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Effects of exenatide on measures of diabetic neuropathy in subjects with type 2 diabetes: results from an 18-month proof-of-concept open-label randomized study

Mamta Jaiswal [a], Catherine L. Martin [b], Morton B. Brown [c], Brian Callaghan [a], James W. Albers [a], Eva L. Feldman [a], Rodica Pop-Busui [b,*]

[a] Department of Neurology, University of Michigan, Ann Arbor, MI
[b] Division of Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[c] Department of Biostatistics, University of Michigan, Ann Arbor, MI

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ABSTRACT

Objective: Experimental studies have reported potential benefit of glucagon-like peptide-1(GLP-1) receptor agonists in preventing diabetic peripheral neuropathy (DPN). We therefore performed a proof-of-concept pilot study to evaluate the effect of exenatide, a GLP-1 agonist, on measures of DPN and cardiovascular autonomic neuropathy (CAN) in patients with type 2 diabetes (T2D).
Research Design and Methods: Forty-six T2D subjects (age 54 ± 10 years, diabetes duration 8 ± 5 years, HbA1c 8.2 ± 1.3%) with mild to moderate DPN at baseline were randomized to receive either twice daily exenatide (n = 22) or daily insulin glargine (n = 24). The subjects, with similar HbA1c levels, were followed for 18 months. The primary end point was the prevalence of confirmed clinical neuropathy (CCN). Changes in measures of CAN, other measures of small fiber neuropathy such as intra-epidermal nerve fiber density (IENFD), and quality of life were also analyzed.
Results: Glucose control was similar in both groups during the study. There were no statistically significant treatment group differences in the prevalence of CCN, IENFD, measures of CAN, nerve conductions studies, or quality of life indices.
Conclusions: In this pilot study of patients with T2D and mild to moderate DPN, 18 months of exenatide treatment had no significant effect on measures of neuropathy compared with glargine treatment.

Diabetic peripheral neuropathy (DPN) affects nearly two-thirds of patients with diabetes and is a major cause of poor quality of life (Tesfaye et al., 2010). Despite the proven efficacy of intensive glucose control in delaying or preventing DPN and cardiovascular autonomic neuropathy (CAN) in patients with type 1 diabetes (T1D) (DCCT, 1993, 1995, 1998), equal efficacy has not been shown in type 2 diabetes (T2D) (Ang, Jaiswal, Martin, & Pop-Busui, 2014; Callaghan, Little, Feldman, & Hughes, 2012). Furthermore, patients may develop DPN and CAN despite good glucose control (Ang et al., 2014).

Among the therapeutic options available for glycemic control in subjects with T2D, glucagon-like peptide 1 (GLP-1) receptor agonists are known to stimulate insulin secretion in response to hyperglycemia, delay gastric emptying, and suppress hepatic glucose release, thus providing significant blood glucose-lowering effects with little increased risk for hypoglycemia or weight gain (Baggio, Huang, Brown, & Drucker, 2004; Yusta et al., 2006). Exenatide, a synthetic form of exendin-4 and the first GLP-1 receptor agonist approved in the US, is an effective glucose-lowering agent in patients with T2D (McCormack, 2014).

Experimental evidence indicates that exenatide may also have direct neuroprotective and neurotrophic effects which are independent of its glycemic effects (Griffioen et al., 2011; Himeno et al., 2011; Kan, Guo, Singh, Singh, & Zochodne, 2012; Luciani et al., 2010; Yamamoto et al., 2002). For instance, GLP-1 receptors are present on dorsal root ganglia (DRG) sensory neurons of diabetic and nondiabetic mice, sciatic nerve axons and Schwann cells, and exendin-4 increases neurite outgrowth of adult sensory neurons in vitro (Kan et al., 2012). In T1D mice with established neuropathy treated with either exendin-4 or high-dose insulin for 4 weeks, exendin-4 improved both sensory electrophysiology and measures of current perception threshold with no effect on hyperglycemia, while high-dose insulin

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* Corresponding author at: University of Michigan, Division of Metabolism, Endocrinology and Diabetes, 5329 Brehm Tower, 1000 Wall Street, Ann Arbor, MI, 48105. Tel.: +1 734 647 9809; fax: +1 734 936 6684.
E-mail address: rpbusui@med.umich.edu (R. Pop-Busui).

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reversed hyperglycemia but only partly improved thermal sensation and epidermal innervation and had no effect on electrophysiological abnormalities (Kan et al., 2012). However, short-term exendin-4 treatment was less effective in T2D mice with neuropathy (Kan et al., 2012). In another study, 4-week exendin-4 treatment in mice with streptozotocin-induced T1D promoted significant neurite outgrowth of DRG neurons and ameliorated the loss of intraepidermal nerve fibers (IENF) (Himeno et al., 2011). It was suggested that these effects were independent of glycemia and possibly mediated via GLP-1 receptor activation and through anti-apoptosis and cAMP signaling pathways (Himeno et al., 2011; Kan et al., 2012), or via stimulating neuronal differentiation in human cells (Luciani et al., 2010). GLP-1 has been also shown to modulate autonomic activity and induce changes in haemodynamic variables. For instance, Griffioen et al. showed that both acute and chronic central administration of exendin-4 increased the resting heart rate and reduced measures of heart rate variability (HRV) in mice, either by altering the inhibition of neurotransmission to cardiac vagal neurons (Griffioen et al., 2011) or up regulation of sympathetic outflow and downstream activation of cardiovascular responses (Yamamoto et al., 2002).

Based on the above experimental evidence, we hypothesized that GLP-1 receptor agonists may have potential beneficial effects on measures of DPN and CAN in humans, something that has not been systematically evaluated. We therefore conducted a pilot, proof-of-concept, randomized, open-label clinical trial to evaluate the effects of exenatide on measures of DPN and CAN in subjects with T2D.

1. Research design and methods

1.1. Study design

This single center, proof-of-concept-pilot, open-label randomized, controlled trial (NCT00855439) was conducted at the University of Michigan between July 2008 and June 2014. The study was reviewed and approved by the University of Michigan Institutional Review Board. All subjects signed a written consent document.

1.2. Study participants

Subjects were eligible to enroll if they were between 18 and 70 years old, had T2D with a hemoglobin A1c (HbA1c) > 7% and fasting blood glucose > 140 mg/dl, had followed a prior stable glucose-lowering regimen that did not include insulin or a GLP-1 receptor agonist, had no known contraindications to treatment with either exenatide or insulin glargine based on FDA prescribing guidelines, and presented with mild-to-moderate DPN as defined by a score of 6 or more on the Michigan Diabetes Neuropathy Scale (MDNS), a validated scale for evaluation of diabetic neuropathy (Feldman et al., 1994) described below in Methods.

Excluded were subjects with a history of kidney, pancreas, or cardiac transplantation, neuropathy independent of diabetes, or any condition other than diabetes associated with neuropathy (e.g. hepatitis C, end stage renal disease, lupus), any lower extremity amputation or severe deformity of lower extremity, HbA1c > 10%, participation in an experimental medication trial within 3 months of starting this study, undergoing therapy for malignant disease other than basal- or squamous cell carcinoma, requiring long-term glucocorticoid therapy, inability or unwillingness to comply with the protocol, and nursing mothers or pregnant women.

1.3. Intervention

Subjects were randomly assigned in a 1:1 ratio to either exenatide (n = 22) or insulin glargine (n = 24) targeting similar levels of glucose control as documented by HbA1c. Exenatide was initiated at a fixed dose of 5 μg twice daily for 4 weeks and then increased to 10 μg twice daily for the remainder of the study. Subjects who did not tolerate the 10 μg dose resumed the reduced 5 μg dose for the duration of the study. Insulin glargine was initiated with 10 units daily and titrated in 2-unit increments to achieve a fasting blood glucose target level of 5.6 mmol/L (100 mg/dL) without recurrent or severe hypoglycemia. The dose of any prior oral agents remained fixed, unless clinical judgment dictated that they should be altered to optimize blood glucose control.

1.4. Assessment of neuropathy

DPN was assessed at baseline and at 12- and 18-month follow-up visits with assessment of symptoms and signs of DPN by a board-certified neurologist as described (Albers et al., 2010), nerve conduction studies of the median (sensory and motor), peroneal motor and sural sensory nerves using a standard protocol, which included replication of baseline limb temperatures at 12 and 18 month assessments (Albers et al., 2010), and quantitative sensory testing for vibration perception (VPT) using the Vibratron II device (Physitemp Instruments, Inc.) as described (Martin et al., 2010).

The rate of IENF reinnervation after capsaicin denervation was used as an exploratory measure of small fiber neuropathy and obtained as described (Polydefkis et al., 2004). Briefly, a baseline skin biopsy was obtained from the distal thigh in a subset of consenting T2D subjects (exenatide = 9, glargine = 11). Capsaicin was applied as a 1% topical cream, and the site was covered with an occlusive dressing for 48 hours. Additional skin biopsies were obtained at 48 hours (to confirm denervation) and at 6 and 12 months of treatment (3 months and 9 months post-capsaicin respectively). All skin biopsies were obtained in a standardized fashion by a single examiner, and all IENFD evaluations were analyzed in a blinded manner by Therapath, Inc (New York, NY). In addition, the MDNS was performed at screening to confirm eligibility as described (Feldman et al., 1994). Briefly the MDNS is a 46-point exam that includes testing for vibration, 10-gram monofilament pressure, pin sensation at the great toe, deep tendon reflexes at knee and ankle, and strength. For all evaluations, 1 point was given for reduction on either side, or 2 points when the response was absent, except for pin sensation where 2 points per side were assigned if sharp sensation was absent.

CAN was evaluated at baseline, 12 months, and 18 months with the gold-standard cardiovascular reflex tests (CARTs) (the deep breathing test and the Valsalva maneuver) (Spallone et al., 2011) and measures of HRV obtained during a 5-minute rest and during CARTs using the ANX 3.1 (ANSAR Inc., Philadelphia, PA). Subjects were required to fast for 8 hours and to abstain from tobacco, caffeine, and alcohol prior to testing. Blood glucose was obtained prior to testing, and testing was rescheduled in the presence of hypoglycemia. Testing was performed with the subjects in a supine position, with the head of the bed elevated no more than 30 degrees. Subjects with demonstrable atrial fibrillation (n = 3 glargine) and subjects with a pacemaker (n = 1 glargine) were excluded from the CART analysis.

Neuropathy specific quality of life was evaluated with the Neuropathy Specific Quality of Life Measure (NeuroQOL) (Vileikyte et al., 2003) at baseline, and at 12 and 18 months of follow up. This self-administered, 39-item validated survey that includes: the overall impact of foot problems on quality of life, overall quality of life and 6 other primary domains: 1) painful symptoms and paresthesias; 2) reduced/lost feeling in the feet; 3) diffuse sensory motor symptoms; 4) limitations in daily activities; 5) interpersonal problems; and 6) emotional burden. For the foot problem-specific item, lower scores indicate less negative impact of foot problems on quality of life, and for overall quality of life higher scores indicate worse quality of life. Within each domain, lower scores indicate worse symptoms or greater adverse effect on quality of life (Vileikyte et al., 2003).