Ginseng and Ginsenoside Re Do Not Improve β-Cell Function or Insulin Sensitivity in Overweight and Obese Subjects With Impaired Glucose Tolerance or Diabetes

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OBJECTIVE—Ginseng and its active component, ginsenoside Re, are popular herbal products that are advocated for treatment of diabetes. The purpose of this study was to determine whether ginseng or ginsenoside Re improves β-cell function and insulin sensitivity (IS) in insulin-resistant subjects.

RESEARCH DESIGN AND METHODS—Overweight or obese subjects (BMI = 34 ± 1 kg/m^2) with impaired glucose tolerance or newly diagnosed type 2 diabetes were randomized to 30 days of treatment with ginseng root extract (8 g/day), ginsenoside Re (250–500 mg/day), or placebo. β-Cell function was assessed as the disposition index (DI) and measured by a frequently sampled oral glucose tolerance test, and IS was assessed as the relative increase in glucose disposal during a hyperinsulinemic-euglycemic clamp procedure plus stable isotope tracer infusion.

RESULTS—Values for DI and IS after therapy (Post) were not different from values before therapy (Pre) in the placebo (DI: Pre, $5.8 \pm 0.9 \times 10^{-3}$ and Post, $5.8 \pm 0.8 \times 10^{-3}$, $P = 0.99$; IS: Pre,165 ± 29% and Post, 185 ± 24%, $P = 0.34$), ginseng (DI: Pre, $7.7 \pm 2.0 \times 10^{-3}$ and Post, $6.0 \pm 0.8 \times 10^{-3}$, $P = 0.29$; IS: Pre, 171 ± 72% and Post,137 ± 59%, $P = 0.88$), and ginsenoside Re (DI: Pre, $7.4 \pm 3.0 \times 10^{-3}$ and Post, $5.9 \pm 1.1 \times 10^{-3}$, $P = 0.50$; IS: Pre, 117 ± 31% and Post, 134 ± 34%, $P = 0.44$) groups. Ginsenosides Re, Rb_1, and Rb_2 were not detectable in plasma after treatment with ginseng root extract or ginsenoside Re.

CONCLUSIONS—Oral ginseng or ginsenoside Re therapy does not improve β-cell function or IS in overweight/obese subjects with impaired glucose tolerance or newly diagnosed diabetes. Poor systemic bioavailability might be responsible for the absence of a therapeutic effect.

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It is estimated that 30% of the U.S. population uses herbs for medicinal purposes. Ginseng root extract (GRE) is one of the most popular herbal products and is used by more than 6 million Americans each year. Ginseng has been a part of Eastern medicine for more than 4,000 years and is purported to prevent and treat diabetes. There are 11 commercially available species of ginseng, but most reports evaluated Asian (*Panax ginseng)* or American (*Panax quinquefolius L.)* ginseng. The physiological effects of ginseng are attributed to its triterpene β-glycosides, known as ginsenosides; more than 150 types of ginsenosides have been identified (1).

Data from studies conducted in animal models and cell culture systems have shown that ginseng extract and specific ginsenosides have beneficial effects on insulin action and glucose metabolism. In diabetic mice, treatment with *P. ginseng* radix or *P. ginseng* (Korean ginseng) stimulates insulin release and improves glucose tolerance and glycemic control (2,3). Ginsenoside Re increases insulin sensitivity (IS) in 3T3-L1 adipocytes (4) and in *ob/ob* mice when administered intraperitoneally (2). It is not clear whether consumption of ginseng or ginsenosides affects IS and glucose homeostasis in humans. Most studies conducted in human subjects only evaluated the effect of a single oral dose of ginseng. Of these studies, most (5–7), but not all (8), found that a single dose lowered blood glucose area under the curve (AUC) during an oral glucose tolerance test (OGTT). Two studies evaluated the effect of more prolonged daily treatment with GRE or ginsenoside Re on glycemic control in subjects with type 2 diabetes (9,10). However, the interpretation of the results from these studies is unclear because of confounding factors that could have influenced the outcome measures, such as changes in body weight and physical activity, changes in diabetes medications, and large drop-out rates.

The purpose of the current study was to conduct a randomized, double-blind, placebo-controlled trial to evaluate the therapeutic potential of ginseng therapy in overweight and obese subjects with impaired glucose tolerance or newly diagnosed type 2 diabetes. Subjects were randomized to 4 weeks of treatment with GRE (Korean red ginseng), ginsenoside Re, or placebo. The euglycemic-hyperinsulinemic clamp procedure in conjunction with stable isotopically labeled tracer infusion and the frequently sampled modified OGTT (FSOGTT) were used to determine *1*) oral glucose tolerance; *2*) glucose and fatty acid kinetics; *3*) insulin action in adipose tissue, liver, and skeletal muscle; and *4*) β-cell function. Because of variability among ginseng

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products, we confirmed that our ginseng extract and ginsenoside Re had biological effects on insulin-mediated glucose uptake in isolated muscle strips (D.H. Han and J.O. Holloszy, submitted for publication).

RESEARCH DESIGN AND METHODS

Study subjects

Fifteen overweight and obese adults (1 man, 14 women; age: 46 ± 3 years, BMI 34 ± 2 kg/m^2) participated in this study. Subjects were identified from the Washington University Volunteer for Health database and completed medical evaluation, blood tests, and a 2-h OGTT. Subjects were required to have a new diagnosis of type 2 diabetes or impaired glucose tolerance and be overweight and/or obese. Potential participants who had any serious medical illnesses were excluded. Subjects had stable weight and were sedentary for at least 3 months before the study. The study was approved by the Human Research Protection Office of Washington University School of Medicine, and written informed consent was obtained from all subjects.

Experimental protocol

Body composition. Body fat mass and fat-free mass (FFM) were determined by using dual-energy X-ray absorptiometry (Hologic QDR 4500; Waltham, MA).

FSOGTT. Subjects were admitted to the Clinical Research Unit at 0700 h after subjects fasted overnight. A catheter was inserted into a hand vein, which was heated to 55°C by using a thermostatically controlled box, to obtain arterialized blood samples. Blood samples were obtained to determine plasma glucose, C-peptide, and insulin concentrations before (−15 min and 0 min) and after (10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 min) consuming a 75-g glucose drink.

Hyperinsulinemic-euglycemic clamp procedure. In the evening on the day of admission, subjects consumed a standard meal, containing 15 kcal/kg FFM at ~1800 h, and then fasted until completion of the clamp procedure. At 0600 h, a catheter was inserted into an antecubital vein of one arm for intravenous infusion, and another catheter was inserted in a vein in the opposite hand, which was heated to 55°C by using a thermostatically controlled box, to obtain arterialized blood samples. At ~0700 h, a primed, continuous infusion of [6,6-$^2H_2$]glucose (infusion rate: 0.25 μmol · min^{-1} · kg^{-1}; priming dose: 22.5 μmol/kg), and a primed, continuous infusion of [1,1,2,3,3-$^2H_5$]glycerol (infusion rate 0.08 μmol · min^{-1} · kg^{-1}; priming dose 1.2 μmol/kg) was maintained for 7 h. At 210 min, insulin was infused at a rate of 50 mU · m^2 body surface area (BSA)$^{-1}$ · min^{-1} (initiated with a two-step priming dose of 200 mU · m^2 BSA^{-1} · min^{-1} for 5 min followed by 100 mU · m^2 BSA^{-1} · min^{-1} for 5 min) for 210 min. Dextrose (20%), enriched with [6,6-$^2H_2$]glucose to ~2.5%, was infused to maintain a plasma glucose concentration of 100 mg/dL. The infusion rates of [$^2H_2$]glucose and [$^2H_5$]glycerol were decreased by 75% during the clamp procedure (from 210 to 420 min) to account for the decline in hepatic glucose production and rate of glycerol release into plasma. Blood samples were obtained before the start of the infusions to determine background plasma glucose and glycerol tracer-to-tracee ratios (TTRs) and every 10 min during the final 30 min of the basal and clamp periods to determine glucose, free fatty acid and insulin concentrations, and substrate kinetics.

Intervention

After baseline studies were completed, subjects were randomly assigned to 4 weeks of treatment with either: *1*) placebo capsules (*n* = 5); *2*) Korean red ginseng extract (Spectrum Laboratories, Gardena, CA) (3 g/day for 2 weeks and then 8 g/day for 2 weeks, *n* = 5); *3*) ginsenoside Re (AIPOP, Gangdown-Do, Korea) (250 mg/day × 2 weeks followed by 500 mg/day × 2 weeks, *n* = 5) (Supplementary Data). The relative content of ginsenoside Re in the GRE used in this study was 13.7 ± 1.4%, which is similar to the ginsenoside Re content reported in previous studies (8,11). We confirmed that the batches of ginseng and ginsenoside Re used in this study had biological activity by demonstrating that incubation with ginseng and ginsenoside Re markedly improved insulin-mediated glucose uptake in isolated epitrochlearis muscles obtained from diet-induced insulin resistant rodents (D.H. Han and J.O. Holloszy, unpublished finding) and rectus abdominus strips obtained from obese subjects undergoing gastric bypass surgery (D.H. Han and J.O. Holloszy, unpublished observations). Randomization to group assignment was performed by The Barnes-Jewish Hospital research pharmacist by using a fixed randomization scheme generated by the Moses-Oakford algorithm, with a block size of three and an allocation ratio of 1:1:1. All subjects, investigators, and laboratory personnel performing the analyses were blinded to group allocation until completion of all primary outcome measures. Subjects were seen once per week by a member of the research team during the intervention to assess compliance by history and pill counts and to check for potential adverse events. Subjects consumed >90% of assigned pills, and no adverse events were reported. At the end of the 4-week period, all baseline studies were repeated. Subjects ingested their study medication (placebo, ginseng, or ginsenoside Re) in the morning 30 min before the start of the FSOGTT and hyperinsulinemic-euglycemic clamp procedure.

Sample processing and analyses

Plasma glucose was measured by using an automated glucose analyzer (YSI, Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin and C-peptide concentrations were measured by radioimmunoassay. Plasma glucose and glycerol TTRs were determined using gas chromatography-mass spectrometry (12).

Plasma ginsenoside Re content was evaluated at every time point during the FSOGTT. An aliquot of 100 μL plasma was acidified with perchloric acid (35%) and centrifuged at 1,100*g* for 30 min. The supernatant was added to a solid-phase cartridge (Oasis HLB 1 cc; Waters Corporation, Milford, MA). After the sample was absorbed by the cartridge, the cartridge was washed with 4 mL water. Ginsenosides were eluted with 1 mL 95% methanol in water and evaporated in a SpeedVac (Savant Instruments, Inc., Farmingdale, NY) at 40°C. The residue was reconstituted in 100 μL 95% methanol. After centrifugation at 20,000*g* for 15 min, ginsenoside Re, Rb_1, and Rb_2 content in the supernatant was evaluated by liquid chromatography/mass spectrometry, as described previously (13). A standard curve was generated using ginsenoside Re of known concentration. This method has a detection limit of 8.0 ng/mL (8.4 nmol/L), which is the minimal concentration of ginseng that is necessary to demonstrate biological activity in vitro (4).

Calculations

FSOGTT. Total AUC for glucose, insulin, and C-peptide during the first 120 min of the FSOGTT were calculated by using the trapezoidal method. Whole-body IS (S_i) was estimated from the FSOGTT by using the oral glucose minimal model, which

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measures the overall effect of insulin to stimulate glucose disposal (14). β-Cell function was evaluated by determining the disposition index (DI), which represents the insulin secretory response in relationship to IS, calculated as the product of the β-cell responsivity index (Φ_o) and S_i (15). DI could not be determined in three subjects (two in the placebo group and one in the ginsenoside Re group), because plasma samples from two subjects were lost and our modeling program was not able to adequately curve-fit the data from one subject.

Tracer kinetics. Steele's equation for steady-state conditions was used to calculate glucose rate of appearance (R_a), glucose rate of disappearance (R_d), and glycerol R_a during the final 30 min of the basal period and the clamp (16). The hepatic IS index was determined as the product of the basal hepatic glucose production rate and basal plasma insulin concentration (17).

Statistical analyses

All outcome measures were analyzed by using a three-way (group × condition) ANOVA with repeated measures using a 3 × 2 factorial design in which the groups are placebo, ginseng extract, and ginsenoside Re and the conditions are basal and high insulin periods during the hyperinsulinemic-euglycemic clamp. Significant *F* ratios from each analysis were followed by post hoc comparisons by the Neuman-Keuls procedure, using the appropriate error terms. A *P* value of ≤ 0.05 was considered statistically significant. All data are reported as means ± SE.

The primary outcome of this study was insulin-stimulated glucose uptake during the hyperinsulinemic-euglycemic clamp procedure. Based on our previous data evaluating the reproducibility of assessing glucose kinetics during a hyperinsulinemic-euglycemic clamp procedure (16), we estimated that five subjects in each group would be needed to detect a 25% improvement in insulin-stimulated glucose disposal, with a power of 0.8 and an α-value of 0.05. A treatment effect of 25% was chosen because this is the effect often observed after weight loss (18) or thiazolidinedione therapy (19). All values are means ± SE.

RESULTS

Subject characteristics and metabolic variables

Study subject characteristics and metabolic variables before and after treatment are shown in Table 1. Body weight and body composition and metabolic variables did not change after the intervention in any group.

FSOGTT

Insulin and glucose AUC during the first 120 min after ingestion of the glucose load were not different between groups at baseline and did not change after therapy in any group (Fig. 1*A* and *C*). Values for S_i (Fig. 1*B*) and DI (Fig. 1*D*) were not different between groups at baseline and did not change after the intervention.

Basal substrate kinetics

Basal glucose R_a after the intervention was not different than values obtained before intervention in the placebo (725 ± 21 versus 682 ± 33 μmol/min), ginseng (865 ± 69 versus 780 ± 99 μmol/min), and ginsenoside Re (635 ± 69 versus 638 ± 99 μmol/min) groups. Similarly, glycerol R_a after the intervention was not different in the placebo (156 ± 8 versus 165 ± 12 μmol/min), ginseng (250 ± 42 versus 248 ± 49 μmol/min), or ginsenoside Re (242 ± 25 versus 221 ± 22 μmol/min) groups. The hepatic IS index after therapy was not different than values obtained before therapy in the placebo, ginseng, and ginsenoside Re groups (Fig. 2*A*).

Hyperinsulinemic-euglycemic clamp procedure

Mean plasma glucose concentrations during the last 30 min of the insulin infusion after treatment were the same as values obtained before treatment in the placebo (96 ± 1 and 93 ± 1 mg/dL), ginsenoside Re (97 ± 1 and 97 ± 1 mg/dL), and ginseng (99 ± 1 and 99 ± 1 mg/dL) groups. Mean plasma insulin concentrations during the last 30 min of insulin infusion after treatment were also the same as values obtained before treatment in the placebo (78 ± 5 and 76 ± 7 μU/mL), ginsenoside Re (88 ± 7 and 89 ± 7 μU/mL), and ginseng (78 ± 12 and 76 ± 10 μU/mL) groups.

Insulin infusion increased the rate of glucose disposal in all groups, but the percent increase above basal was not affected by placebo, ginsenoside Re, or ginseng therapy (Fig. 2*B*). Endogenous glucose production rates decreased in all groups during insulin infusion but the relative suppression in glucose R_a did not change with treatment in any group (Fig. 2*C*). The decrease in glycerol R_a during insulin infusion was also the same after as before therapy in all groups (Fig. 2*D*).

Plasma ginsenoside concentration

Plasma concentrations of ginsenoside Re, Rb_1, and Rb_2 were not detectable in blood

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Table 1—*Study subject characteristics and metabolic variables before and after treatment*

	Before	After	Before	After	Before	After
Sex (male/female)	1/4	—	0/5	—	0/5	—
Race (African American/Caucasian)	2/3	—	1/4	—	3/2	—
Weight (kg)	88 ± 8	90 ± 7	98 ± 11	98 ± 11	89 ± 4	91 ± 5
BMI (kg/m^2)	31 ± 1	32 ± 1	35 ± 3	35 ± 3	36 ± 2	37 ± 2
Fat mass (% body wt)	40 ± 3	40 ± 4	40 ± 5	40 ± 4	43 ± 2	43 ± 2
Glucose (mg/dL)	94.1 ± 1.8	95.6 ± 3.2	96.0 ± 6.6	98.2 ± 3.7	94.5 ± 2.4	95.5 ± 4.3
Insulin (μU/mL)	7.3 ± 1.4	8.0 ± 1.8	11.1 ± 4.0	12.1 ± 3.5	11.2 ± 1.3	11.9 ± 2.4
HbA_{1c} (%)	5.9 ± 0.2	5.9 ± 0.1	5.5 ± 0.1	5.7 ± 0.1	5.8 ± 0.8	5.9 ± 0.1
Total cholesterol (mg/dL)	214 ± 21	202 ± 15	164 ± 27	165 ± 27	206 ± 32	204 ± 26
Triglyceride (mg/dL)	130 ± 24	120 ± 27	135 ± 36	128 ± 29	126 ± 23	139 ± 31
HDL cholesterol (mg/dL)	47 ± 5	46 ± 5	46 ± 6	44 ± 5	52 ± 6	50 ± 6
LDL cholesterol (mg/dL)	140 ± 20	132 ± 12	88 ± 20	96 ± 21	143 ± 27	126 ± 19

Data are means ± SE.

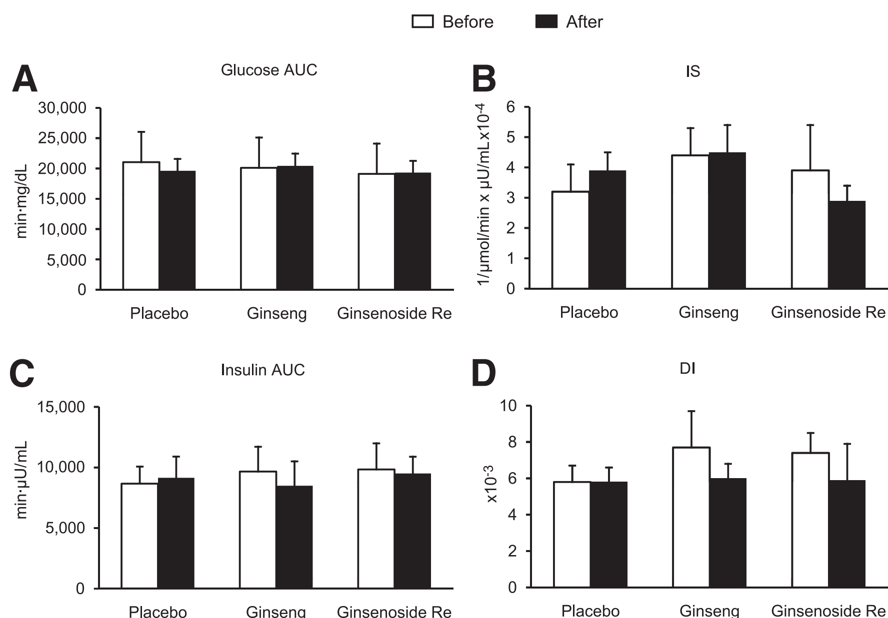

Figure 1—*Glucose* (A) *and insulin* (C) *AUC obtained during the first 2 h of the 5-h FSOGTT, and IS* (B) *and DI* (D), *assessed by the FSOGTT before (white bars) and after (black bars) treatment with placebo, ginseng, or ginsenoside Re. Values are means ± SE.*

samples obtained from 30 min to 6 h after ingesting the morning dose of ginseng or ginsenoside Re during the day of the FSOGTT and from 30 min to 7.5 h after ingesting the morning dose of ginseng or ginsenoside Re during the day of the hyperinsulinemic-euglycemic clamp procedure. The method used to assess ginsenoside concentrations has a lower limit of detection of 8.0 ng/mL (8.4 nmol/L), which is below the minimal concentration of ginsenoside Re and Rb_1 necessary to increase IS in vitro (4).

CONCLUSIONS—Ginseng is a popular herbal therapy that is purported to be effective in both the prevention and treatment of diabetes. Data from studies conducted in animal models have identified ginsenoside Re as a component of ginseng that affects IS and improves glycemic control (2). Therefore, we conducted a double-blind, randomized, placebo-controlled study to determine whether treatment with ginseng or ginsenoside Re improves oral glucose tolerance, β-cell function, and IS in humans. Only subjects with impaired glucose tolerance or newly diagnosed type 2 diabetes, who presumably have more reversible metabolic dysfunction, were studied to increase our ability to detect a beneficial effect of therapy. Moreover, we used specific sources of ginseng and ginsenoside Re that we found improved skeletal muscle IS in vitro in rodent and human muscle strips. Our data demonstrate that 4 weeks of oral ginseng and ginsenoside Re therapy do not improve oral glucose tolerance, β-cell function, or multiorgan IS. These results refute the popular notion that ingestion of ginseng and its putative active ginsenoside component has beneficial metabolic effects on glucose homeostasis.

Data from studies conducted in 3T3-L1 adipocytes and in obese, insulin-resistant rodent models have found that GRE and several ginsenoside species (Re, Rb_1) improve insulin-stimulated glucose disposal (2,20). In most of these animal studies, ginseng and ginsenosides were given intraperitoneally. Oral administration of ginseng or ginsenosides has also been reported to improve oral glucose tolerance and increase insulin-stimulated glucose disposal (21,22). However, the results from these studies are confounded by concomitant weight loss, so it is unclear whether the improvements in IS occurred because of weight loss or because of the insulin-sensitizing properties of ginsenosides. Few studies have evaluated the effect of ginseng in human subjects, and the interpretation of data from these studies is difficult because of differences in experimental design and contradictory results among studies. A single dose of oral ginseng given ~40 min before glucose ingestion reduced the glucose AUC during an OGTT by ~20% in some studies (23) but had no beneficial effect in others (8). Longer term oral ginseng therapy was evaluated in subjects with type 2 diabetes in two studies. In one study, ginseng treatment (6 g/day for 12 weeks) lowered plasma insulin concentration but did not change HbA_{1c} (10), whereas ginseng treatment (100–200 mg/day for 8 weeks) in the other study was associated with a decrease in fasting plasma glucose concentration (9). However, the interpretation of the results from both studies is

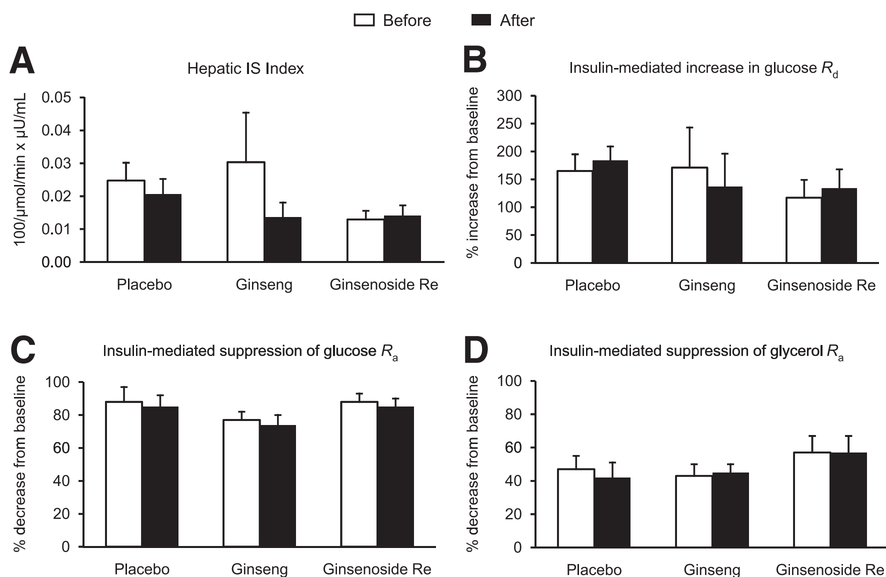

Figure 2—*Hepatic IS index* (A), *insulin-mediated increase in glucose* R_d (B), *insulin-mediated suppression of glucose* R_a (C), *and insulin-mediated suppression glycerol* R_a (D) *during the hyperinsulinemic-euglycemic clamp procedure before (white bars) and after (black bars) treatment with placebo, ginseng, or ginsenoside Re therapy. Values are means ± SE.*

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confounded by either a large drop-out rate (10) or concomitant weight loss (9). Oral ginseng therapy (3 g/day for 14 days) did not improve insulin-mediated glucose disposal, assessed by using the hyperinsulinemic-euglycemic clamp procedure, in subjects with indinavir-induced skeletal muscle insulin resistance (24).

We were unable to detect ginsenoside Re, Rb_1, or Rb_2 in plasma in our subjects, even though they were prescribed large daily oral doses of ginseng and ginsenoside Re for 30 days and ingested the last dose ~30 min before a series of blood samples were obtained to assess blood concentrations. The method we used to measure ginsenoside Re, Rb_1, or Rb_2 has a threshold of detection of 8 ng/mL, which is below the minimal concentration necessary for biological activity in vitro (4). Therefore, our results suggest that ginsenoside Re is poorly absorbed from oral ingestion of ginseng or ginsenoside Re itself. The limited systemic bioavailability of ginseng Re in our subjects helps explain the discrepancy between our findings and the positive effects observed in studies that involved intraperitoneal ginseng injection (2) or in vitro incubation with ginseng (4,20). Data from pharmacokinetic studies conducted in rodents and people have found that absorption of ginseng metabolites is poor after oral ingestion (13,25). Plasma ginseng or ginsenoside concentrations were not reported in previous studies that found metabolic benefits of ginseng therapy in study subjects. We are aware of only one study that evaluated oral ginsenoside absorption in human subjects (13). This study was conducted in two subjects who were studied for 12 h after ingesting GRE. Ginsenoside Rb_1 and Rb_1 were detected at very low levels in plasma (~5 nmol/L) in one subject, but ginseng components were not detected in the other subject. Very low levels of ginsenoside Re were found in urine for up to 3 h after ingestion. The poor absorption of orally ingested ginsenosides is likely related to its saponin ring structure, which is poorly soluble in aqueous solutions. In addition, protopanaxtriols (e.g., ginsenoside Re) are rapidly hydrolyzed to ginsenoside Rb_1 in mildly acidic conditions, such as in the stomach, suggesting that the bioavailability of orally administered ginsenoside Re is particularly poor. Our results, in conjunction with data from other studies, suggest that oral ginsenoside products are too poorly absorbed to provide adequate systemic availability to influence metabolic function. We cannot exclude the possibility that other ginsenosides and their metabolites or nonginsenoside components of GRE are bioavailable when given enterally.

Although it is possible that our study missed a therapeutic effect of ginseng or ginsenoside Re because of the small number of study subjects, we believe that this is unlikely. We used the hyperinsulinemic-euglycemic clamp procedure, in conjunction with stable isotopically labeled tracer infusion, to evaluate IS. We have demonstrated that this procedure is very sensitive and reproducible (16) and would allow us to detect a 25% improvement in insulin-stimulated glucose disposal in the current study with a power of 0.8. Our data did not even detect a trend toward treatment-induced improvement in any of our study outcome measures. Ginsenoside composition varies between commercially available products, so our study cannot eliminate the possibility that other ginseng products could have metabolic benefits.

In summary, despite the popular use of ginseng products to improve glucose homeostasis and treat type 2 diabetes, we found no evidence that oral ginseng or ginsenoside Re therapy improves β-cell function or IS in subjects with impaired glucose tolerance or newly diagnosed type 2 diabetes. Although parenteral ginseng and ginsenoside Re can markedly enhance insulin action in animal models, our data suggest that minimal bioavailability after oral ingestion limits its therapeutic efficacy in people.

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No potential conflicts of interest relevant to this article were reported.

D.N.R. performed experiments, researched data, and wrote the manuscript. B.W.P. analyzed data, contributed to the discussion, and reviewed and edited the manuscript. A.O. analyzed data and contributed to the discussion. J.O.H. researched data and reviewed and edited the manuscript. K.S.P. analyzed data, contributed to the discussion, and reviewed and edited the manuscript. S.K. analyzed data, edited and reviewed the manuscript, and contributed to the discussion.

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