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Review

Treatment induced neuropathy of diabetes

Christopher H. Gibbons

Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Palmer 111, Boston, MA 02215, United States of America

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ABSTRACT

Background: Treatment induced neuropathy of diabetes (TIND) is an iatrogenic painful sensory and autonomic neuropathy. Although the prevalence is not known, it is seen in up to 10% of tertiary cases referred for evaluation of diabetic neuropathy.

Evidence: TIND is associated with a decrease in the glycosylated hemoglobin A1C in individuals with long-standing hyperglycemia. TIND is more common in individuals with type 1 diabetes, but can occur in anyone with diabetes through the use of insulin, oral hypoglycemic medications or diet control. There is an acute or subacute onset of neuropathy that is linked to the change in glucose control. Although the primary clinical manifestation is neuropathic pain there is a concurrent development of autonomic dysfunction, retinopathy and nephropathy.

Conclusion: TIND is more common than previously suspected. The number of cases reported over the past 10 years is much greater than historical literature predicted. Increased attention to target glucose control as a physician metric could suggest a possible explanation for the increased in TIND cases reported in recent years. At present, supportive care is the only recommended treatment. Future research is necessary to define the underlying mechanism, prevent development and to guide treatment recommendations.

1. Introduction

The name 'Treatment induced neuropathy of diabetes' is a relatively recent addition to an older body of literature (Gibbons and Freeman, 2010). The first case description of the disease entity dates back to 1933 when a woman who was diagnosed with diabetes developed severe pain shortly after initiating insulin therapy (Caravati, 1933). The insulin was discontinued, and the pain resolved shortly thereafter. Another trial of insulin in this same patient again resulted in the rapid onset of burning pain. At that time it was hypothesized that this was an allergic reaction to insulin, and thus the term 'insulin neuritis' was introduced. The description of insulin neuritis has been used over the last 80 years across a few small case reports where similar clinical presentations have been described. The most frequent clinical description is the acute onset of severe pain in the setting of improved glycemic control (Kihara et al., 1994; Tesfaye et al., 1996; Dabby et al., 2009). However, the literature also includes other similar reports that have been labeled 'acute painful neuropathy', 'diabetic neuropathic cachexia' or other similar variations on these names (Ellenberg, 1974; Gade et al., 1980; Massey, 1982; Blau, 1983; Llewelyn et al., 1986; Llewelyn et al., 1988; Knopp et al., 2013). In general, the overall characteristics of these cases are very similar: they generally involve individuals with type 1 diabetes who historically have poor glycemic control, and then have a rapid improvement in glycemic control, typically caused by treatment with insulin. Within a few days to weeks of the glucose control, there is the onset of severe burning and lancinating pain in a length-dependent or diffuse fashion (Ellenberg, 1974; Gade et al., 1980; Massey, 1982; Blau, 1983; Llewelyn et al., 1986; Llewelyn et al., 1988; Knopp et al., 2013).

Over the 80 year history of the disorder the total number of cases reported in the literature was quite small, suggesting that the disease was very rare and not necessarily relevant to most patients or physicians. In 2010 we described 16 individuals with diabetes that developed the onset of neuropathic pain after an improvement in glucose control (Gibbons and Freeman, 2010). One of the major differences in our case study was the fact that it included individuals with both type 1 and type 2 diabetes, and not all subjects were taking insulin. A few of the subjects achieved major changes to glucose control simply through severe dietary restriction (Gibbons and Freeman, 2010). Thus, the name 'treatment induced neuropathy of diabetes (TIND)' was suggested as a more accurate name, rather than insulin neuritis. It was also noted that individuals with TIND also developed autonomic neuropathy, in addition to the painful peripheral neuropathy. There was also a concurrent development of nephropathy and proliferative retinopathy, suggesting that a diffuse microvascular process was occurring (Gibbons and Freeman, 2010). To date, the number of individuals at risk for TIND is unknown, and the general prevalence in the population is not described.

This paper will review the relevant publications on treatment

E-mail address: cgibbons@bidmc.harvard.edu.

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induced neuropathy of diabetes with a focus on the most recent reports of prevalence, clinical findings, mechanisms and treatment options.

2. Potential mechanisms of TIND

There are several theories that exist surrounding the potential pathophysiology of TIND. One potential mechanism is the development of a 'relative' hypoglycemia in an individual with chronic and sustained hyperglycemia that results in an energy dependent failure of axonal transport. Controlled studies of modest hypoglycemia in humans using an insulin clamp have resulted in the development of tactile hyperalgesia and transient autonomic dysfunction associated with the release of pro-inflammatory cytokines (Gibbons et al., 2012). Other proposed mechanisms include the development of arteriovenous shunt that result in endoneurial ischemia and firing of regenerating nerve fibers (Llewelyn et al., 1986; Llewelyn et al., 1988; Tesfaye et al., 1996). Development of an animal model of TIND may provide greater understanding of the potential pathophysiological mechanisms of the disease (Nicodemus et al., 2017).

3. Epidemiology of TIND

The prevalence of TIND in the general population is unknown. Several abstracts presented at recent international meetings have highlighted the scientific interest in this phenomenon, but the results from these abstracts have not yet been published. Thus, the only data currently available is based on smaller, non-population based studies or secondary outcomes gleaned from larger clinical trials with other overlapping microvascular outcomes of interest.

Our group conducted a review of all records of patients seen with diabetic neuropathy over 5 years (Gibbons and Freeman, 2015). In order to standardize the operational definition of TIND, subjects included in the study had to meet the following criteria to be classified as having TIND: 1) to have the onset of either neuropathic pain or autonomic dysfunction within 8 weeks of a decrease in average glucose values, 2) having neuropathic pain of at least 3 points on a 10 point Likert scale or autonomic dysfunction that was severe enough to require medical attention, 3) the change in glucose control resulted in a decrease in hemoglobin A1C (HbA1C) of 2 points or more over a 3 month period of time (Gibbons and Freeman, 2015). Over a period of 5 years 954 patients were evaluated for a diagnosis of diabetic neuropathy, and 104/954 (10.9% of the total evaluated) met study criteria for TIND. The number of patients with probable TIND in this single study was greater than the total number of patients reported over the prior 80 years. The study was conducted though a single medical center at two enrollment sites, so was unable to investigate the prevalence of this disorder in the broader population of individuals with diabetes. However, the frequency with which it was seen did challenge the presumption that this was a rare disorder (Gibbons and Freeman, 2015).

In the diabetic ophthalmology literature, it was noted within the Diabetes Control and Complications Trial (DCCT) a small subset of individuals developed diabetic retinopathy after institution of aggressive glycemic control (Lauritzen et al., 1983; Kroc Collaborative Study, 1984; Dahl-Jorgensen et al., 1985). This was described as 'early worsening retinopathy'. Since these initial studies, early worsening retinopathy has been reported with individuals with both type 1 and type 2 diabetes (Group, 1998; Henricsson et al., 1999; Chantelau and Meyer-Schwickerath, 2003). In the original DCCT trial, early worsening retinopathy occurred in 22% of the intensive therapy group, vs. 13% in the conventional therapy group (Lauritzen et al., 1983, Kroc Collaborative Study, 1984, Dahl-Jorgensen et al., 1985). The findings from these studies suggest that TIND may be more frequent than previously estimated.

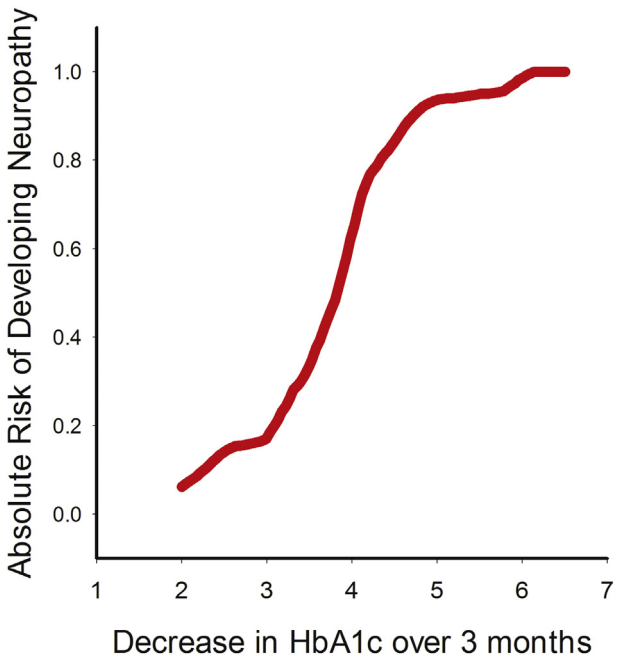

Fig. 1. Risk of TIND. The absolute risk of developing TIND by change in HbA1C is visually depicted. A 2 point decrease in the HbA1C over 3 months carries an approximately 10% risk of TIND. A 4 point decrease in the HbA1C over 3 months results in a 50% risk of TIND, while a 5 point change in the HbA1C in 3 months carries a > 90% risk of TIND.

4. Risks of TIND development

Of the 104 individuals in the retrospective analysis that developed TIND, there was a relationship between neuropathy development and change in HbA1C (Gibbons and Freeman, 2015). All patients completed HbA1C testing every 3 months as part of their routine clinical management of their diabetes. An analysis of the rate of HbA1C change versus development of neuropathy was performed to determine the absolute risk of TIND in this population (Gibbons and Freeman, 2015). Of the individuals with a decrease in their HbA1C of 2 points or more over 3 months, those with smaller changes in glucose had a lower incidence of TIND than those with greater changes in their HbA1C. This data is visually displayed in Fig. 1: a risk analysis curve plots TIND development against the change in HbA1C (Gibbons and Freeman, 2015). With more modest changes in HbA1C, the absolute risk of developing TIND was 10% or less. However, greater changes in HbA1C increased the risk of TIND to > 50%. With a decrease in HbA1C of 5 percentage points or more in 3 months the absolute risk of developing TIND was > 90% (Gibbons and Freeman, 2015). As seen in Fig. 2, as the HbA1C fell to a greater degree, the distribution and severity of the pain increased.

The information gathered from the DCCT ophthalmology studies suggests that with every percentage point drop in glycosylated hemoglobin (HbA1C), there was a 1.6-fold increase in the risk of early worsening retinopathy (Lim et al., 2019). It was also noted that the magnitude of the decrease in HbA1C was also closely tied to the initial HbA1C, so it was difficult to determine which of the HbA1C characteristics was the primary driver of retinopathy development (Lim et al., 2019).

These findings strongly support a link between large fluctuations in average glycemic control and risks of microvascular complications including neuropathy and retinopathy. A number of questions remain about the associated risks, and these include 1) the duration of hyperglycemia that is necessary before someone is at risk for TIND or early worsening retinopathy, 2) it is the initial HbA1C or the change in HbA1C that puts individuals at risk and 3) are there other comorbid

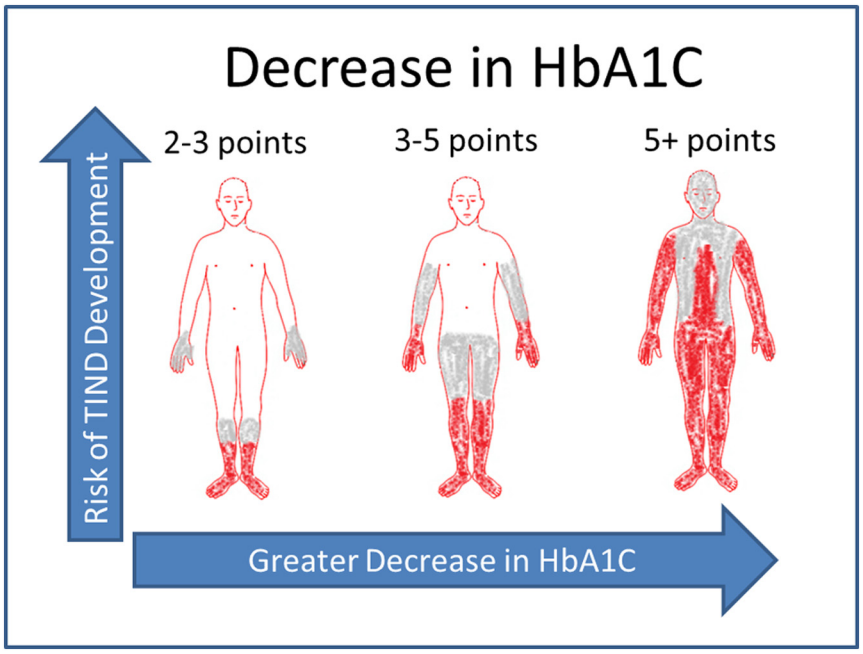

Fig. 2. Clinical Phenotype in TIND. A small change in HbA1C results in a stocking/glove distribution of pain (red area seen in all patients, grey seen in some patients) while a larger change in HbA1C over 3 months results in a larger distribution of neuropathic pain that can cover most of the body when the HbA1C change exceeds 5 points in 3 months. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

conditions that modify the risk of TIND development, or are required for TIND development.

Thus far, there is little data available in the literature to suggest that a particular type of treatment for diabetes triggers TIND. The magnitude of the change in HbA1C and initial HbA1C appear be the major associated risk factors for TIND. How the change in HbA1C occurs does not seem to matter (i.e. TIND could develop with insulin, oral hypoglycemic medications or even dietary restriction), although it should be noted that insulin will cause a more rapid change in the individuals not previously exposed to it (Gibbons and Freeman, 2010; Gibbons and Freeman, 2015). Those individuals with type 1 diabetes who developed TIND in our study typically had a longstanding history of hyperglycemia, frequently extending back several years. The duration of hyperglycemia in individuals with type 2 diabetes is often challenging to ascertain due to incomplete information about disease and symptom onset (Gibbons and Freeman, 2015). We did not detect TIND in any individual with hyperglycemia of a < 6 months duration (Gibbons and Freeman, 2010; Gibbons and Freeman, 2015). It therefore appears, based on incomplete data, that individuals with short term fluctuation in glycemic control are not likely to develop TIND.

5. Demographics of individuals with TIND

Without true epidemiologic data, it is difficult to state concrete findings. The demographic distribution of patients who developed TIND in the retrospective study was made up disproportionately of those with type 1diabetes (73%), with a mean age of 25 years, and 79% of those were female (Gibbons and Freeman, 2015). Estimating that ~5% of people with diabetes have type 1 diabetes, it suggests a 50 fold increase in risk of developing TIND with type 1 diabetes, and a 5 fold increase in risk for women (CDC, 2011). Given that there is only one small, single center, study to date, further investigation into the demographics of this disorder are required to confirm these findings.

Those individuals with type 2 diabetes tended to be older (> 50 years) and have an equal distribution of males and females. Individuals with type 2 diabetes could be using insulin, oral hypoglycemic medications or just diet control alone (Gibbons and Freeman, 2015).

We did note that among those individuals with type 1 diabetes that developed TIND eating disorders were a common co-morbidity. More than 80% of individuals reported a history of diabetic anorexia or diabulemia (intentionally withholding insulin in order to lose weight) (Gibbons and Freeman, 2015). None of the individuals with type 2 diabetes in our study had a history of eating disorders. The prevalence of eating disorders among individuals with type 1 diabetes is approximately 30% (this number includes anorexia, bulimia and other forms of eating disorders) (Colton et al., 2015; de Groot et al., 2016). Diabulimia is known to carry a very high morbidity, but it is unclear how common this is in individuals who do not develop TIND (Torjesen, 2019).

5. Symptoms and signs of TIND

The most common symptom of TIND is the onset of neuropathic pain in an acute or subacute time frame 2–8 weeks after the change in glucose control. The characteristic used to describe pain typically include the terms 'burning' or 'lancinating/lightning'. The pain presents in a length-dependent fashion, and the distribution of pain is typically associated with the magnitude of the change in HbA1C. In addition to reports of spontaneous pain, there is typically pain evoked by contact. On examination, the pain is characterized by both allodynia and hyperalgesia (Gibbons and Freeman, 2010; Gibbons and Freeman, 2015).

In addition to neuropathic pain, there are a variety of autonomic symptoms that are present in individuals with TIND. Autonomic symptoms tend to appear in a similar time frame, with an acute to subacute onset, although it is often difficult for patients to identify an exact date where symptoms began because they are often more insidious than the development of pain. This is in part because the autonomic manifestations are frequently dismissed due to the severity and attention to neuropathic pain. However, with detailed questioning symptoms of dysautonomia will frequently be reported (Gibbons and Freeman, 2010). Common autonomic manifestations of TIND include orthostatic intolerance, orthostatic hypotension with syncope, postprandial fullness, hyperhidrosis, anhidrosis, and erectile dysfunction.

For patients with TIND that complete formal testing of autonomic function moderate dysfunction of the sympathetic and parasympathetic systems will be noted, although severe autonomic failure may be noted in some cases. There is a relationship between severity of autonomic failure and the decrease in HbA1C (Gibbons and Freeman, 2015).

6. Associated microvascular complications of TIND

As noted in the initial description of TIND (Gibbons and Freeman, 2010), a number of other microvascular manifestations can occur in addition to autonomic and peripheral neuropathy (Gibbons and Freeman, 2015). As noted in our study, the development of retinopathy was a common co-morbid complication that occurred in individuals that developed TIND. More than half of the group with TIND had no retinopathy and only 3% of the individuals had proliferative retinopathy prior to the decrease in their HbA1C. After development of TIND, 90% of the group had either severe non-proliferative or proliferative retinopathy (Gibbons and Freeman, 2015).

Renal function is also impaired in individuals who develop TIND. Microalbuminuria was detected in 17% prior to development of TIND. In contrast, 1 year after the development of TIND 84% of individuals had microalbuminuria detected on testing. It should be noted that microalbuminuria is a poor surrogate for renal function, but is an indication of renal damage. A small group of individuals (8%) with TIND did have a significant increase in their serum creatinine levels and in some cases required hemodialysis (Gibbons and Freeman, 2015; Gibbons, 2017).

7. Management of symptoms associated with TIND

Many patients with TIND will report severe neuropathic pain. Although this can be treated using the same medications as painful diabetic neuropathy, there are a couple of items to consider for effective management. In some cases, the neuropathic pain will be much more severe than is routinely identified in painful diabetic neuropathy. In some cases of TIND, maximizing treatment with a single neuropathic pain agent may help (Hovaguimian and Gibbons, 2011). However, in many cases the use of a 2nd, or even a 3rd medication for treatment of neuropathic pain must be considered (Peltier et al., 2014). Although tricyclic antidepressant medications can be used, the anticholinergic side effects may worsen any orthostatic hypotension that develops in the setting of autonomic neuropathy in TIND. Eventually neuropathic pain may resolve with stable glycemic control, although this often takes 12–24 months. Improvements in neuropathic pain should be monitored every few months so that appropriate reductions in the use of neuropathic pain medications occur as tolerated.

8. Outcomes

Unfortunately there is limited information on the long term outcomes of patients who have developed TIND. From the ophthalmology literature we know that individuals with early worsening retinopathy tend to recover with treatment (Lim et al., 2019). It appears that the long term impact of early worsening retinopathy is balanced by the societal benefits achieved by better glycemic control (Lim et al., 2019). The evidence of long term outcomes in TIND is less clear. The only longitudinal follow up data comes from a single center with follow up of 26 individuals with type 1 diabetes that developed TIND (Gibbons, 2017). The majority of the individuals in this longitudinal follow-up study (22/26) were female and had a mean age of 34 years.

Of this cohort, ~75% maintained stable glucose control during the 8 years of follow up post development of TIND. Clinically, they reported a gradual reduction in both severity and distribution of neuropathic pain over 18–36 months (Gibbons, 2017). In parallel, there was an improvement reported autonomic symptoms, including orthostatic intolerance, postprandial fullness, anhidrosis, hyperhidrosis and erectile dysfunction. However, the symptoms did not entirely resolve. Other microvascular complications that occurred in parallel (retinopathy and nephropathy) also tended to improve over time (Gibbons, 2017).

The remaining 25% of individuals that did not maintain stable glycemic control had a very different long-term outcome. There were periods of sustained hyperglycemia followed by periods of improved glycemic control. These fluctuations resulted in a pattern of progressive worsening of neuropathy, retinopathy and nephropathy (Gibbons, 2017). Although encompassing a very small proportion of the individuals who have diabetes, the associated medical expenses, morbidity and mortality with this group were significant because of severe loss of visional, amputations and renal failure (Gibbons, 2017).

9. Conclusions

Treatment induced neuropathy of diabetes is a relatively unrecognized iatrogenic complication of aggressive glucose control. Although detected in up to 10% of patients referred for evaluation of diabetic neuropathy at a tertiary referral center, the actual prevalence of the disorder in the general population is not known (Gibbons and Freeman, 2015). The most common clinical scenario is the acute to subacute onset of neuropathic pain associated with a clinically significant decline in HbA1C. Autonomic symptoms are typically present, although often underreported. In some cases the autonomic symptoms may be the presenting feature. The number of cases of TIND reported over the past 10 years, compared to the prior 80 years, does suggest a change in underlying population risks, although physician recognition could play a role in the reported increase. One possible theory about the increase in TIND is that physician metrics and payer reimbursement have now been tied to patient outcomes, such as the HbA1C score.(Pop-Busui et al., 2009; Albers et al., 2010; Pop-Busui et al., 2010) Although quality metrics are important ways to encourage positive outcomes, the heightened pressure to bring HbA1C scores into the recommended range could theoretically have resulted in greater numbers of individuals at risk for TIND. (Albers et al., 2010; Gibbons et al., 2013).

At present, there is insufficient data to recommend a standard approach to safely reducing the HbA1C in someone with chronic hyperglycemia. Based on both the early worsening retinopathy and TIND data, a target change in HbA1C would be < 1 percentage point change over 1 month, although a 1 point change every 3 months would offer an even lower risk. (Group, 1998; Chantelau et al., 2010; Gibbons and Freeman, 2015; Gibbons, 2017; Lim et al., 2019) There are multiple challenges with implementing slow rates of glycemic change to prevent TIND: 1) the known risk of complications to many patients with ongoing hyperglycemia, where the complications rates are high and well established and 2) the financial pressure from insurance companies to achieve target A1C levels rapidly in order to avoid 'nonpayment penalties'. The management of an individual that has developed TIND is limited to those with type 1 diabetes, and stable glycemic control is recommended. There are no longitudinal follow up studies of people with type 2 diabetes and TIND, although recommending stable glucose control seems to be an uncontroversial recommendation.

One of the challenges is to merge the data from the DCCT and EDIC trials that support intensive glycemic control, with the risks of TIND that appear to occur with rapid glycemic control. (Group, 1993; Pop-Busui et al., 2010; Gibbons and Freeman, 2015) The longitudinal studies of subjects with type 1 diabetes in the DCCT and EDIC trials have a reduction in microvascular complications with 'intensive' glycemic control. However, in most cases the HbA1C change was only about 2 percentage points. (Group, 1993; Pop-Busui et al., 2010) Despite the modest changes in HbA1C, 'early worsening retinopathy' was detected in almost 22% of individuals. (Group, 1998; Davis et al., 2007; Lim et al., 2019) In contrast, individuals with TIND typically have severe hyperglycemia (with HbA1C values typically $> 10\%$), and a change in HbA1C of $> 3\%$ over 3 months. (Gibbons and Freeman, 2010; Gibbons and Freeman, 2015; Gibbons, 2017) Therefore, the need for prospective testing of rates of glycemic change should be investigated in order to provide adequate information about outcomes. There is a critical need for continued research into the pathophysiology, natural history, treatment and prevention of TIND.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of competing interest

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