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Diabetic Neuropathy: One disease or two?

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Abstract

Purpose of review—To compare and contrast the evidence for the effect of glucose control on the prevention of neuropathy in type 1 (T1DM) and type 2 (T2DM) diabetes mellitus.

Recent findings—In T1DM, multiple clinical trials have demonstrated a large benefit from enhanced glucose control, whereas the benefit in T2DM is much more modest. Epidemiologic and laboratory evidence exists to support factors other than hyperglycemia in the development of neuropathy including obesity, hypertension, dyslipidemia, inflammation, and insulin resistance.

Summary—T1DM neuropathy and T2DM neuropathy are fundamentally different. In T1DM, glucose control has a large effect on the prevention of neuropathy; therefore future efforts should continue to concentrate on this avenue of treatment. In contrast, in T2DM, glucose control has a small effect on the prevention of neuropathy; as a result, more research is needed to define the underlying mechanisms for the development of neuropathy. Understanding these mechanisms may lead to novel therapeutic approaches to prevent or treat diabetic neuropathy.

Keywords

Neuropathy; Type 1 diabetes; Type 2 diabetes; Metabolic syndrome

Introduction

The 2011 Diabetes Fact Sheet published by the Centers for Disease Control confirms what is now popular knowledge: the United States is experiencing a diabetes epidemic (1*). Twenty-five million Americans, or over 8% of the population, have diabetes mellitus, and 1.9 million new cases were diagnosed in 2010. Of these individuals, 5% have type 1 diabetes mellitus (T1DM), a disease of children and young adults characterized by an autoimmune destruction of pancreatic islet cells with loss of pancreatic insulin production. The remaining 95% of individuals have type 2 diabetes mellitus (T2DM). T2DM is a metabolic disease with high pancreatic insulin production in the setting of insulin resistance, a condition where muscle, fat and liver cells are poorly responsive to insulin. Along the spectrum of insulin resistance lies a third metabolic disorder, impaired glucose tolerance (IGT), referred to as “pre-diabetes.” Systemic glucose metabolism is abnormal in IGT, but not to the degree of T2DM. The Center for Disease Control estimates there are 79 million

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Americans with IGT (1*). In total, over 100 million Americans have either pre-diabetes or diabetes, and this number continues to climb, especially among minority populations.

Diabetic polyneuropathy (DN) is the most common complication of both T1DM and T2DM with an estimated lifetime prevalence of 60% (1*, 2**). DN is a length-dependent disorder of peripheral nerve fibers, characterized by a distal-to-proximal loss of peripheral nerve axons and, in turn, neural function. While the mechanisms underlying T1DM and T2DM are distinct, it is generally held that DN is due to hyperglycemic damage, regardless of the type of diabetes (2**, 3**, 4**). Only recently has the diabetes community begun to question this idea.

In this opinion piece, we will summarize available results from T1DM and T2DM glucose intervention trials, which suggest that glycemic control is a more important driver of T1DM DN than T2DM DN. Recent findings will be presented that suggest that obesity, hypertension, dyslipidemia, inflammation, and insulin resistance are contributory to T2DM DN to an equal if not greater degree than hyperglycemia. This concept will be further highlighted by discussing the results of newly published transcriptomic data which identifies lipid metabolism and inflammation pathways as key regulators of human nerve damage. We will conclude with a summary opinion that there are differences between the underlying disease mechanisms of DN in T1DM and T2DM, and that treatment of DN requires early but distinct therapeutic interventions depending on the type of diabetes.

The Burden of Disease

IGT neuropathy (IGTN) is reported at rates that vary between 8 to 30%, although these data remain controversial and require further research (4**). Both IGTN and DN are length-dependent disorders of peripheral nerve fibers, characterized by a distal-to-proximal loss of peripheral nerve axons and, in turn, function. IGTN and new onset DN represent a disease spectrum beginning with early symptoms of distal foot pain and thermal sensitivity reflecting early damage to small myelinated and unmyelinated fibers. As pre-diabetes transitions to T2DM, and as T1DM and T2DM patients experience continued metabolic injury, there is a gradual loss of the small myelinated and unmyelinated fibers. With this loss, foot pain is replaced by foot numbness and proprioceptive loss as large caliber myelinated fibers undergo metabolic injury. Eventually there is a confluence of fiber damage and loss leading to the development of an insensate foot. At this stage, individuals with DN experience falls, ulcers and even amputations, leading to impaired quality of life (4**). Consequently, DN has a high societal cost, estimated at \$50 billion in 2007, comprising 25% of the total direct and indirect costs of T1DM and T2DM (1*).

Defining DN for Clinical Trials

While DN is prevalent, disabling and costly, research in the field has been hampered by the lack of a uniform set of criteria to define DN. Criteria were developed 25 years ago by a panel of neurologists and diabetologists but proved too costly and time consuming for clinical trials, and as a result, each trial has used different outcome measures. There are sufficient similarities between the different approaches to allow for a reasonable comparison

of the results for this opinion piece, but a more ideal comparison would involve the same clinical parameters.

To address this problem, a second group of experts, known as the Toronto Expert Panel on Diabetic Neuropathy convened and published revised criteria in 2011 (5**). These criteria are less complex than the previous criteria and provide a new, more widely accepted framework for future studies. The highlights of the criteria are presented in Table 1.

T1DM and DN

The Diabetes Control and Complications Trial (DCCT), the largest T1DM intervention trial, was designed to determine if intensive glycemic control would alter the development and progression of microvascular complications in T1DM. Subjects in a primary prevention cohort (diabetes < 5 years) and subjects in a secondary prevention cohort (diabetes < 15 years) were randomized to intensive versus conventional therapy, which resulted in respective hemoglobin A_{1c} (HbA_{1c}) values of 7.2% versus 9% during the 6.5 year mean follow-up. DN was diagnosed by history, focused neurological examination, and nerve conduction studies (same criteria as in Table 1). The risk of developing DN was reduced in the intensive treatment group by 69% in the primary prevention cohort and 57% in secondary prevention cohort, with an overall risk reduction of 60% (6).

After completion of the DCCT, long-term observational follow-up of 1,375 of the 1,425 DCCT patients occurred in the Epidemiology of Diabetes Complications and Interventions Cohort (EDIC) study (7). DN was assessed annually in EDIC using the Michigan Neuropathy Screening Instrument (MNSI). While glycemic control merged in EDIC with an average HbA_{1c} of 8% for both the intensive and conventional treatment arms, the beneficial effects of prior intensive treatment persisted for 8 years. Patients in the initial DCCT-intensive cohort had a significant risk reduction for developing DN when compared to patients in the initial DCCT-conventional cohort, and this effect was reconfirmed 16 years later, using the more stringent initial DCCT protocol for the diagnosis of DN (7).

Four other T1DM studies of at least 40 subjects or more have directly targeted glycemic control and reported the effects of glycemic intervention on DN. These studies enrolled substantially smaller numbers of T1DN patients than DCCT/EDIC and also employed varying criteria for DN diagnosis. All studies, however, reached the same conclusion: improved glycemic control results in preserved nerve function and/or decreases the likelihood of developing DN (3**). The T1DM DN studies are summarized in Table 2.

T2DM and DN

There are 5 T2DM glucose intervention studies with at least 150 subjects that examined subjects for DN (Table 2). In the United Kingdom Prospective Diabetes Study (UKPDS), 3,867 newly diagnosed T2DM subjects were randomized into either intensive treatment with an oral hypoglycemic agent or insulin, or conventional treatment with diet. After 10 years, intensive treatment resulted in approximately 1% lower HbA_{1c} versus conventional treatment but there was no significant difference in the development of DN between the two groups, which had similar lipid and blood pressure profiles (12). A statistically significant

effect on DN was eventually seen in this cohort, but only at 15 years. This finding, at first unexpected in light of the earlier robust DCCT results, was supported by a second smaller T2DM study, the VA Cooperative Study, which demonstrated no difference in the prevalence of DN in 153 men with T2DM over a 2 year period comparing standard and intensive glycemic control (13). A larger study of 1791 T2DM veterans found no statistically significant effect of glucose control (HbA_{1c} 8.4% versus HbA_{1c} 6.9 comparing conventional to intensive therapy) on DN over a 5 year period (15). In 2003, similar results were reported in the Steno-2 Study of 160 T2DM subjects (14). The most recent and largest trial, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, randomized 10,251 subjects: 5,128 to intensive glycemic control (HbA_{1c} of < 6.0%) and 5,123 to standard control (7.0-7.9%). Intensive therapy was stopped before study end because of higher mortality, and subjects were placed on standard therapy. Using the MNSI for diagnosis of DN, there was a 0.7% per year reduction in the risk of developing DN in T2DM subjects in the intensive group, and a modest 5% relative risk reduction after a median follow-up of 3.7 years, but this result did not reach statistical significance (16). While four of these five studies reported a small reduction in neuropathy in the enhanced glucose control group compared to conventional therapy, only the UKPDS revealed a statistically significant result. Therefore, these 5 studies were the first large scale trials to suggest that independent factors other than glycemic control are critical to the development of DN.

T2DM clusters with other risk factors for coronary heart disease including obesity, hypertension, and dyslipidemia; individuals with multiple of these factors are diagnosed with the metabolic syndrome. The common association of T2DM with other aspects of the metabolic syndrome has led to investigations into the effects of the metabolic syndrome and its components on neuropathy. Costa et al and the Metascreen study team both used cross sectional designs to demonstrate an association between the metabolic syndrome and neuropathy (17, 18). Smith et al discovered that patients with idiopathic neuropathy with and without impaired glucose tolerance had the same prevalence of metabolic syndrome components (19). The implication of this study is that metabolic syndrome components other than impaired glucose tolerance may play a role in neuropathy. Other groups have demonstrated an independent association between obesity, hypertension, LDL, HDL, and/or hypertriglyceridemia with neuropathy (4**). All of these studies point to factors other than glucose control in the development of neuropathy in patients with T2DM.

Lipids, Inflammation, Insulin Resistance and DN

In the mid-1990's, multiple clinical trials for DN were completed using changes in sural nerve morphology as the primary endpoint. Unfortunately, no agent successfully halted or reversed the course of DN. Our laboratory is in possession of a repository of these sural nerve biopsies, as well as accompanying blood chemistries and clinical data (20). We analyzed the demographic data from subjects who had undergone serial sural nerve biopsies, separated in time by a period of one year, for predictive correlates of loss of sural nerve myelinated fiber density (MFD). High-throughput microarray technology is used to measure the abundance of different mRNA species in tissues. We used this technology to assess neural gene regulation during DN in a subset of sural nerve biopsies. We completed microarray analyses on 36 sural nerve biopsies collected at the end of the clinical trials.

These samples were selected from two groups of subjects: those with progressive DN defined as a decrease in MFD of $> 500/\text{mm}^2$ myelinated fibers over a one year period, and those with non-progressive DN defined as a decrease of MFD $< 100/\text{mm}^2$ myelinated fibers over a one year period. A series of bioinformatics analyses identified 532 differentially expressed genes (DEG) between patient samples with progressive versus non-progressive DN, and found these were functionally enriched in pathways involving lipid metabolism and inflammatory responses. A literature-derived co-citation network of the DEGs revealed gene sub-networks centered on apolipoprotein E (APOE) and peroxisome proliferator-activated receptor gamma (PPAR γ), again suggesting crucial regulatory roles for lipids in DN progression (21**). These results in man were recently replicated in a recent transcriptomics study of peripheral nerves from a T2DM animal model (22*). Microarray analysis of sciatic nerves from mice with T2DM and DN revealed that genes associated with lipid metabolism, and immune response are highly dysregulated by diabetes, similar to the genes affected in man (21**).

As discussed in an earlier section, T2DM patients are insulin resistant. Insulin resistance is defined as a state of decreased responsiveness of tissues such as muscle, fat and liver to normal circulating levels of insulin. These tissues are dependent on insulin for glucose uptake. In contrast, neurons are not insulin dependent for glucose uptake, but they are insulin responsive. In the case of neurons, insulin is an essential growth factor and has important roles in neuronal development and survival (2**). A newly emerging concept is that neurons can develop insulin resistance, similar to other tissues, and considering the important neurotrophic role of insulin, it is possible that perturbation of insulin signaling secondary to insulin resistance, results in neuronal damage and contributes to the pathogenesis of DN. We recently demonstrated that disruption of insulin signaling due to insulin resistance makes neurons more vulnerable to metabolic insults and may contribute to the development of DN (23*). This in part could be due to a change in the responsiveness of essential intracellular docking proteins, known as insulin receptor substrates (IRS) in neurons in the presence of diabetes (24).

Conclusion

We contend that a synthesis of recent published results in context with past studies strongly suggests that strict glucose control alone is not enough to ameliorate the onset and progression of T2DM DN. With the global increase in IGT and T2DM being described as epidemic, the need for fresh DN prevention strategies is clear. We advocate that more research is required to understand new mechanisms of nerve injury, including lipotoxicity, inflammation and neuronal insulin resistance, as our incomplete understanding of disease mechanisms is one reason for a lack of effective interventions. As we await results from ongoing and future studies, we advocate following the American Diabetes Association guidelines for the aggressive treatment of T2DM, as well as other components of the metabolic syndrome such as obesity, hypertension, and dyslipidemia (25). DN in patients with T1DM has a more robust association with glycemic control, and we suggest a focus on glycemic control in these individuals will continue to be beneficial.

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Key Points

- Diabetic neuropathy is common, disabling, and costly
- Glucose control in T1DM has a large effect on the prevention of neuropathy
- In T2DM, glucose control only has a small effect on the prevention of neuropathy
- Emerging evidence points to obesity, hypertension, dyslipidemia, inflammation, and insulin resistance as potential mechanisms for the development of neuropathy

Table 1

Defining criteria for DN according to The Toronto Expert Panel on Diabetic Neuropathy (5**)

Classification	Characteristics
Possible Clinical DN	Symptoms <i>or</i> signs of DN. Symptoms can be positive (pain) or negative (loss of sensation) in the feet. Signs can include symmetrical decreased sensory loss in the feet or decreased or absent ankle reflexes.
Possible Clinical DN	A combination of symptoms <i>and</i> signs of DN, as described above, with any two or more of the following: neuropathic symptoms, decreased sensation, or decreased or absent ankle reflexes.
Confirmed Clinical DN	An abnormal nerve conduction study <i>and</i> a symptom or sign of DN, as described above.
Subclinical DN (Stage 1a)	An abnormal nerve conduction study with no signs <i>or</i> symptoms of DN.

Table 2

Glycemic Intervention Differentially Affects DN in T1DM versus T2DM

	Trial size	Length of study (years)	Positive effects of enhanced glycemic control?
T1DM			
Holman et al (8)	74	2	Yes
Dahl-Jorgensen et al (9)	45	2	Yes
DCCT (6)	1,441	5	Yes
Reichard et al (10)	102	7.5	Yes
Linn et al (11)	49	5	Yes
T2DM			
UKPDS (12)	3,867	10	No *
Azad et al (13)	153	2	No
Gaede et al (14)	160	8	No
Duckworth et al (15)	1,791	5.6	No
Ismail-Beigi et al (16)	10,251	3.7	No

* The UKPDS did not show a statistically significant benefit at 9 or 12 years but did show a benefit at 15 years of follow up. Of note, only 227 subjects were evaluated for neuropathy at 15 years.