Very-low dose pre-meal whey protein microgels reduce postprandial glucose in type 2 diabetes: a randomized, placebo-controlled crossover study

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Disclosures, Author Information, and Acknowledgement

Author	Institution	Conflicts of interest
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Roberto Zagury, MD	Human Performance Lab, Rio de Janeiro, Brazil	Received speakers fee from NHSc
Bo Ahrén, MD	Lund University, Sweden	None
Joel Neutel, MD	Orange County Research Center, USA	Received investigator fee from NHSc
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Emilie Perrin, MSc	SOCAR Research SA, Switzerland	Employment SOCAR, who has done analytical work paid by NHSc
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Luiz Henrique de Gregório, MD	IBPClin, Rio de Janeiro, Brazil	None

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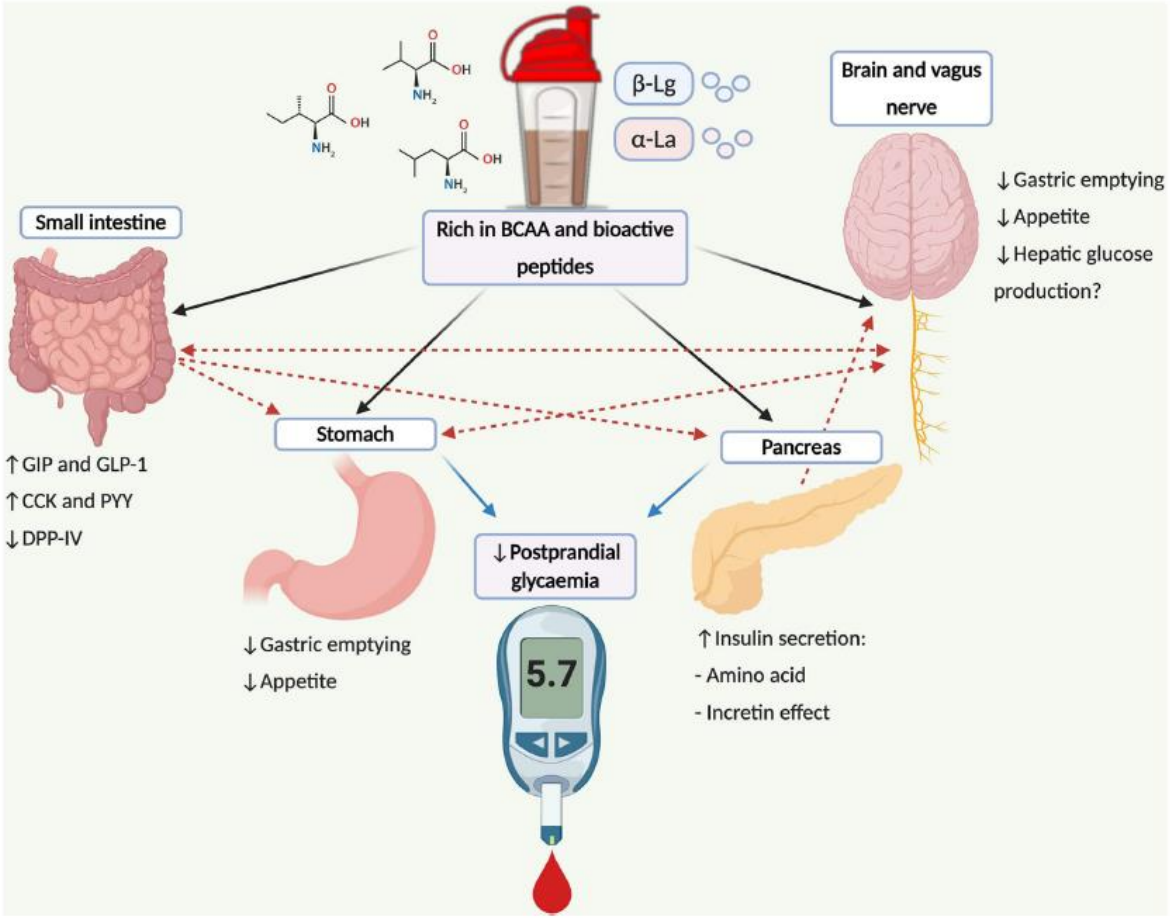
Background: Metabolic effects of Whey Proteins (WP) in Type 2 Diabetes (T2D)

WP augment several interconnected mechanisms for postprandial glucose (PPG) regulation



Smith K, Bowden Davies KA, Stevenson EJ and West DJ . The Clinical Application of Mealtime Whey Protein for the Treatment of Postprandial Hyperglycaemia for People With Type 2 Diabetes: A Long Whey to Go. Front. Nutr. 2020; 7:587843.

Role of WP in glucose management for T2D

- WPs are rich in
  - branched chain amino acids (BCAA)
    - leucine, isoleucine, and valine
  - bioactive peptides
    - e.g., α –La (lactalbumin) and β –Lg (lactoglobulin)
- that can stimulate secretion of incretin peptides and insulin
  - bioactive peptides may also inhibit DPP-IV activity

- Incretin peptides (e.g., GLP-1) stimulate β -cell activity, augmenting the release of insulin, and can contribute to delay gastric emptying and regulate the transit of food via central-related mechanisms

Background: Whey Proteins in T2D – Current Limitations

Limitations with traditional WP formulas to regulate PPG

- 1) Pre-meal timing of WP
  - Most studies have presented WP 30 min before the nutrient challenge, which is unlikely to replicate free-living behaviors (compliance, forgetfulness and the burden of having to plan ahead)
- 2) Dosing of WP
  - Evidence to date has primarily presented large WP doses (20–50 g), entailing a significant caloric load

Select WP studies in T2D

WP dose	Time ahead of meal	Effect on glucose	Effect on GLP-1
50 g[1] (220 Cal)	30 min	↓	↑
25 g[2] (89 Cal)	30 min	↓ (peak) ↔ (AUC)	↑
20 g[3] (74 Cal)	15 min	↔	↔ (GIP ↑)
15 g[4] (68 Cal)	With meal	↓ (CGM)	↔

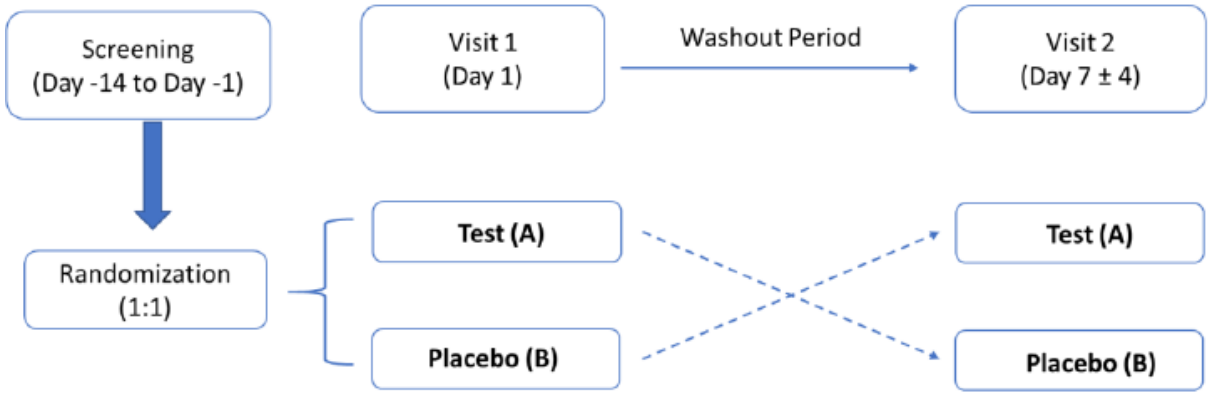
1: Diabetologia 2014;57:1807-1811
2: Diabetes Care 2016;39:511-517
3: Nutrients 2018;10:122
4: Am J Clin Nutr 2018;107:550–557

Objective

- **To assess if a novel WP formulation can allow for**
  - A smaller time-window between WP intake and subsequent meal
    - *Study question: Can a WP formulation taken closer to the meal maintain its efficacy?*
  - Using a lower protein dose
    - *Study question: Can a WP protein formulation with less proteins, that do not contribute significantly to the daily caloric intake, maintain its efficacy?*
- **Novel WP formulation**
  - The novel WP formulation was prepared with a proprietary technology (micelle-technology) that generated a WP microgel (WPM) intended to make the WP more readily available
  - The technology allowed for:
    - A high WP concentration
    - Presenting the WP in a liquid matrix that does not gel

Methods

- NCT04639726
- Mechanistic, exploratory, randomized, investigator-blinded, placebo-controlled, single-center, crossover study
- Intervention:
  - WPM (10 g, 40 kcal)
  - placebo (0 kcal)



- The WPM was provided as a 125 mL shot to be taken 15 min ahead of a 250 g pizza lunch meal
  - 622 kcal (29.0 g protein, 22.6 g fat, 72.6 g carbohydrates)

- Postprandial (PP) glucose and insulin response over 4 hours, and incretin response (intact glucagon-like peptide [GLP]-1, peptide-YY [PYY], glucose-dependent insulinotropic polypeptide [GIP]) over 2 hours were assessed in blood, and the difference between WPM and placebo were assessed by comparing incremental areas under the curve (iAUC) between the two interventions

Inclusion/exclusion criterion and timelines

Inclusion criteria

A. Willing and able to sign written informed consent prior to study entry.

B. Male or female, >18 years of age.

C. T2D with HbA1c 6.5 – 10.0%

D. Treatment naïve or on active therapy with metformin at a daily dose of 1000-3000mg at screening.

E. Hematocrit ≥ 34/40% for females/males

F. Hemoglobin ≥ 11.0/13.5 g/dL for females/males.

Timelines

First participant entered: Sept 29 2020

Last participant completed: Oct 26 2020

Exclusion criteria

A. Fasting plasma glucose > 220mg/dl at screening.

B. eGFR of < 60mL/min/1.73m^2

C. BMI > 40 kg/m^2

D. Elevated liver transaminase > 3 ULN at screening.

E. Ongoing or recent (i.e. < 3 month) treatment with any oral or injectable glucose-lowering drug other than metformin.

F. Ongoing or recent (i.e. < 3 month) weight loss interventions (e.g. dietary weight loss programs) or any history of bariatric surgery or any documented weight loss > 5% within previous 6 months.

G. Ongoing or recent (i.e. < 3 month) treatment with anorectic drugs, systemic steroids, medications known to affect gastric motility, or any condition known to affect gastro-intestinal integrity and food absorption.

H. Major medical/surgical event requiring hospitalization in the last 3 months.

I. Donation of blood or significant amount of blood loss within 8 weeks prior to screening. Patients must also agree to not donate blood within 8 weeks after their last visit.

Baseline characteristics of the 26 participants

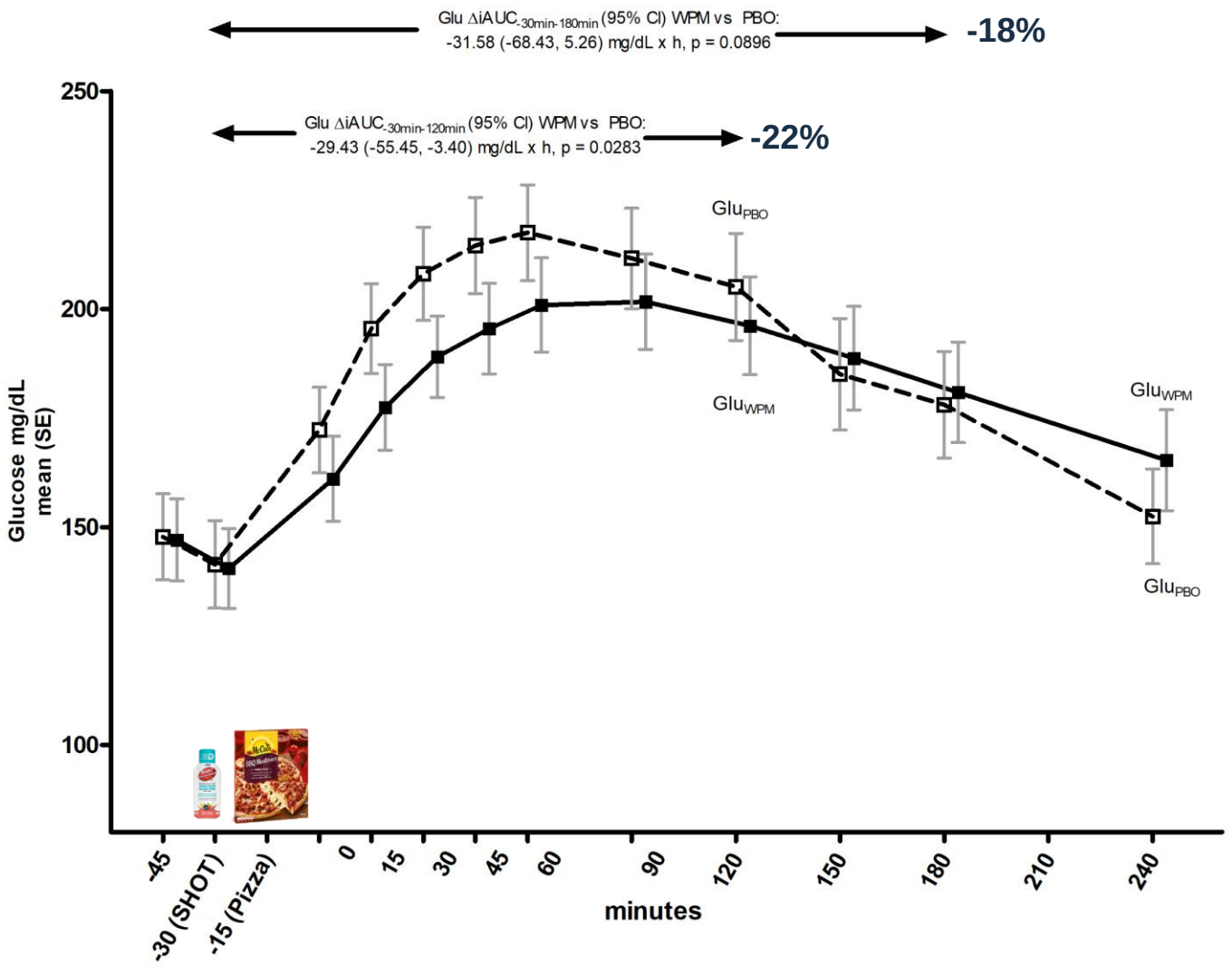
	n (%)
Sex	
Female	14 (54%)
Male	12 (46%)
Ethnicity	
Hispanic or Latino	9 (34.6%)
Not hispanic or Latino	17 (65.4%)
Race	
Asian	3 (11.5%)
Black or African American	4 (15.4%)
White	19 (73.1%)

	Mean (SD), or n (%)
Age, years	62.0 (8.3)
Weight, kg	82.9 (15.0)
Body Mass Index, kg/m^2	29.2 (4.8)
Waist circumference, cm	101.3 (12.7)
HbA1c, %	7.5* (1.1)
Fasting plasma glucose, mg/dL	139.9** (42.9)
Total cholesterol, mg/dL	180.4*** (50.0)
Triglycerides, mg/dL	159**** (62)
Systolic/diastolic blood pressure, mmHg	129 (12)/77 (9)
eGFR (MDRD-formula), mL/min/1.73m^2	99.1 (24.7)
Medications	
Metformin	19 (73%)
Glimepiride	1 (4%)
Statins	8 (31%)

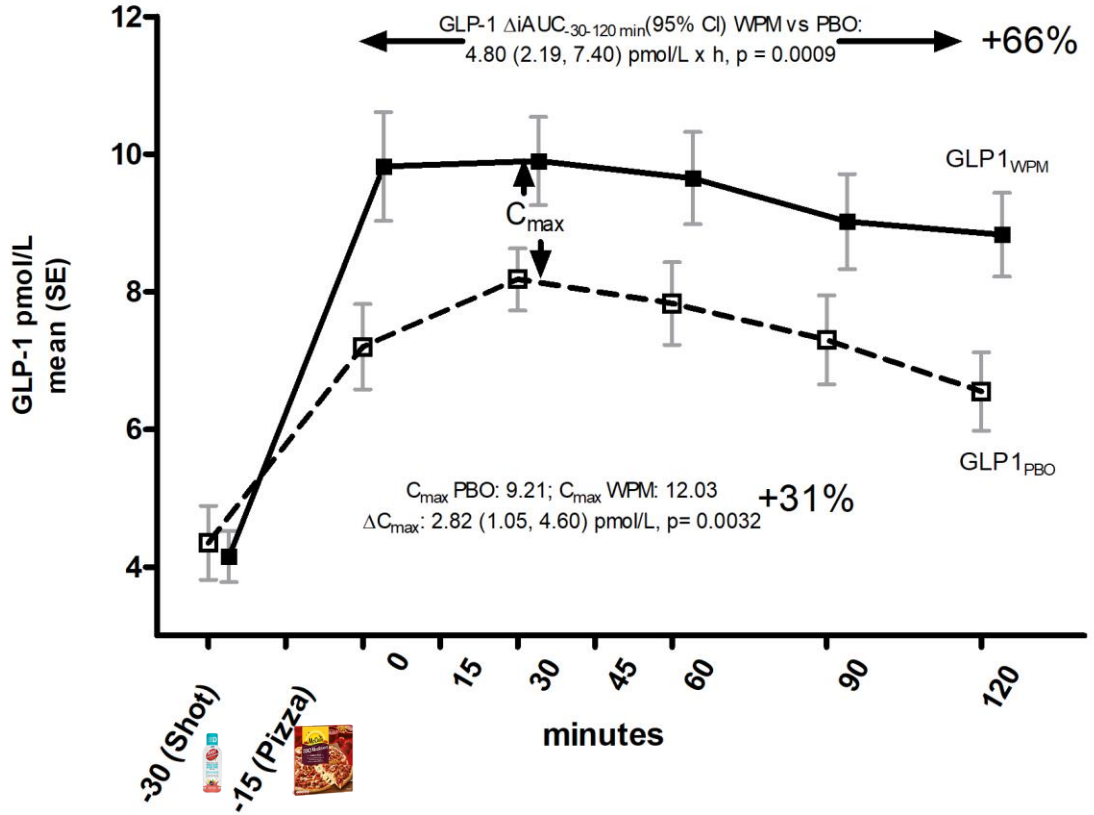
*58 mmol/mol; Old HbA1c = 0,0915 New + 2,15%
**7.8 mmol/L; mg/dL to mmol/L glucose: multiply with 0.0555
***4.7 mmol/L; multiply by 0.02586
*****1.8 mmol/L; multiply by 0.01129

Results: effects on glucose and incretin response

Glucose



Total GLP-1

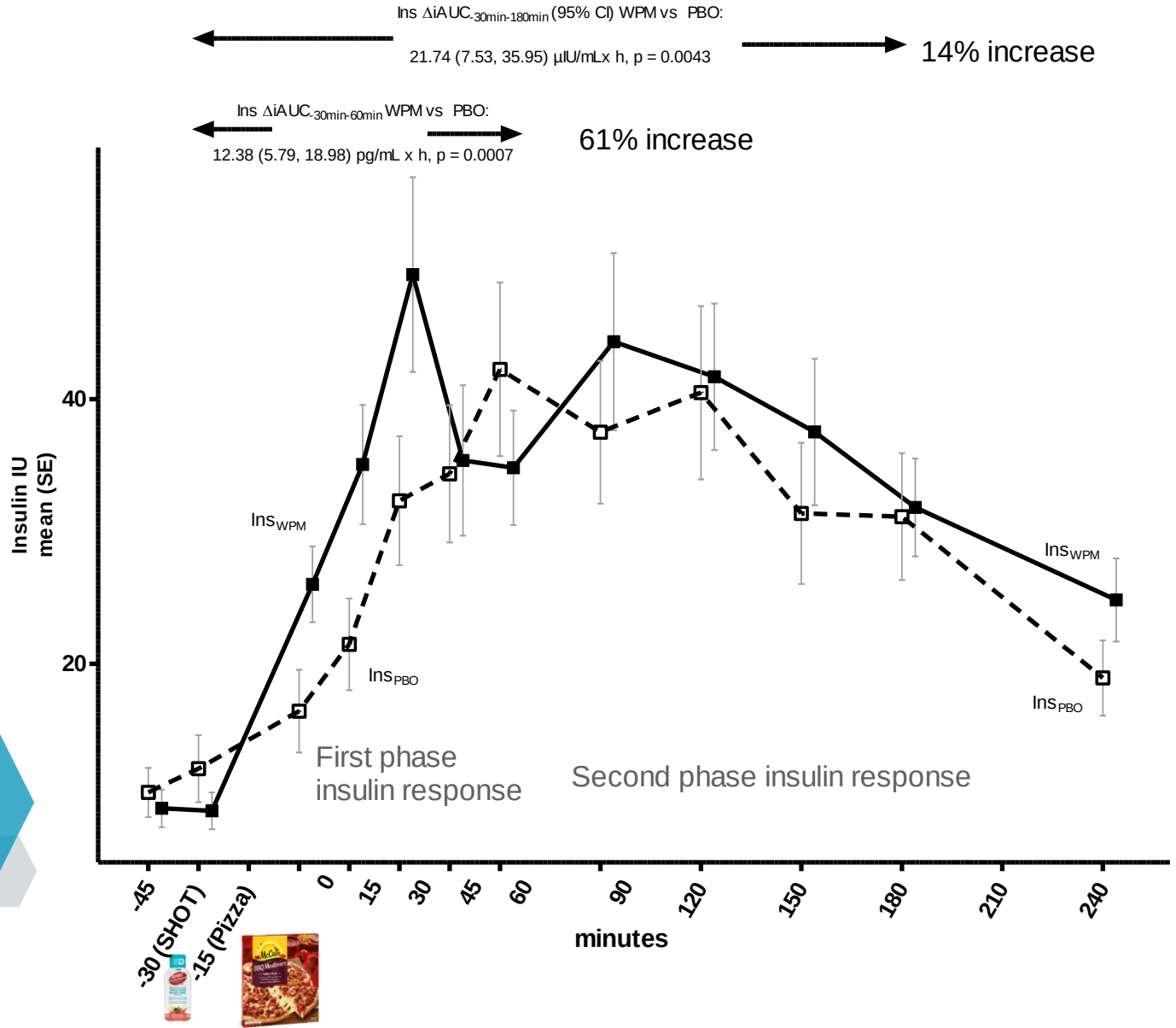


PYY and GIP

No differential effect on PYY and GIP, ΔiAUC $_{\text{-30-120 min}}$

- PYY: 5.21 [-1.14, 11.56] pmol/Lxh, p=0.1035
- GIP: 8.52 [-15.27, 32.31] pmol/Lxh, p=0.4668

Results: effects on insulin response



Interpretation:

10 g WPM provided 15 min ahead of a meal increased insulin response in people with type 2 diabetes

- iAUC 0-1h: +61% (p=0.0007)
- iAUC 0-3h: +14% (p=0.0043)

Conclusion

- Compared to placebo, 125 mL of 10 g WPM taken 15 minutes ahead of a meal significantly increased early insulin secretion by 61% at 1h and 30% at 3h, while altering the early postprandial glucose trajectory and reduced the 2h incremental area under the curve by 22%, while significantly increasing maximum GLP-1 level by 31% and 2h overall GLP-1 exposure by 66%

- The reduction observed in early glycemic burden and augmented early insulin and sustained GLP-1 response, supports its use as a convenient pre-meal shot to improve postprandial metabolic profile in type 2 diabetes

- Longer term studies are needed to understand the full translational metabolic impact of this novel WPM formulation