landmark trial in diabetes remission is the Diabetes Remission Clinical Trial (DiRECT) conducted across primary care practices in the UK. It was designed to determine whether a structured, intensive weight management program, delivered in a routine primary care setting, is a viable treatment for achieving durable normoglycemia. Other aims were to understand the mechanistic basis of remission and to identify psychological predictors of response.

In 36 (24%) participants in the intervention group, there was a weight loss of ≥15 kg at the end of 12 months as compared to none in

the control group (p<0.0001), with 68 (46%) participants achieving diabetes remission in the intervention group and 6 (4%) participants in the control group. The mean body weight loss was 10 kg and 1 kg in the intervention and control groups, respectively. The remission rate was proportional to the weight loss achieved in the study participants; none among the 76 participants who gained weight, (6 from 89 participants, 7%), (19 of 56 participants, 34%), (16 of 28 participants, 57%) and (31 of 36 participants, 86%) who lost 0-5 kg, 5-10 kg, 10-15 kg and >15 kg, respectively. There were 9 serious adverse events reported by 7 (4%) of 157 participants in the intervention group, while there were 2 serious adverse events reported by 2 (1%) participants in the control group, with none leading to withdrawal from the study. After 24 months in the DIRECT trial, 17 (11%) and 3 (2%) participants in the intervention and control groups, respectively, lost weight to the tune of 15 kg (aOR 7.49, 95% CI 2.05 to 27.32, p=0.0023) or more. Then, 53 (36%) and 5 (3%) participants in the intervention and control groups, respectively, attained diabetes remission (OR 25.82, 8.25 to 80.84, p <0.0001). The post-hoc analysis, including all study participants, revealed that of the 45 participants of the 272 (where data was known) who maintained at least 10 kg weight loss, 29 (64%) had attained diabetes remission, with 36 (24%) of the 149 participants from the intervention group maintained at least 10 kg weight loss. Serious adverse events were similar to those reported at 12 months and less in the intervention group as compared to the control group (nine versus 22) at the end of 24 months (9). After the 2nd year, participants in the intervention group (101 of the 149, 68%) were offered low-intensity support for 3 more years; thus, 95 (94%) of the 101 participants agreed to participate in the DIRECT extension trial. Amongst these participants, 54 were randomized to the non-extension group with the intervention being withdrawn. At the end of 5 years of this DIRECT extension trial (n=85), a mean weight loss of 6.1 kg was noted, with 11 (13%) of 85 participants achieving remission and benefits in HbA1c, blood pressure and lipids. Thus, diabetes remission appeared to be a pragmatic target for motivated patients, as the sustained remissions were found to be associated with the extent of weight loss maintained (10).

In a retrospective, observational study of people with T2DM who underwent metabolic and bariatric surgery, there were assessments to see the incidence of durable remission and relapse of diabetes rates ten years post-surgery and also to assess predictive factors for remission. Among the ninety-five patients (mean age 48.8±9.1 years, mean HbA1c 7.0±1.5%) included, the rate of complete diabetes remission was 31% at the end of ten years of follow-up, partial remission was at 15% and late recurrence after initial remission was at 24%. At this ten-year follow-up, it was also observed that patients maintained lower fasting plasma glucose (p<0.001), HbA1c (p<0.001), number of anti-diabetic agents (p<0.001) and incidence of insulin therapy (p<0.001). It was concluded that preoperatively, those with a lower HbA1c and taking a lesser number of antidiabetic agents were able to maintain remission for longer period. This study clearly proved that significant improvement and sustainable remission were achievable with metabolic and bariatric surgery (11).

With limited evidence from randomized, controlled trials evaluating and comparing surgical with nonsurgical modalities for remission of diabetes, the Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial was undertaken in one hundred and fifty persons living with diabetes and a BMI of 27-43 kg/m². The trial subjects were assigned to either of the two arms in the trial, with one arm receiving intensive medical therapy alone and the other arm receiving intensive medical therapy plus Roux-en-Y gastric bypass/sleeve gastrectomy. The primary endpoint was achieving an HbA1c ≤6% with or without the use of diabetes medications at the end of five years. From the total number enrolled (except one death during the five-year follow-up period), 134 patients (90%) completed the entire study. Baseline characteristics included a mean age

of 49±8 years, 66% females, a mean HbA1c of 9.2±1.5% and a mean BMI of 37±3.5 years. The results included achievement of the primary endpoint by 2 of 38 (5%) participants in the medical therapy alone arm, 14 of 49 (29%) participants and 11 of 47 participants (23%) in the surgical plus medical therapy arm with gastric bypass and sleeve gastrectomy, respectively. At the end of the 5-year follow-up period, participants achieved a greater reduction in HbA1c (2.1% vs. 0.3%, p=0.03), body weight by 23%, 19% and 5%, triglycerides by 40%, 29% and 8%, HDL cholesterol by 32%, 30% and 7%, decreased insulin use by 35%, 34% and 13% and greater quality of life measures in the gastric bypass, sleeve gastrectomy and medical therapy alone arms, respectively ($P<0.05$ for all comparisons). No major late surgical complications were observed, except for one reoperation. Thus, the surgical arm with medical intervention fared far better for remission than medical-therapy alone in diabetes patients with a BMI between 27 and 43 kg/m² (12).

A large systematic review and meta-analysis to evaluate the long-term (≥5 years) outcomes of bariatric surgery on remission of diabetes along with microvascular and macrovascular complications and mortality in T2DM found that among the ten trials (one randomized controlled trial and nine cohorts) included in this review, there was increased diabetes remission (RR = 5.90; 95% CI 3.75-9.28), reduced microvascular (RR = 0.37, 95% CI 0.30-0.46) and macrovascular (RR = 0.52, 95% CI 0.44-0.61) complications and mortality (RR = 0.21, 95% CI 0.20-0.21) post-bariatric surgery as compared to any other non-surgical treatment. Thus, it was observed that there are better remission rates and lower risks of microvascular and macrovascular complications in T2DM patients in the surgical group as compared to those who underwent non-surgical interventions for diabetes after 5 years of follow-up (13).

The Swedish Obese Subjects (SOS) study is the largest study of bariatric surgery and diabetes remission conducted as a prospective, controlled design with two comparative arms; i.e. in one arm, 2010 obese subjects with T2DM underwent gastric bypass (13.2%), banding procedures (18.7%), or vertical banded gastroplasty (68.1%) and 2037 matched control subjects received usual care. A total of 4032 subjects were analyzed by stratification based on baseline glycemic status (euglycemia n=2838, prediabetes n=591, screen-detected diabetes n=246, established diabetes n=357) for microvascular events including retinopathy, diabetic kidney disease and neuropathy (whichever occurred first). At the 15-year follow-up of the study, approximately 21% of subjects from the surgery arm achieved and had maintained complete diabetes remission in comparison to 2% in the control group, with sustained benefits in weight loss, glycemic control and beta cell function (14).

Overall, as compared to the control arm that reported 374 events, there were 224 first-time microvascular events (complications of the eyes, kidneys, or nerves, whichever event occurred first) in the surgery group, corresponding to an incidence rate of 10.9 and 6.3 events per 1000 person-years, respectively (HR, 0.56; 95% CI 0.48-0.66, $p<0.0001$).

In those who had prediabetes at baseline and continued to remain diabetes-free at the end of 15 years, there was an increased reduction of microvascular complications as compared to those who developed diabetes during the 15-year follow-up, highlighting the need to prevent diabetes to reduce microvascular complications. The rates were also lower in those who not only remained diabetes-free but also those who maintained lower fasting glucose levels in the surgery arm as compared to the controls. The results also demonstrated the reduction of microvascular events in obese individuals with or without diabetes at the time they underwent surgery. The surgical intervention was more beneficial in those with prediabetes as compared to those with diabetes or normal blood glucose at baseline.

Thus, the SOS study is one of the longest follow-up data on bariatric surgery and remission, with insights on the complications. The study had an extension up to 15 years, highlighting the

need for early intervention for increased weight loss with surgical interventions predicting better remission rates and also underscoring the importance of medical management and regular follow-up (14).

A large consortium, ARMMS-T2D (Alliance of Randomized Trials of Medicine versus Metabolic Surgery in Type 2 Diabetes), investigated the durability and the long-term effectiveness of metabolic surgery compared with medical/lifestyle management in a prospective observational study including 316 people with T2DM, of whom 195 had previously undergone surgery and 121 had undergone medical/lifestyle therapy in the STAMPEDE, TRIABETES, SLIMM-T2D and CROSSROADS trials. While the primary outcome was to determine the rate of diabetes remission at 3 years in these individuals, the secondary outcomes included other parameters like glycemic control, weight, biomarkers and a reduction in comorbidities. On completion of three years, 256 patients, mean age 50 ± 50±8.3 years, BMI 36.5 ± 3.6kg/m² and duration of diabetes 8.8 ± 5.7 years, were analysed. A statistically significant greater number of individuals achieved diabetes remission post-surgery, i.e., 60/160 (37.5%) individuals, as compared to 2/76 (2.6%) with medical/lifestyle therapy ($p<0.001$), with greater reductions in HbA1c, fasting plasma glucose and BMI and lower use of medications for diabetes, hypertension, or dyslipidemia observed in the former cohort as compared to the latter one. Thus, this large study with the three-year follow-up demonstrated that metabolic surgery was more effective for diabetes remission than medical/lifestyle interventions, including in individuals with class 1 obesity, who may not commonly undergo surgery (15).

Thus, there is overwhelming evidence with bariatric surgery, with medical and lifestyle interventions in the form of low-calorie and low-carbohydrate diets is effective for diabetes remission and also reduces complications associated with diabetes. Due consideration to the patient and physician perspectives must be given to enable varied choices for someone living with diabetes or even newly diagnosed diabetes (16).

LESSONS FROM THE SCIENTIFIC EVIDENCE

Diabetes remission occurs with weight loss of at least 15 kgs or 15% of the baseline body weight, regardless of the method selected to achieve the same. From the large number of randomized controlled trials, the systematic reviews and meta-analyses, it is clear that bariatric surgery is the most effective tool for inducing weight loss and maintenance over time as compared to pharmacological or dietary interventions. While guidelines describing the standard of care are implemented for all patients, there may be a subset of individuals willing to adopt the methods necessary for remission. Besides, the concept of personal fat threshold offers hope even to relatively lean individuals developing diabetes, especially important in the Indian scenario.

A review of the literature has suggested that there are certain predictors of more diabetes remission:

- Highly motivated person living with diabetes
- Shorter duration of diabetes (6 years or less)
- HbA1c moderately high and not overtly high at baseline
- Men achieving remission is likelier than women due to greater weight loss achieved in men
- High body weight and BMI
- High levels of C-peptide/insulin secretion and those persons not on insulin therapy (17)

In terms of those persons with diabetes who achieve remission, those who manage to maintain the weight loss will have a sustained remission of diabetes. Persons who are regular with the follow-up have a greater likelihood of maintaining the remission. Thus, the key to achieving successful remission is patient selection and setting up expectations for patients.

PATIENT PERSPECTIVES

Even though interventions aimed at remission of diabetes are not a part of first-line standard of

care as per guidelines, a choice should be offered to people living with diabetes. Upon release of the results from the Counterpoint study, the communication received by the study team from people living with diabetes was overwhelming, with more than eight hundred letters, emails and phone calls sharing personal disappointment at being diagnosed with diabetes, relief at finding a potential path to remit diabetes and the lack of knowledge for a successful outcome. With the optimal patient selection and guidance provided, diabetes remission may be achieved more frequently (18).

Remission of diabetes must be offered to people with Type 2 diabetes, especially those who are highly motivated to undertake sustained efforts to achieve optimal health status and remit the condition. Even patients with a longer duration of diabetes and on insulin therapy or with a normal BMI may be able to achieve remission or at least a reduction in the number of medications by appropriate dietary choices with decreased carbohydrate intake. Even if complete remission is not achieved, use of a lesser number of medications or lower doses with improvement in health is akin to a success (17).

REFERENCES:

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. Lancet. 2024; 23;2077-2093.
2. Shibib L, Al-Qaisi M, Ahmed A, et al. Reversal and Remission of T2DM - An Update for Practitioners. Vasc Health Risk Manag. 2022;18: 417-443.
3. Rolek B, Haber M, Gajewska M, Rogula S, Pietrasik A, Gąsecka A. SGLT2 Inhibitors vs. GLP-1 Agonists to Treat the Heart, the Kidneys and the Brain. J Cardiovasc Dev Dis. 2023;10 :322.
4. Roden M., Shulman G.I. The integrative biology of Type 2 diabetes. Nature. 2019; 576:51–60.
5. Taylor R. Calorie restriction for long-term remission of Type 2 diabetes. Clin Med (Lond). 2019; 19:37-42.
6. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of Type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia. 2011;54 :2506-14.
7. Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very low-calorie diet and 6 months of weight stability in Type 2 diabetes: Pathophysiological changes in responders and non-responders. *Diabetes* Care. 2016; 39:158–65.
8. Taylor R, Irvine KM, Barnes AC, et al. Remission of Type 2 Diabetes after Weight Loss in "Normal" Weight People—The ReTUNE Study. Diabetes 1. 2022; 71 (Supplement 1): 218–LB.
9. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of Type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391:541-551.
10. Lean ME, Leslie WS, Barnes AC, et al. 5-year follow-up of the randomised Diabetes Remission Clinical Trial (DiRECT) of continued support for weight loss maintenance in the UK: an extension study. Lancet Diabetes Endocrinol. 2024;12 :233-246.
11. Meira I, Menino J, Ferreira P, et al. Diabetes Remission After Bariatric Surgery: A 10-Year Follow-Up Study. Obes Surg. 2025;35 :161-169.
12. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, Navaneethan SD, Singh RP, Pothier CE, Nissen SE, Kashyap SR for the STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes. N Engl J Med. 2017; 376: 641-651.
13. Sheng B, Truong K, Spitler H, Zhang Lu, Tong X, Chen L. The Long-Term Effects of Bariatric Surgery on Type 2 Diabetes Remission, Microvascular and Macrovascular Complications and Mortality: A Systematic Review and Meta-Analysis. Obes Surg 2017; 27:2724-2732.
14. Sjöholm K, Svensson PA, Taube M, Jacobson Pandersson-Assarsson JC, Carlsson LMS, Peltonen M. Evaluation of Prediction Models for Type 2 Diabetes Relapse After Post-bariatric Surgery Remission: A Post hoc Analysis of 15-Year Follow-up Data from the Swedish Obese Subjects (SOS) Study. Obes Surg. 2020; 30:3955-3960.
15. Kirwan JP, Courcoulas AP, Cummings DE, Goldfine AB, Kashyap SR, Simonson DC, Arterburn DE, Gourash WF, Vernon AH, Jakicic JM, Patti ME, Wolski K, Schauer PR. Diabetes Remission in the Alliance of Randomized Trials of Medicine Versus Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D). Diabetes Care. 2022; 45:1574-1583.
16. Anny H. Xiang, Enrique Trigo, Mayra Martinez, et al, RISE Consortium; Impact of Gastric Banding Versus Metformin on β-Cell Function in Adults with Impaired Glucose Tolerance or Mild Type 2 Diabetes. Diabetes Care 1 December 2018; 41: 2544–2551.
17. Ko JH, Kim TN. Type 2 Diabetes Remission with Significant Weight Loss: Definition and Evidence-Based Interventions. J Obes Metab Syndr. 2022; 31:123-133.
18. Leslie WS, Ford I, Sattar N, Hollingsworth KG, et al. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. BMC Fam Pract. 2016; 17:20.

EARLY INSULIN INITIATION TO PRESERVE BETA-CELL FUNCTION IN TYPE 2 DIABETES MELLITUS

Shubhda Bhanot*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and a gradual decline in pancreatic beta-cell function. Research indicates that at the onset of Type 2 diabetes, over 70% of the β-cell mass is depleted, with the loss commencing at least a decade before the diagnosis of overt diabetes. Limiting the stress or workload of β-cells may salvage them and preserve their function for a longer period of time.

One suggested method to save a dying β cell is to initiate early insulin therapy. Emerging evidence suggests that early initiation of insulin therapy may offer benefits beyond glycemic control, including the preservation of beta-cell function. This approach is sometimes called "transient intensive insulin therapy (TIIT)" and aims to improve glycemic control, protect beta cells and potentially reduce long-term complications associated with diabetes (1).

This article reviews the rationale, supporting evidence and clinical implications of early insulin therapy in T2DM, with a focus on its role in altering disease progression.

T2DM is traditionally managed with lifestyle modifications and stepwise pharmacologic escalation, often delaying insulin therapy until other treatments fail, unlike in Type 1 diabetes mellitus (T1DM), where insulin is immediately initiated on diagnosis. This usually is due to the patient's reluctance and psychological barriers towards insulin. Sometimes clinicians may hesitate to initiate insulin due to misconceptions about insulin's safety or effectiveness or the healthcare physician may not have the required support or knowledge to use insulin in specific patient groups. Clinicians or patients may even have concerns about hypoglycemia or weight gain associated with insulin. However, due to these perceptions, we may miss a crucial window during which beta-cell function can be preserved by appropriate therapy. Early insulin initiation is increasingly being considered not just as a rescue therapy but as a strategic intervention to modify the natural history of T2DM.

In patients with newly diagnosed T2DM, early insulin therapy may modify the disease's clinical trajectory by restoring β-cell function and encouraging prolonged glycemic remission (2).

PATHOPHYSIOLOGY OF BETA-CELL DECLINE IN T2DM

The key characteristic of T2DM advancement is the gradual failure of pancreatic beta cells, which is influenced by chronic high blood glucose levels (glucotoxicity), increased free fatty acids (lipotoxicity) and heightened oxidative and endoplasmic reticulum stress. These elements result in diminished insulin secretion, beta-cell death and a decrease in beta-cell mass.

Maintaining beta-cell function is essential for achieving long-term blood glucose control. Unfortunately, at the point of diagnosis, approximately 50%-70% of beta-cell functionality has already been lost. Therefore, interventions focused on early restoration of normal blood glucose levels may alleviate metabolic stress and help retain residual beta-cell function.

Prompt insulin administration has the ability to not only offer blood glucose control and salvage beta cells but also minimize microvascular and macrovascular issues (3). Insulin is the most effective treatment for reducing high blood glucose and pivotal studies indicate that attaining early glycemic control can postpone or prevent

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long-term complications of diabetes through the "legacy effect" or "metabolic memory" (4).

Interestingly, it has been observed that lowering the demand for insulin can slow the progression from the insulin-resistant phase to impaired glucose tolerance (IGT) and diabetes. Weight loss and increased physical activity can enhance insulin sensitivity, thereby helping to maintain beta-cell function.

A strategy that combines diet and exercise with medications developed to lessen insulin demand can be employed to preserve beta-cell function and avert the onset of diabetes.

COMPARISON WITH OTHER THERAPIES

Thiazolidinedione

Pioglitazone is an effective insulin sensitizer. This is expected to reduce insulin demand and thus reduce the metabolic strain on beta cells.

Metformin

Metformin improves insulin sensitivity and has some anti-inflammatory properties. While it may indirectly reduce beta cell stress, it does not directly enhance beta cell function or prevent apoptosis.

Sulfonylureas

Sulfonylureas promote insulin release by depolarizing the membranes of beta cells. Although initially effective, they may be associated with beta cell exhaustion and increased apoptosis over time.

DPP-4 Inhibitors and GLP-1 Receptor Agonists

These incretin-based therapies enhance glucose-dependent insulin secretion and have shown modest beta cell preservation in preclinical and short-term clinical studies. GLP-1 receptor agonists might reduce apoptosis and promote neogenesis of beta cells in animal studies (7).

SGLT2 Inhibitors

SGLT2 inhibitors lower blood glucose via increased urinary glucose excretion. Some studies suggest they may reduce glucotoxicity and promote beta cell rest, though direct evidence for beta cell preservation is limited.

Table 1 shows urgent situations (1 to 5) where insulin therapy must be indicated. In long term therapy, need for insulin is shown in items 6,7,8 of this table.

Table 1

When to Initiate Insulin in Type 2 Diabetes (T2DM)

Summary Table (2023–2024 ADA and EASD Guidelines) (5)

Sr. No.	Clinical Scenario	Recommended Action	Rationale / Notes
1.	**Newly diagnosed T2DM with severe hyperglycemia**	Start insulin immediately	If A1C ≥ 10% or FPG ≥ 300 mg/dL or symptomatic (e.g., weight loss, ketosis)
2.	**Catabolic symptoms present** (e.g., weight loss, polyuria, polydipsia)	Start insulin	Indicates insulin deficiency; rule out Type 1 diabetes
3.	**Hospitalization or acute illness**	Initiate insulin temporarily	Preferred for glycemic control during stress, surgery, or infections
4.	**Pregnancy in diabetes**	Insulin is main-stay of therapy	Safe and effective for gestational and pregestational T2DM
5.	**Intolerance or contraindications to other agents**	Start insulin earlier	For example, if metformin or GLP-1 RA are not tolerated
6.	**T2DM uncontrolled on oral agents and/or GLP-1 RA**	Add basal insulin	If A1C remains above goal (>7%) after 3–6 months of optimized therapy
7.	**Persistent A1C > 9% despite dual/ triple therapy**	Add or initiate insulin	Especially if on maximum tolerated doses of non-insulin agents
8.	**Patient preference or lifestyle needs**	Consider insulin	Shared decision-making important

RATIONALE FOR EARLY INSULIN INITIATION

Reduction of Glucotoxicity and Lipotoxicity

Glucotoxicity and lipotoxicity have been acknowledged for a long time to harm both β-cell performance and insulin sensitivity. Glucolipotoxicity refers to the damaging effects that result from high levels of glucose and free fatty acids on the mass and functionality of β-cells. It indicates the harmful interaction of increased glucose and free fatty acids affecting both the mass and operation of β-cells. Insulin therapy rapidly lowers blood glucose and reduces lipolysis, thus alleviating the metabolic stress on beta cells.

It is important to avoid high blood glucose levels in people who have just been diagnosed with diabetes in order to reduce the risk of future health problems like microvascular and macrovascular complications. Therefore, four current guidelines advocate prompt implementation of lifestyle modifications, with or without the introduction of metformin and the subsequent addition of second- and third-line therapies if earlier interventions do not succeed in reaching or sustaining the target. The objectives for managing hyperglycemia in individuals recently diagnosed with Type 2 diabetes are to obtain near-normal glucose control as soon as possible to protect β-cell function and uphold long-term normoglycemia.

Resting Beta cells

In Type 2 diabetes, initiating early intensive insulin treatment has demonstrated potential in maintaining the function of β-cells. For instance, a study involving newly diagnosed Type 2 diabetes patients treated with premix insulin for 8 weeks observed significant reductions in HbA1c levels and improvements in C-peptide responses, indicating enhanced β-cell function (8).

Long-Term Benefits: Research indicates that early insulin therapy can lead to sustained glycemic control and β-cell function preservation. A study reported that patients who received early intensive insulin therapy maintained improved β-cell function for at least 3.5 years post-diagnosis.

Mechanistic Insights: The concept of β-cell rest posits that exogenous insulin reduces the secretory demand on β-cells, allowing them to recover and function more effectively. It is conceivable that a resting cell with lower metabolic activity is less likely to damage by any toxin cellular antibodies or ischemic insult. This approach may also mitigate the harmful effects of chronic hyperglycemia on β-cell health.

Reduction in pro-inflammatory Cytokines

Inflammatory cytokines play a crucial role in the development of diabetes, especially in the impairment of pancreatic β-cells and the onset of insulin resistance. Early initiation of insulin therapy may mitigate these inflammatory effects, preserve β-cell function and improve glycemic control.

Chronic low-grade inflammation is a significant contributor to the emergence of insulin resistance, which is a defining feature of T2DM. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) are found at higher levels in obesity and lead to insulin resistance by disrupting insulin signaling pathways within adipose tissue, liver and skeletal muscle. These cytokines are produced by immune cells like macrophages that infiltrate metabolic tissues in response to overnutrition and adipocyte stress. Early initiation of insulin therapy in newly diagnosed T2DM patients has been shown to have beneficial effects beyond glycemic control. Short-term intensive insulin therapy can reduce levels of pro-inflammatory cytokines and improve endothelial function, which are important factors in cardiovascular health. For instance, a study demonstrated that early insulin therapy decreased biomarkers related to low-grade inflammation and endothelial dysfunction, suggesting a potential role in mitigating cardiovascular risk. Another study found that intensive insulin therapy could decrease pro-inflammatory cytokines such as TNF-α and IL-6 in patients, indicating an anti-inflammatory effect of insulin treatment.

CLINICAL EVIDENCE SUPPORTING EARLY INSULIN THERAPY

The ORIGIN Trial (3)

The Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial (n=12,500) demonstrated that early insulin glargine use in people with dysglycemia was safe and maintained glycemic control over time without increased risk of cardiovascular events.

Chinese Newly Diagnosed Diabetes Study (2)

In this study, newly diagnosed T2DM patients received intensive insulin therapy for 2-3 weeks, resulting in near-normal glycemia and partial restoration of beta-cell function. Follow-up showed sustained glycemic remission in a significant proportion of patients without ongoing pharmacotherapy.

UKPDS Findings (6)

Although the UKPDS did not specifically investigate early insulin use, it highlighted the progressive nature of beta-cell dysfunction and the importance of early intensive glycemic control in reducing complications.

CHALLENGES IN EARLY INSULIN INITIATION

Early insulin initiation is often postponed, even though efficacy has been proved. This is due to the barriers from the clinician's perspective to initiate early insulin therapy.

Clinical Inertia

Clinical inertia, defined as the failure to initiate or intensify therapy despite un-met treatment goals is a significant barrier. This may stem from overreliance on oral medications, fear of patient's acceptance, or uncertainty about the appropriate timing for insulin initiation.

Time Constraints and Workflow Limitations

Initiating insulin requires detailed patient education, dosage planning and follow-up tasks that are often time-consuming. In busy clinic settings, limited consultation time makes it challenging to address insulin therapy adequately.

Lack of Confidence or Training

Some primary care providers may feel inadequately trained in insulin therapy, especially when dealing with complex regimens. Fear of hypoglycemia, dosing errors and titration uncertainty can discourage clinicians from initiating insulin early.

Patient-Related Factors

Clinicians often encounter resistance from patients who associate insulin with disease severity or personal failure. Concerns about injections, fear of hypoglycemia and lifestyle restrictions can complicate the decision-making process, causing clinicians to delay insulin discussion.

Systemic and Logistical Barriers

Insulin initiation may be hindered by lack of access to diabetes educators, poor coordination between care teams and insufficient reimbursement for insulin management services. Additionally, high medication costs may influence clinical decisions.

Psychological and Communication Barriers

Discussing insulin therapy requires sensitivity and strong communication skills. Clinicians may avoid conversations that could provoke emotional responses or erode trust, particularly if they feel unprepared to address psychological resistance.

The Influence of Early Insulin Treatment on Quality of Life

Quality of life (QoL) serves as a crucial indicator of the effectiveness of T2DM management. Many people think that using insulin can lower quality of life (QoL), which makes doctors hesitant to start it on time. However, studies that looked at QoL for up to 4 years in T2DM found that starting insulin early does not harm QoL (10).

A 24-week study utilizing questionnaires evaluated treatment satisfaction and QoL for initiating insulin at bedtime compared to adjusted oral medication in 366 individuals with T2DM. QoL was assessed using the Audit of Diabetes-Dependent Quality of Life (ADDQoL), which includes 13 items related to physical functioning,

symptoms, psychological well-being, social well-being, role activities and personal constructs (11). The assessment of the ADDQoL showed a notable enhancement in the quality of life for patients receiving early insulin treatment at Week 12 and Week 24 in comparison to those undergoing adjusted oral therapy.

STRATEGIES TO OVERCOME BARRIERS

Education and Training: Enhancing clinician confidence through ongoing education and practical insulin management workshops.

Multidisciplinary Support: Integrating diabetes educators and pharmacists into the care team to provide patient support and reduce provider burden.

Decision-Support Tools: Utilizing electronic health record prompts and standardized insulin initiation protocols to guide clinical decisions.

Patient-Centered Communication:
Employing motivational interviewing and shared decision-making to align treatment goals with patient values.

CONCLUSION

Early insulin initiation in T2DM presents a paradigm shift from its traditional role as a last resort to a proactive strategy aimed at preserving beta-cell function. Clinical trials support its safety and efficacy, particularly in newly diagnosed individuals with severe hyperglycemia. While challenges remain, particularly around patient acceptance, a tailored approach to early insulin therapy may alter the course of T2DM and improve long-term outcomes.

REFERENCES

1. Ilkova H, Glaser B, Tunçkale A, Bagriaçik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed Type 2 diabetic patients by transient intensive insulin treatment. Diabetes Care. 1997; 20:1353-6.
2. Weng, J., Li, Y., Xu, W., et al. Effect of intensive insulin therapy on β-cell function and glycemic control in newly diagnosed Type 2 diabetes: A multicentre randomized parallel-group trial. *The Lancet*. 2008; 371:1753–1760.
3. Gerstein, H. C., Bosch, J., Dagenais, G. R., et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *The New England Journal of Medicine*. 2012; 367:319–328.
4. Samajdar SS, Mukherjee S, Tripathi SK, *et al.* Early Initiation of Insulin Therapy in Newly Diagnosed Patients with Type 2 Diabetes and Exploring the Legacy Effect—A Single-arm Prospective Observational Study. Bengal Physician Journal 2020;7 :52–54.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in Type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012; 35:1364-79.
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with Type 2 diabetes. *The Lancet*.1998; 352:837–853.
7. DeFronzo, R. A. From the triumvirate to the ominous octet: A new paradigm for the treatment of Type 2 diabetes mellitus. *Diabetes*.2009; 58: 773–795.
8. Riddle, M. C., et al. Early insulin therapy for Type 2 diabetes: Evidence supporting the concept of beta-cell preservation. *Diabetes Care*.2013; 36: S264–S269.
9. Khunti K, Wolden ML, Thorsted BL, et al. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care.* 2013; 36 :3411-7.
10. Alvarsson M, Sundkvist G, Lager I, et al. Effects of insulin vs. glibenclamide in recently diagnosed patients with type 2 diabetes: a 4-year follow-up. Diabetes Obes Metab. 2008 ;10 :421-9.
11. Houlden R. Ross S. Harris S. Yale JF. Sauriol L. Gerstein HC. Treatment satisfaction and quality of life using an early insulinization strategy with insulin glargine compared to an adjusted oral therapy in the management of Type 2 diabetes: the Canadian INSIGHT Study. Diabetes Res Clin Pract. 2007; 78:254–258.

NEUROPATHIES IN DIABETES MELLITUS

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INTRODUCTION

Diabetes mellitus (DM) is a group of disorders characterized by impaired insulin secretion or resistance, leading to excessive glucose production, glucose underutilization and resulting in hyperglycemia (1). Type 2 diabetes, linked to poor lifestyle, is more common than Type 1, caused by pancreatic beta-cell destruction. Other types include gestational and diabetes from specific causes. Diagnosis is based on high plasma glucose or HbA1c levels. As per the American Diabetes Association (ADA), a patient has diabetes if either HbA1c≥6.5%, or fasting blood sugar levels are ≥126 mg/dL, or 2-hour plasma glucose values of ≥200 mg/dL during a 75g oral glucose tolerance test (OGTT) or a random blood sugar of ≥200 mg/dL (in an individual with classic symptoms of hyperglycemia or hyperglycemic crisis) and HbA1c≥ 6.5% (1).

OVERVIEW OF ALL TYPES OF NEUROPATHIES (DIABETIC AND NON-DIABETIC)

Peripheral neuropathies are a group of disorders occurring due to damage to the peripheral nerve cells and/or fibers, which may include the cranial nerves, spinal nerve roots and ganglia, plexus, autonomic nerves, sensory, motor and mixed nerves (2). Neuropathies have multitudes of presentations, causes and pathophysiology. The types of neuropathies are numerous; classifying them based on specific variables, like onset and progression, anatomical distribution, etiology, pathophysiology (electrodiagnostic findings) and type of nerve involvement, gives a clarity and ease of approach to make a proper diagnosis. The different types of neuropathies are listed.

CLASSIFICATIONS OF NEUROPATHIES

CLINICAL ELEMENT

Onset and Progression

Acute (< 4 weeks)

Differential Diagnoses: Guillain-Barré syndrome (GBS), Vasculitis, Toxin exposure, diabetic radiculoplexopathy, Hepatitis B and C associated neuropathies, Critical illness neuropathy, Lyme disease neuropathy, Rheumatologic neuropathies

Subacute (4-8 weeks)

Differential Diagnoses: Chronic inflammatory demyelinating polyneuropathy (CIDP), Paraproteinemic neuropathy, Paraneoplastic neuropathy, Mononeuritis multiplex, Rheumatologic neuropathies

Chronic (> 8 weeks)

Differential Diagnoses: Metabolic (diabetic) neuropathies, Nutritional (Vitamin B_{12} deficiency), Alcohol-related neuropathy, Treatment related neuropathy, Hereditary neuropathies, Human immunodeficiency virus (HIV) neuropathy, Multifocal motor neuropathy (MMN), Uremic neuropathy

Anatomical Distribution

Symmetric length dependent

Differential Diagnoses: Metabolic (diabetic) neuropathies, Nutritional (Vitamin B_{12} deficiency), Alcohol-related neuropathy, Toxin exposure (heavy metals), Chemotherapy-related neuropathy, Hereditary neuropathies (Charcot-Marie-Tooth disease, familial amyloidosis), HIV neuropathy, Vasculitis, Uremic neuropathy

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Symmetric proximal (non-length dependent)

Differential Diagnoses: CIDP, GBS, Hypothyroidism, Diabetes, Infections (HIV/AIDS, Lyme disease, diphtheria), Malignancies, Porphyria, Vincristine exposure

Focal

Differential Diagnoses: Entrapment/compressive neuropathies, Direct trauma to nerves, such as repeated minor trauma, traction, injection, cold exposure, burns, radiation, Amyloidosis. Acromegaly, Ischemic lesions, Leprosy, Myxedema, Neoplastic infiltration, Rheumatoid arthritis, Sarcoidosis

Multifocal (Mononeuritis multiplex)

Differential Diagnoses:

Axonal Mononeuropathy Multiplex

- Vasculitis, Diabetes mellitus, Sarcoidosis, Leprosy, HIV-1 infection

Demyelinating Mononeuropathy Multiplex

- Multifocal motor neuropathy, Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) variant of CIDP, Multiple compressive neuropathies (hypothyroidism, diabetes), Hereditary neuropathy with liability to pressure palsies (HNPPs)

Predominant upper limb involvement

Differential Diagnoses: MMN, MADSAM, Lead toxicity, Porphyria, Tangier disease, Familial amyloid neuropathy Type 2, Hereditary motor neuropathy (uncommon forms)

Monomelic

Differential Diagnoses: Focal compression neuropathy, Radiculopathy, Plexopathy, Diabetic amyotrophy

Neuropathies with cranial nerve involvement

Differential Diagnoses: Guillain-Barré syndrome, Infections (HIV/AIDS, Lyme disease, diphtheria), Neoplastic invasion of the skull base or meninges, Sarcoidosis

Sensorimotor Involvement

Predominant sensory

Differential Diagnoses: Toxin exposure, Metabolic (Diabetic) neuropathy, Nutritional (Vitamin B_{12} deficiency), Alcohol-related neuropathy, Amyloidosis, HIV neuropathy, Uremic neuropathy

Pure motor

Differential Diagnoses: MMN, Acute motor axonal neuropathy (AMAN) variant of GBS, Lead toxicity, Hereditary motor neuropathy, Porphyria

Predominant early motor alongside sensory

Differential Diagnoses: Guillain-Barré syndrome (GBS), Chronic inflammatory demyelinating polyneuropathy (CIDP), Paraproteinemic neuropathy, Diabetic amyotrophy

Predominant autonomic

Differential Diagnoses:

Acute

- Acute pan-dysautonomic neuropathy (autoimmune, paraneoplastic), GBS, Porphyria, Toxic: vincristine, Vacor (rodenticide)

Chronic

- Diabetes mellitus, Amyloid neuropathy (familial and primary), Paraneoplastic sensory neuronopathy (malignant inflammatory sensory polyganglionopathy), HIV-related autonomic neuropathy, Hereditary sensory and autonomic neuropathy (HSAN)

Type of Nerve Fiber

Small fiber neuropathies

Differential Diagnoses: Diabetes mellitus and impaired glucose tolerance, Sjögren (sicca) syndrome, Celiac disease, Familial amyloidosis, HIV-associated sensory neuropathy, HSAN, Fabry disease, Tangier disease, Idiopathic small-fiber neuropathy

Large fiber neuropathies

Differential Diagnoses:

- Sensory neuronopathies (polyganglionopathies):

- ✓ Paraneoplastic sensory neuronopathy (malignant inflammatory sensory polyganglionopathy), Sjögren syndrome, Idiopathic

- Toxic (cisplatin and analogs, vitamin B6 excess)
- Chronic immune sensory polyradiculopathy
- Demyelinating polyradiculoneuropathies:
  - ✓ GBS (Miller-Fisher variant)
  - ✓ Immunoglobulin M monoclonal gammopathy Myelin-Associated Glycoprotein (MAG) antibody
- Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins and anti-GD1b disialosyl antibodies (CANOMAD), Tabes dorsalis

Mixed

Differential Diagnoses: Diabetic neuropathy, Chemotherapy related neuropathy, HIV neuropathy

Pathophysiology

Axonal loss

Differential Diagnoses: Vitamin deficiency (Vitamin B_{12}, Vitamin E, Folic acid), Inherited (CMT 2 & CMT X), Drug and Toxin (Alcohol, vincristine, dapsone, statins), Autoimmune (Sjogren's syndrome, systemic lupus erythematosus, vasculitis), Metabolic polyneuropathies (Diabetic, Uremic neuropathy, hypothyroidism), Infective (HIV neuropathy, Hepatitis C, Lyme disease), Paraneoplastic (Carcinoma lung, ovary)

Segmental demyelinating

Differential Diagnoses: GBS, CIDP,

Paraproteinemic neuropathies: IgM Anti-myelin associated glycoprotein (MAG) paraprotein

Diffuse demyelinating

Differential Diagnoses: POEMs syndrome, Charcot-Marie-Tooth disease, Hereditary neuropathies (Leukodystrophies, Refsum disease, etc.)

EPIDEMIOLOGY

As per the new data published in The Lancet, the worldwide prevalence of adults living with diabetes has quadrupled since 1990, surpassing 800 million (3). Diabetes mellitus leads to significant morbidity and mortality, mainly due to macrovascular complications (coronary artery, peripheral vascular, cerebrovascular disease) and microvascular complications (retinopathy, nephropathy, neuropathy).

Diabetic neuropathy can have myriad presentations, which often causes a challenge in recognizing it. The neuropathies associated with diabetes fall into five categories:

1. Length-dependent axonal polyneuropathy, the most prevalent form, which may involve selective damage to small-diameter unmyelinated axons, large myelinated axons, or both
2. Acute diabetic neuropathies, including radiculoplexus neuropathy and treatment-induced neuropathies
3. Mononeuropathies, including individual cranial or peripheral nerves
4. Autonomic neuropathies
5. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) (4–6)

Type 1 diabetes neuropathy is closely linked to glycemic control, with optimal management reducing risk by 78% (4,5,7). In Type 2 diabetes, hyperglycemia plays a lesser role, with intensive control lowering neuropathy risk by only 5–9% (5). Neuropathy is more prevalent at diagnosis in Type 2 diabetes, with prevalence rising from 8% to 42% over 10 years in well-controlled cases and from 0% to 68% over 4 years in poorly controlled cases (5). Metabolic syndrome components-hypertriglyceridemia, hypertension, obesity, low HDL and tobacco use are key contributors (6).

DISTAL SYMMETRIC POLYNEUROPATHY OF DIABETES

Distal symmetric polyneuropathy (DSPN) affects one-third of diabetics (8,9), defined as peripheral

nerve dysfunction after ruling out other causes (10). It follows a length-dependent pattern, impacting ~30% more in Type 2 diabetes (11). While age is a key risk, 22% of young Type 1 diabetics develop DSPN (12,13). Other risks include disease duration, severity, obesity and metabolic syndrome (14). Individuals of African origin may have higher risk (15).

DSPN causes symmetric paresthesia, starting in the toes and spreading in a stocking-glove pattern (16). Symptoms include stabbing pain, tingling, numbness and burning (17). Atypical features (asymmetry, sudden onset, motor signs) suggest alternative diagnoses (18). Up to 50% are asymptomatic (19), while 25% develop painful polyneuropathy (8-9). Examination shows small and large fiber damage both affected early (8,20,21).

DIAGNOSIS

Clinical history and neurologic examination support the diagnosis of DSPN, requiring electrodiagnostic testing only for atypical features. Nerve conduction studies often show axonal loss, with low sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitude responses, slightly prolonged distal latencies and slowed conduction velocities, affecting sensory more than motor studies (17). For atypical cases, further testing is recommended.

MANAGEMENT

Diabetic sensorimotor polyneuropathy (DSPN) is a chronic and progressive condition that cannot be reversed, but it can be managed and controlled effectively with appropriate treatment strategies. The goal of therapy is to slow the progression of nerve damage, alleviate symptoms and improve the patient's quality of life. DSPN is primarily caused by long-term hyperglycemia, which leads to nerve damage due to metabolic disturbances, poor circulation and impaired nerve repair. While the damage to the nerves is irreversible, interventions such as strict glycemic control, pharmacotherapy and symptomatic treatment can help manage symptoms, reduce pain and prevent further complications. Managing DSPN primarily requires creating awareness. Patients are often diagnosed with diabetes after presenting with neuropathy, providing an opportunity to address poorly managed risk factors. Management is threefold, including intervention for risk factors and glycemic control, pathogenetically oriented pharmacotherapy and symptomatic pain relief.

Combining glycemic control with weight loss and dietary modifications shows potential benefits. In Type 1 diabetes, improved glycemic control reduces DSPN incidence by 78% (7,22,23), while in Type 2 diabetes, the reduction is only 5-8% (24,25).

Pathogenetic pharmacotherapy for DSPN includes alpha-lipoic acid (ALA, antioxidant) and benfotiamine (thiamine derivative), both licensed and approved for treatment (26,27). Multiple meta-analyses show that 600mg-1800mg of ALA per day reduces main DSPN symptoms (pain, numbness) (26,28–35). The BEDIP(36) and BENDIP (37) demonstrate symptom improvement, with high-dose benfotiamine most effective for pain. Benfotiamine can be started at 600 mg/day and maintained at the same dose, with a maximum of 600 mg/day. Both agents are helpful in addressing the underlying biochemical imbalances that contribute to nerve damage but do not reverse existing neuropathy. Both ALA and benfotiamine have favorable safety profiles for long-term treatment (38).

DSPN management focuses on pain relief (Table 1). The 2022 American Academy of Neurology (AAN) guideline endorses four drug classes for painful DSPN: gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs) tricyclic antidepressants (TCAs) and sodium channel blockers (oxcarbazepine and lamotrigine) (39). The OPTION-DM (Optimal Pathway for Treating Neuropathic Pain in Diabetes Mellitus) trial found amitriptyline, duloxetine, pregabalin and gabapentin comparably efficacious for treating DSPN, with improved pain control when adding a second agent for non-responders (40). The management of painful DSPN typically begins with first-line agents, including Gabapentin and Pregabalin, both of which are α2δ calcium channel ligands. These drugs help to reduce the hyperexcitability of the nerves and are usually initiated at doses ranging from 300 mg/day to 600 mg/day.

TABLE 1:

PHARMACOTHERAPEUTIC MANAGEMENT OF DSPN (26–38,41–49)

DRUG	CLASS	INITIAL DOSE (mg/d)	MAINTAINENCE DOSE (mg/d)	MAXIMUM DOSE (mg/d)
PATHOGENETICALLY ORIENTED PHARMACOTHERAPY				
Alpha-lipoic acid Benfotiamine	Anti-oxidant Thiamine derivative	600mg 600mg	600 600mg	1800 600
SYMPTOMATIC TREATMENT FOR PAINFUL DSPN				
1ST line agents:				
Gabapentin Pregabalin Duloxetine Venlafaxine Amitriptyline	α2δ Calcium channel ligand α2δ Calcium channel ligand SNRI SNRI TCA	300-600 75-150 30 37.5 10-25	1200-3000 150-450 60 150-225 25-100	3600 (if no renal impairment) 600 (if no renal impairment) 120 375 150 (caution above 100mg)
2nd line agents:				
Tramadol	Weak μ opioid & SNRI	50-100	100-200	400
3rd line agents:				
Oxycodone Tapentadol	Strong μ opioid Strong μ opioid & SNRI	10-20 50-100	20-50 Up to 200	400 500
Topical analgesics Capsaicin 8% Patch	TRPV1 agonist	Plaster applied for 30 min every 60–90 days		716 (equivalent to 4 plasters)

Abbreviations: DSPN: diabetic sensorimotor polyneuropathy; TRPV1: Transient receptor potential vanilloid-1; SRI: Serotonin reuptake inhibitors; SNRI: serotonin-norepinephrine reuptake inhibitors; TCA: tricyclic antidepressants

The maintenance dose for Gabapentin can go up to 1200-3600 mg/day and for Pregabalin, it ranges from 150-450 mg/day, with a maximum dose of 600 mg/day (if no renal impairment). Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is another first-line agent, with an initial dose of 30 mg/day, a maintenance dose of 60 mg/day and a maximum dose of 120 mg/day.

Second-line agents include Tramadol, a weak opioid with SNRI properties, which can be initiated at 50-100 mg/day and increased to 100-200 mg/day, with a maximum dose of 400 mg/day. In more refractory cases, third-line agents such as Oxycodone (a strong opioid) and Tapentadol (a strong opioid combined with SNRI activity) can be considered. Oxycodone starts at 10-20 mg/day, with a maximum of 400 mg/day, while Tapentadol is initiated at 50-100 mg/day and increased to 200 mg/day, with a maximum of 500 mg/day. These opioids, however, are typically used cautiously due to their potential for dependence and side effects.

For some patients, the Capsaicin 8% patch may provide relief. This treatment, applied for 30 minutes, every 60-90 days, acts as a TRPV1 agonist, desensitizing pain receptors. The dose is usually equivalent to 4 plasters applied over the affected area and it is an option for those who may not respond well to systemic treatments. Cognitive behavioral therapy, mindfulness and exercise may also help (50). Patients should wear hard-soled shoes, inspect their feet daily and seek prompt care for foot injuries to prevent ulcers or amputations.

The goal of treatment in DSPN is to control symptoms rather than reverse the damage. Early intervention, especially with pathogenetically oriented therapies like Alpha-lipoic acid and

Benfotiamine, along with symptomatic treatments for pain, can significantly improve patient comfort and functional status. However, it is important to understand that these treatments can only manage the condition and reduce the symptoms. They cannot halt or reverse the underlying nerve damage caused by prolonged hyperglycemia. Regular monitoring and individualized treatment plans are essential to optimizing the management of DSPN and preventing its progression.

NEUROPATHY ASSOCIATED WITH METABOLIC SYNDROME AND PREDIABETES

Prediabetes, defined by an HbA1c of 5.7%–6.4%, can precede Type 2 diabetes by years. Evidence shows an increased risk of polyneuropathy in prediabetes (51). Metabolic syndrome, which includes insulin resistance, high triglycerides, low HDL, central obesity and hypertension, increases the risk of DSPN. Prevalence of neuropathy in prediabetes is around 10% (52). DSPN symptoms in prediabetes mirror those in Type 2 diabetes. Some may experience autonomic dysfunction, like tachycardia. Small unmyelinated fibers are especially vulnerable.

SMALL FIBRE NEUROPATHY IN DIABETES

Small fibre neuropathy (SFN) affects Aδ and C fibres, which make up 79.6% to 91.4% of peripheral nerve fibres. These fibres are crucial for temperature and pain perception, sweating, blood flow and autonomic regulation. Impairment of these functions is linked to foot ulcerations in diabetes and when the autonomic system is affected, it is often referred to as autonomic neuropathy (53). The nerve conduction studies may be normal and specialized bedside testing may be required to arrive at a diagnosis.

The various methods for assessing small fiber neuropathy (SFN) and its function include both non-invasive and invasive techniques, each with varying equipment needs, time requirements and limitations. Non-invasive methods like Laser Doppler imager (LDIFLARE), quantitative sudomotor testing (QST), Sudoscan and Neuropad provide useful data on nerve function, with varying levels of sensitivity, specificity and ease of use. Invasive methods such as skin biopsy and sural nerve biopsy offer detailed structural information on nerve damage but require specialized equipment, trained personnel and are more time-consuming. Tests like microneurography and corneal confocal microscopy are more research-focused, providing valuable insights but requiring skilled operators and extensive equipment. While these techniques offer varying degrees of diagnostic value, none can replace the need for patient cooperation and some have limited availability or higher costs (53).

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN), or diabetic amyotrophy, is a rare Type 2 diabetes complication and may exceed GBS/CIDP prevalence (54).

Risk factors include stroke, high BMI, autoimmune diseases (thyroiditis, IBD, psoriasis) (55). The disease typically occurs in the sixth decade (male-to-female 3:2), approximately three years post-diagnosis (56,57).

Patients present with sudden, unilateral thigh and hip pain (burning, tightness, or allodynia), which may spread to the opposite side over weeks to months, followed by weakness and muscle atrophy, leading to difficulty walking. In most cases, the patients are able to recall the date when their symptoms began. These patients have absent knee jerks, although ankle jerks are usually preserved but can be lost with underlying DSPN, which may coexist, with about a quarter of the cases having associated autonomic dysfunction (57).

Unlike DSPN, patients with DLRPN often have well-controlled diabetes and are sometimes diagnosed with DLRPN as the first symptom (58). Diagnosis is primarily based on clinical history and examination, as laboratory tests are typically normal. Nerve biopsy, though not routinely recommended, may reveal

focal or multifocal nerve fiber degeneration, perivascular mononuclear inflammation and neovascularization in the epineurium, suggesting that microvasculitis of individual nerves may be the underlying pathophysiology (59–61). Nerve conduction studies often show low-amplitude or absent CMAPs in the typically from the femoral nerve, along with involvement of tibial and peroneal nerves and low-amplitude or absent SNAPs in the sural nerve, with limb asymmetry, while electromyography shows increased insertional activity, fibrillation potentials and reduced motor unit recruitment from the muscles supplied by the femoral nerve or the lumbosacral plexus (62,63). MRI of the lower spine is typically normal, with plexus MRI showing increased T2 signal and nerve thickening. Later stages may reveal muscle oedema, atrophy and fatty infiltration (63,64,65). Cerebrospinal fluid (CSF) examination if done, shows elevated protein levels (63,66).

DLRPN is a monophasic neuropathy, with most patients achieving recovery to some degree over 18 to 24 months, few returning to normal (67). There is no established effective treatment and while immunotherapy is a potential option, evidence is scarce. A multicenter, double-blind clinical trial for intravenous methylprednisolone found no significant difference between the steroid and placebo groups, though the authors noted delayed treatment may have impacted results (68). Patients treated early with steroids reported better pain relief, suggesting intravenous methylprednisolone may benefit those with early disease and refractory pain (68,69). Steroid use may affect glycemic control, so the treatment plan should be reviewed with the patient's primary physician or endocrinologist.

TREATMENT-INDUCED NEUROPATHY OF DIABETES

An ironic entity in the era of advising patients to maintain glycemic control to avoid a diabetic neuropathy, which is the treatment-induced neuropathy of diabetes (TIND), which can be induced by sudden aggressive diabetic control in patients with a history of prolonged hyperglycemia. First described in 1993, the term was finally proposed after 2010, with the recognition of insulin neuritis which was secondary not only to insulin treatment but also to rapid reduction in glucose concentration (70–72). This small fiber neuropathy was considered to be a rare condition, however in a retrospective chart review of patients assessed for diabetic neuropathy, 10.9% were diagnosed with treatment-induced diabetic neuropathy (73), suggesting a higher prevalence.

With a reported mean age of 35 years at onset, TIND has a slight male preponderance, associated with Type 1 diabetes more than Type 2. Cases reported having diabetes for more than 5 years, most of them relying on insulin (74). Patients often present with length dependent burning and stabbing neuropathic pain that begins abruptly and intensely 2-6 weeks after improvement of glycemic control (75). Autonomic manifestations may also occur. The pathophysiology of treatment-induced neuropathy of diabetes is yet to be fully understood. It is probably related to microcirculatory changes during hyperglycemia that is not restored as quickly as hypoglycemia leading to endoneural ischemia and ectopic depolarization upon normoglycemia (76).

Management focuses on preventing progression and managing symptoms. Stable glucose control (avoiding hypoglycemia) may improve neuropathy, but full resolution isn't guaranteed. Analgesic therapy is essential to manage pain. In severe TIND cases, increasing the dose of a single agent or adding additional drugs may be required (74,76). Labile glycemia can worsen symptoms, so vigilant glucose control is essential. Patient and physician education is equally important, especially for prevention.

DIABETIC TRUNCAL NEUROPATHY

Diabetic truncal neuropathy, described in 1978, presents as sudden, severe unilateral pain mimicking thoracic or abdominal pathology. It occurs in long-standing Type 2 diabetes, resolves within months and rarely involves motor

function, though abdominal wall protrusion may occur (77).

AUTONOMIC NEUROPATHIES

Autonomic neuropathies produce a range of symptoms due to their impact on various organ systems. This term encompasses cardiovascular autonomic neuropathy, gastroparesis, constipation, bladder dysfunction and sexual and sudomotor dysfunction. Of these, cardiovascular autonomic neuropathy carries a huge burden of morbidity and mortality and hence has been studied in more detail (Table 2).

Cardiovascular autonomic neuropathy affects both sympathetic and parasympathetic nerves, starting with vagal nerve dysfunction, leading to increased resting heart rate and reduced heart rate variability to stress (78). In later stages, damage to sympathetic vasomotor nerves causes orthostatic hypotension (defined as a fall in blood pressure of >20mm Hg systolic and 10 mm Hg diastolic) (79), although some authors suggest a 30mm Hg systolic blood pressure fall as appropriate based on normal population values (80,81). Cardiovascular autonomic neuropathy in diabetes increases mortality, with orthostatic hypotension contributing to a 27-56% mortality rate (82).

TABLE 2:

AUTONOMIC NEUROPATHIES IN DIABETES

	TYPE	PREVALENCE	CLINICAL FEATURES	INVESTIGATIONS
1.	**Cardiovascular autonomic neuropathy** (83,84)	Type 1 diabetes: 29-54% Tye 2 diabetes: 12-73%	Exercise intolerance Dizziness Syncope	Standard cardiovascular autonomic reflex tests: ✓ Beat-to-beat heart rate variation ✓ Heart rate response to standing ✓ Heart rate response to Valsalva maneuver ✓ Systolic blood pressure response to standing ✓ Diastolic blood pressure response to isometric exercise
2.	**Gastrointestinal autonomic neuropathy** (81,85)	Type 1 diabetes: 22-55% Tye 2 diabetes: 30% (variable in different studies)	Nausea Bloating Fullness Watery nocturnal-diarrhea	✓ Scintigraphy (gold standard) ✓ Upper gastrointestinal barium radiographic study ✓ 13C-breath tests ✓ Ultrasonography for serial changes in antral area ✓ Magnetic resonance imaging ✓ Antroduodenal manometry ✓ Gastric barostat ✓ Electrogastrogram(EGG)
3.	**Urinary dysfunction** (86)	39-61%	Hesitancy Urgency Incontinence Lack of full bladder awareness Retention	Urodynamic studies
4.	**Genital dysfunction** (87,88)	Erectile dysfunction – 45% Female sexual dysfunction – 42%	Erectile dysfunction Vaginal dryness Painful intercourse	International index of erectile dysfunction Female sexual function index
5.	**Sudomotor dysfunction** (89,90)	30.2%	Proximal hyperhidrosis Anhidrosis	Dynamic sweat tests

Gastroparesis in diabetes delays stomach emptying, complicates glycemic control and is treated with small meals, metoclopramide and improved glucose control (91).

Diabetic urogenital autonomic neuropathies cause bladder and sexual dysfunction, including urgency, incontinence, erectile dysfunction and vaginal dryness, complicating treatment due to neuropathy and medication side effects (92,93).

Sudomotor dysfunction in diabetic neuropathy causes hyperhidrosis, with treatment focusing on thermoregulation and managing symptoms like gustatory sweating (93).

FOCAL NEUROPATHIES IN DIABETES

Entrapment neuropathies (EN) are common in diabetes and may be the earliest sign of nerve involvement, especially in the upper limbs. These neuropathies, including median mononeuropathy at the wrist (carpal tunnel syndrome), ulnar mononeuropathy at the elbow (cubital tunnel syndrome) and fibular (peroneal) mononeuropathy are caused by metabolic changes from abnormal glucose metabolism, making nerves more susceptible to entrapment (94). Diabetic cranial neuropathies are rare but unequivocally associated with diabetes, affecting less than 1% of patients. Cranial nerves III, VI and VII are most commonly involved. Diabetic cranial neuropathies often present early and have a favorable prognosis (95).

DIABETES AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

The relationship between chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and diabetes is complex and has been the subject of ongoing debate. Studies have reported a higher prevalence of CIDP in diabetic patients, with some suggesting an 11-fold increased risk compared to non-diabetic patients (96). However, other studies have found mixed results, with some indicating no significant association between CIDP and DM (97, 98). Real-world data suggest a higher prevalence of CIDP in diabetic patients, particularly in older adults, but it remains unclear whether this is due to diabetes itself or the age factor (99).

However, CIDP and DM both share an increased prevalence in older adults (above 50 years of age), making it challenging to definitively determine whether diabetes directly increases the risk of CIDP or whether the age factor contributes more significantly.

DIAGNOSTIC CHALLENGES IN CIDP WITH DM

Diagnosis of CIDP in patients with diabetes is complicated by the presence of concomitant diabetic neuropathy (DPN) and axonal damage, which can obscure electrophysiological findings that are critical for diagnosing CIDP. Electrophysiological testing can be affected by diabetic polyneuropathy, leading to false positives or misinterpretations of CIDP. CSF protein elevation, often used to diagnose CIDP, may also be seen in DPN, further complicating the diagnostic process. Additionally, axonal loss in diabetic neuropathy can mimic the features of CIDP, including motor slowing and sensory loss, making it difficult to differentiate the two conditions, especially when clinical presentation overlaps.

A proposed screening tool combines clinical, electrophysiological and laboratory parameters to help differentiate CIDP from DPN in patients with diabetes. This tool, though not validated in larger populations, has shown promise in small cohorts (100). The tool takes into account progressive/relapsing motor weakness (2–6 months), distal CMAP duration and evidence of demyelination on nerve conduction studies. Corneal confocal microscopy, which is being explored as a potential biomarker, may help differentiate CIDP from DPN, as it can detect nerve fiber loss typical of CIDP, whereas DPN typically shows more small fiber damage.

Differentiating CIDP from DPN in patients with diabetes is critical because CIDP is treatable, whereas DPN is not. The rising prevalence of DM worldwide necessitates more accurate diagnostic tools to determine which patients have

a treatable neuropathy (CIDP) versus a non-treatable one (DPN). The goal remains to identify which diabetic patients have CIDP, a treatable autoimmune neuropathy so that they can receive the appropriate immunomodulatory treatment and improve their clinical outcomes.

CONCLUSION

Neuropathy in different forms is a growing complication of diabetes mellitus. It can range from the classical distal symmetrical polyneuropathy to autonomic neuropathies, acute forms like lumbosacral radicuoplexopathy and treatment-induced neuropathy and even chronic inflammatory demyelinating polyneuropathy. In this review, we discussed the five main types of neuropathies seen in diabetes, with the current understanding about their diagnosis and management. Identification and prevention early in the course of these neuropathies play a crucial role in battling the morbidity and possible mortality associated with them, especially where disease-modifying agents are not available.

REFERENCES

1. ElSayed NA, Aleppo G, Bannuru RR, et al. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47: S20–42.
2. Remiche G, Kadhim H, Maris C, Mavroudakis N. Peripheral neuropathies, from diagnosis to treatment, review of the literature and lessons from the local experience. Rev Med Brux. 2013; 34:211–20.
3. Zhou B, Rayner AW, Gregg EW, Sheffer KE, Carrillo-Larco RM, Bennett JE. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. The Lancet. 2024; 404:2077–93.
4. Feldman EL, Callaghan BC, Pop-Busui R, et al. Diabetic neuropathy. Nat Rev Dis Primers. 2019; 5: 41.
5. Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017; 40 :136–54.
6. Eid S, Sas KM, Abcouwer SF, et al. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. Diabetologia. 2019;62 :1539–49.
7. Linn T, Ortac K, Laube H, Federlin K. Intensive therapy in adult insulin-dependent diabetes mellitus is associated with improved insulin sensitivity and reserve: A randomized, controlled, prospective study over 5 years in newly diagnosed patients. Metabolism. 1996;45 :1508–13.
8. Ziegler D, Tesfaye S, Spallone V, et al. Screening, diagnosis and management of diabetic sensorimotor polyneuropathy in clinical practice: International expert consensus recommendations. Diabetes Res Clin Pract. 2022; 186:109063.
9. Ziegler D, Papanas N, Vinik AI, Shaw JE. Epidemiology of polyneuropathy in diabetes and prediabetes. Handb Clin Neurol. 2014; 126:3–22.
10. Lee CG, Ciarleglio A, Edelstein SL, et al. Prevalence of Distal Symmetrical Polyneuropathy by Diabetes Prevention Program Treatment Group, Diabetes Status, Duration of Diabetesand Cumulative Glycemic Exposure. Diabetes Care. 2024; 47:810–7.
11. Sun J, Wang Y, Zhang X, Zhu S, He H. Prevalence of peripheral neuropathy in patients with diabetes: A systematic review and meta-analysis. Prim Care Diabetes. 2020; 14:435–44.
12. Christensen DH, Knudsen ST, Gylfadottir SS, et al. Metabolic Factors, Lifestyle Habitsand Possible Polyneuropathy in Early Type 2 Diabetes: A Nationwide Study of 5,249 Patients in the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) Cohort. Diabetes Care. 2020; 43:1266–75.
13. Jaiswal M, Divers J, Dabelea D, et al. Prevalence of and Risk Factors for Diabetic Peripheral Neuropathy in Youth with Type 1 and Type 2 Diabetes: SEARCH for Diabetes in Youth Study. Diabetes Care. 2017; 40:1226–32.
14. Callaghan BC, Gao L, Li Y, et al. Diabetes and obesity are the main metabolic drivers of peripheral neuropathy. Ann Clin Transl Neurol. 2018; 5:397–405.
15. Hicks CW, Wang D, Windham BG, Matsushita K, Selvin E. Prevalence of peripheral neuropathy defined by monofilament insensitivity in middle-aged and older adults in two US cohorts. Sci Rep. 2021; 11:19159.
16. Gylfadottir SS, Weeracharoenkul Dandersen ST, Niruthisard S, Suwanwalaikorn S, Jensen TS. Painful and non-painful diabetic polyneuropathy: Clinical characteristics and diagnostic issues. J Diabetes Investig. 2019; 10:1148–57.
17. Abbott CA, Malik RA, van Ross ERE, Kulkarni J, Boulton AJM. Prevalence and Characteristics of Painful Diabetic Neuropathy in a Large Community-Based Diabetic Population in the U.K. Diabetes Care. 2011; 34:2220–4.
18. Tesfaye S, Boulton AJM, Dyck PJ, et al. Diabetic Neuropathies: Update on Definitions, Diagnostic Criteria, Estimation of Severityand Treatments. Diabetes Care. 2010; 33:2285–93.
19. Microvascular Complications and Foot Care: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020; 43:135–51.
20. Spallone V, Greco C. Painful and Painless Diabetic Neuropathy: One Disease or Two? Curr Diab Rep. 2013; 13:533–49.
21. Ziegler D, Papanas N, Zhivov A, et al. Early Detection of Nerve Fiber Loss by Corneal Confocal Microscopy and Skin

Biopsy in Recently Diagnosed Type 2 Diabetes. Diabetes. 2014; 63:2454–63.

22. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. New England Journal of Medicine. 1993; 329:977–86.

23. Effect of intensive diabetes treatment on nerve conduction in the diabetes control and complications trial. Ann Neurol. 1995; 38:869–80.

24. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: clinical manifestations and current treatments. Lancet Neurol. 2012; 11:521–34.

25. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycemia on microvascular outcomes in Type 2 diabetes: an analysis of the ACCORD randomised trial. The Lancet. 2010; 376:419–30.

26. Papanas N, Ziegler D. Efficacy of α-lipoic acid in diabetic neuropathy. Expert Opin Pharmacother. 2014; 15:2721–31.

27. Balakumar P, Rohilla A, Krishan P, Solairaj P, Thangathirupathi A. The multifaceted therapeutic potential of benfotiamine. Pharmacol Res. 2010; 61:482–8.

28. El-Nahas MR, Elkannishy G, Abdelhafez H, Elkhamisy ET, El-Sehrawy AA. Oral Alpha Lipoic Acid Treatment for Symptomatic Diabetic Peripheral Neuropathy: A Randomized Double-Blinded Placebo-Controlled Study. Endocr Metab Immune Disord Drug Targets. 2020; 20:1531–4.

29. Ziegler D, Low PA, Litchy WJ, et al. Efficacy and Safety of Antioxidant Treatment With α-Lipoic Acid Over 4 Years in Diabetic Polyneuropathy. Diabetes Care. 2011; 34:2054–60.

30. Ziegler D, Nowak H, Kempler P, Vargha P, Low PA. Treatment of symptomatic diabetic polyneuropathy with the antioxidant α-lipoic acid: a meta-analysis. Diabetic Medicine. 2004; 21:114–21.

31. Rutkove S, McIlduff. Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. Ther Clin Risk Manag. 2011;377.

32. Mijnhout GS, Kollen BJ, Alkhalaf A, Kleefstra N, Bilo HJG. Alpha Lipoic Acid for Symptomatic Peripheral Neuropathy in Patients with Diabetes: A Meta-Analysis of Randomized Controlled Trials. Int J Endocrinol. 2012; 2012:1–8.

33. Amato Nesbit S, Sharma R, Waldfogel JM, et al. Non-pharmacologic treatments for symptoms of diabetic peripheral neuropathy: a systematic review. Curr Med Res Opin. 2019; 35:15–25.

34. Nguyen N, Takemoto JK. A Case for Alpha-Lipoic Acid as an Alternative Treatment for Diabetic Polyneuropathy. Journal of Pharmacy & Pharmaceutical Sciences. 2018; 21:192s–9s.

35. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic Review and Meta-Analysis of Pharmacological Therapies for Painful Diabetic Peripheral Neuropathy. Pain Practice 2014; 14:167–84.

36. Haupt E, Ledermann H, Köpcke W. Benfotiamine in the treatment of diabetic polyneuropathy – a three-week randomized, controlled pilot study (BEDIP Study). Int Journal of Clinical Pharmacology and Therapeutics. 2005; 43:71–7.

37. Stracke H, Gaus W, Achenbach U, Federlin K, Bretzel RG. Benfotiamine in Diabetic Polyneuropathy (BENDIP): Results of a Randomised, Double Blind, Placebo-controlled Clinical Study. Experimental and Clinical Endocrinology & Diabetes 2008;116:600–5.

38. Ziegler D. Pathogenetic treatments for diabetic peripheral neuropathy. Diabetes Res Clin Pract. 2023; 206:110764.

39. Price R, Smith D, Franklin G, et al. Oral and Topical Treatment of Painful Diabetic Polyneuropathy: Practice Guideline Update Summary. Neurology 2022;98 :31–43.

40. Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptylineand duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial. The Lancet. 2022;400 :680–90.

41. Quilici S, Chancellor J, Löthgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol. 2009; 9:6.

42. Liampas A, Rekatsina M, Vadalouca A, Paladini A, Varrassi G, Zis P. Pharmacological Management of Painful Peripheral Neuropathies: A Systematic Review. Pain Ther 2021; 10:55–68.

43. Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2017;2020 (2).

44. Waldfogel JM, Nesbit SA, Dy SM, et al. Pharmacotherapy for diabetic peripheral neuropathy pain and quality of life. Neurology. 2017; 88:1958–67.

45. Vilar S, Castillo JM, Martínez PVM, Reina M, Pabón M. Therapeutic alternatives in painful diabetic neuropathy: a meta-analysis of randomized controlled trials. Korean J Pain. 2018; 31:253–60.

46. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database of Systematic Reviews 2019; 2019(5).

47. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic Interventions for Painful Diabetic Neuropathy. Ann Intern Med. 2014; 161:639–49.

48. Gaskell H, Derry S, Stannard C, Moore RA. Oxycodone for neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2016;2016 (7).

49. Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% Patch in Painful Diabetic Peripheral Neuropathy: A Randomized, Double-Blind, Placebo-Controlled Study. J Pain 2017;18 :42–53.

50. van Laake-Geelen CCM, Smeets RJEM, Quadflieg SPAB, Kleijnen J, Verbunt JA. The effect of exercise therapy combined with psychological therapy on physical activity and quality of life in patients with painful diabetic neuropathy: a systematic review. Scand J Pain. 2019; 19:433–9.

51. Papanas N, Ziegler D. Prediabetic Neuropathy: Does It Exist? Curr Diab Rep. 2012; 12:376–83.

52. Ziegler D, Rathmann W, Dickhaus T, Meisinger C, Mielck A. Neuropathic Pain in Diabetes, Prediabetes and Normal Glucose Tolerance: The MONICA/KORA Augsburg Surveys S2 and S3. Pain Medicine. 2009; 10:393–400.

53. Sharma S, Vas P, Rayman G. Small Fiber Neuropathy in Diabetes Polyneuropathy: Is It Time to Change? J Diabetes Sci Technol. 2022; 16:321–31.

54. Ng PS, Dyck PJ, Laughlin RS, Thapa P, Pinto M V., Dyck PJB. Lumbosacral radiculoplexus neuropathy. Neurology. 2019;92.

55. Pinto M V., Ng P, Laughlin RS, et al. Risk factors for lumbosacral radiculoplexus neuropathy. Muscle Nerve. 2022; 65:593–8.

56. Albers JW, Jacobson RD, Smyth DL. Diabetic Amyotrophy: From the Basics to the Bedside. European Medical Journal. 2020;94–103.

57. Agarwal A, Srivastava MVP, Vishnu VY. Diabetic Amyotrophy (Bruns-Garland Syndrome). Ann Indian Acad Neurol. 2022; 25:841–4.

58. Barohn RJ. The Bruns-Garland Syndrome (Diabetic Amyotrophy). Arch Neurol. 1991;48:1130.

59. Dyck PJB, Norell JE, Dyck PJ. Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. Neurology. 1999; 53:2113–2113.

60. Said G, Goulon-Goeau C, Lacroix C, Moulonguet A. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. Ann Neurol.1994; 35:559–69.

61. Pascoe MK, Low PA, Windebank AJ, Litchy WJ. Subacute Diabetic Proximal Neuropathy. Mayo Clin Proc. 1997; 72:1123–32.

62. Llewelyn D, Llewelyn JG. Diabetic amyotrophy: a painful radiculoplexus neuropathy. Pract Neurol. 2019; 19:164–7.

63. Pasnoor M, Dimachkie MM, Barohn RJ. Diabetic Neuropathy Part 2. Neurol Clin. 2013; 31:447–62.

64. Ku V, Cox C, Mikeska A, MacKay B. Magnetic Resonance Neurography for Evaluation of Peripheral Nerves. J Brachial Plex Peripher Nerve Inj. 2021;16: e17–23.

65. Hlis R, Poh F, Bryarly M, Xi Y, Chhabra A. Quantitative assessment of diabetic amyotrophy using magnetic resonance neurography—a case-control analysis. Eur Radiol 2019; 29:5910–9.

66. Massie R, Mauermann ML, Staff NP, et al. Diabetic cervical radiculoplexus neuropathy: a distinct syndrome expanding the spectrum of diabetic radiculoplexus neuropathies. Brain 2012; 135:3074–88.

67. Glenn MD, Jabari D. Diabetic Lumbosacral Radiculoplexus Neuropathy (Diabetic Amyotrophy). Neurol Clin 2020; 38:553–64.

68. Tracy JA, Engelstad JK, Dyck PJB. Microvasculitis in Diabetic Lumbosacral Radiculoplexus Neuropathy. J Clin Neuromuscul Dis. 2009; 11:44–8.

69. Kilfoyle D, Kelkar P, Parry GJ. Pulsed Methylprednisolone Is a Safe and Effective Treatment for Diabetic Amyotrophy. J Clin Neuromuscul Dis. 2003; 4:168–70.

70. Tesfaye S, Malik R, Harris N, et al. Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glycaemic control (insulin neuritis). Diabetologia. 1996; 39:329–35.

71. Dabby R, Sadeh M, Lampl Y, Gilad R, Watemberg N. Acute painful neuropathy induced by rapid correction of serum glucose levels in diabetic patients. Biomedicine & Pharmacotherapy. 2009; 63:707–9.

72. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: A reversible painful autonomic neuropathy. Ann Neurol. 2010; 67:534–41.

73. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain. 2015; 138:43–52.

74. Quiroz-Aldave JE, Concepción-Zavaleta MJ, del Carmen Durand-Vásquez M, et al. Treatment-induced neuropathy of diabetes: an update. Practical Diabetes. 2023; 40:28–35.

75. Elafros MAandersen H, Bennett DL, et al. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis and new treatments. Lancet Neurol. 2022; 21:922–36.

76. Gibbons CH. Treatment induced neuropathy of diabetes. Autonomic Neuroscience. 2020; 226:102668.

77. Ellenberg M. Diabetic Truncal Mononeuropathy — A New Clinical Syndrome. Diabetes Care.1978;1:10–3.

78. Duque A, Mediano MFF, De Lorenzo A, Rodrigues Jr LF. Cardiovascular autonomic neuropathy in diabetes: Pathophysiology, clinical assessment and implications. World J Diabetes. 2021; 12:855–67.

79. Consensus statement on the definition of orthostatic hypotension, pure autonomic failureand multiple system atrophy. Neurology 1996;46(5):1470–1470. 10.1212/WNL.46.5.1470

80. Ziegler D, Laux G, Dannehl K, et al. Assessment of Cardiovascular Autonomic Function: Age-related Normal Ranges and Reproducibility of Spectral Analysis, Vector Analysisand Standard Tests of Heart Rate Variation and Blood Pressure Responses. Diabetic Medicine. 1992; 9:166–75.

81. Spallone V, Bellavere F, Scionti L, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic

autonomic neuropathy□. Nutrition, Metabolism and Cardiovascular Diseases. 2011; 21:69–78.

82. Freeman R. Diabetic autonomic neuropathy. 2014. p. 63–79.
83. Eleftheriadou A, Spallone V, Tahrani AA, Alam U. Cardiovascular autonomic neuropathy in diabetes: an update with a focus on management. Diabetologia. 2024; 67:2611–25.
84. Agashe S, Petak S. Cardiac Autonomic Neuropathy in Diabetes Mellitus. Methodist Debakey Cardiovasc J. 2018; 14:251.
85. Parkman HP, Hasler WL, Fisher RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology. 2004; 127:1592–622.
86. Brown JS, Wessells H, Chancellor MB, et al. Urologic Complications of Diabetes. Diabetes Care. 2005; 28:177–85.
87. Wessells H, Braffett BH, Holt SK, et al. Burden of Urological Complications in Men and Women with Long-standing Type 1 Diabetes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort. Diabetes Care. 2018; 41:2170–7.
88. Agochukwu-Mmonu N, Pop-Busui R, Wessells H, Sarma A V. Autonomic neuropathy and urologic complications in diabetes. Autonomic Neuroscience. 2020; 229:102736.
89. CHEN X, YANG X, XU W, et al. 426-P: Sudomotor Dysfunction Is Associated with Decreased Cardiac Diastolic Function in Patients with Type 2 Diabetes. Diabetes 2021;70(Supplement_1).
90. Provitera V, Nolano M, Caporaso G, Stancanelli A, Santoro L, Kennedy WR. Evaluation of sudomotor function in diabetes using the dynamic sweat test. Neurology. 2010; 74:50–6.
91. Horváth VJ, Izbéki F, Lengyel C, Kempler P, Várkonyi T. Diabetic Gastroparesis: Functional/Morphologic Background, Diagnosisand Treatment Options. Curr Diab Rep. 2014; 14:527.
92. Hayes R, Dennerstein L. The Impact of Aging on Sexual Function and Sexual Dysfunction in Women: A Review of Population-Based Studies. J Sex Med. 2005; 2:317–30.
93. Kempler P, Amarenco G, Freeman R, et al. Management strategies for gastrointestinal, erectile, bladderand sudomotor dysfunction in patients with diabetes. Diabetes Metab Res Rev. 2011; 27:665–77.
94. Rota E, Morelli N. Entrapment neuropathies in diabetes mellitus. World J Diabetes. 2016; 7:342.
95. Menon D, Bril V. Diabetic Cranial Neuropathies. In: The Cranial Nerves in Neurology. Cham: Springer International Publishing; 2023. p. 161–70.
96. Sharma KR. Demyelinating Neuropathy in Diabetes Mellitus. Arch Neurol. 2002; 59:758.
97. Dyck PJB, Engelstad JK, Norell JE, et al. Inflammatory neuropathies in diabetes mellitus: The radiculoplexus neuropathies and diabetic CIDP. Journal of the Peripheral Nervous System: The Official Journal of The Peripheral Nerve Society. 2010; 15:241–93.
98. Laughlin RS, Dyck PJ, Melton LJ, Leibson C, Ransom J, Dyck PJB. Incidence and prevalence of CIDP and the association of diabetes mellitus. Neurology. 2009;73 :39–45.
99. Bril V, Blanchette CM, Noone JM, Runken MC, Gelinas D, Russell JW. The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. J Diabetes Complications. 2016; 30:1401–7.
100. Lotan I, Hellman MA, Steiner I. Diagnostic criteria of chronic inflammatory demyelinating polyneuropathy in diabetes mellitus. Acta Neurol Scand. 2015; 132:278–83.

QUESTIONS AND ANSWERS

Q. Why is BMI an inadequate measure of obesity? What are the improved ways to identify and understand obesity?

A. Obesity is defined by an excessive buildup of body fat that can negatively impact health. Body Mass Index (BMI), is a common method to assess body fat, calculated by dividing weight in kilograms by the square of height in meters (kg/m²). While BMI is widely used as a screening tool to estimate body fat levels, it does not directly measure fat and therefore cannot accurately diagnose overweight or obesity.

BMI has notable limitations. It tends to overestimate fat in individuals with high muscle mass, such as athletes, or in those with fluid retention and underestimates fat in individuals with low muscle mass, such as the elderly or those with sarcopenia. Its sensitivity and specificity are relatively low and it does not always account for age-related changes in body composition. As people age, they typically lose muscle mass while body fat increases, changes that BMI may not accurately reflect.

In assessing fat distribution, waist-to-height ratio (WHtR) offers advantages over waist circumference (WC) alone. Although WC is commonly recommended to evaluate abdominal fat and predict the risk of cardiometabolic diseases, WHtR is considered more accurate indicator of relative abdominal fat.

WHtR categories:

0.4 to 0.49	Healthy fat distribution, low health risk
0.5 to 0.59	Elevated fat distribution, increased health risk
0.6 and above	High central fat distribution, significant health risk

For estimating body composition, Bioelectrical Impedance Analysis (BIA) is a quick, non-invasive and cost-effective technique. It works by sending a low-level electrical current through the body and measuring the resistance (impedance) of biological tissues. Since different tissues conduct electricity differently, BIA can estimate body water, fat mass and muscle mass, which are then used to calculate body fat percentage and hydration status.

Another method for assessing body composition is digital anthropometry, which can be more visually informative than numerical data like BMI or WC. This method uses either 2D digital photography or 3D optical imaging to provide non-invasive, accurate and detailed measurements of body shape and composition.

Although digital anthropometry and BIA are currently underutilized, they are recommended for broader use in the future to offer more precise assessments of body fat and composition.

Dr. Dina Mithani

Q. Is their evidence supporting the use of cinnamon or other spices and herbs in controlling diabetes?

A. Yes, there is some evidence suggesting that cinnamon and to a lesser extent, certain other spices and herbs, play a role in managing Type 2 diabetes.

Several studies have shown that cinnamon *(C. zeylanicum)*, extracted from the inner bark of the cinnamon tree, contains widely varying levels of natural coumarin, a compound with anticoagulant properties. Recent research has shown that it may help in controlling hyperglycemia, high blood pressure and high cholesterol.

Ranasinghe et al. did a systematic meta-analysis study of the therapeutic qualities of cinnamon and found that it had several positive effects both in-vitro and in-vivo. A daily consumption of 1–6 g of cinnamon demonstrated a decrease in serum

glucose levels after a period of 40 days. Cinnamon also has cinnamaldehyde and procyanidin. However, the most suitable type for treating Type 2 DM is the Chinese cinnamon, *Cinnamomum cassia,* as reported by Sanlier and Gencer in 2020. In another trial, Crawford P. in 2009 reported that 109 patients with Type 2 DM showed a lower hemoglobin A1c level with cinnamon vs those who received regular medication. Cinnamon lowered HbA1c by 0.83% (95% CI, 0.46-1.20) while usual care lowered HbA1c by 0.37% (95% CI, 0.15-0.59).

One study added 3 g/day cinnamon capsules to patients already on oral antidiabetic medicines (like metformin or sulfonylureas). Over 90 days, it produced a modest improvement with a 0.2 % drop in HbA1c compared to placebo. Another study concluded that cinnamon significantly reduces fasting blood glucose (SMD ≈ –1.32), insulin resistance and HbA1c (SMD ≈ –0.67) in Type 2 diabetes.

Other spices and herbs are also known to demonstrate certain effects: For eg. berberine is known for improving first phase insulin secretion. Fenugreek has shown potential in improving blood sugar control. *Gymnema sylvestre* used traditionally in India for diabetes management has shown some promising results. Ginger is known to have anti-inflammatory properties and aid in glucose metabolism. Turmeric contains curcumin, which has anti-cancer, anti-inflammatory and antioxidant effects. Alpha-lipoic acid, found in organ meats (liver and kidney) and green vegetables (spinach and broccoli) may also help improve insulin sensitivity.

A study conducted by the Research Society for the Study of Diabetes in India (RSSDI) examined efficacy of fenugreek powder in controlling blood sugar levels in people with diabetes. Participants who consumed 20 g of fenugreek powder each day showed a notable decrease in their fasting blood sugar levels. In contrast, those taking 10g did not demonstrate a statistically significant change in fasting blood sugar compared to the control group. However, there were no significant differences in HbA1c levels among all groups.

In conclusion, cinnamon as well as many other herbs shows potential in diabetes management. This still needs further research. Their role in prevention and treatment in the early phases of Type 2 DM appears promising and must be explored further (Chandalia HB. JAPI, 2025).

It is recommended to consult a healthcare professional to understand whether and how to incorporate herbs and spices at a therapeutic level.

Jayshri Jain

RECIPES

SEMOLINA SANDWICH

INGREDIENTS

60 gm Semolina (Rava)

50 gm Rolled Oats flour

60 gm Skim Curd

100 gm Finely chopped vegetables (Carrot, Capsicum, Onion, Methi)

15 gm Coriander leaves

15 gm skim Paneer

1 tsp Groundnut oil

Black pepper to taste

Salt to taste

METHOD

- Mix semolina, oats flour, curd, black pepper, salt and enough water to form a thick batter.
- Fold in the finely chopped vegetables and coriander, mixing gently to combine evenly.
- Rest the batter for 10–15 minutes.
- Grease sandwich maker lightly with oil spray.
- Pour little batter, layer with a little paneer and cover with more batter.
- Grill or cook till golden brown and cooked through (about 5–7 mins).
- Serve hot with homemade mint chutney or plain curd.

PROVIDES 2 SERVINGS

Nutritional Information Per Serving

Energy (Kcal)	Carbohydrate (gm)	Protein (gm)	Fat (gm)	GI
254	32	12	5	Low

SPECIAL FEATURES

- Fibre-rich
- Low Glycemic Index

Jincy Sajan

BAJRA PANEER CHILLA

INGREDIENTS

20 gm Bajra flour
30 gm skim Curd
30 gm skim paneer (grated)
Ginger (chopped): 2 cloves
1 Chilli (chopped)
50 gm Onion (chopped)
50 gm Tomato (chopped)
50 gm Carrot (grated)
50 gm Capsicum (chopped)
100 gm Palak (chopped)
1 tsp Sesame seeds
1 tsp Dhaniya powder
1 tsp Groundnut oil
Salt as per taste

METHOD

- Take bajra flour, curd, garlic, green chilli, carrot, onion, capsicum, tomato, palak, salt and add water to make a thick batter.
- Let the mixture sit for 10 minutes.
- Chop ginger, chilli, onion, tomato, capsicum and palak finely.
- In a greased iron pan, add the batter and top with grated paneer. Sprinkle sesame seeds. Let one side of the Bajra chilla cook to golden-brown, then flip and cook similarly on the other side.
- Serve hot with green chutney.

PROVIDES 1 SERVING

Energy	Protein	Carbohydrate	Fat	GI
339	13	24	7	Low

SPECIAL FEATURES

- Fibre-rich
- Low Glycemic Index

Harshini Thakur

HOW KNOWLEDGEABLE ARE YOU?

1. **A major disadvantage of the use of sulfonylureas in patients with diabetes is:**
   A. Vitamin B_{12} malabsorption
   B. Weight loss
   C. Risk of hypoglycemia
   D. Risk of urinary tract infections

2. **What is the recommended blood sugar level before meals for someone with Type 2 diabetes?**
   A. Above 180 mg/dL
   B. Between 80 and 130 mg/dL
   C. Below 50 mg/dL
   D. Any level is acceptable

3. **Which of the following is not a primary mechanism of action for GLP-1 receptor agonists?**
   A. Directly stimulating insulin secretion from beta cells
   B. Induce delayed gastric emptying
   C. Reduce appetite through hypothalamic nuclei
   D. Increases glycosuria

4. **SGLT2 inhibitors are not associated with:**
   A. Weight loss
   B. Glycosuria
   C. Hypoglycemia
   D. Vaginal infections

5. **Which of following is true?**
   A. GLP-1 receptor agonists are not usually associated with hypoglycemia
   B. Sulphonylurea is associated with weight loss
   C. Insulin is associated with weight loss
   D. Elderly diabetes patients should have the same diabetes treatment targets as younger patients.
   E. Impaired awareness of hypoglycemia (IAH) affects only Type 1 diabetic patients

6. **Which medication should be discontinued when starting oral semaglutide?**
   A. Metformin
   B. Sulfonylureas
   C. DPP-4 inhibitors
   D. SGLT-2 inhibitors
   E. None of the above

7. **KDIGO/ADA guidelines in management of patients with diabetes and CKD recommend all of the following except:**
   A. A comprehensive strategy including healthy lifestyle, reduction of CV risk and glycemic control and appropriate reno-protective drugs
   B. Metformin is recommended as the first-line antihyperglycemic drug according to level of renal function
   C. Addition of a SGLT-2 inhibitor regardless of level of renal function
   D. Appropriate target HbA1c according to level of renal function
   E. GLP-1 receptor agonist is the preferred added agent if HbA1c target is not achieved with Metformin (when permissible) and SGLT-2 inhibitor

8. **Which of the following is false about oral semaglutide:**
   A. 7 mg or 14 mg is indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes
   B. It is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia Syndrome Type 2 (MEN 2)
   C. Routine monitoring of serum calcitonin or using thyroid ultrasound is of proven value for early detection of MTC in patients
   D. It is not indicated for use in patients with Type 1 diabetes
   E. The most common adverse reactions, reported in ≥5 percent of patients treated, are nausea, abdominal pain, diarrhoea, decreased appetite, vomiting and constipation

9. **Among female children and adolescents, the first sign of Type 1 diabetes may be:**
   A. Rapid weight gain
   B. Constipation
   C. Genital candidiasis
   D. Insomnia

10. **Which of the following measures does not help to prevent diabetes complications?**
    A. Controlling blood glucose
    B. Controlling blood pressure and blood lipids
    C. Eliminating all carbohydrates from the diet
    D. Prompt detection of diabetic eye and kidney disease

ANSWERS:

1.	C	2.	B	3.	D
4.	C	5.	A	6.	C
7.	B	8.	D	9.	C
10.	C				

MYTHS AND FACTS

Myth: Fat loss from exercise does not improve diabetes if weight stays the same.

Fact: There are benefits of exercise that go beyond weight reduction. Exercise improves insulin sensitivity, glucose uptake by muscles and HbA1c levels, which is independent of weight loss.

Aerobic and resistance training both help regulate blood glucose: Studies indicate that physical activity can reduce liver fat, improve lipid profiles and overall is beneficial for managing diabetes. A 2016 study in Standards of Diabetes Care found that people with Type 2 diabetes showed improvement in insulin sensitivity and enhanced glycemic control after exercise training without weight loss.

Fat Loss as Compared to Weight Loss: Fat loss can occur without a lot of weight loss, especially if there is gain in muscle mass at the same time. Visceral fat, is particularly harmful in Type 2 diabetes and reducing it improves insulin sensitivity, even if total body weight does show no change.

Visceral vs. Subcutaneous Fat: Decrease in visceral fat improves diabetes markers more than losing subcutaneous fat. A reduction in visceral fat can improve HbA1c and fasting glucose.

Myth 2: High-protein diets are the best for diabetics

Fact: Protein plays a vital role in a diabetic diet, but it is crucial to strike a balance. While excessive protein intake, especially from animal sources, can strain the kidneys, many Indian diets tend to be protein-deficient due to the high carbohydrate content of their diet. Aiming for 0.8-1.0 g/kg body weight of protein, tailored to individual needs and activity levels, can help manage diabetes effectively. A balanced diet that includes diverse protein sources such as legumes, dairy, nuts and lean meats is ideal. Opt for lean proteins like fish, chicken, tofu and low-fat dairy and limit high-fat or processed meats to minimize risk of heart disease.

Rima Ved

Myth 3: Diabetes often leads to amputation of lower limbs

Fact: It is a fact that diabetes is a significant risk factor for lower limb amputations, especially in individuals with poorly controlled blood glucose levels, high triglyceride and tobacco abuse. Diabetic neuropathy and peripheral artery disease, both complications of diabetes, increase the likelihood of foot ulcers that may not heal, leading to infection and ultimately, amputation.

Foot care is an important part of diabetes management. It can prevent lot of amputations:

Examination of feet every day: Inspection of feet daily for blisters, cuts, cracks, sores, redness, tenderness or swelling. One can use a hand mirror to see the bottom of the feet if there is difficulty in seeing the feet.

Clean feet daily: Rinse feet in lukewarm (not hot) water each day. Pat them dry gently in between the toes.

Apply talcum powder to maintain dryness of the skin between the toes. Apply a moisturizing cream or lotion to the feet to maintain soft skin. Avoiding fissures in dry skin aids in blocking bacteria from entering.

Cut toenails carefully: Cut nails straight across. Ask someone to help if toenails cannot be trimmed by oneself.

Avoid walking without shoes: To protect feet from injury, refrain from going without footwear, even within home.

Put on clean, dry socks: Opt for socks made of fabric that absorbs moisture away from the skin. Go for cotton and unique acrylic fibers, excluding nylon. Avoid wearing socks with tight elastic bands as these bands limit blood flow. Avoid socks that have seams which might cause skin irritation.

Purchase shoes that fit well: Opt for comfortable footwear that offers support and cushioning for the heel, arch and ball of your foot. Avoid tightfitting shoes and high heels or narrow footwear that squeezes the toes.

Major amputations have become rare in a centre for diabetes care. Effective management and consistent care can avoid a majority of complications, such as amputations.

Jayshri Jain

DIABETES EDUCATOR CERTIFICATE COURSE

Dr Chandalia's DENMARC in association with Help Defeat Diabetes Trust (HDDT) presents to you a Certificate course for Diabetes Educators (CDE)!

Help Defeat Diabetes Trust (HDDT) is a registered, non-profit public trust, having amongst its many objectives, the main objective of promoting education and awareness about diabetes among people from different fields.

Who can enroll?

Graduates in Nutrition, Doctors, Nursing, Pharmacy, Occupational and Physiotherapy.

What is the duration of the course?

6 months, including 300 Hours of hands-on training and experience with a recognized mentor in your own town (see this on our website).

How can I do this course from my place of residence?

A suitable Mentor can be selected from the registrant's locality under whom the training can be done.

How will I get the course material?

All course material is available online on our website.

What are the course fees?

The standard fee for the course are INR 10,000/-

Where can I get more information about this course?

Kindly visit our website **http://www.helpdefeatdiabetes.org** or you can get in touch with us on our email id: heldefeatdiabetesinfo@gmail.com.

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- To secure highest marks in the current year.

For further details visit helpdefeatdiabetes.org

MEMBERSHIP FORM

Association of Diabetes Educators (ADE)

(For eligibility criteria: Check Website www.diabeteseducatorsindia.com)
(Kindly print, duly fill, scan and upload)

Name ……..……Age:……Gender:……

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……

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Educational Qualifications:……..……

……

Work Experience: ……...……

……

Currently employed at: ….……

……

Certificates attached: ……

……

How do you wish to participate in the ADE activities?

- o Update my knowledge and skills
- o As a faculty in ADE's Educational Activities
- o Organizational Activities as Office Bearer

Please pay the membership fees through NEFT / RTGS/online to the following bank account. The details are as follows:

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Account type: Savings Account

Name of the bank: Bank of India

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