

No common denominator: Plant-based diets and treatment-induced neuropathy of diabetes

Maximilian Andreas Storz

MD and independent author based in 72076 Tübingen, Baden-Württemberg, Germany



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ABSTRACT

Treatment-induced neuropathy of diabetes is a poorly understood and underestimated iatrogenic complication of aggressive glycemic control in individuals suffering from diabetes. Symptoms, including severe neuropathic pain and autonomic dysfunction, usually follow an abrupt improvement in glycemic control. The latter is usually triggered by pharmacotherapy, however, treatment-induced neuropathy of diabetes (TIND) has also been associated with severe dietary restriction.

Dietary modifications are of paramount importance in the treatment of type 2 diabetes. Hereby, calorie restriction and fasting diets as well as plant-based diets enjoy uninterrupted popularity. While cases of TIND have been reported with (very) low calorie diets, a case of TIND in the context of a whole-food plant-based diet has not been published to the best of my knowledge.

Is this a simple coincidence or is there potentially a reason behind it? The hypothesis presented in this paper is that whole-food plant-based diets and TIND do not share a common denominator. Both evidence in support and evidence against this, admittedly, speculative hypothesis, is presented in this manuscript. A special focus is put on HbA1c dynamics with plant-based diets and reduced medication needs.

Text

Treatment-induced neuropathy of diabetes (TIND) is a poorly understood and underestimated iatrogenic complication of aggressive glycemic control in individuals suffering from type 1 or type 2 diabetes [1,2]. In patients with longstanding chronic hyperglycemia, TIND may be triggered by a rapid decline in blood glucose levels or a rapid improvement in HbA1c levels respectively [3]. The disease can affect both adults and children [4].

Symptoms may include acute and severe neuropathic pain as well as features of autonomic dysfunction [5]. They usually follow an abrupt and rapid improvement in glycemic control, often triggered by pharmacotherapy including rapid correction of serum glucose with insulin or administration of oral hypoglycemic agents [6–8]. In some cases, however, TIND has also been associated with severe dietary restriction [6].

In the treatment of type 2 diabetes, dietary modifications are of paramount importance [9]. In this context, low and very-low calorie diets have been shown to improve insulin sensitivity and pancreatic β -cell function [10–12]. However, patients on a very low-calorie diet often report side effects, such as nausea, fatigue and constipation [13]. Moreover, very-low-calorie diets seem to increase the risk of symptomatic gallstones requiring hospitalization or cholecystectomy [14,15].

Reviewing their potential to rapidly correct dysregulated glucose homeostasis and insulin resistance, very-low-calorie diets may also increase the risk of TIND.

In 2010, Gibbons and Freeman reported a case of TIND in the context of severe dietary restriction [16]. By restricting himself to a 500 calorie per day diet, a patient intentionally lost 21 lbs in 2 months. He suffered from type 2 diabetes and had an initial HbA1c of 12.1%. Within just a week of dietary restriction, his average daily blood glucose dropped from approximately 402 mg/dl to 126 mg/dl. Four weeks after starting his diet, the patient noted tingling and another two weeks later, he reported pain.

Another nutritional approach in the management and treatment of type 2 diabetes is a whole-food plant-based diet. Plant-based diets (PBDs) emphasize legumes, whole grains, vegetables, fruits, nuts, and seeds while discouraging most (or all) animal products [17]. PBDs have been shown to reduce HbA1c levels and are inversely associated with risk of developing diabetes [18,19]. Within the last two decades, plant-based nutrition has increased in popularity in the general population and a variety of studies investigated on its beneficial effects in the treatment of type 2 diabetes [20,21]. To the best of my knowledge, a case report of TIND in the context of a whole-food plant-based diet has not been published so far.

E-mail address: storzm815@gmail.com.

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The hypothesis

Why is this? Why is there apparently no published case of a patient developing TIND under a supervised whole-food plant-based diet? Is it because TIND is underdiagnosed and under-recognized? Is it because TIND used to be considered rare and diagnostic guidelines are limited? While all these aspects must be considered, I had a lot of conversations with experienced physicians and dietitians that frequently prescribe PBDs. None of them reported a single case of TIND. A surprise? I doubt it.

It is my hypothesis that a well-planned whole-food PBD and TIND do not have a common denominator.

Please allow me to explain this in detail and present both evidence in support and evidence against this, admittedly, speculative hypothesis.

PBDs and HbA1c levels

Although TIND is still insufficiently understood, it appears that high and fast HbA1c reductions may predispose patients to develop the disease. In 2015, Gibbons and Freeman reported that approximately 11% of patients who had a decrease in HbA1c > 2% percentage points over 3 months developed TIND [22].

Reviewing the kinetics of an average HbA1c reduction under an isocaloric whole-food PBD, one would not expect such a rigorously fast drop within 3 months. A meta-analysis by Yokoyama et al. revealed that a vegetarian dietary pattern reduced HbA1c levels by 0.4 percentage point in patients with type 2 diabetes [18]. The magnitude of the effect size of this dietary modification is approximately one-half of that seen with the oral antidiabetic drug metformin.

Other studies published after the meta-analysis by Yokoyama et al. revealed comparable results. In 2016, Lee et al. reported the effects of a brown rice based vegan diet on glycemic control in patients suffering from type 2 diabetes [23]. The authors noted a statistically significant reduction in HbA1c levels by 0.5% within 12 weeks. A sub-analysis considering only participants with high compliance revealed a larger HbA1c level reduction (−0.9%). Recently, Ramal et al. published a study that investigated the impact of a PBD in Latinos with type 2 diabetes living in medically underserved areas [24]. The authors paired a high-fiber and low-fat PBD with lifestyle support. While baseline measurements revealed poor metabolic control (HbA1c 8.53), mean HbA1c levels decreased to 7.31% after six months. This constitutes a reduction in mean HbA1c levels of 1.22% within half a year. Another study by Barnard and colleagues revealed a significant reduction in HbA1c levels by −0.40 percentage point after a 20-week nutrition intervention with a low-fat vegan diet [25].

Reviewing the relevant studies in this field, it appears that a PBD has the potential to reliably reduce HbA1c levels in patients suffering from type 2 diabetes. Of note, this reduction seems to be sound and sustainable, yet not excessive enough to increase the risk of TIND in the first three months. In 2017, Gibbons suggested a conservative approach to glycemic control in individuals with longstanding hyperglycemia in order to avoid TIND. According to Gibbons, the rate of change in HbA1C should not exceed 3 percentage points in 3 months [3]. The expected HbA1c reduction of a PBD within the first months of application in the management of type 2 diabetes is in full compliance with this recommendation (Fig. 1).

Unlike low- and very-low calorie diets, PBDs do usually not restrict calorie intake. The great majority of clinical studies investigating the effects of a PBD in terms of a HbA1c reduction had a neutral energy balance [27]. Although PBDs either strictly limit or fully exclude the intake of animal products, they do not restrict total food intake in general. On the other hand, the caloric restriction of low and very-low calorie diets may lead to a more aggressive and faster HbA1c reduction predisposing patients to TIND.

In short, it seems very unlikely that one would exceed the HbA1c-

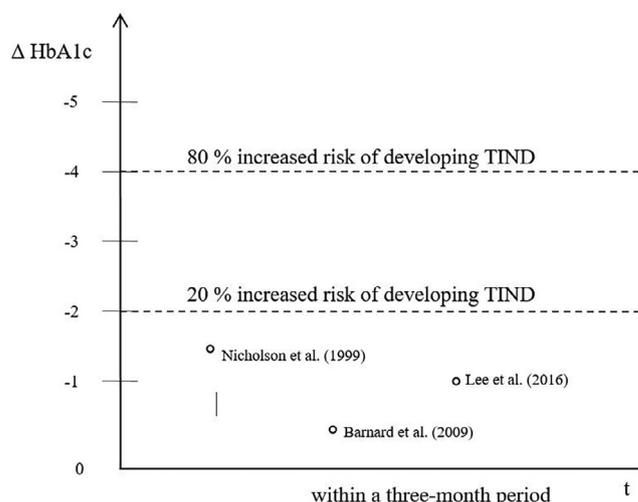


Fig. 1. HbA1c reductions over 3 months and the absolute risk of TIND – a schematic illustration. Modified, according to Gibbons and Freeman [22]. The total HbA1c reduction of three clinical studies using a low-fat PBD (with high patient compliance) are shown for comparison [20,23,26].

reduction threshold suggest by Gibbons [3] using a non-hypocaloric whole-food PBD.

PBDs and medication needs

Physicians and dietitians prescribing PBDs often refer to type 2 diabetes as a lifestyle disease that should to be treated using sustainable lifestyle modifications. Instead of prescribing medication immediately, more and more physicians use a lifestyle modification approach in the first place. In this case, a PBD and exercise are the foundations for proper medical care.

The McDougall program for instance discourages patients from taking oral antidiabetics [28,29]. As part of the program, the daily insulin dosage is often reduced and switched from multiple shots daily to a single dose of long-acting insulin [28]. On the same time, patients are asked to change to a low-fat PBD along with regular exercise. The aim of this less aggressive treatment approach is a more gradual and yet sustainable HbA1c improvement. The rationale behind this approach is that several landmark studies showed that the use of intensive therapy to target normal glycated hemoglobin levels increased mortality in patients with type 2 diabetes [30].

Some oral hypoglycemic agents (Sulfonylurea and Metformin) are expected to decrease HbA1c levels by 1.0–2.0% when used as a monotherapy [31,32]. Combining these drugs in the first place may lead to high HbA1c reductions within a short time frame. Ultimately, this may result in a higher risk of developing TIND.

PBDs on the other hand are associated with a reduction in “medication needs” [33–35]. Over time, blood glucose levels do generally decrease in patients adhering to the guidelines of a low-fat PBD [35]. This often requires a reduction in oral hypoglycemic agent (and insulin) use. While it may take longer to correct HbA1c levels in patients with type 2 diabetes with this more “natural” approach, sustainable changes are the hallmark of the whole-food PBD-approach.

The again, some patients on a typical western diet will not change their eating patterns once they are told that medication will correct their blood sugar and HbA1c levels “for them”. Instead, they will continue consuming a high-fat and high-sugar diet including large amounts of processed foods. In this case, metabolic control and laboratory findings (blood glucose and HbA1c levels) will not improve. On the contrary, they will eventually be even worse, putting physicians under pressure to intensify the current treatment regime. In such cases, another oral hypoglycemic agent will be added or the daily insulin dosage

will be increased to achieve normoglycaemia. The result? A rigorous pharmacological treatment regime with the potential for a dramatically fast and pronounced HbA1c reduction resulting in an increased risk of developing TIND.

Limitations

Up until today, TIND is poorly and insufficiently understood. The exact pathophysiological mechanism still remains unclear [22]. Moreover, the disease is presumably underdiagnosed and under-recognized [7]. Awareness of this entity among physicians may be insufficient and there is a possibility that some clinicians may not consider the relationship between changes in glycemic control and the development of an acute neuropathy [22].

Although an association between TIND an initiation of a PBD has not been reported yet, one may not exclude that this could happen in the future. Plant-based nutrition has experienced an increase interest in the medical community within the last years and it is likely that more papers dealing with its clinical implication will be published in the near future.

It must be emphasized that the hypothesis mentioned above refers explicitly to non-hypocaloric plant-based diets under medical supervision. Unsupervised and hypocaloric PBDs may lead to a more rapid reduction in HbA1c levels and a consecutively increased risk of TIND. Patients with a poorly-controlled type 2 diabetes need to see a physician on a regular basis once they start with a PBD. Medication, both daily insulin dosage and oral hypoglycemic agents, must be constantly adjusted and re-evaluated since whole-food PBDs will effectively lower the patient's blood glucose levels. If this does not happen, the blood glucose lowering effects of a PBD and the medication will add up and the combined effect will lead to recurrent hypoglycemic episodes and an aggressive HbA1c reduction. This, in turn, may also increase the risk of developing TIND.

Conclusions

There is evidence from clinical and observational studies that a whole-food plant-based diet may effectively reduce blood glucose and HbA1c levels in patients suffering from poorly controlled type 2 diabetes. Of note, this reduction happens gradually over time and the results seem to be sustainable. There is a lack of cases associating TIND with PBDs in the literature.

Evidence in the literature backs up the hypothesis that a PBD and TIND do not share a common denominator, namely an abrupt improvement in glycemic control. Due to the rather gradual than abrupt HbA1c improvements with a whole-food PBD, this dietary modification might be a suitable therapeutic option for patients at high risk of developing TIND (e.g. those with poor metabolic control and high HbA1c levels).

Declaration of Competing Interest

The author received no specific funding for this work. I hereby confirm, that the manuscript has not been accepted elsewhere for publication. The author declares that there is no conflict of interest. The author reports no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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