Licorice extract supplementation effects on chronic diabetic neuropathy pain: a pilot study

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Abstract:

Background:

Diabetic neuropathy is a common and often debilitating condition for which available treatments are limited. Because a low-fat plant-based diet has been shown to improve glycemic control in individuals with type 2 diabetes, we hypothesized that such a diet would reduce painful symptoms of diabetic neuropathy.

Methods:

In this 42-week pilot study,9 individuals with type 2 diabetes and painful diabetic neuropathy were assigned to: The group was asked to consume Licorice root extract with weekly meetings for support and pain monitoring . At baseline, midpoint and 42 weeks, clinical, laboratory and questionnaire data were collected. Questionnaires included an analog ‘worst pain' scale, Michigan Neuropathy Screening Instrument, global impression scale, Short Form McGill Pain Questionnaire.

Results:

After 42 weeks, body weight change with the intervention was −1.4 kg (95% confidence interval (CI) −2.4 to −0.4, $P<0.001$) in an effect size analysis. The difference in change in pain, as measured by the McGill pain questionnaire, was −7.1 points (95% CI −15.1 to −0.5, $P=0.04$). Michigan Neuropathy Screening Instrument questionnaire score change was −1.4 points (95% CI −2.1 to −0.4 $P=0.03$).

Conclusions:

Improvements were seen in most clinical and pain measures in 7 out of 9 participants . This pilot study suggests the potential value of Licorice root extract intervention, for treating painful diabetic neuropathy.

Backround

Diabetic peripheral neuropathy occurs in up to 60% of individuals with type 2 diabetes(1) and is associated with significant morbidity, including gait disturbances, amputations, anxiety, depression and reduced quality of life.(2,3) The condition manifests with damage to the terminal branches of peripheral nerves and usually first affects small fibers that are responsible for translating pain, light touch and

temperature. As neuropathy progresses, large fibers responsible for reflexes and muscle tone are affected, leading to balance and gait problems. Most patients with diabetic peripheral neuropathy present with pain, numbness, or abnormal, spontaneous or induced sensations in the lower extremities. Pain occurs in 15–30% of cases.(4).

Uncontrolled interventions typically improve glycemic control (5) and other factors associated with type 2 diabetes and its complications. Glycemic control appears to have a key role in the risk of complications(6). In intervention trials using licorice root extract , improvements in CIMT, blood lipid concentrations and blood pressure(in press) have been consistently observed.

One uncontrolled unpublished intervention study showed promising results in individuals with diabetic neuropathy using Licorice. We therefore hypothesized that a Licorice intervention can reduce diabetic neuropathy pain and conducted a uncontrolled, pilot study to test this hypothesis. This study was intended to investigate the efficacy of this approach and the suitability of the overall method, permitting larger trials to follow. The study was not intended to elucidate the mechanisms by which the intervention might lead to clinical changes or to separate which parts of the intervention might be responsible for any observed benefit.

Materials and methods

Participants and recruitment

Participants were recruited in the Kiryat Ata Family Practice Academic Clinic. Inclusion criteria were age 18–65 years, diagnosis of type 2 diabetes, and diagnosis or symptoms of painful diabetic neuropathy for at least 6 months. Exclusion criteria were vitamin B12 deficiency, alcohol consumption of more than two drinks per day, use of recreational drugs in the past 6 months, pregnancy, unstable medical or psychiatric illness, current adherence to a vegan diet and inability or unwillingness to participate in all components of the study. Participants were screened for B12 deficiency, which can cause neuropathy independent of diabetes. Criteria for deficiency were a B12 level of <200 pg ml^{-1} .

A screening interview was conducted to determine eligibility. Participants were determined to have symptoms of painful diabetic neuropathy if they described in the screening interview painful sensations in the hands or feet, including tingling, burning or freezing.

9 participants were assigned to the intervention. However, examinations for the Michigan Neuropathy Screening Instrument (7) were performed by an independent clinician (the resident in Kiryat ata clinic).

Study design and procedures

The intervention group was instructed to take the licorice root extract and attend weekly doctor-patient meeting for 20 weeks and after - twice a month. The study

duration was chosen to be comparable to that of previous studies demonstrating clinically significant effects other interventions

Participants were asked to keep their diabetes medications constant when possible, but to follow the advice of their personal physician regarding medication use (for example, in the case of hypoglycemia).

Dependent variables

Body weight was measured in light clothing and without shoes using a digital scale accurate to 0.1 kg. Blood pressure was measured 3 times, using a digital sphygmomanometer. The first measurement was disregarded, and the mean of the remaining two measurements was calculated. Blood glucose, HbA1c (percent hemoglobin A1c) and plasma lipid concentrations were measured by standard methods

Sensory perception was assessed by monofilament sensation, vibration perception and ankle reflex as part of the Michigan Neuropathy Screening Instrument physical assessment and pin-prick and touch pressure were assessed.

Our primary outcomes were pain and sensory symptoms as measured by visual analog ‘worst pain' scale, global impression scale,(8) Short Form McGill Pain Questionnaire,(9,10) Michigan Neuropathy Screening Instrument questionnaire . The visual analog scale was a 10-cm line anchored by ‘No pain' and ‘Pain as bad as it could possibly be' on either end, and participants were asked to rate their worst pain in the preceding 2 weeks. The visual analog scale was completed with an interviewer.

The patient's global impression of change (PGIC) question assesses subjective pain improvement by asking participants to rate symptom change on a scale of 1–7 from ‘no change' to ‘a great deal better.(8)

Participants were asked to provide weekly ratings for average pain, worst pain and night pain on an 10-point numerical scale.

Mood and depression were measured by the Beck Depression Inventory (BDI(11))

Statistical analysis

Since little has been published on the effects of Licorich on pain in diabetic neuropathy and no prior controlled studies using Licorich were found, a power analysis could not be based on the previous research. Therefore, we chose an exploratory approach that did not limit sample size and accepted all volunteers who met the participation criteria.

For pain scales, body weight and lipid concentrations (total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol and triglycerides), baseline descriptive statistics were calculated. For normally distributed data, two-tailed Student's *T*-tests for independent samples were calculated for 42-week changes in the group. Since primary outcomes were based on the 42-week study endpoint, statistical approaches that evaluate changes over time were not used.

Results

Recruitment

16 participants were interviewed and 9 were enrolled. Recruitment periods were October 2014 to January 2015. The participant group had a mean age of 57 years . At baseline, seven participants were taking medications for diabetic neuropathy symptoms, including pregabalin, gabapentin, duloxetine, bupropion and escitalopram. There were no significant study-related adverse effects. The study ended as per the protocol.

Changes on clinical measurements

Mean HbA1c declined in the intervention group by 0.4 percentage point over 20 weeks, (P=0.09). Despite the request that participants not change medications, several did have medication adjustments, typically due to hypoglycemia. Glucose-lowering medications were reduced for 4 participants and increased for two by their primary physicians.

Total cholesterol declined 12.1 mg dl^{-1} in the group (P=0.20).

Changes in perceived pain and neuropathy symptoms

Pain, as measured by the Short Form McGill Pain Questionnaire, declined by 7.1 points in the intervention group over 42 weeks. The largest decline was seen in the sensory subscore . Pain as measured by the Neuropathy Total Symptom Score and visual analog pain scale declined in the group. (P=0.70).

Complete remission(75 to 100%) of burning pain and an improved sense of touch was reported by 7 of participants, while one of the remaining participants reported partial symptomatic relief and one no relief

During the study, seven participants were taking medications for neuropathy, and two eliminated such medications. One participant began and then stopped taking pregabalin.

Changes in mood

No significant changes were observed in the Beck Depression Inventory over the 42 weeks.

Discussion

In this 42-week diet intervention and HbA1c declined slightly in the group. Significant improvements in pain were observed in the intervention group, as measured by the Quality of Life questionnaire, Short Form McGill Pain Questionnaire.

Complete remission of burning pain and an improved sense of touch was reported by 7 of participants, while one of the remaining participants reported partial(35%) symptomatic relief and one no relief. Other favorable changes included , decreased blood lipid concentrations and reduced need for medications for blood pressure . Since nerve damage occurs over the course of years, a longer study might be expected to show greater improvements in pain and neuropathy symptoms.

The mechanism(s) by which the Licorice improves neuropathy pain may involve improved insulin sensitivity, leading to better glucose control. In addition, diabetic neuropathy is associated with hypertension, dyslipidemia and blood supply to small peripheral nerves , all of which can be ameliorated with Licorice. (in press)

Medication changes in the intervention group may have obscured some improvements in glucose control, blood lipids and blood pressure. Most of the participants who altered diabetes medications did so because of hyperglycemia. It is possible that some changes in pain and other symptoms were in part related to changes in symptom management medication that occurred during the 42 weeks.

This pilot study has some strengths. It was conducted with community volunteers; therefore, the results are readily translatable to applications outside the research setting.

Further studies are needed to identify the specific mechanisms by which the intervention may lead to physical and symptomatic improvements. The self-reported nature of pain is an intrinsic limitation of pain research. Also, the definition of painful diabetic neuropathy as an inclusion criterion may have been insufficiently precise.

In conclusion, this pilot study suggests the potential of Licorice root extract for treating diabetic neuropathy and provides findings that can be used to guide further studies. A further trial might be a useful means of assessing the effects of Licorice root supplement in a more intensive scientific intervention in this otherwise intractable and debilitating chronic disease.

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