

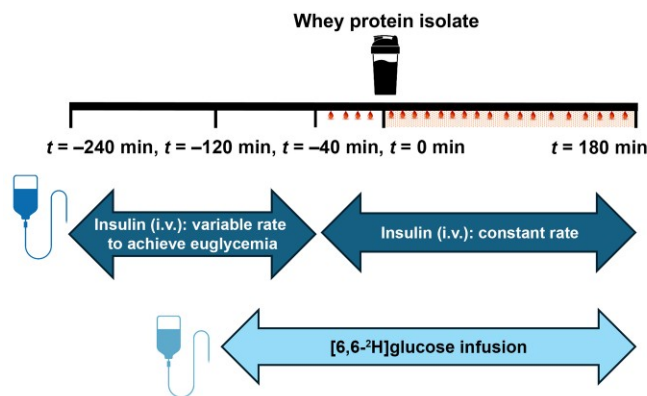
## Whey Protein Ingestion Stimulates Glucagon Secretion and Raises Blood Glucose Levels in Adults With Type 1 Diabetes

Giang M. Dao, Sam Zhao, Cara Schofield, Sara Vogrin, Declan T. Hennessy, Carmel E. Smart, Dessi P. Zaharieva, David N. O'Neal, Clinton R. Bruce, Greg M. Kowalski, and Dale J. Morrison

*Diabetes* 2026;75(7):1–12 | <https://doi.org/10.2337/db26-0059>

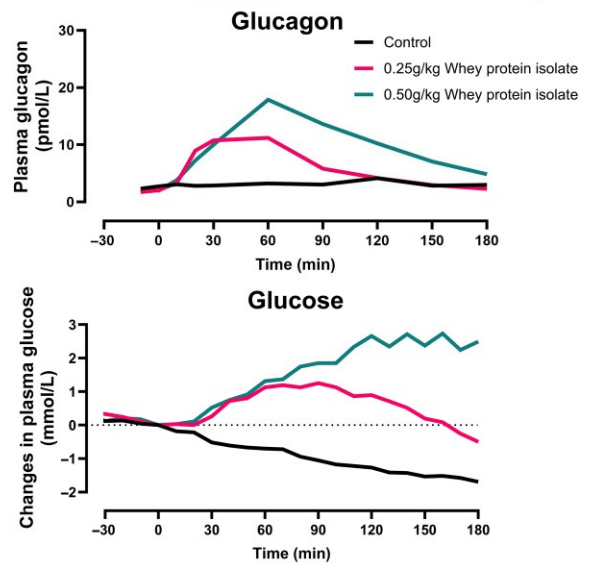
### Whey Protein Ingestion Stimulates Glucagon Secretion and Raises Blood Glucose Levels in Adults With Type 1 Diabetes

#### Methods



In participants with type 1 diabetes receiving constant i.v. insulin infusion, whey protein ingestion stimulated glucagon secretion, resulting in a sustained rise in blood glucose levels. This highlights the possibility of using whey protein isolate as a tool to manage hypoglycemia.

#### Results





# Whey Protein Ingestion Stimulates Glucagon Secretion and Raises Blood Glucose Levels in Adults With Type 1 Diabetes

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**This study characterized the dose effect of whey protein isolate (WPI) ingestion on glucagon secretion, glycemia, and the underlying mechanisms in adults with type 1 diabetes. Twelve insulin pump-treated adults with type 1 diabetes (mean  $\pm$  SD age  $47.3 \pm 16.4$  years; BMI  $26.1 \pm 3.8$  kg/m<sup>2</sup>) and six adults without diabetes (age  $36.2 \pm 20.9$  years; BMI  $27.3 \pm 5.8$  kg/m<sup>2</sup>) received 1) control (water), 2) low-dose WPI (0.25 g/kg), or and 3) high-dose WPI (0.5 g/kg). Those with diabetes replaced subcutaneous insulin with fixed-rate i.v. insulin. [6,6-<sup>2</sup>H]glucose infusion was used to measure glucose flux. In participants with type 1 diabetes, low- and high-dose WPI raised plasma glucagon by approximately five- and approximately nine-fold, respectively. Endogenous glucose production increased by  $\sim 50\%$  (peak) for both WPI doses, with the high dose producing more sustained stimulation. Plasma glucose decreased by a median (interquartile range) of  $\sim 1.7$  (2.0, 1.0) mmol/L for control but increased by 1.3 (1, 1.7) and 3.1 (2.5, 3.3) mmol/L for the low and high doses, respectively. Participants with and without diabetes had similar increases in amino acids, glucagon, glucagon-like peptide 1, and glucose-dependent insulinotropic polypeptide. This study highlights the substantial glucagon-stimulating and glycemic effects of WPI, which could be clinically useful for hypoglycemia management in type 1 diabetes.**

In individuals with type 1 diabetes, emerging evidence indicates that protein ingestion can substantially influence

## ARTICLE HIGHLIGHTS

- The effect of protein ingestion on glucagon and glycemic responses in individuals with type 1 diabetes is not well characterized.
- This study examined how ingestion of varying amounts of fast-absorbing whey protein (in the absence of other macronutrients) affected glucagon secretion, glucose levels, and associated metabolic hormone levels in adults with type 1 diabetes.
- Whey protein ingestion stimulated glucagon secretion and endogenous glucose production and increased blood glucose in adults with type 1 diabetes. Our findings highlight the potential of whey protein as a tool to support glycemic management and mitigate hypoglycemia in type 1 diabetes.

postprandial glucose levels; however, this effect remains poorly understood (1). In those without type 1 diabetes, protein ingestion stimulates both insulin and glucagon secretion, which act synergistically to promote amino acid disposal (1–5). In this setting, the glucose-raising actions of glucagon are offset by insulin, maintaining stable glycemia (2,5); while in a mixed meal, protein may reduce postprandial glycemia via insulin- and incretin-potentiating properties and delayed gastric emptying (6,7). However,

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Received 15 January 2026 and accepted 1 April 2026

This article contains supplementary material online at <https://doi.org/10.2337/figshare.31918842>.

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protein ingestion presents a unique physiological challenge for individuals with type 1 diabetes because of an absence of endogenous insulin secretion. Although their glucagon response to exercise and hypoglycemia is often impaired (8–10), the response to amino acid and protein ingestion remains intact (11–13). Therefore, the unopposed glucagon response after protein ingestion, combined with elevated circulating amino acids (gluconeogenic substrates), might stimulate endogenous glucose production (EGP) and raise glucose levels in type 1 diabetes (1).

Literature regarding the glycemic action of protein in type 1 diabetes is unclear, reflected in the limited guidelines on insulin administration for protein ingestion (1). This in part stems from the limited and conflicting findings regarding the glycemic action of protein in type 1 diabetes, which is likely due to past studies using varying protein sources. Specifically, the magnitude of the glucagon response to protein ingestion positively correlates with the rate of amino acid appearance in circulation (1,14). This might explain why some studies using slow-absorbing protein (e.g., casein) showed no glycemic effects (15), whereas fast-absorbing protein (e.g., whey) increased glucose concentrations by up to 3.5 mmol/L, with glycemia remaining elevated above baseline for up to 8 h (16). Although adding protein to mixed meals in people with type 1 diabetes has been demonstrated to increase glucose levels in the late postprandial period (17–19), the specific actions of protein may have been masked by other macronutrients.

Given the glucagon-stimulating and glucose-raising properties of protein in individuals with type 1 diabetes, protein ingestion could potentially be used therapeutically for mitigating hypoglycemia. Whey protein, a rapidly absorbed milk-derived protein fraction, potently stimulates glucagon secretion (6) and is therefore an excellent candidate as a glycemia-modifying tool in individuals with type 1 diabetes (1). We aimed to determine, under controlled laboratory conditions, the effects of varying doses of whey protein isolate (WPI) ingestion on blood glucagon and glucose concentrations, glucose flux (including EGP), and incretin responses and compare these with effects in individuals without diabetes.

## RESEARCH DESIGN AND METHODS

A randomized crossover study was performed in adults with type 1 diabetes who consumed test drinks containing two doses of WPI. Inclusion criteria were age >18 years, type 1 diabetes duration  $\geq 1$  year, established on insulin pump therapy and using a continuous glucose monitoring system, HbA<sub>1c</sub> <10%, no additional metabolic or renal conditions, no medications affecting glucose metabolism, no history of gastroparesis, and no allergy or intolerance to WPI. Participants avoided strenuous exercise and alcohol 24 h before each study session. A comparator group without diabetes was also included (age >18 years, no metabolic conditions, and no medications affecting glucose metabolism).

The study was approved by the St Vincent's Hospital Melbourne Human Research Ethics Committee, Melbourne, Victoria, Australia, and informed consent was obtained.

## Participants

Fourteen adults with type 1 diabetes and seven without diabetes were recruited. Two participants with type 1 were excluded (one withdrew and the other was excluded for protocol nonadherence), and one without diabetes withdrew for personal reasons.

## Study Design and Procedures

All participants completed three study visits ( $\geq 3$  days apart) in random order, ingesting either water (200 mL; control), low-dose WPI (0.25 g/kg), or high-dose WPI (0.5 g/kg) dissolved in 200 mL water (<0.04 g carbohydrates/g; WPI 90 [French vanilla]; True Protein, Brookvale, NSW, Australia). Amino acid composition of the WPI is shown in Supplementary Fig. 1.

## Protocol for Participants With Type 1 Diabetes

Participants arrived at the clinical laboratory at 7:30 A.M. after an overnight (10–12 h) fast. On arrival, participants disconnected their subcutaneous insulin pump. A cannula was inserted into a dorsal hand vein for arterialized blood sample collection using a heated box (50–55°C). A second cannula was inserted into an antecubital vein for insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark) and [6,6-<sup>2</sup>H]glucose (Cambridge Isotope Laboratories, Inc., Tewksbury, MA) infusions. A variable i.v. insulin infusion was initiated and continued for  $\sim 4$  h, providing adequate washout of exogenous subcutaneous insulin while permitting the establishment of glucose tracer equilibration and optimization of the insulin infusion rate to achieve stable glycemia (20,21). After  $\sim 2$  h (at least 2 h before drink ingestion), [6,6-<sup>2</sup>H]glucose infusion was initiated as a primed, glycemia-adjusted bolus ( $[\text{blood glucose concentration (mmol/L)}/5.5] \times 6$  mg/kg administered over 5 min), followed by a continuous infusion (0.06 mg/kg/min) that was maintained until the end of the trial. During this tracer equilibration period (minimum 2 h) and on achievement of a stable (30–40 min) baseline blood glucose concentration (mean  $\pm$  SD  $6.7 \pm 1.0$  mmol/L [min 4.1, max 9.5 mmol/L]), the i.v. insulin infusion rate was fixed and remained constant for the remainder of the trial. During this steady baseline period, blood samples were collected in BD Vacutainer EDTA tubes every 10 min for  $\sim 40$  min (at  $-40$ ,  $-30$ ,  $-20$ ,  $10$ , and  $0$  min) to determine baseline concentrations of metabolites, hormones, and tracer enrichment. At  $t = 0$  min, participants ingested the test drink, and thereafter, blood samples were collected every 10 min for 180 min. At any point, if blood glucose dropped <4.0 mmol/L, the trial was terminated. Blood samples were immediately placed on ice and subsequently centrifuged at 2,000 rpm for 10 min at

4°C. Plasma was collected and stored at -80°C for additional analyses.

### Protocol for Participants Without Diabetes

Participants without diabetes followed a similar protocol to those with type 1 diabetes but did not undergo the i.v. insulin infusion. The 2-h [6,6-<sup>2</sup>H]glucose tracer equilibration period was initiated immediately on cannulation, followed by test drink ingestion at  $t = 0$  min and a 3-h postprandial period. Blood samples were collected every 10 min from -40 to 180 min.

### Plasma Glucose Analysis

Plasma glucose concentrations and tracer enrichment were measured via gas chromatography-mass spectrometry (GC-MS; Agilent Technologies, Santa Clara, CA) using the isotope dilution method as previously described (2). Briefly, plasma was analyzed using methane-positive chemical ionization GC-MS, with glucose measured as the methyloxime pentapropionate derivative and raw data undergoing correction for natural isotopic background abundance skew (22).

### Plasma Metabolite and Hormone Analysis

Plasma concentrations of amino acids, urea,  $\beta$ -hydroxybutyrate, pyruvate, and lactate were simultaneously measured via electron ionization GC-MS (Agilent Technologies), using the isotope dilution method and methyloxime-*tert*-butyldimethylsilyl derivatization, as previously described (5). Free fatty acid (FFA) concentrations were determined by a colorimetric assay (NEFA-C; Wako Chemicals, Richmond, VA). Plasma concentrations of hormones were measured using commercial ELISA kits: insulin (ALPCO, Salem, NH), glucagon (Merckodia, Uppsala, Sweden), total glucagon-like peptide 1 (GLP-1; Merckodia), and total glucose-dependent insulinotropic polypeptide (GIP; Merckodia).

### Outcomes and Power Calculation

The primary outcome was plasma glucagon concentration after WPI ingestion, and the secondary outcomes were plasma concentrations of glucose, GLP-1, GIP, FFA, and amino acids, as well as glucose fluxes. Based on data from Paramalingam et al. (16), in which ingestion of 50 g WPI postexercise increased plasma glucagon from 27.3 to 82.6 ng/l (SD 26.9), the current sample size of 12 would provide 80% power ( $\alpha = 0.05$ ; intraparticipant correlation  $r = 0.5$ ) to detect the minimum difference of 22 ng/L (6.3 pmol/L).

### Calculation and Statistical Analysis

Glucose fluxes (EGP and  $R_d$ ) were calculated using Steele's non-steady-state equation (23). Data are presented as median (interquartile range). Baseline-subtracted area under the curve (bsAUC) was calculated as the area above baseline subtracted by the area under baseline. Baseline was defined as the mean of -10 and 0 min. For the three main interventions, pairwise comparisons were performed using the

Wilcoxon signed rank test. Participants with type 1 diabetes were compared with controls using the rank sum test. No multiple-comparison adjustments were made. Statistical significance was set at a two-tailed  $P$  value of  $<0.05$ . Analyses were performed using Stata 18 (StataCorp, LLC, College Station, TX).

### Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## RESULTS

Twelve adults with type 1 diabetes ( $n = 7$  men;  $n = 5$  women) and six without type 1 diabetes ( $n = 3$ men;  $n = 3$  women) were included in the analysis. Participant characteristics are listed in Table 1. Because of sample processing issues, plasma insulin data were only available for nine participants with type 1 diabetes and five participants without diabetes.

### Plasma Hormones and Metabolites

In participants with type 1 diabetes, both low and high WPI doses produced a rapid and robust increase in glucagon concentrations (peaking at ~5.5- and approximately ninefold above basal, respectively), with the high dose causing a significantly larger peak increase and bsAUC ( $P < 0.001$ ) (Fig. 1A and Table 2). Plasma insulin and FFA concentrations remained stable throughout all visits (Fig. 1C and H). Additionally, in the control condition, plasma levels of total amino acids, glucagon, GLP-1, and GIP remained at baseline throughout the experimental period (Fig. 1A, E, I, and K). Compared with low-dose WPI, high-dose WPI produced larger integrated GLP-1 and GIP responses (bsAUC;  $P = 0.002$  for both GLP-1 and GIP), although only GLP-1 reached a higher absolute peak concentration (Table 2). Compared with ingestion of low-dose WPI, high-dose WPI ingestion resulted in a greater bsAUC in plasma total amino acid concentrations ( $P < 0.5$ ) (Fig. 1E and Table 2), including all essential (Fig. 2) and most nonessential amino acids (Fig. 3A-K), as well as urea concentrations (Fig. 3L). Postprandial levels of lactate, pyruvate, and  $\beta$ -hydroxybutyrate did not differ between any of the interventions (Fig. 3M-O).

In control participants without diabetes, WPI ingestion raised insulin levels by ~4.1-fold basal for the low dose and by sixfold for the high dose (Fig. 1D). Compared with participants with type 1 diabetes, participants without diabetes had markedly lower (~15 vs. ~5  $\mu$ IU/mL) baseline plasma insulin concentrations (Fig. 1C and D). In contrast, participants without diabetes had comparable plasma total amino acid, glucagon, GLP-1, and GIP responses compared with those with type 1 diabetes, as demonstrated by similar bsAUC and peak concentration changes for these parameters across all visits (Table 3). Plasma concentrations of individual amino acids and metabolites in those without type 1 diabetes are shown in Supplementary Figs. 1 and 2.

**Table 1—Baseline characteristics and average ingested macronutrient amount for participants with and without type 1 diabetes**

	With type 1 diabetes	Without type 1 diabetes
Total <i>n</i>	12	6
Sex		
Male	7	3
Female	5	3
Age, years	47.3 ± 16.4	36.2 ± 20.9
BMI, kg/m <sup>2</sup>	26.1 ± 3.8	27.3 ± 5.8
Diabetes duration, years	28.1 ± 11.5	NA
HbA <sub>1c</sub> , %	6.7 ± 0.5	NA
Protein amount for low-dose WPI, g	20.0 ± 3.3	20.1 ± 3.7
Protein amount for high-dose WPI, g	39.9 ± 6.6	40.2 ± 7.4

Values are mean ± SD unless otherwise indicated. NA, not applicable.

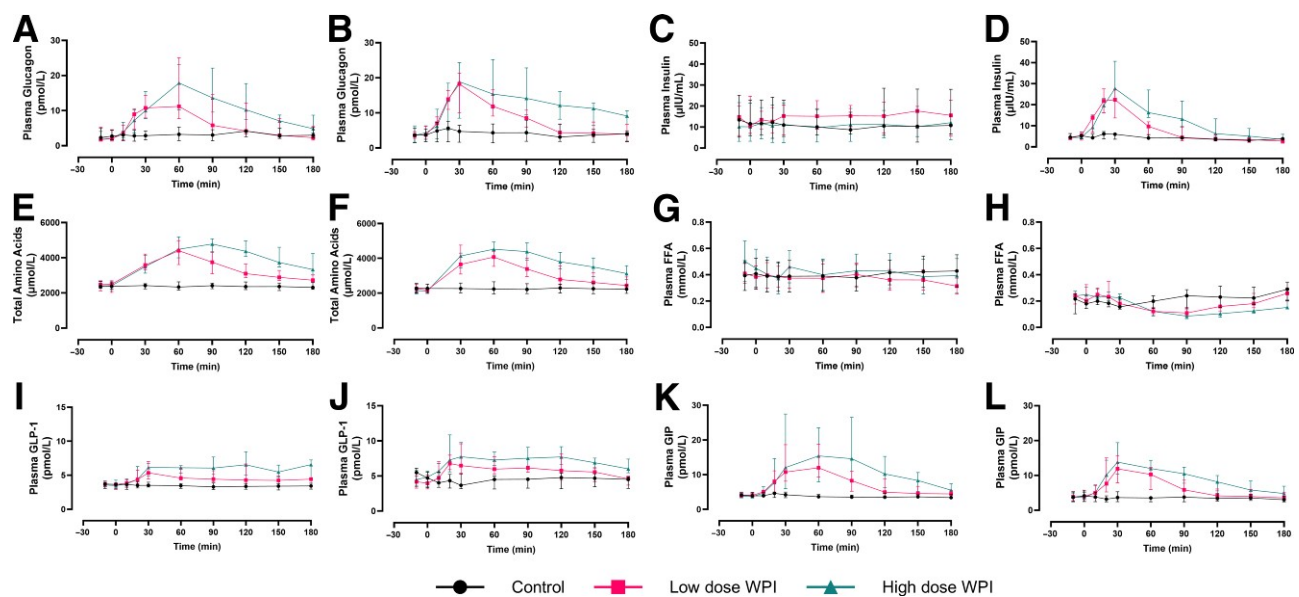
### Plasma Glucose

In participants with type 1 diabetes, plasma glucose declined steadily in the control condition by a median (interquartile range) of 1.7 (2.0, 1.0) mmol/L at 180 min. In contrast, both the low- and high-dose WPI trials produced significant elevations in glucose levels, as evidenced by an increased bsAUC compared with control ( $P < 0.001$ ) (Table 2). Furthermore, bsAUC was greater in the high- versus low-dose trials ( $P = 0.027$ ) (Table 2). Absolute increases in glucose levels were comparable between low- and high-dose trials in the first 90 min (Table 2), and whereas glucose levels returned to baseline at the end of the experiment in the low-dose trial, glucose remained elevated at 180 min in the high-dose trial (Fig. 4A and C). By comparison, participants

without diabetes had stable baseline glucose concentrations throughout all experimental conditions (Fig. 4B and D).

### Glucose Flux

Baseline EGP was similar across all visits in participants with type 1 diabetes (Fig. 4G). Although the control condition produced a steady decline in EGP throughout the study, EGP was stimulated by up to ~50% above baseline after WPI ingestion, with the peak EGP increase being comparable between the low- and high-dose trials (Fig. 4G). Comparing the low and high doses, EGP was similar in the first 60 min post-ingestion, and whereas EGP returned to baseline at the end of the experiment for the low dose, it remained elevated above baseline beyond 180 min in the



**Figure 1—**Plasma concentrations of glucagon (A and B), insulin (C and D), total amino acids (E and F), FFAs (G and H), total GLP-1 (I and J), and total GIP (K and L) in participants with ( $n = 12$ ) (A, C, E, G, I, and K) and without ( $n = 6$ ) (B, D, F, H, J, and L) type 1 diabetes after ingestion of control (water), low-dose WPI, and high-dose WPI. Data are presented as median and interquartile range.

**Table 2—Glycemic, hormonal, and glucose flux outcomes for participants with type 1 diabetes ( $n = 12$ ) after ingestion of water (control), low-dose WPI (0.25 g/kg), or high-dose WPI (0.5 g/kg)**

	Control (water) ( $n = 12$ )	Low-dose WPI ( $n = 12$ )	High-dose WPI ( $n = 12$ )	<i>P</i>		
				Control vs. low	Control vs. high	Low vs. high
<b>Plasma glucose, mmol/L</b>						
bsAUC*	−1.1 (−1.5, −0.66)	0.55 (0.21, 1)	1.6 (1.3, 1.7)	<0.001	<0.001	0.027
Absolute peak increase	−0.02 (−0.07, 0.07)	1.3 (1, 1.7)	3.1 (2.5, 3.3)	<0.001	<0.001	0.027
<b>EGP, mg/kg/min</b>						
bsAUC*	−0.24 (−0.44, −0.1)	0.5 (0.2, 0.7)	0.85 (0.63, 0.98)	<0.001	<0.001	0.002
Absolute peak increase	0.21 (0.09, 0.41)	1.3 (0.77, 1.5)	1.4 (1.2, 1.7)	<0.001	<0.001	0.042
<b>R<sub>d</sub>, mg/kg/min</b>						
bsAUC*	−0.12 (−0.26, −0.02)	0.29 (0.1, 0.4)	0.32 (0.13, 0.5)	0.002	<0.001	0.339
Absolute peak increase	0.51 (0.18, 0.59)	0.78 (0.6, 1.1)	1 (0.68, 1.3)	0.002	0.001	0.266
<b>Total amino acids, μmol/L</b>						
bsAUC*	−47 (−91, −14)	946 (870, 1,183)	1,666 (1,408, 1,899)	<0.001	<0.001	<0.001
Absolute peak increase	28 (5.6, 66)	1,794 (1,548, 2,507)	2,312 (2,230, 2,946)	<0.001	<0.001	<0.001
<b>Glucagon, pmol/L</b>						
bsAUC*	0.14 (−0.02, 0.81)	4.1 (2.8, 7.2)	8.1 (5.5, 13)	<0.001	<0.001	<0.001
Absolute peak increase	1.1 (0.45, 1.7)	11 (7.9, 19)	15 (11, 22)	<0.001	<0.001	0.021
<b>Insulin, μIU/mL</b>						
bsAUC*	0.45 (−1.1, 2.3)	1.8 (−1, 3.1)	0.43 (−0.55, 1.8)	0.203	0.82	0.322
Absolute peak increase	2 (0.96, 3.7)	5.3 (2.4, 6)	2.9 (1, 6.2)	0.004	0.359	0.432
<b>FFAs, mmol/L</b>						
bsAUC*	−0.004 (−0.063, 0.026)	0.005 (−0.086, 0.033)	−0.061 (−0.12, 0.005)	0.622	0.176	0.47
Absolute peak increase	0.074 (0.046, 0.14)	0.1 (0, 0.17)	0.054 (0.009, 0.1)	0.91	0.791	0.301
<b>GLP-1, pmol/L</b>						
bsAUC*	−0.08 (−0.25, −0.01)	0.99 (0.62, 1.4)	2.1 (1.6, 3.2)	0.001	0.001	0.001
Absolute peak increase	0.14 (0.03, 0.22)	1.7 (1.2, 2.7)	4.1 (2.4, 5.2)	0.001	0.001	0.001
<b>GIP, pmol/L</b>						
bsAUC*	0.06 (−0.36, 0.14)	3.8 (2.2, 6.5)	7.4 (3.9, 13)	<0.001	<0.001	<0.001
Absolute peak increase	0.4 (0.08, 0.75)	8.1 (7.1, 18)	12 (6.5, 26)	<0.001	<0.001	0.151

Values are median (interquartile range). \*Units for bsAUC: [(unit of the outcome) × min]/min.

high-dose trials (Fig. 4G). R<sub>d</sub> remained unchanged in the control condition but modestly increased in the WPI conditions (Fig. 4I). The peak increase in R<sub>d</sub> and the pattern of rise were comparable between the low- and high-dose WPI conditions (Fig. 4I and Table 2).

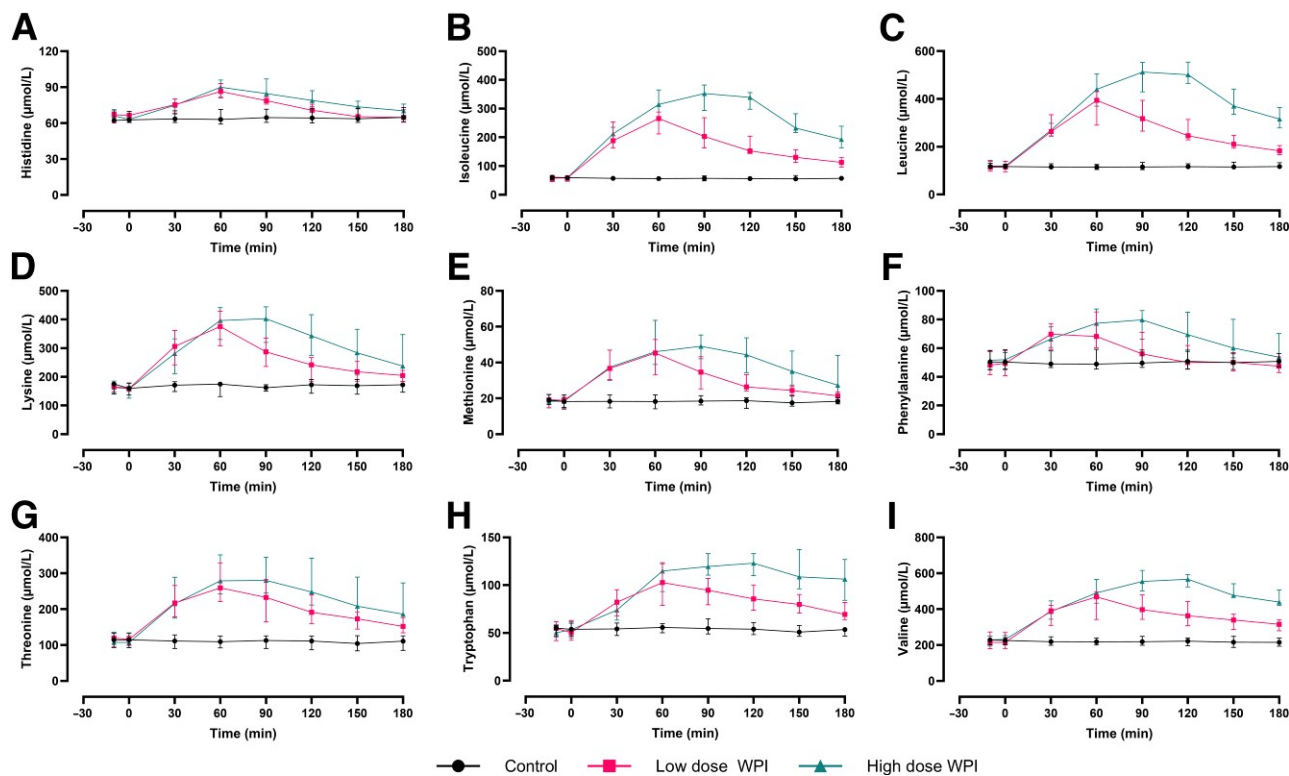
In participants without diabetes, EGP increased above baseline by ~25% in both low- and high-dose WPI trials (Fig. 4H). The stimulation of EGP was matched by an equal increase in R<sub>d</sub>, which was similar (~25% above baseline) for both WPI conditions (Fig. 4J). Accordingly, compared with participants with type 1 diabetes, those without diabetes had proportional stimulation of both EGP and R<sub>d</sub> during both low- and high-dose WPI trials, resulting in stable postprandial glycemia (Fig. 4B, H, and J and Table 3). However, EGP stimulation tended to be greater in those with type 1 diabetes, particularly with high-dose WPI, as evidenced by the higher absolute EGP at 30 ( $P < 0.05$ ) and 60 min ( $P = 0.062$ ) in the low-dose trial and higher bsAUC

( $P < 0.05$ ) and absolute EGP at 30–90 min ( $P < 0.05$ ) in the high-dose trial.

## DISCUSSION

Under carefully controlled conditions, we provide robust evidence that WPI ingestion in adults with type 1 diabetes increases plasma glucagon concentrations, an effect that seems to be dose responsive and comparable to that seen in individuals without diabetes. This robust glucagon response in turn raises EGP and plasma glucose concentrations, an effect that can be sustained for at least 3 h with high-dose WPI. Together, these data highlight the potent glucoregulatory action of WPI ingestion in individuals with type 1 diabetes, which could potentially be explored for preventing hypoglycemia in this population.

To our knowledge, this is the first study to demonstrate a glucagon response to varying doses of ingested WPI in adults with type 1 diabetes, confirming that individuals with



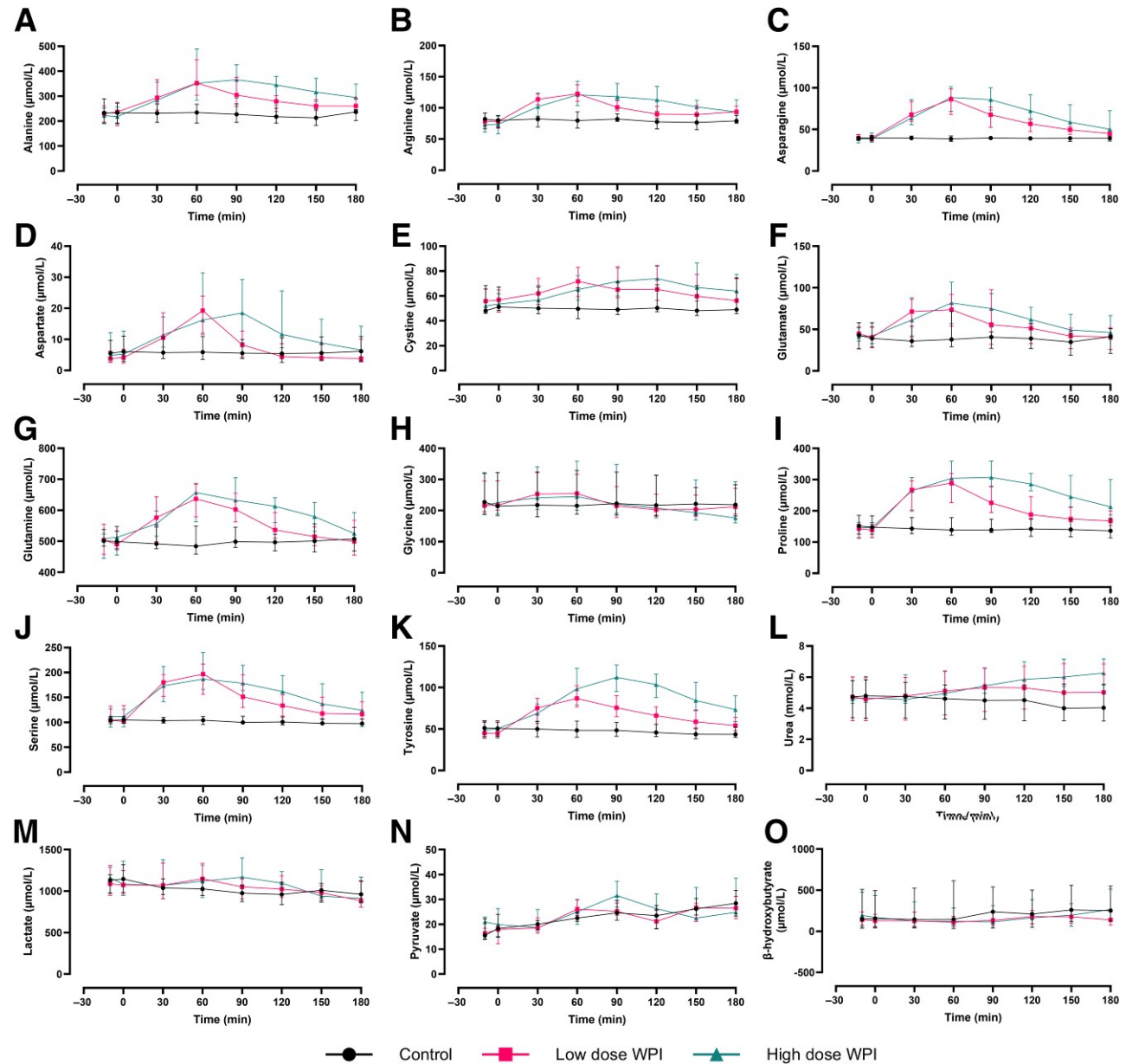
**Figure 2**—Plasma concentrations of essential amino acids histidine (A), isoleucine (B), leucine (C), lysine (D), methionine (E), phenylalanine (F), threonine (G), tryptophan (H), and valine (I) in participants with type 1 diabetes after ingestion of control (water), low-dose WPI, and high-dose WPI. Data are presented as median and interquartile range.

type 1 diabetes have an intact glucagon response to amino acids, despite often having an impaired glucagon response to other stimuli, such as hypoglycemia or exercise (8,10,24). This is consistent with the mechanism by which amino acids stimulate glucagon secretion, which is independent of the upstream insulin signaling (i.e., intraislet communication) that is absent in type 1 diabetes (25). Indeed, amino acids can stimulate glucagon secretion by acting on G-protein-coupled receptors, or they are directly transported into the  $\alpha$ -cell, where they can stimulate glucagon secretion directly by depolarizing the cell or indirectly by fueling the glucagon secretory pathway (26). It is worth noting that the amino acid composition along with the absorption rate determines the extent of the glucagon response (1). Indeed, previous studies using single amino acid ingestion or i.v. infusion have demonstrated that glucagon is most strongly stimulated by amino acids such as glycine, arginine, phenylalanine, and alanine, in which glycine seems to have the strongest effect (27,28). Although the underlying mechanism is unclear, it could be due to the fact that glycine can stimulate glucagon via dedicated glycine receptors on  $\alpha$ -cells and is not dependent on generic amino acid transport-linked depolarization (29,30). In our study, glycine was the only amino acid that did not increase after WPI ingestion, which is consistent with the low glycine content in WPI. To this end, future work comparing WPI and other protein sources with varying amino acid compositions, such as glycine-

rich gelatin or collagen, may be of interest in determining which protein sources produce the greatest magnitude of glucoregulatory effect.

Although we demonstrated an overall comparable magnitude of the WPI-induced glucagon response between those with and without type 1 diabetes, the kinetics of the response did tend to differ slightly. The glucagon response to both low- and high-dose WPI seemed to be slower in those with type 1 diabetes compared with controls without diabetes, reaching its peak at  $\sim 60$  min post-ingestion, compared with  $\sim 30$  min in those without diabetes. Although speculative, this delay could reflect the lack of intraislet communication to stimulate glucagon secretion resulting from absent endogenous insulin (25) or relatively slower gastric emptying, which has previously been reported in individuals with type 1 diabetes (31,32). Additional studies on the underlying mechanisms of these temporal differences may be of interest.

Consistent with findings from others (33), our participants with type 1 diabetes exhibited similar fasting and postprandial levels of GIP and GLP-1 to those without diabetes. Although our study design did not allow us to determine the contribution of the incretin hormones to glycemia post-WPI ingestion, we hypothesize that this may occur via the  $\alpha$ -cell. Indeed, GIP is known to stimulate, whereas GLP-1 tends to suppress, glucagon secretion (34,35). Future work exploring the contribution of the incretins in modulating the glucagon and/or glycemic responses to protein



**Figure 3**—Plasma concentrations of nonessential amino acids and metabolites alanine (A), arginine (B), asparagine (C), aspartate (D), cystine (E), glutamate (F), glutamine (G), glycine (H), proline (I), serine (J), tyrosine (K), urea (L), lactate (M), pyruvate (N), and  $\beta$ -hydroxybutyrate (O) in participants with type 1 diabetes participants after ingestion of water (control), low-dose WPI, and high-dose WPI. Data are presented as median and interquartile range.

ingestion in type 1 diabetes may be of interest, especially given recent heightened interest in incretin-based therapies in diabetes.

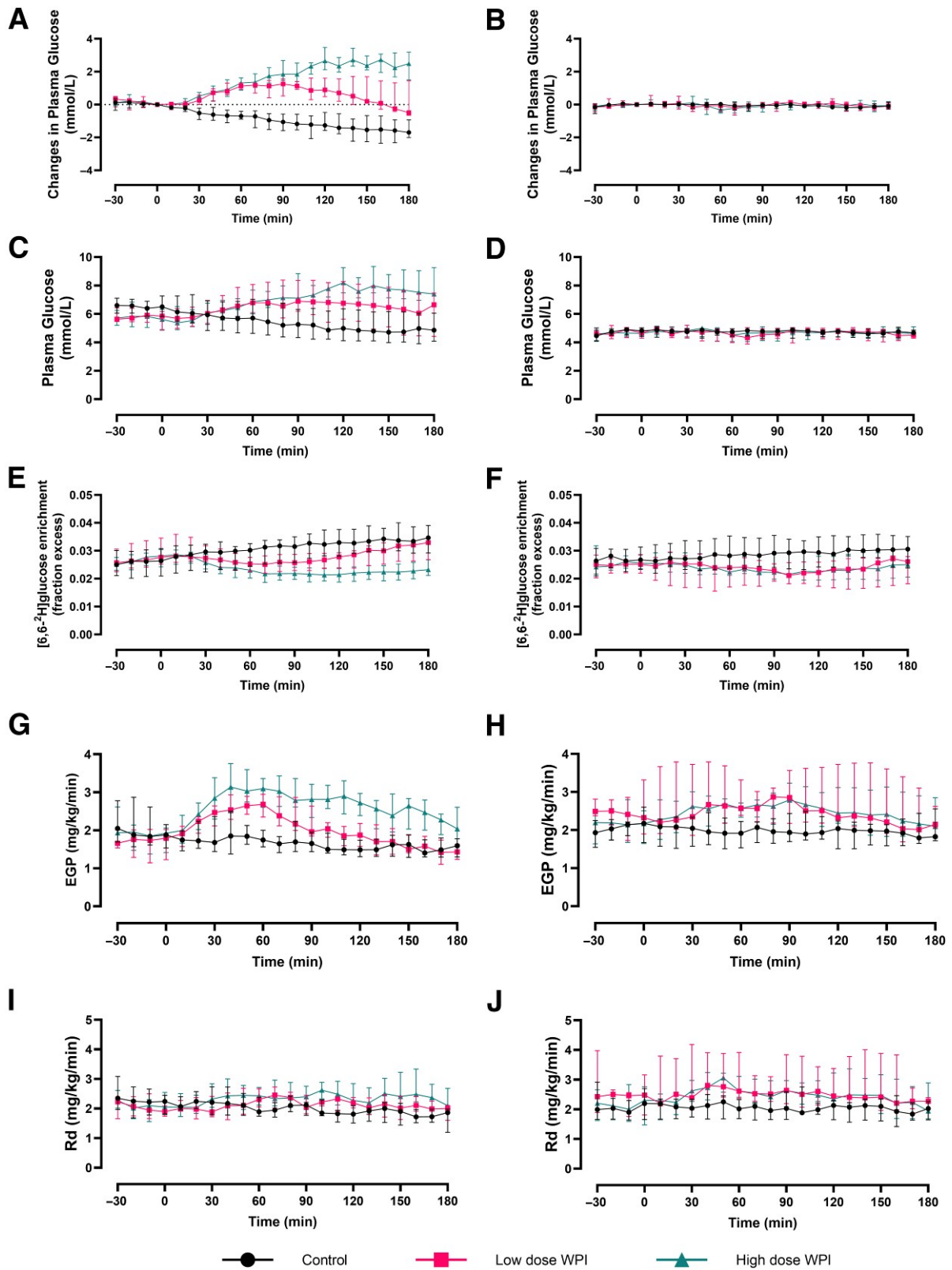
Interestingly, despite the dose effect of the glucagon response, the corresponding increase in plasma glucose did not continue to rise proportionally at the higher WPI dose. Although high-dose WPI prolonged the duration of the glycemic effect, the magnitude of the response seemed to plateau, suggesting that additional glucagon release at high protein amounts does not further amplify the peak plasma glucose response. Given  $R_d$  was similar throughout the postprandial period for all protein ingestion groups,

the glycemic effect of WPI was ultimately determined by the magnitude and temporal kinetics of EGP stimulation. Indeed, during the first 60 min after WPI ingestion, the peak increase in EGP and rate of rise in plasma glucose were similar for both WPI doses tested. The lack of a larger peak in EGP at a higher protein dose, despite greater circulating glucagon, suggests a saturation threshold for stimulating EGP, which seems to occur at or below 0.25 g/kg. However, compared with low-dose WPI, higher-dose WPI extended the duration of EGP elevation, producing a more sustained glycemic effect.

**Table 3—Glycemic, hormonal, and glucose flux outcomes for participants with (*n* = 12) and without (*n* = 6) type 1 diabetes after ingestion of water (control), low-dose WPI (0.25 g/kg), and high-dose WPI (0.5 g/kg)**

	Control		Low-dose WPI		High-dose WPI		<i>P</i>
	With type 1 diabetes	Without type 1 diabetes	With type 1 diabetes	Without type 1 diabetes	With type 1 diabetes	Without type 1 diabetes	
		<i>P</i>		<i>P</i>		<i>P</i>	
Glucose, mmol/L							
bsAUC*	-1.10 (-1.50, -0.66)	-0.10 (-0.12, -0.06)	0.55 (0.21, 1.00)	-0.07 (-0.2, -0.02)	1.60 (1.30, 1.70)	0.03 (-0.12, 0.07)	<b>&lt;0.001</b>
Absolute peak increase	-0.02 (-0.07, 0.07)	0.13 (0.08, 0.33)	1.30 (1.00, 1.70)	0.18 (0.14, 0.30)	3.10 (2.50, 3.30)	0.23 (0.16, 0.55)	<b>&lt;0.001</b>
EGP, mg/kg/min							
bsAUC*	-0.24 (-0.44, -0.10)	-0.20 (-0.21, 0.02)	0.50 (0.20, 0.70)	0.08 (-0.06, 0.20)	0.85 (0.63, 0.98)	0.39 (0.32, 0.52)	<b>0.007</b>
Absolute peak increase	0.21 (0.09, 0.41)	0.23 (0.07, 0.44)	1.30 (0.77, 1.50)	0.52 (0.31, 1.50)	1.40 (1.20, 1.70)	0.84 (0.71, 0.94)	<b>0.049</b>
R <sub>G</sub> , mg/kg/min							
bsAUC*	-0.12 (-0.26, -0.02)	-0.02 (-0.17, 0.09)	0.29 (0.10, 0.40)	0.18 (-0.09, 0.76)	0.32 (0.13, 0.50)	0.42 (0.32, 0.64)	0.510
Absolute peak increase	0.51 (0.18, 0.59)	0.55 (0.16, 0.68)	0.78 (0.60, 1.10)	1.30 (0.43, 1.60)	1 (0.68, 1.30)	1.10 (0.96, 1.40)	0.640
Total Amino Acids, μmol/L							
bsAUC*	-47 (-91, -14)	8.5 (-30, 34)	946 (870, 1,183)	907 (778, 1,263)	1,666 (1,408, 1,899)	1,754 (1,408, 1,925)	1.000
Absolute peak increase	28 (5.6, 66)	51 (36, 63)	1,794 (1,548, 2,507)	1,884 (1,560, 2,196)	2,312 (2,230, 2,946)	2,452 (2,232, 2,846)	0.710
Glucagon, pmol/L							
bsAUC*	0.14 (-0.02, 0.81)	0.39 (0.03, 0.74)	4.10 (2.80, 7.20)	4.90 (3.70, 5.20)	8.10 (5.50, 13.00)	8.50 (7.20, 11.00)	0.930
Absolute peak increase	1.10 (0.45, 1.70)	2.10 (0.96, 3.60)	11.00 (7.90, 19.00)	13.00 (11.00, 17.00)	15.00 (11.00, 22.00)	15.00 (14.00, 18.00)	0.930
Insulin, μU/mL							
bsAUC*	0.45 (-1.10, 2.30)	-0.57 (-1.50, -0.36)	1.80 (-1.00, 3.10)	3.20 (3.00, 3.60)	0.43 (-0.55, 1.80)	6.80 (6.60, 8.50)	<b>0.002</b>
Absolute peak increase	2.00 (0.96, 3.70)	0.83 (0.63, 1.40)	5.30 (2.40, 6.00)	21.00 (18.00, 21.00)	2.90 (1.00, 6.20)	24.00 (19.00, 25.00)	<b>0.002</b>
FFAs, mmol/L							
bsAUC*	-0.00 (-0.06, 0.03)	0.04 (0.00, 0.08)	0.00 (-0.09, 0.03)	-0.05 (-0.07, -0.03)	-0.06 (-0.12, 0.00)	-0.09 (-0.12, -0.08)	0.220
Absolute peak increase	0.07 (0.05, 0.14)	0.13 (0.06, 0.14)	0.10 (0.00, 0.17)	0.07 (0.06, 0.09)	0.05 (0.01, 0.10)	0.02 (-0.02, 0.07)	0.260
GLP-1, pmol/L							
bsAUC*	-0.08 (-0.25, -0.01)	-0.35 (-0.63, -0.16)	0.99 (0.62, 1.40)	1.60 (1.40, 2.50)	2.10 (1.60, 3.20)	2.50 (2.10, 3.30)	0.310
Absolute peak increase	0.14 (0.03, 0.22)	0.17 (-0.08, 0.45)	1.70 (1.20, 2.70)	4.40 (2.80, 5.10)	4.10 (2.40, 5.20)	4.40 (3.40, 5.00)	0.420
GIP, pmol/L							
bsAUC*	0.06 (-0.36, 0.14)	-0.02 (-0.58, 0.16)	3.80 (2.20, 6.50)	2.70 (1.30, 3.50)	7.40 (3.90, 13.00)	5.20 (3.70, 6.60)	0.400
Absolute peak increase	0.40 (0.08, 0.75)	0.36 (0.04, 1.10)	8.10 (7.10, 18.00)	7.60 (4.30, 11.00)	12.00 (6.50, 26.00)	11.00 (8.70, 14.00)	0.850

Values are median (interquartile range). Bold font indicates significance. \*Units for bsAUC: (unit of the outcome) × min/min.



**Figure 4**—Glycemic outcome, glucose flux, and plasma glucose tracer enrichment. Changes in plasma glucose ( $\Delta$ ) from baseline ( $t = 0$  min) (A and B), plasma glucose concentration (C and D), plasma [6,6- $^2$ H]glucose enrichment (E and F), rate of EGP (G and H), and  $R_d$  (I and J) in participants with ( $n = 12$ ) (A, C, E, G, and I) and without ( $n = 6$ ) (B, D, F, H, and J) type 1 diabetes after ingestion of water (control), low-dose WPI, and high-dose WPI. Data are presented as median and interquartile range.

The WPI-induced glycemic response observed here was robust under laboratory-controlled conditions. This is clearly demonstrated by the fact that in light of the  $\sim 1.5$  mmol/L decline in glucose seen in the control condition, WPI not only prevented this decrease but actively increased glycemia. Previous studies using 50 g WPI have demonstrated increases in plasma glucose levels of 2–3 mmol/L (16,36), indicating that the magnitude and kinetics of the glycemic response observed here are broadly consistent with previous work. Nonetheless, our data contradict those of Paterson et al. (17), who reported no significant glycemic effect with 12.5, 25, or 50 g WPI. However, participants in this study were not using a fixed insulin infusion, and a significant glycemic rise in the control (water ingestion) group and no glycemic changes after ingestion of 10 g carbohydrate were reported, indicating high data variability (37). Notably, higher doses of WPI (75 and 100 g) produced significant increases in blood glucose with kinetics similar to those observed here, suggesting that the effects of lower doses may have been masked. This variability likely reflects the fluctuations in glucose commonly seen in individuals with type 1 diabetes under free-living conditions and underscores the importance of controlled experimental conditions for accurately detecting dose-dependent glycemic effects of protein.

Although our study design allows us to accurately capture EGP stimulation, the contribution of glycogenolysis and gluconeogenesis to EGP remains unclear. Speculatively, given the high gluconeogenic substrate availability (e.g., alanine and arginine) and relatively low liver glycogen from the 14- to 16-h fast, it is likely that gluconeogenesis was a major contributor to EGP (38). This is important because the stimulating effect of glucagon on gluconeogenesis is significantly more delayed compared with glycogenolysis, which occurs within minutes (38). As such, the WPI-induced EGP and glycemic responses observed here may vary depending on the existing hepatic glycogen content and likely differ significantly from those induced by pure glucagon injection, given the injection does not simultaneously increase gluconeogenic substrate availability (unlike WPI ingestion).

Collectively, our findings may have valuable clinical implications for glycemic management in individuals with type 1 diabetes, particularly in the context of hypoglycemia prevention. Hypoglycemia is a significant issue for those living with type 1 diabetes, especially in situations where insulin requirements change rapidly (e.g., during or after exercise) or during sleep (39). Additionally, the counterregulatory glucagon response to hypoglycemia is often impaired in those with type 1 diabetes, likely because of the diminishing upstream paracrine signals from  $\beta$ -cells (25). In contrast, because the glucagon response to amino acids is intact, WPI can create a buffer to protect against hypoglycemia through its potent glucagon- and EGP-stimulating properties. Moreover, the resultant gradual yet sustained glycemic effect is in contrast to currently recommended strategies (carbohydrate feeding or reducing meal-time insulin bolus),

which induce rapid and robust glycemic rises and can result in hyperglycemia and increased glycemic variability (39). It is worth noting that although WPI may be useful as a proactive strategy for hypoglycemia prevention, it is likely less suitable for hypoglycemia rescue because of its moderate and relatively delayed glycemic effect, compared with fast-acting carbohydrate, which can increase plasma glucose by up to 2–3 mmol/L within 15 min, although with a much shorter duration of effect (40). Given glucose levels only started to rise  $\sim 30$  min post-WPI ingestion in the current study, we speculate that WPI could be most useful as a standalone supplement at  $\sim 30$  min before exercise, or immediately at bedtime, to help mitigate hypoglycemia risk. Nonetheless, further research into the use of WPI for hypoglycemia management in exercise or sleep contexts is warranted.

A key strength of the study is that we demonstrated the glucoregulatory effect of WPI in adults with type 1 diabetes in a laboratory-controlled setting with constant i.v. insulin infusion. Nonetheless, there are limitations. Firstly, given the glycemic effect of WPI can last up to 6–12 h (16,36,37), our relatively short (3 h) experimental period was likely not sufficient to demonstrate the full duration of the glycemic outcomes from WPI ingestion. Secondly, the gradual decline in glucose levels by  $\sim 1.5$  mmol/L over 3 h in the control condition indicates that a metabolic steady state was not maintained, despite a fixed i.v. basal insulin infusion rate. Because participants had stable baseline glucose levels  $\sim 1$  h before the intervention, this decline may be related to variations in insulin requirements across the day and over continued fasting. Indeed, on average, insulin requirements in those with type 1 diabetes tend to be highest in the morning and decrease gradually by 25–30% from 11 A.M. onward (41). Therefore, results regarding the magnitude of glucose rise in the WPI conditions should be interpreted accordingly. Thirdly, antecedent hypoglycemia was also not controlled for, which is known to effect subsequent counterregulatory glucagon responses, although given the mechanism of protein-induced glucagon secretion seems distinct from normal glucose counterregulation (29), we do not believe this would have meaningfully affected the results. Fourthly, although the fixed basal insulin infusion rate was largely consistent between visits within participants, there were still some instances of day-to-day variability. Although modest, these small differences in basal insulin could influence the glucagon and glycemic response. Finally, it is noteworthy that WPI does not represent all dietary proteins, and the kinetics and magnitude of the glycemic response can differ significantly between protein sources, depending on the composition and rate of digestion (1).

In conclusion, in adults with type 1 diabetes, WPI ingestion produced a robust and sustained increase in glucagon secretion that seemed to be dose responsive and comparable to that in those without type 1 diabetes, ultimately leading to increased EGP and plasma glucose concentrations. The glycemic impact of WPI ingestion is clearly illustrated

by its ability to not only counteract the steady decline in glucose in the control condition but also actively raise glucose levels. Compared with carbohydrate, the temporal profile of the WPI-induced glycemic response may confer a physiological advantage: WPI produces a moderate yet prolonged increase in plasma glucose, providing a more controlled, sustained, and physiologically favorable response. These findings highlight the potential of whey protein as a tool to support glycemic management and mitigate hypoglycemia in type 1 diabetes.

**Acknowledgments.** The authors thank all participants for their time and commitment to this study and True Protein for supplying the WPI for this study.

**Funding.** G.M.D. was supported by an Australian Government Research Training Program Scholarship. This investigator-initiated study was supported by the Leona M. and Harry B. Helmsley Charitable Trust (grant 2311-06395) and by the Australian Diabetes Society. True Protein supplied the WPI used in the study. D.P.Z. and D.J.M. have received research support from the Leona M. and Harry B. Helmsley Charitable Trust.

The study funders were not involved in the design of the study; the collection, analysis, or interpretation of data; or writing the report and did not impose any restrictions regarding the publication of the report.

**Duality of Interest.** D.N.O. has received honoraria from Medtronic, Insulet, Abbott, Novo Nordisk, and Sanofi and research support from Medtronic, Insulet, Dexcom, Roche, GlySense, BioCapillary, and Endogenex and serves on advisory boards for Medtronic, Insulet, Abbott, Ypsomed, Novo Nordisk, and Sanofi. C.E.S. has received speaker honoraria from Medtronic, Sanofi, and Eli Lilly and served on advisory boards for Abbott and Medtronic. D.P.Z. has received honoraria for speaking engagements from Ascensia Diabetes, Insulet, Medtronic, and Dexcom and serves on an advisory board for Dexcom. D.J.M. has received honoraria from Medtronic. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** G.M.D., S.Z., C.S., D.T.H., C.R.B., G.M.K., and D.J.M. contributed to implementation of the study and data generation. G.M.D., S.V., C.E.S., D.P.Z., D.N.O., C.R.B., G.M.K., and D.J.M. contributed to conceptualization and study design. G.M.D., S.V., and D.J.M. contributed to data analysis. G.M.D. and D.J.M. wrote the initial manuscript draft. All authors critically reviewed the manuscript and approved the final version. D.J.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** Data from this article were presented at the 25th Australasian Diabetes Congress, Broadbeach, Queensland, Australia, 20 August 2025; 85th American Diabetes Association Scientific Sessions, Chicago, IL, 20 June 2025; 1st Asian Conference on Innovative Therapies for Diabetes Management of Advanced Technologies & Treatments for Diabetes Asia, Singapore, 19 November 2024; 60th Annual Meeting of the European Association for the Study of Diabetes, Madrid, Spain, 9 September 2024; and 24th Australasian Diabetes Congress, Perth, Western Australia, 21 August 2024.

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