

Administration of resveratrol for 5 wk has no effect on glucagon-like peptide 1 secretion, gastric emptying, or glycemic control in type 2 diabetes: a randomized controlled trial^{1,2}

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ABSTRACT

Background: Resveratrol has been reported to lower glycemia in rodent models of type 2 diabetes associated with the stimulation of glucagon-like peptide 1 (GLP-1), which is known to slow gastric emptying, stimulate insulin secretion, and suppress glucagon secretion and energy intake.

Objective: We evaluated the effects of 5 wk of resveratrol treatment on GLP-1 secretion, gastric emptying, and glycemic control in type 2 diabetes.

Design: Fourteen patients with diet-controlled type-2 diabetes [mean \pm SEM glycated hemoglobin (HbA1c): $6.4 \pm 0.2\%$ (46.4 ± 2.2 mmol/mol)] received resveratrol (500 mg twice daily) or a placebo over two 5-wk intervention periods with a 5-wk washout period in between in a double-blind, randomized, crossover design. Before and after each intervention period (4 visits), body weight and HbA1c were measured, and patients were evaluated after an overnight fast with a standardized mashed-potato meal labeled with $100 \mu\text{g }^{13}\text{C}$ -octanoic acid to measure blood glucose and plasma GLP-1 concentrations and gastric emptying (breath test) over 240 min. Daily energy intake was estimated from 3-d food diaries during the week before each visit.

Results: Fasting and postprandial blood glucose and plasma total GLP-1 as well as gastric emptying were similar at each assessment, and the change in each variable from weeks 0 to 5 did not differ between resveratrol and placebo groups. Similarly, changes in HbA1c, daily energy intake, and body weight after 5 wk did not differ between the 2 treatments.

Conclusions: In patients with diet-controlled type 2 diabetes, 5 wk of twice-daily 500 mg-resveratrol supplementation had no effect on GLP-1 secretion, glycemic control, gastric emptying, body weight, or energy intake. Our observations do not support the use of resveratrol for improving glycemic control. This trial was registered at www.anzctr.org.au as ACTRN12613000717752. *Am J Clin Nutr* doi: 10.3945/ajcn.115.117440.

Keywords: blood glucose, GLP-1, HbA1c, incretin, resveratrol

INTRODUCTION

Glycated hemoglobin (HbA1c),⁷ which is a predictor of the incidence and progression of microvascular (1) and probably

macrovascular (2) complications in type 2 diabetes, reflects overall glycemic control and, in the majority of patients whose diabetes is relatively well controlled (i.e., HbA1c $\leq 7.5\%$), is predominantly determined by postprandial rather than fasting hyperglycemia (3). Patients with comparable HbA1c concentrations but larger daily glycemic fluctuations appear to be at greater cardiovascular disease risk (4). Therefore, the reduction of postprandial glycemic excursions represents a priority in the management of type 2 diabetes.

Postprandial glycemia is determined, among other factors, by the release of the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) from intestinal K and L cells, respectively. These hormones stimulate insulin secretion in a glucose-dependent manner in health (5, 6). The insulinotropic activity of GIP is markedly impaired in type 2 diabetes, whereas that of GLP-1 is largely preserved (7). Moreover, GLP-1 suppresses glucagon secretion and energy intake (8) and slows gastric emptying (9), the latter of which represents a key mechanism by which short-acting GLP-1 receptor agonists can specifically target postprandial hyperglycemia (10).

Resveratrol, which is a phytoalexin derived from plants including red grapes, has recently generated substantial interest as a safe and inexpensive dietary supplement with potential health benefits in relation to obesity and type 2 diabetes as well as

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⁷ Abbreviations used: GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin.

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cardiovascular disease, cognitive decline, and certain cancers on the basis of data from animal studies, albeit with less strong evidence in humans (11). In patients with type 2 diabetes, the addition of resveratrol to usual therapy for 6–12 wk has been reported to reduce fasting blood glucose and HbA1c modestly (12, 13). Suggested mechanisms to account for these effects include the augmentation of insulin secretion through an action on sulfonylurea receptors (14) and the enhancement of insulin sensitivity (15, 16). In a high-fat-fed mouse model of diabetes, supplementation with resveratrol (60 mg/kg per day) for 5 wk was reported to improve oral glucose tolerance and insulin secretion, and was associated with a 3-fold increase in GLP-1 concentrations in the portal vein accompanied by substantial increases in colonic proglucagon messenger RNA and GLP-1 contents (17). However, to our knowledge, the effects of resveratrol on GLP-1 secretion have hitherto not been evaluated in patients with type 2 diabetes. We hypothesized that supplementation with resveratrol for 5 wk in patients with type 2 diabetes would increase both fasting and postprandial GLP-1 concentrations and, accordingly, lower both fasting and postprandial blood glucose concentrations and slow gastric emptying.

METHODS

Subjects

Fourteen patients with type 2 diabetes that was diagnosed by WHO criteria and managed by diet alone [10 men and 4 women; mean \pm SEM age: 67.5 ± 1.6 y; BMI (in kg/m^2): 27.7 ± 1.4 ; known duration of diabetes: 5 ± 1 y; and baseline HbA1c: $6.4 \pm 0.2\%$ (46.4 ± 2.2 mmol/mol)], were studied after each individual provided written informed consent. None of the subjects had evidence of microvascular or macrovascular complications or any other significant comorbidity, was a smoker, or was taking a medication known to affect gastrointestinal or cardiovascular function. The study protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and was conducted in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Protocol

After an initial screening visit, each patient was treated with 500-mg oral resveratrol or placebo (microcrystalline cellulose) capsules twice daily for two 5-wk treatment periods in a double-blind, randomized, crossover design with a 5-wk washout period between treatments. This dose of resveratrol was chosen to approximate the human equivalent of the dose shown to enhance GLP-1 release in rodents (17, 18). Random assignment was performed by the hospital pharmacy with established software. Food consumption was assessed with the use of a 3-d food diary that was kept by patients in the second half of the week before each visit and analyzed with FoodWorks software (FoodWorks 3.01; Xyris Software) to calculate energy and macronutrient intakes. Adherence to treatment was reinforced by weekly telephone calls and evaluated by counting the number of capsules that remained on the final day of each treatment period.

After the screening visit, each patient attended the Royal Adelaide Hospital at 0800 on the first day and the final day of each treatment period after an overnight fast for a total of 4 study

visits. On the evening before each visit (~ 1900), patients consumed a standardized beef-lasagna meal (2472 kJ; McCain Foods Proprietary Ltd.) with bread, a nonalcoholic beverage, and a piece of fruit. After the meal, water was allowed until 2200.

At each visit, body weight was recorded, and the food diary was collected. At the end of each treatment period (visits 2 and 4), the last dose of resveratrol or the placebo was administered 30 min before the test meal. A cannula was inserted into a forearm vein for repeated blood sampling, and a baseline breath sample was collected. Patients consumed a standardized meal within 10 min that consisted of 65 g dry powdered potato and 20 g glucose reconstituted with 250 mL H_2O together with an egg yolk labeled with $100 \mu\text{g}$ ^{13}C -octanoic acid (energy content: 368.5 kcal). $T = 0$ min was defined as the time of finishing the meal. Breath samples were collected every 5 min for the first hour and every 15 min until $T = 240$ min to measure the concentration of $^{13}\text{CO}_2$ in expired air to calculate the rate of gastric emptying (19). Venous blood samples (~ 13 mL) were taken immediately before the meal ($T = -10$ min) and at $T = 15, 30, 45, 60, 90, 120, 150, 180$, and 240 min for measurements of blood glucose and GLP-1 with the use of established assays (20). At $T = -10$ min, an additional 4 mL blood was collected for the measurement of HbA1c.

Measurements

Blood glucose concentrations were measured by the glucose oxidase method with the use of a glucometer (MediSense Optium meter; MediSense Inc.). Plasma total GLP-1 was measured with the use of radioimmunoassay (GLPIT-36HK; Millipore) with

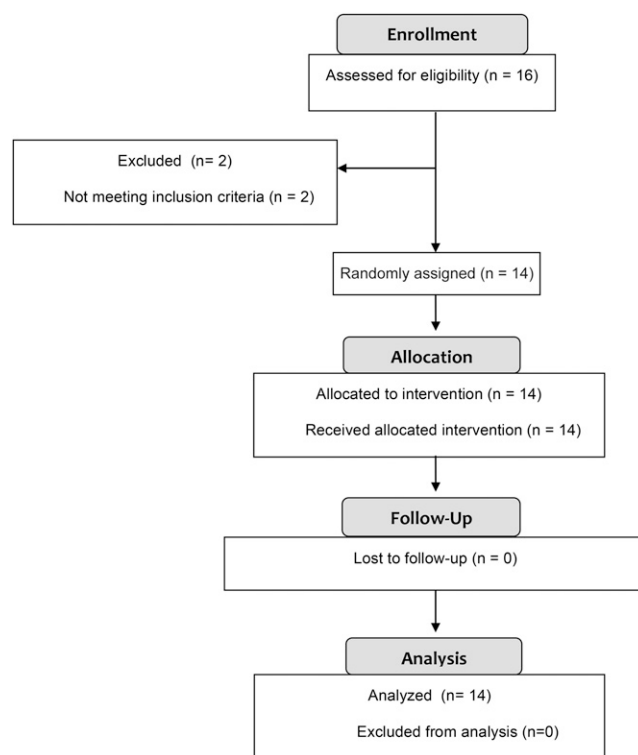


FIGURE 1 CONSORT diagram outlining the number of subjects involved in enrollment, intervention allocation, follow-up, and data analysis. CONSORT, Consolidated Standards of Reporting Trials.

TABLE 1

Fasting and peak values and AUCs at baseline (week 0) and after 5 wk of treatment (week 5) with resveratrol (500 mg twice daily) or a placebo for total plasma GLP-1 and blood glucose concentrations, HbA1c, gastric half-emptying, daily energy intake, and body weight in 14 patients with type 2 diabetes¹

	Resveratrol (500 mg twice daily) (n = 14)		Placebo (500 mg twice daily) (n = 14)		P (Δ resveratrol vs. Δ placebo)
	Week 0	Week 5	Week 0	Week 5	
Fasting GLP-1, pmol/L	36.8 \pm 6.7	35.4 \pm 6.5	36.7 \pm 5.9	34.1 \pm 4.8	0.64
Peak GLP-1, pmol/L	52.7 \pm 6.1	55.1 \pm 6.4	51.2 \pm 6.3	47.6 \pm 4.3	0.13
GLP-1 AUC, pmol \cdot L ⁻¹ \cdot min ⁻¹	8944 \pm 872	8746 \pm 913	8664 \pm 965	8476 \pm 809	0.98
Fasting glucose, mmol/L	8.1 \pm 0.3	7.8 \pm 0.3	8.2 \pm 0.3	7.8 \pm 0.3	0.21
Peak glucose, mmol \cdot L ⁻¹ \cdot min ⁻¹	13.5 \pm 0.9	13.6 \pm 0.8	13.6 \pm 0.8	13.5 \pm 0.9	0.80
Glucose AUC, mmol \cdot L ⁻¹ \cdot min ⁻¹	2513 \pm 193	2545 \pm 161	2521 \pm 177	2469 \pm 204	0.32
HbA1c, % (mmol/mol)	6.26 \pm 0.17 (44.9 \pm 1.9)	6.24 \pm 0.16 (44.7 \pm 1.7)	6.31 \pm 0.18 (45.5 \pm 2.0)	6.18 \pm 0.17 (44.0 \pm 1.9)	0.29
Gastric half-emptying time, min	165 \pm 12	163 \pm 14	164 \pm 12	157 \pm 18	0.62
Energy intake, kJ/d	8343 \pm 690	9249 \pm 960	7497 \pm 774	7871 \pm 554	0.55
Body weight, kg	81.1 \pm 3.7	81.2 \pm 3.8	81.1 \pm 4.1	80.8 \pm 4.0	0.43

¹All values are means \pm SEMs. Student's paired *t* test, which was adjusted for the period, was used to compare the changes of these variables between weeks 0 and 5 of resveratrol and placebo treatments (Δ resveratrol vs. Δ placebo). GLP-1, glucagon-like peptide 1; HbA1c, glycated hemoglobin.

a sensitivity of 3 pmol/L and intra-assay and interassay CVs of 7.9% and 6.9%, respectively. HbA1c was measured by a commercial laboratory (SA Pathology). Gastric emptying was assessed by measuring ¹³CO₂ concentrations in breath samples with the use of an isotope-ratio mass spectrometer (ABCA 2020; Europa Scientific) with an on-line gas chromatographic purification system. This method has previously been validated against scintigraphy (21). The half-emptying time of the test meal was calculated with the use of the formula described by Ghooes et al. (22).

Calculations and statistical analysis

On the basis of a previous study (23), we estimated that a sample size of 14 subjects would have 80% power (at $\alpha = 0.05$) to detect a 50% difference in the postprandial AUC for plasma total GLP-1, which was the primary endpoint. AUCs for plasma GLP-1 and blood glucose concentrations were calculated with the use of the trapezoidal rule; changes in the latter were a secondary endpoint. Other secondary endpoints were fasting and peak postprandial GLP-1 and blood glucose concentrations, HbA1c, gastric emptying, daily energy intake, and body weight. Absolute changes in each variable between weeks 0 and 5 of each intervention were calculated for the analysis. Carryover effects from one intervention period to the other were excluded with the use of the methods reported by Wellek et al. (24). The presence of treatment effects was analyzed with the use of period-adjusted *t* tests to account for the crossover design (24). All analyses were performed with SPSS 21 software (IBM Corp.). Data are expressed as means \pm SEMs; *P* < 0.05 was considered statistically significant.

RESULTS

Subjects consumed 98.6% of resveratrol capsules and 99% of placebo capsules during each intervention. All subjects tolerated

the study well, and none of the subjects reported adverse effects (Figure 1).

Plasma total GLP-1 concentrations

At each study visit, GLP-1 concentrations increased substantially (*P* < 0.001 for each visit) in response to the test meal before declining thereafter. Neither the change in AUC nor the change in fasting and peak GLP-1 concentrations from weeks 0 to 5 differed between resveratrol and placebo groups (Table 1, Figure 2A).

Blood glucose concentrations

At each study visit, blood glucose concentrations increased substantially (*P* < 0.001 for each visit) in response to the test meal before declining to below the baseline at *T* = 240 min (*P* < 0.05 for each visit). Neither the change in AUC nor the change in fasting and peak blood glucose concentrations from weeks 0 to 5 differed between resveratrol and placebo groups (Table 1, Figure 2B).

HbA1c, gastric emptying, energy intake, and body weight

HbA1c, the gastric half-emptying time, energy intake, and body weight were all similar at weeks 0 and 5 of each intervention. The change in each of these outcome measures from weeks 0 to 5 did not differ between resveratrol and placebo groups (Table 1).

DISCUSSION

In this double-blind, randomized, crossover study of patients with type 2 diabetes that was managed by diet alone, we showed that resveratrol administered at a dose of 500 mg twice daily for 5 wk had no effect on GLP-1 secretion, glycemic control, gastric emptying, or body weight and did not suppress energy intake.

To our knowledge, the effect of resveratrol supplementation on GLP-1 release and gastric emptying in type 2 diabetes has not

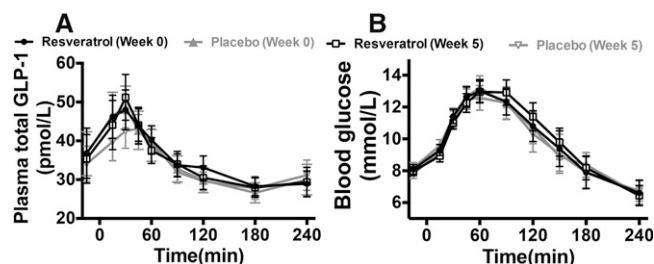


FIGURE 2 Mean \pm SEM effects of resveratrol (500 mg twice daily) or a placebo for 5 wk on plasma GLP-1 concentrations (A) and blood glucose concentrations (B) before and after the test meal in 14 patients with type 2 diabetes. Changes in the AUC and both fasting and peak concentrations from weeks 0 to 5 did not differ between resveratrol and placebo groups for either GLP-1 or blood glucose concentrations (period-adjusted Student's paired *t* test). GLP-1, glucagon-like peptide 1.

been evaluated previously. Resveratrol was shown to augment GLP-1 release in a high-fat-fed mouse model of diabetes; because the oral bioavailability of resveratrol is low (25), it was suggested that the accumulation of resveratrol or its metabolites in the epithelial cells of the digestive tract could account for this response (17). In a recent report, the administration of resveratrol for 30 d suppressed postprandial glucagon secretion but did not affect fasting or postprandial plasma GIP or GLP-1 concentrations in obese nondiabetic subjects (26); the dose of resveratrol used in the study (150 mg/d) was substantially lower than that used in our study or those of other groups (11). Even with the relatively higher dose used in our study, resveratrol did not have any effect on GLP-1 release, and therefore, it was not surprising that gastric emptying was also unaffected.

The dose of resveratrol (1 g/d) used in our study was reported to have lowered both fasting blood glucose and HbA1c, although modestly, in a group of poorly controlled type 2 patients [baseline HbA1c: $8.6 \pm 1.4\%$ (70.5 ± 15.3 mmol/mol)] (12). A lower dose of resveratrol (250 mg/d) given for 3 mo in another randomized, placebo-controlled, double-blind, parallel clinical trial in patients with poorly controlled type 2 diabetes [HbA1c at baseline $\sim 9.9\%$ (85 mmol/mol)] was reported to result in a modest mean reduction of HbA1c of 0.3% (13), whereas the same dose of resveratrol had no effect on HbA1c in a different open-label study (27). The patients in these previous reports were less well controlled than those included in our study, and all of them were controlled with the use of oral hypoglycemic agents, including metformin, which is known to stimulate GLP-1 release and could potentially interact with resveratrol. It should be acknowledged that the duration of our intervention would likely have been too brief to show an effect on HbA1c, and our study was not adequately powered for this endpoint. However, the fact that we observed no trend whatsoever for a reduction in glycemia before or after the standardized test meal, which we have previously shown to be very sensitive to interventions (20), made it unlikely that a larger sample size or longer intervention would have altered our findings.

In an open-label study that involved overweight or obese subjects with impaired glucose tolerance, resveratrol (1–2 g/d) improved insulin sensitivity as well as postprandial glycemia (28). However, a more recent study that involved resveratrol supplementation (500 mg/d) for 4 wk in obese, nondiabetic subjects failed to show any effect on insulin sensitivity (29). In this study, insulin sensitivity was evaluated with the use of the

euglycemic hyperinsulinemic clamp technique, which is more accurate than the HOMA-IR models that were used in the previous study (28). In our study, we did not measure plasma insulin concentrations, but we believe it unlikely that the concentrations would have been altered by resveratrol because of the lack of an effect on fasting or postprandial blood glucose.

Other metabolic effects of resveratrol, including changes in resting metabolic rate, lipids, and inflammatory markers have been apparent only in obese subjects (30) and not in subjects with lower BMI (31). It is possible that resveratrol failed to influence metabolism in our study because our patients were not obese. Similarly, animal data have suggested that resveratrol can induce weight loss (32), and this effect has also previously been reported in patients with the metabolic syndrome (33). However, we did not observe any effect on body weight or any suppression of total daily energy intake.

The limitations of our study included the relatively small sample size; however, the number of subjects studied was calculated to have 80% power to show a change in plasma GLP-1 concentrations if any substantial effect existed. There was no suggestion of any effect on either GLP-1 concentrations or glycemia, and thus, it is unlikely that increasing the sample size would have altered our results. Second, we studied only nonobese patients with well-controlled type 2 diabetes; it is uncertain whether these observations can be generalized to patients with poorly controlled diabetes or to the obese. Third, the treatment period of 5 wk was relatively brief but consistent with both animal (17) and human (12) studies in which resveratrol supplementation has stimulated GLP-1 secretion or improved glycemia. Fourth, the dose of resveratrol selected was toward the higher end of the range reported in human studies, but we cannot be certain that a higher or even lower dose would not have been more efficacious. Finally, we did not measure resveratrol metabolites as a marker of compliance, but we believe good compliance was achieved on the basis of telephone calls and capsule counts.

In conclusion, our observations do not support the stimulation of GLP-1 release as a mechanism of action of resveratrol in humans and suggest that resveratrol is unlikely to improve glycemic control in nonobese patients with type 2 diabetes that is controlled by diet and life-style management alone.

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The authors' responsibilities were as follows—SST: was involved in the subject recruitment, coordination, data collection, and interpretation; statistical analysis; and drafting of the manuscript; TW: was involved in the data interpretation, statistical analysis, and drafting of the manuscript; MJB and HLC: assisted in the recruitment and data collection; SS: was involved in the data analysis; KLJ and MH: were involved in the conception and design of the study and data interpretation; CKR: was involved in the conception and design of the study and data interpretation and had overall responsibility for the study; and all authors: critically reviewed the manuscript and approved the final version of the manuscript. None of the authors reported a conflict of interest related to the study.

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