Patients with Type 1 Diabetes and the Effect of C-Peptide on Diabetic Neuropathy

Simona Cernea*

Diabetes, Nutrition and Metabolic Diseases Outpatient Unit, Emergency County Clinical Hospital, Târgu Mureș, Romania

Corresponding Author*

Simona Cernea

Diabetes, Nutrition and Metabolic Diseases Outpatient Unit, Emergency County Clinical Hospital, Târgu Mureș, Romania

Phone: +408210923764

E-mail: cerneasimona@umfst.ro

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Abstract

Contrary to what was previously believed, new research demonstrates that proinsulin C-peptide has significant physiological effects and exhibits the traits of a bioactive peptide. Studies in type1 diabetes, both in humans and in animal models, show that replacement amounts of C-peptide can enhance peripheral nerve function and delay or reverse the onset of aberrant nerve anatomical changes. C-peptide replacement improves peripheral nerve function in diabetes type 1 patients with early-stage neuropathy as measured by sensory nerve conduction velocity and quantitative sensory testing. Similar to this, autonomic nerve dysfunction is improved after receiving C peptide for up to three months. The mechanisms of action are related to the capacity of C-peptide to reverse diabetes-induced reductions in endoneurial blood flow, in -ATPase activity, and in the modulation of neurotropic factors. This has been evaluated in animal models of type1 diabetes, and the improved nerve function is accompanied by reversal or prevention of nerve structural changes. The results put together show that C-peptide might be a novel option for treating neuropathy in type 1 diabetes.

Keywords: Autonomic neuropathy; Diabetic peripheral neuropathy; Painful diabetic neuropathy; Bioactive peptide

Introduction

One of the most prevalent long-term consequences of diabetes mellitus is neuropathy. Patients with type 1 and type2 diabetes are also affected, but type1 diabetes has a faster progression and more severe symptoms. Clinical examination findings of sensory, motor, and autonomic impairments, whether or not associated with symptoms, are used to identify diabetic neuropathy. A diagnosis may only be made by examination in up to 50% of patients, or occasionally when a patient exhibits a painless foot ulcer. While some individuals may not express symptoms, others may acknowledge to having numb or lifeless feet when questioned [1]. The sensory loss of vibration, pressure, pain, and temperature perception, mediated by small and large fibres, as well as the absence of ankle reflexes, are typically discovered during a thorough neurological examination of the lower limb. Signs of peripheral sympathetic autonomic dysfunction, which can include a warm or cold foot, sometimes with dilated dorsal foot veins, dry skin, and the presence of calluses under pressure-bearing areas, are frequently seen in patients with diabetes in addition to autonomic neuropathy manifestations, such as impaired cardiovascular and gastrointestinal functions. Although diabetic neuropathies can manifest as fast reversible hyperglycemic neuropathy, localised or multifocal neuropathies, and persistent distal symmetric polyneuropathy, these are not the most clinically significant forms (DSPN) [2].

The distal axonal degeneration of the "dying-back" type, which is most pronounced in the lower limbs, is one of the structural abnormalities that are associated with the DSPN. Early in the course of the condition, however, tiny fibre sensory impairment is also present. In general, diabetic individuals have a 30% prevalence of DSPN; however the percentage varies significantly throughout the literature depending on how diabetic neuropathy is defined and how its presence is evaluated. Both clinical tests and patient symptom assessments are regarded as crucial instruments in the assessment of neuropathy status, however both methods have weak repeatability and specificity because they heavily rely on subjective elements [3]. In addition to being valid means for detecting neuropathy, assessments utilising more objective polyneuropathy markers, such as vibration perception threshold (VPT) and nerve conduction velocity (NCV), may also be used to predict mortality in diabetes patients. Indirect and direct metabolic effects of hyperglycemia, such as oxidative stress, increased polyol pathway metabolism, and the production of advanced glycation end products, contribute to the pathophysiology of diabetic neuropathy [4].

Additionally, decreased nerve Na+, K+-ATPase activity and microvascular anomalies are associated with diabetic neuropathy (e.g., reduced endoneurial perfusion). Specific structural nerve abnormalities that are uncommon in type 2 diabetes are connected with type 1 diabetes. Axonal atrophy and distinctive nodal and paranodal alterations are among these anomalies, which together lead to the steady decline in nerve conduction velocity. In contrast, type 2 diabetes has a milder form of axonal degeneration and shows little to no nodal and paranodal abnormalities. However, type 2 diabetes frequently develops insulin and C-peptide deficiency over time, and at this point it is most likely that the type 2 DSPN will start to exhibit traits resembling those of type 1 neuropathy [5].

The evidence that is now available indicates that C-peptide insufficiency is a significant contributor to the recognisable structural abnormalities in type 1 diabetes. According to this premise, numerous studies have shown that while neuropathy cannot be prevented, the advancement of diabetes problems can be slowed down with greater metabolic control and more aggressive insulin therapy. The course of diabetic neuropathy in type 1 diabetes is therefore likely to be influenced by additional variables, such as C-peptide insufficiency. In the recent decades, data have been provided showing that C-peptide has major physiological impacts. It demonstrates that, contrary to what was previously believed, C-peptide exhibits the qualities of a bioactive peptide. Endothelial nitric oxide synthase (eNOS) and Na+, K+-ATPase are stimulated when C-peptide binds specifically to the membranes of different cell types, such as endothelial, renal, and nerve cells [6].

This intracellular signalling cascade is then activated. Recent research also shows that C-peptide promotes a number of transcriptional factors in addition to a number of neurotropic factors. Thus, it has been established that giving patients who lack endogenous C-peptide an exogenous replacement dose of C-peptide restores the reduced blood flow in a number of tissues and improves renal and neurological function, the latter of which is discussed below. A long-standing clinical finding is that patients with type 2 diabetes who maintain low levels of endogenous C-peptide and insulin secretion are less likely to experience microvascular long-term complications affecting the kidneys, eyes, or nervous system. This is in contrast to type 1 diabetes patients whose beta-cell secretion completely stops [7].

Discussion

Although there haven't been many investigations on the clinical effects of C-peptide on nerve function, a number of preclinical studies have found that it has a major impact on the structural and functional changes in nerves

brought on by diabetes. The available clinical data show that C-peptide has positive effects on peripheral and autonomic nerve function in people with type 1 diabetes. Thus, C-peptide replacement (1.8 mg/day) or placebo was administered for three months along with the patients' regular insulin therapy in a double-blind, placebo-controlled study involving 46 type 1 diabetes patients with an average age of 29 years and an average duration of diabetes of about 10 years [8]. These patients also had reduced sensory nerve and motor nerve conduction velocities (NCV) but no other signs of neuropathy. During the course of the investigation, the peroneal nerve's sensory nerve conduction velocity gradually rose, but not the peroneal nerve's motor nerve conduction velocity. After three months, the rise reached 2.7 m/s, which represents an 80% repair of the patients' initial conduction velocity deficit. Even though these patients' baseline perception thresholds were largely normal, this alteration was accompanied by an improvement in vibration perception as measured on the dorsum of the foot. Since vibration perception in this anatomical location is predominantly mediated by the big sural nerve fibres, this improvement is consistent with better sural nerve function [9].

A recently concluded clinical trial including individuals with diabetic neuropathy has verified and expanded the improvement in nerve function seen in this early patient cohort. The trial, which included 161 type 1 diabetes patients with an average age of 44 years and a mean duration of diabetes of 29 years, was a double-blind, placebo-controlled, randomised multicenter study (according to the San Antonio criteria). After 6 months of C-peptide replacement therapy, there was a statistically significant improvement in SCV for the patients receiving C-peptide, amounting to m/s assessed as peak velocities and m/s for the initial response (the velocity change from baseline for the patients receiving C-peptide). At baseline, their sensory nerve conduction velocity assessed in the sural nerve (SCV) was on average 2.6 SD below normal. . These modifications, however, did not statistically vary from the modification in the placebo group. When compared to the placebo group, the group receiving C-peptide had statistically substantially more responders (defined as patients with an improvement in peak SCV > 1 m/s) (37% against 19%, resp., p .032). However, given that the trial lasted little more than 6 months, it is possible that individuals who were relatively less afflicted at baseline may have a larger chance of improving. It is interesting that of the enrolled patients, several had significant nerve conduction impairments at baseline. Consequently, a subgroup analysis was carried out in the subset of individuals whose baseline SCV was the least impacted (half of the patient population). There was an improvement in vibration perception in the C-peptide treated patients along with these improvements in sural nerve conduction velocity, but there was no statistically significant change in motor nerve conduction velocity [10].

Additionally, there was a tendency for neurological exam results to rise after C-peptide. The combination of these data shows that C-peptide administration in patients with type 1 diabetes results in a therapeutic improvement of diabetes-induced peripheral nerve dysfunction; 3-6 months of C-peptide replacement to patients with early stage neuropathy resulted in approximately 1.5 m/s in sensory nerve conduction velocity, along with other signs of nerve function improvements. After three to six months of C-peptide replacement therapy (red bar) or placebo (grey bar) for type 1 diabetic patients, there was a change in the peak sensory nerve conduction velocity in the sural nerves. The figure displays compiled data [11].

Additionally, there is proof that giving C-peptide to type 1 individual who have autonomic neuropathy symptoms has positive consequences. Reduced heart rate variability (HRV) during deep breathing, a measurement with a high degree of consistency that predominantly reflects vagal function, can be used to assess a patient's autonomic nerve function insufficiency. In a double-blind trial, patients were observed twice while under normoglycemic circumstances and throughout a 3-hour intravenous infusion of either human C-peptide or saline. When plasma concentrations were returned to physiological levels by the C-peptide infusion, the HRV was lowered by% (normal reference value: 24%) at baseline. However, following the saline infusion, there was no change in the HRV (p .001). When C-peptide was administered for three hours to participants who had a lower heart rate brake index prior to the trial, the heart rate brake index following a tilting manoeuvre also improved. In line with these findings, type 1 diabetes patients who received C-peptide replacement for three months experienced a 20% improvement in HRV, compared to the same patients who received placebo treatment, who experienced no change or a minor decline in their HRV [12].

Conclusion

The macro and microvascular consequences of diabetes were the main emphasis of this research, and some important conclusions were reached using a summary analysis: Diabetic individuals are more likely to experience vascular problems due to the high incidence of diabetes in emerging nations and the relative paucity of therapeutic technology. The prevention of vascular problems is further complicated by the patients' generally limited awareness and compliance. There are a lot of diabetes people that are undiagnosed, according to a sample survey. Although there has been a trend toward a relative improvement in the prevalence of diabetic vascular problems in industrialised countries and regions, the resources required for the improved medical technology will be a significant burden on society. The prevention of diabetic vascular problems is also faced with a number of novel challenges. For instance, the prevalence of associated disorders has increased as a result of a younger generation of diabetes patients. Nevertheless, it is challenging to lower the prevalence of diabetes as the world's population ages, and numerous studies have noted an increase in the impact of gestational diabetes.

Diabetes problems can be prevented and controlled by a multistep process that involves both patients and medical staff working together. The government and other relevant departments should take action for illness prevention at the same time. The following actions can also help to control the onset of diabetes and its vascular complications: (1) When it comes to lifestyle choices, diabetic patients are urged to eat fewer calories overall, consume less salt and oil while increasing the amount of fiber-rich foods and high-quality protein in their diets, engage in the proper amount of exercise, and cut back on their cigarette and alcohol use. (2) Patients with less severe illnesses should closely regulate their blood pressure, blood lipids, and blood sugar levels. Severe vascular problems should be actively treated with medication, any necessary surgery, and improved diabetes care procedures. (3) Clinicians should implement a chronic disease management system for prompt follow-up and disease monitoring and offer individualised control strategies based on precision medicine's tenets.

Conflict of Interest

None

Acknowledgement

None

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