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Case Report

Hypoglycemia by Ginseng in type 2 Diabetic Patient: Case Report

Angelo Michele Carella*, Teresa Marinelli, Armando Melfitano, Michele Di Pumpo, Matteo Conte and Angelo Benvenuto

Internal Medicine Department, "T. Masselli-Mascia" Hospital - San Severo (Foggia), Italy

***Address for Correspondence:** Angelo Michele Carella, Internal Medicine Department, T. Masselli-Mascia Hospital, San Severo (Foggia), Italy, Email: mic.carella@virgilio.it

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ABSTRACT

Ginseng extracts are often used as adaptogen to improve mental performances and well being, helping to overcome stress. Thus, in our times a lot of ginseng extracts are continuously produced and sold into commercial channels. Both Asian and Korean red ginseng (Panax ginseng) and American ginseng (Panax quinquefolius) are the most extensively used and researched. Both Panax ginseng and Panax quinquefolium contain different types of saponins, also known as ginsenosides, which are the substances that give ginseng medicinal properties. Human and animal studies showed that ginseng extracts can also have hypoglycemic effects. The mechanisms by which ginseng reduces blood glucose levels are unclear; some mechanisms have been proposed to explain its hypoglycemic effect, especially modulating effects on insulin sensitization and/or insulin secretion and regulating actions on digestion and intestinal absorption. We describe a case of hypoglycemia by ginseng in type 2 diabetic patient treated with oral hypoglycemic agents. Although, in order to provide better assessments of a sure anti-diabetic efficacy of ginseng, larger and longer randomized controlled clinical trials will be required, in our case we think that we have enough evidence to believe that the cause of hypoglycemia was ginseng. Obviously, this report should not be taken as a proof of the hypoglycemic effect of ginseng, nor it wants to be a suggestion to use ginseng in the treatment of diabetes; instead, it wants to be an alert for patients and clinicians to avoid hypoglycemia in daily clinical practice.

INTRODUCTION

Ginseng, traditionally considered a tonic herb, has been used in Chinese medicine for thousands of years and now it is often used as adaptogen to improve mental performances and well being, helping to overcome stress [1]. Thus, in our times a lot of ginseng extracts are continuously produced and sold into commercial channels [2].

Several species of ginseng have been identified, but Asian and Korean red ginseng (Panax ginseng) and American ginseng (Panax quinquefolius) are the most extensively used and researched. Both Panax ginseng and Panax quinquefolium contain in different amounts several types of saponins, also known as ginsenosides, which are the substances that give ginseng medicinal properties [1]. Human and animal studies showed that ginseng extracts can also have hypoglycemic effects [3-5].

In this report we describe a case of hypoglycemia by ginseng in type 2 diabetic patient treated with oral hypoglycemic agents.

CASE REPORT

66-year-old male with type 2 diabetes comes to our observation referring, in previous 72 hours, two episodes of postprandial symptomatic hypoglycemia, consisting of profuse sweating, tremors, pulse-pounding and transient blurred vision. In the previous hypoglycemic episode the blood glucose test measured glucose value of 47 mg/dL and he was treated as outpatients with glucose 10% intravenous infusions. In the second episode the value of glycemia was 32 mg/dL, so the patient was hospitalized.

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At admission the patient reported uncomplicated type 2 diabetes treated from some years with metformin 1000 mg three times a day, with meals, and repaglinide 1 mg before lunch and dinner; moreover the patient reported to take a normoglycemic diet of approximately 1.700 calories per day; no alcohol consumption was reported. The patient did not take other medications to treat other conditions, since he did not report other concomitant diseases. He was a sedentary lifestyle patient, overweight (Body Mass Index=28,3 kg/m^2), in retirement from two years, with poor compliance to glycemic self-monitoring. However, three months before the patient had done laboratory tests that revealed glycosylated hemoglobin (Hb_{A1c}) level of 46 mmol/mol and c-peptide value of 3.7 ng/mL.

During hospitalization all standard baseline investigations were normal: no abnormalities were found in basal electrocardiogram, standard thoracic radiographs, carotid and peripheral arterial echo-doppler and in ocular fund; blood pressure monitoring recorded a normotensive profile; all standard laboratory parameters were in normal range; Hb_{A1c} level was 44 mmol/mol and c-peptide value was 3.4 ng/mL. Both fasting and postprandial blood glycemic values were in target range, and no hypoglycemia was registered, although we modified oral hypoglycemic agent therapy by suspending repaglinide and introducing sitagliptin 100 mg daily. Normoglycemic diet of 1.700 calories per day was confirmed. On the sixth day the patient was discharged and the diagnosis was "iatrogenic hypoglycemia".

Approximately ten days later, the patient returned to our observation referring another hypoglycemic episode with blood glycemic value of 51 mg/dL. Thus we reexamine him in details, as outpatient, and a more careful drug history revealed that the patient, as well as having regularly performed hypoglycemic therapy prescribed at discharge, had begun to take dietary supplements containing ginseng. Moreover, the patient truthfully stated that he started to take ginseng (extract G115 from roots of Panax ginseng, 200 mg orally three times a day) about 10 days before hospitalization, because of fatigue and decreased libido that had arisen few months before. At admission the patient omitted this anamnestic detail considering it irrelevant; however, he denied having taken ginseng during hospitalization. The patient was strongly advised not to take ginseng extract later and to continue glycemic self-monitoring; oral hypoglycemic therapy was not modified. In the subsequent 6-month follow-up the patient no longer registered hypoglycemic episodes, maintaining adequate glycemic control.

DISCUSSION

In vitro and animal models indicate that ginseng might have hypoglycemic action [3-5]; similar effect has been reported in several human studies [6-9]. One of these studies showed that 200 mg per day of orally unspecified type of ginseng, in eight weeks, led to an improvement of Hb A1c values in noninsulin-dependent diabetic patients [6]. Other studies have shown that American ginseng was effective in reducing post-prandial glycemia in both diabetic [7,8] and non-diabetic subjects [7,9], although in healthy subjects this reduction was time dependent but not dose dependent; actually, in non-diabetics the hypoglycemic effect was obtained only when ginseng was given 40 minutes before oral glucose challenge test while doses of ginseng within the range of 1-3 g were equally effective [9]. In a randomized, double-blind, placebo-controlled study, the administration of Korean red ginseng 2 g/meal (6 g/day) for 12 weeks maintained good glycemic control and improved glucose and insulin regulation in type 2 diabetic patients [10]. In another randomized, double-blind, placebo-controlled, crossover trial Panax ginseng at the dose of 2×369 mg three times daily for 4 weeks reduced insulin resistance in type 2 diabetics [11]. However, it has been shown that the anti-hyperglycemic efficacy of ginseng varies across species and is correlated to their ginsenoside composition [12].

Data from recent meta-analysis of randomized controlled clinical trials assert that ginseng modestly yet significantly improves fasting blood glucose in subjects with and without diabetes, although the analysis had highlighted several methodological limitations including short duration of the trials, use of unstandardized ginseng preparations with potentially varying potencies, well controlled glycemia of participants at baseline and changes in diabetic medications that could have influenced the outcomes [13]. Thus, in order to provide better assessments of a sure anti-diabetic efficacy of ginseng, larger and longer randomized controlled trials using standardized ginseng preparations are required.

In our case the patient experienced hypoglycemic episodes before hospitalization and after discharge, when he took ginseng extracts; no hypoglycemia occurred during hospitalization, when our patient has not taken ginseng. During hospitalization we have modified the hypoglycemic therapy, believing that hypoglycemia was due to repaglinide, drug known for its action stimulating release of insulin from the pancreas; nevertheless, after discharge hypoglycemia occurred while the patient was taking metformin and sitagliptin, two drugs that rarely cause hypoglycemia [14]. Thus we think there are enough evidence to believe that the cause of hypoglycemia was ginseng; moreover, after discontinuation of ginseng the patient no longer experienced hypoglycemia. A positive interaction between ginseng extracts and oral antidiabetic agents might nevertheless be a possibility.

The mechanisms by which ginseng reduces blood glucose levels are unclear; some mechanisms have been proposed to explain its hypoglycemic activity, especially modulating effects on insulin sensitization [5,15] and/or insulin secretion [16] and a regulating action on digestion and intestinal absorption [17,18].

Active components of ginseng which may play an important mediating role in these postulated processes include its polysaccharide (ginsenans), peptidoglycan (panaxans), and ginsenoside profiles. Most pharmacological actions of ginseng, however, are attributed to the involvement of ginsenosides, of which there are 3 classes: 20(S)-protopanaxadiols, 20(S)-protopanaxatriols, and oleanic acid-ginsenoside [19].

It is known that the early phase of insulin secretion requires nitric oxide [20] and there is evidence that ginsenosides are able to modulate nitric oxide synthesis [21]. Moreover, it has been shown in animal studies that ginsenosides increases glucose uptake into sheep erythrocytes [15] and into adipocytes or skeletal muscle cells through glucose transporter-4 (GLUT4) overexpression [22,23], consequent to increased activity of peroxisome proliferator-activated receptor gamma (PPAR-γ) [24,25].

Several studies have shown that ginsenosides can ameliorate metabolic diseases such as diabetes, obesity and nonalcoholic fatty liver disease via AMP-activated protein kinase (AMPK) signaling pathway [23,26-30]; moreover it has been also shown that ginsenoside-Rb2 intensifies the activity of glucokinase and phosphofructokinase, two rate-limiting glycolytic enzymes, while decreases the activity of glucose-6-phophatase, a rate limiting gluconeogenic enzyme [31,32]. Other studies demonstrate both American and Korean red ginseng increase insulin production and secretion through inhibition of cytokine-induced β-cell apoptosis [33,34] and presumably by acting on ATP-sensitive K+ channels [35].

Finally, in other studies, ginseng has been able to inhibit gastric secretion in rats [18] and to reduce sugar absorption in isolated rat and human duodenal samples [36]; these observations may suggest a delaying or inhibiting effect on the intestinal absorption of carbohydrates. On the other hand, in some clinical trials [37,38] ginseng was found to have no effect on any glucoregulatory parameter investigated, including insulin sensitivity, suggesting that the use of ginseng has no effect on glucose regulation.

Obviously our report should not be taken as a proof of the hypoglycemic effect of ginseng, nor wants to be a suggestion to use ginseng in the treatment of diabetes; instead, it wants to be an alert for patients and clinicians to avoid hypoglycemia, particularly in diabetic patients with optimal glycemic control and treated with antidiabetic drugs stimulating insulin secretion.

CONCLUSION

Although data from animal and in vitro studies have shown that ginseng extract and its active components can have hypoglycemic activity and beneficial effects on glucose and lipid metabolism, the results from clinical studies are unclear because of confounding factors which could have influenced the outcomes. Therefore, in order to provide better assessments of a sure anti-diabetic efficacy of ginseng larger and longer randomized controlled clinical trials will be required. However, we think the potential hypoglycemic effect of ginseng should be taken into account in daily clinical practice to avoid hypoglycemia, particularly in diabetic patients with optimal glycemic control and in those treated with antidiabetic drugs stimulating insulin secretion.

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