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The prevalence and impact of low faecal elastase-1 in community-based patients with type 2 diabetes

Michael D. Riceman [a], Michelle Bound [a], Jacqueline Grivell [a], Seva Hatzinikolas [a], Samuel Piotto [a], Nam Q. Nguyen [b,d], Karen L. Jones [a,b,c], Michael Horowitz [a,b,c], Christopher K. Rayner [a,b,d], Liza K. Phillips [a,b,c,*]

[a] Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia
[b] National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Translating Nutritional Science to Good Health, The University of Adelaide, Adelaide, Australia
[c] Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia
[d] Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, Australia

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ABSTRACT

Aims: To determine the prevalence of low faecal elastase-1 (FE-1) (≤200 μg/g) in type 2 diabetes (T2DM), and to test the hypothesis that pancreatic enzyme replacement therapy (PERT) would reduce postprandial glycaemia after a high-fat, high-carbohydrate meal in T2DM subjects with low FE-1.

Methods: Of 109 community-based patients who submitted stool samples, 10 had low FE-1 and 8 were recruited (6 male, 2 female, 67.8 ± 3.0 years). Participants were given a high-fat, high-carbohydrate meal (718 kcal) with either pancrelipase (50,000 units) or placebo in a randomised, double-blind, crossover fashion. The primary outcome was the difference in postprandial glycaemia following PERT vs placebo, as evaluated by the incremental area under the postprandial plasma glucose curve (iAUC). Secondary outcomes included differences in gastric half-emptying time (T50) measured using scintigraphy, and C-peptide iAUC.

Results: The prevalence of low FE-1 in T2DM was 9.2% (95% CI 3.8–14.6%). There was no difference in postprandial glycaemia iAUC (P = 0.38), gastric emptying T50 (P = 0.69) or C-peptide iAUC (P = 0.25) after PERT compared to placebo.

Conclusions: Decreased FE-1 has a relatively low prevalence in community-based patients with T2DM, and PERT does not reduce postprandial glycaemia in these patients.

Clinical Trial Registration Number: ACTRN12617000349347.

1. Introduction

Postprandial glycaemia is increasingly recognised as an important treatment target in the management of type 2 diabetes (T2DM) [1–3]. Although postprandial glycaemic excursions are determined by a number of factors, the 'incretin' hormones and the rate of gastric emptying are of particular relevance. The incretins, glucagon-like peptide-1 (GLP-1) and

* Corresponding author at: Level 5 AHMS Building, Corner North Tce & George St, University of Adelaide, Adelaide, SA 5005, Australia.
E-mail address: liza.phillips@adelaide.edu.au (L.K. Phillips).

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glucose-dependent insulinotropic polypeptide (GIP), are released from the gut after nutrient stimulation and augment postprandial insulin secretion in a glucose dependent fashion [4]. GLP-1 also slows gastric emptying [5], with previous studies identifying that the rate of gastric emptying accounts for 30–40% of the variance of peak postprandial glycaemia following oral glucose in health and T2DM [6].

Secretion of the incretins and slowing of gastric emptying after a high-fat meal are dependent on the exposure of intestinal enteroendocrine cells to fatty acids, produced upon digestion of fat by pancreatic lipase [7]. Accordingly, GIP and GLP-1 responses to fatty meals are markedly attenuated [8] and gastric emptying accelerated [9] by lipase inhibition. Normal pancreatic exocrine function is, therefore, essential to stimulate incretin hormone release and generate feedback that slows gastric emptying and limits postprandial glycaemia.

There is recent evidence to suggest that there may be a high prevalence of pancreatic exocrine insufficiency (PEI) in T2DM [10]. The majority of reports have centred on PEI diagnosed by indirect tests of pancreatic function, particularly faecal elastase-1 (FE-1) [10], rather than direct exocrine function tests [11,12]. It is unclear whether this high prevalence reflects under-recognition of chronic pancreatic disease causing diabetes of the exocrine pancreas (type 3c diabetes) [13–15], or is secondary to diabetes itself and represents a novel pathological entity, 'diabetic exocrine pancreatopathy' [10], or both.

FE-1 is a proteolytic enzyme that binds to bile salts during its passage through the gut, is pancreas-specific, and is not degraded within the lumen [16]. FE-1 levels correlate well with pancreatic output of elastase-1, as well as that of other enzymes including lipase and amylase [17]. Measurement of FE-1 has, therefore, been proposed as a screening investigation for PEI. A recent meta-analysis reported that 28% of subjects with T2DM had FE-1 < 200 μg/g compared with 13% of non-diabetic controls. Furthermore, the more stringent cut-off of FE-1 < 100 μg/g, suggesting severe PEI, was met by 14% of subjects with T2DM vs 3% of controls [10]. However, the reported prevalence of PEI using FE-1 in T2DM has been derived largely from the hospital setting and has varied widely [10,18–23].

In patients with T2DM and low FE-1, pancreatic enzyme replacement therapy (PERT) would potentially represent a novel therapeutic approach to reduce postprandial glycaemia through the enhanced secretion of incretin hormones and slowing of gastric emptying. Several studies have evaluated the effect of PERT on postprandial glycaemia in groups with PEI in conditions other than T2DM. For example, acute treatment with PERT in subjects with cystic fibrosis and known PEI increased plasma incretin concentrations, slowed gastric emptying, and reduced the postprandial glycaemic excursion substantially without change in insulin secretion [24,25]. In subjects with known chronic pancreatitis, steatorrhoea and impaired glucose tolerance, acute administration of PERT stimulated GIP and insulin secretion and also reduced postprandial glycaemia [26]. However, there was no change in postprandial glycaemia in another study of patients with chronic pancreatitis given PERT despite a rise in postprandial GLP-1 [27]. In a 16-week randomised placebo-controlled trial of PERT in people with T1DM and FE-1 <100 μg/g there was also no difference in postprandial glycaemia or HbA1c [28]. Importantly, no studies have investigated the impact of PERT on postprandial glycaemia in people with T2DM and low FE-1.

The aims of this study were to determine (i) the prevalence of low FE-1 (≤200 μg/g) in community-based patients with T2DM and (ii) the effects of PERT on postprandial glycaemia, C-peptide and gastric emptying in patients with T2DM and low FE-1 concentrations.

2. Subjects, materials and methods

2.1. Screening

Volunteers aged 40–80 years with a history of T2DM were recruited through flyers in general practice clinics, hospitals, and our university, and through community diabetes seminars and outpatient diabetes clinics. Exclusion criteria included a history of pancreatic disease, previous gastric or pancreatic surgery, use of a GLP-1 receptor agonist or any other medication known to affect gastrointestinal motility, current daily intake of >20 g of alcohol, cigarette smoking, pregnancy or iron deficiency.

Eligible participants were sent an information package and a stool sample kit for FE-1 measurement. Those found to have FE-1 ≤200 μg/g were screened to exclude renal or hepatic disease, and iron-deficiency anaemia. HbA1c was also measured.

2.2. Participant assessment

Eligible participants visited our clinical research facility for a screening visit, where microvascular complications of neuropathy and retinopathy, height, weight, waist circumference and autonomic nerve function were assessed. A modified gastrointestinal symptom questionnaire was completed [29], fasting fat-soluble vitamins measured, and magnetic resonance cholangiopancreatography (MRCP) performed. Participants with normal FE-1 were also invited to complete the gastrointestinal symptom questionnaire.

2.3. Study protocol

The study design was a 2-day, randomised, double-blind, crossover trial of PERT vs placebo. The participants' regular medication was managed by an endocrinologist and kept consistent over the two study days. Informed consent was obtained initially by telephone and subsequently in writing at the time of stool sample submission. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and all studies were performed in accordance with the Declaration of Helsinki. The study was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12617000349347).

Participants ate a standardised beef lasagna meal the evening prior to each study day (590 kcal; McCain Foods Pty Ltd, Victoria, Australia), then consumed only water until midnight, before fasting until they attended our facility the following morning (12 h fast for solids, 8 h for liquids). On the morning of the study, participants consumed a high fat/high

carbohydrate mashed potato meal (718 kcal; 29.5 g carbohydrate, 65.5 g fat, 3.9 g protein) within 10 min. The meal comprised 65 g powdered potato (Deb Instant Mashed Potato, Continental, Australia), 1 egg yolk containing 100 μL ^{13}C-octanoate, 20 g glucose and 60 g olive oil, reconstituted with 250 mL water, and was labelled with 20 MBq ^{99m}Tc-calcium phytate. Immediately afterwards (t = 0 min), they drank 50–100 mL water with two capsules, either PERT (Creon® 25,000 [Mylan Health, Germany] containing lipase 25,000U, protease 1000U, amylase 18,000U) or matching placebo (microcrystalline cellulose). Over the following 6 h, plasma was sampled frequently for glucose and C-peptide measurements and appetite scores were collected. After a 'washout' period of 7–17 days, they returned for the second study day.

2.4. Study measurements

2.4.1. Faecal elastase-1

FE-1 was measured using an enzyme-linked immunosorbent assay (ELISA) (Pancreatic Elastase 1, ScheBo Biotech, Giessen, Germany), with an upper limit of detection of 500 μg/g. FE-1 concentrations were not adjusted for stool water content.

2.4.2. Autonomic nerve function

Autonomic nerve function was assessed using standardised cardiovascular reflex tests (variation in heart rate during deep breathing, heart rate response to standing, and fall in systolic blood pressure in response to standing). Each test result was graded as 0 = normal, 1 = borderline, or 2 = abnormal. A score of ≥3 was considered to indicate autonomic dysfunction [30].

2.4.3. Questionnaires

The gastrointestinal symptom questionnaire was adapted from a standard questionnaire [29]. Symptoms (anorexia, nausea, early satiation, upper abdominal discomfort/distension, vomiting, abdominal pain, dysphagia, heartburn and acid regurgitation) were graded as 0 (none), 1 (mild; the symptom could be ignored), 2 (moderate; the symptom could not be ignored, but did not influence daily activities), or 3 (severe; the symptom influenced daily activities). A total symptom score was calculated, with a potential maximum score of 27. The frequency of bowel motions (number per week) was recorded, and their consistency graded using the Bristol Stool Chart [31]. The frequency of greasy stools and/or stools that are difficult to flush was reported as occurring 'never', 'occasionally' or 'frequently' as a marker of steatorrhoea.

When comparing results between participants with low and normal FE-1, all gastrointestinal symptoms were dichotomised i.e. either 'present' (more than 0) or 'absent'.

Diabetic neuropathy was assessed using the Michigan Neuropathy Screening Instrument, with a score of >2/15 suggestive of neuropathy [32]. Retinopathy was assessed as present or absent by patient recall.

During the two study days, feelings of hunger, fullness, desire to eat, projected consumption ('how much food do you think you could eat?') and nausea ('I feel sick') were measured using validated 100 mm visual analogue scales (VAS) [33] at 15-minute intervals for 2 h then every 30 min for the remainder of the study.

2.4.4. Fat-soluble vitamins, plasma glucose and C-peptide concentrations

Fasting blood was taken on the morning of the first study day for measurement of fat-soluble vitamins. During the crossover study, unless otherwise stated, blood was sampled at t = −15, 0, 15, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min for measurement of plasma glucose and C-peptide.

Vitamins A and E were measured by reverse-phase high performance liquid chromatography (Agilent Technologies Inc, CA, USA). They were deemed deficient if <1.0 μmol/L and <12 μmol/L respectively. 25-hydroxy vitamin D was measured by liquid chromatography tandem-mass spectrometry using a TLX-4 4-channel HPLC and TSQ Quantum Access Max Mass Spectrometer (ThermoFisher Scientific Inc, MA, USA), and was deemed deficient if <50 nmol/L [34]. The international normalised ratio (INR) (as a surrogate for Vitamin K) was measured using the Sta R Max® Hemostasis Analyzer (Diagnostica Stago Inc, NJ, USA).

Plasma glucose concentrations were determined with the glucose oxidase method using a YSI 2900 Biochemistry Analyzer (YSI, Xylem, OH, USA), and plasma C-peptide concentrations were determined using an ELISA immunoassay (10-1136-01, Mercodia; Uppsala, Sweden).

2.4.5. Gastric emptying

Gastric emptying was measured over 6 h postprandially using a standardised, single-isotope (^{99m}Tc-calcium phytate) scintigraphic test [35]. The meal also contained ^{13}C-octanoate to allow concurrent assessment of gastric emptying using a breath test technique, but we report only the scintigraphic data here, given that it represents the 'gold standard' [36].

Radioisotopic data were acquired with participants seated with their back against a gamma camera (e.cam Signature Series, Siemens or Genie, GE Healthcare Technologies) at 1-minute intervals for the first hour and at 3-minute intervals thereafter, for a total of 240 min. Static 3-min images were then performed at 300 and 360 min. Data were corrected for patient movement, radionuclide decay and γ-ray attenuation, as described previously [35]. A region-of-interest was drawn for the total stomach, and gastric emptying curves, expressed as percent retention over time, were derived, allowing the quantification of the gastric half-emptying time (T50) [35].

2.5. Statistical methods

Prevalence data are reported with 95% confidence intervals. Participant demographic information was analysed using descriptive statistics.

Anthropometric data from participants with low and normal FE-1 were compared using unpaired *t*-tests, and gastrointestinal symptoms were compared using Pearson Chi-Square tests.

The primary outcome of the randomised controlled trial was the difference in postprandial glycaemia as evaluated by the incremental area under the glucose curve (iAUC) following PERT vs placebo. Secondary outcomes were differences in gastric emptying T50, C-peptide iAUC, and scores for appetite, satiety and nausea (total AUC) following PERT vs placebo. iAUC and AUC were calculated using the trape-

zoidal rule [37]. Paired t-tests (two-tailed) were used to compare sample means of baseline and peak plasma glucose, glucose and C-peptide iAUC, gastric emptying T50, and VAS baseline scores and AUC. As one study was terminated prematurely at t = 300 min due to hypoglycaemia, all data after t = 300 min were disregarded.

Based on previous data generated by our research group using mashed potato meals in subjects with cystic fibrosis [25] and an updated estimate of within-subject variability, we calculated that a sample size of 8 was able to detect a 30% reduction in glucose iAUC at $\alpha = 0.05$ with 98% power.

Data are presented as mean values ± standard error of the mean (SEM) unless otherwise stated. $P < 0.05$ was considered significant in all analyses. All analyses were performed using SPSS Statistics (Version 24; IBM Corp., USA).

3. Results

3.1. *Prevalence of low FE-1 in T2DM*

Initial contact was made with 514 people with T2DM and 109 stool samples were ultimately received for FE-1 analysis; reasons for exclusion are outlined in Fig. 1. The median FE-1 concentration was 470 μg/g (range 61–500 μg/g) (Fig. 2). Ten participants had low FE-1 (≤200 μg/g) (prevalence 9.2% [95% CI 3.8–14.6%]) and 4 had very low FE-1 (≤100 μg/g) (prevalence 3.7% [95% CI 0.2–7.2%]).

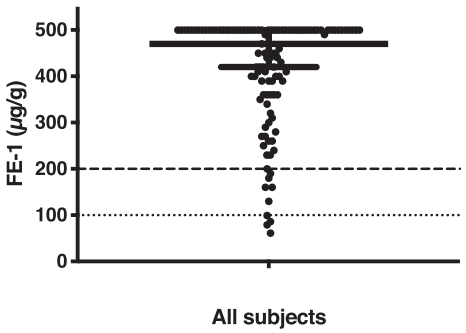
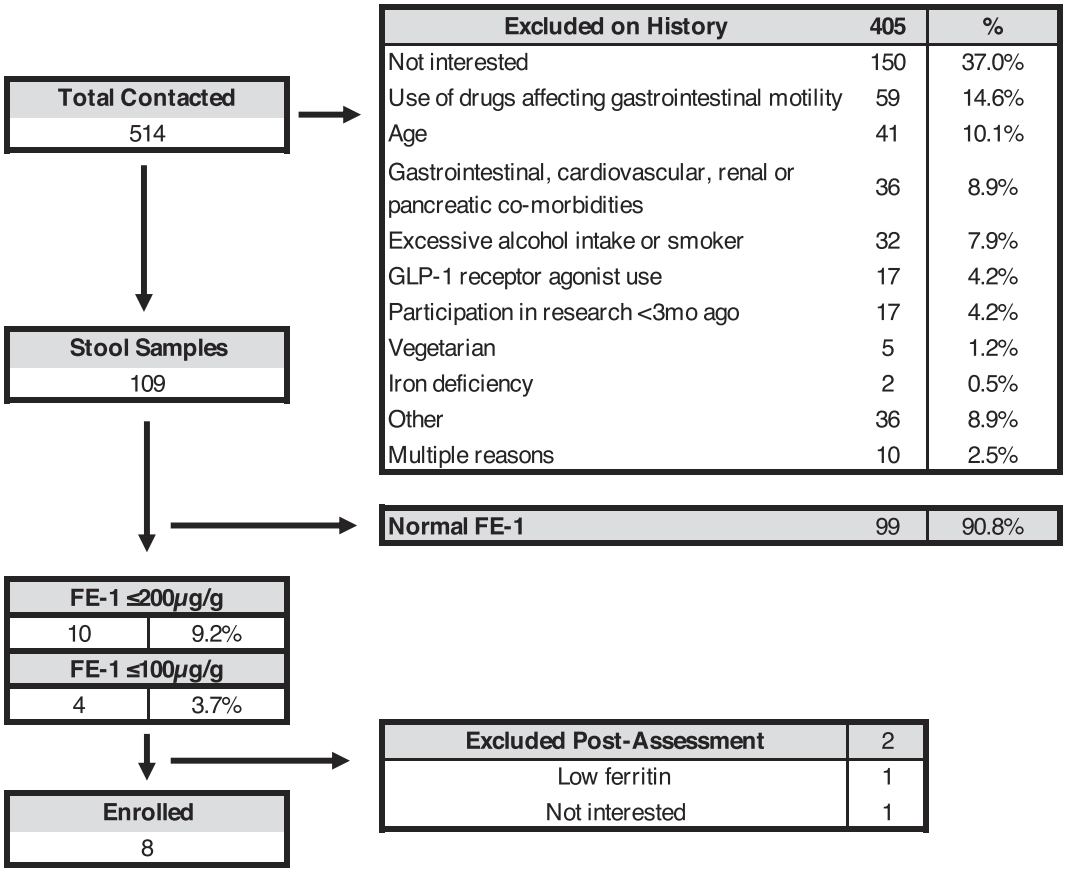


Fig. 2 – FE-1 Distribution: Measurement of FE-1 in stool samples from 109 patients with T2DM. Solid lines indicate median and 95% CI; dashed line indicates 200 μg/g (cut-off for PEI); dotted line indicates 100 μg/g (cut-off for severe PEI).

3.2. *Impact of low FE-1 in T2DM*

3.2.1. *Participant demographics*

Eight participants with low FE-1 were enrolled into the study (6 male, 2 female, age 67.8 ± 3.0 years, duration of known dia-



Excluded on History	405	%
Not interested	150	37.0%
Use of drugs affecting gastrointestinal motility	59	14.6%
Age	41	10.1%
Gastrointestinal, cardiovascular, renal or pancreatic co-morbidities	36	8.9%
Excessive alcohol intake or smoker	32	7.9%
GLP-1 receptor agonist use	17	4.2%
Participation in research <3mo ago	17	4.2%
Vegetarian	5	1.2%
Iron deficiency	2	0.5%
Other	36	8.9%
Multiple reasons	10	2.5%

Normal FE-1	99	90.8%

Excluded Post-Assessment	2
Low ferritin	1
Not interested	1

Fig. 1 – Consort Diagram: Community-based volunteers with T2DM were screened through history; those who met the eligibility criteria were invited to submit a stool sample for FE-1 assay. Participants with FE-1 ≤200 μg/g were then screened for abnormal renal and hepatic function, haemoglobin and iron studies and if still eligible, were enrolled into the randomised controlled trial comparing PERT with placebo. 'Other' reasons included incorrect contact details or language barrier.

Table 1 – Participant demographics and biochemical results.

ID	Sex	Age (Yrs)	Duration of diabetes (Yrs)	Medications[†]	BMI[‡] (kg/m^2)	Waist circumference (cm)	FE-1 (μg/g)	HbA1c (%) (mmol/mol)	25(OH) Vit D (>50 nmol/L)
Participant 1	M	70	25	**Insulin aspart** Metformin SGLT2 inhibitor	32.5	112	86	7.7 *(61)*	52
Participant 2	M	56	13	**Metformin SGLT2[§] inhibitor** Sulphonylurea	30.2	109	130	7.6 *(60)*	65
Participant 3	F	77	18	**Metformin Sulphonylurea** SGLT2 inhibitor	31.6	102	180	8.5 *(69)*	55
Participant 4	M	75	10	Metformin DPP-IV[¶] inhibitor Sulphonylurea	32.8	110	160	8.0 *(64)*	49
Participant 5	M	55	8	**Metformin SGLT2 inhibitor**	31.5	115	61	6.0 *(42)*	118
Participant 6	M	69	4	–	26.5	92	99	5.9 *(41)*	34
Participant 7	F	66	1	–	36.5	95	200	5.8 *(40)*	72
Participant 8	M	74	6	Metformin SGLT2 inhibitor	29.9	108	79	8.8 *(73)*	39

Participant information acquired on history, physical examination and initial investigations. Vitamin D was measured from a fasting sample on the morning of the first study day. *Participant 9* was excluded due to low ferritin and *Participant 10* declined further involvement.

† Only diabetic medications are reported; those highlighted in bold were taken during the study days.

‡ BMI – body mass index.

§ SGLT2 – Sodium-glucose transporter 2.

¶ DPP-IV – dipeptidyl peptidase-4.

betes 10.6 ± 2.8 years, HbA1c 7.3 ± 0.4% [56 ± 5 mmol/mol], BMI 31.4 ± 1.0 kg/m^2) (Table 1). One participant was on insulin, six on oral hypoglycaemic therapy, and two were managed by diet alone. One participant had a history of diabetic neuropathy, while none had a history of retinopathy or evidence of cardiovascular autonomic dysfunction. No participant was currently drinking >20 g alcohol per day, although one participant had consumed >100 g alcohol 5 days a week for approximately 15 years until 10 years prior. One participant also had a history of cholecystectomy.

3.2.2. *Clinical evidence of PEI*

Of the 8 participants enrolled, the mean gastrointestinal symptom score was 3.3 ± 0.8: 2 participants (25%) reported mild nausea, and 2 (25%) and 1 (13%) respectively reported mild and moderate 'discomfort or distension in the upper abdomen'; 4 (50%) reported 'feeling full after eating only a little food' (i.e. early satiation) to a mild degree and 2 (25%) to a moderate degree. The mean number of bowel actions per week was 6.7 ± 1.1 and the median Bristol Stool Chart score was 3.5 (range 2–5). Two participants reported occasional greasy stools and three reported 'stool that is difficult to flush' occasionally. Vitamin D deficiency was present in 3 participants (37.5%) (Table 1), however there was no deficiency of any other fat-soluble vitamin. Five participants had an abnormal pancreas on MRCP, with a fatty atrophic pancreas (4 participants) and/or pancreatic cysts (4 participants).

Of the 99 participants who had normal FE-1 levels, 49 participants (28 male, 21 female, aged 65.3 ± 1.1 years, duration of diabetes 10.2 ± 0.9 years) also completed a gastrointestinal symptom questionnaire; the remaining 50 declined to do so. When compared to the participants with normal FE-1, those with low FE-1 were more likely to report early satiation (75% vs 29%, P = 0.012). There were no differences in BMI (31.4 ± 1.0 kg/m^2 vs 31.1 ± 0.8 kg/m^2, P = 0.87), the number of bowel actions per week (6.7 ± 1.1 vs 9.5 ± 0.7, P = 0.17), or the prevalence of nausea (25% vs 27%, P = 0.90), abdominal discomfort (38% vs 42%, P = 0.82), greasy stools (25% vs 37%, P = 0.51), or stools that are difficult to flush (38% vs 40%, P = 0.88).

3.2.3. *Crossover study*

The studies were well tolerated. Three adverse events were reported: postprandial hypotension and pre-syncope (placebo day), musculoskeletal back pain (PERT day), and hypoglycaemia at t = 300 (placebo day) leading to premature cessation of that study day.

3.2.4. *Plasma glucose and C-Peptide*

Baseline and peak plasma glucose were comparable between the placebo and PERT days (baseline 7.9 ± 0.6 mmol/L and 7.5 ± 0.5 mmol/L [P = 0.29] respectively; peak 12.6 ± 0.7 mmol/L and 12.5 ± 0.6 mmol/L [P = 0.71] respectively). Over 5 h, the iAUC for plasma glucose did not differ between the placebo day (654.4 ± 63.7 mmol L^{-1} min) and the PERT day (692.7 ± 51.9 mmol L^{-1} min) (P = 0.38) (Fig. 3a).

There was no difference in plasma C-peptide iAUC between the placebo and PERT days (281 ± 60.5 nmol L^{-1} min vs 300 ± 63.6 nmol L^{-1} min, P = 0.25) (Fig. 3b).

3.2.5. *Gastric emptying*

Gastric emptying T50 did not differ between the PERT and placebo days (79.5 ± 10.7 min vs 81.1 ± 9.2 min, P = 0.69) (Fig. 3c).

3.2.6. *Appetite and gastrointestinal perceptions*

All VAS scores were similar between the two days (P > 0.05). Participants reported minimal nausea during the study (data not shown).

4. Discussion

In this community-based study of patients with T2DM, the prevalence of FE-1 ≤200 μg/g and ≤100 μg/g was 9.2% and 3.7% respectively, and in people with FE-1 ≤200 μg/g, there was no effect of acute administration of PERT on gastric emptying, postprandial glycaemia or C-peptide concentrations.

The prevalence of low FE-1 in T2DM in our study is substantially less than the figure of 28% in a recent meta-analysis of seven studies [10]. Like those studies, we reported FE-1 values that were unadjusted for stool water content; if anything, correction for water content would have further diminished the prevalence of low FE-1. The difference from previous studies may potentially reflect recruitment of a healthier, community-dwelling population, since low FE-1 has previously been associated with poor glycaemic control, increased BMI, and the presence of vascular disease [18,22], and previous studies have recruited patients predominantly from the hospital setting [18,20,23]. Moreover, patients with diabetes of the exocrine pancreas (T3cDM), who are particularly likely to have low FE-1, are known frequently to be misclassified as T2DM [15,38]. Given that we excluded patients with a history of pancreatic disease or surgery and excessive current alcohol intake, our estimate of the prevalence of low FE-1 in T2DM is likely to be conservative.

There was minimal clinical evidence of PEI in participants with low FE-1 and T2DM. All were overweight or obese, whereas PEI is typically associated with malnutrition. Gastrointestinal symptoms, which are known to occur frequently in T2DM [39], were only reported by a minority of participants with low FE-1, were generally mild, and were not more preva-

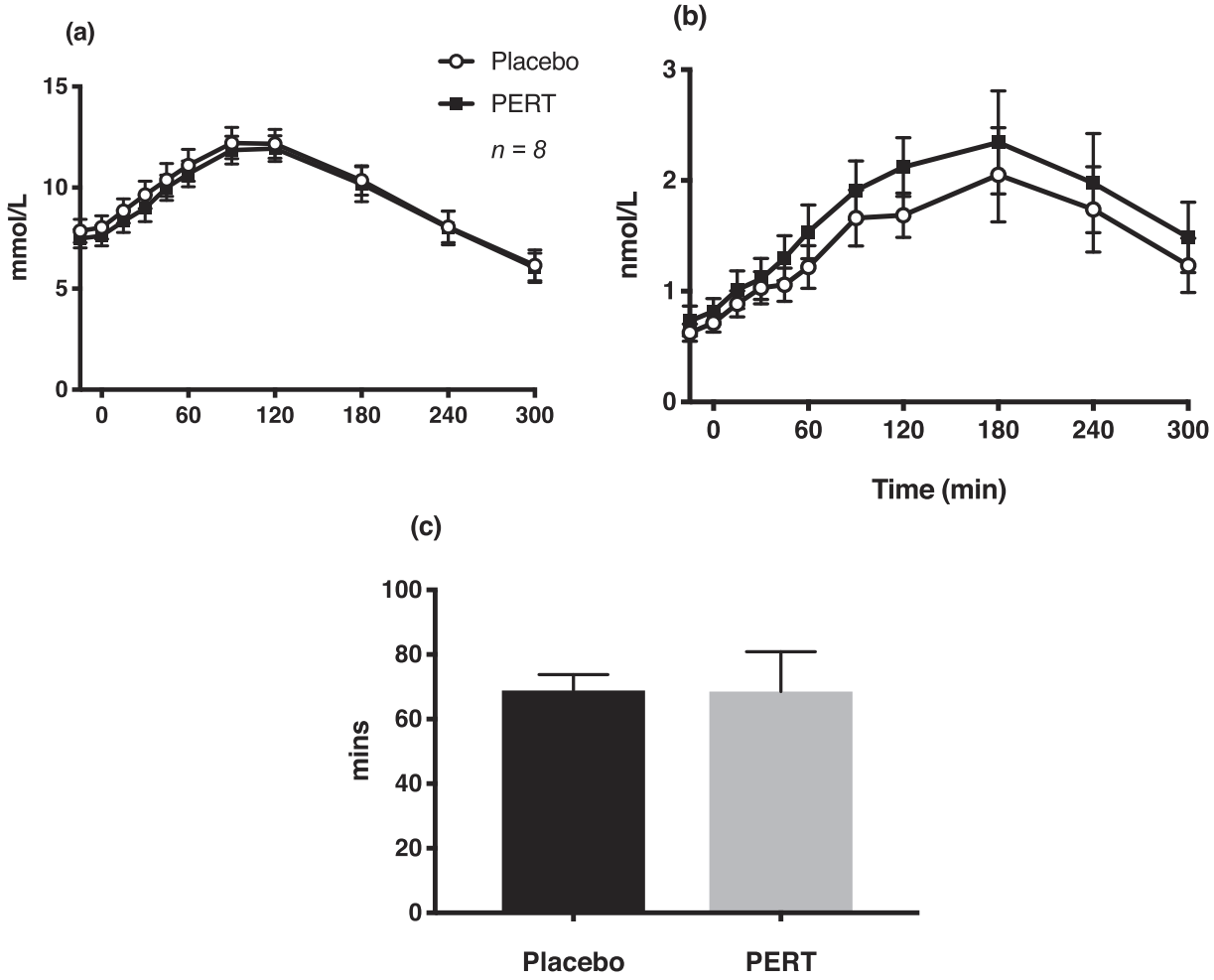


Fig. 3 – There was no difference in (a) plasma glucose iAUC (P = 0.38), (b) plasma C-peptide iAUC (P = 0.25), or (c) gastric half-emptying time (T50) (P = 0.69) between the placebo and PERT days in n = 8 patients with T2DM and low FE-1 after a high carbohydrate/high fat meal with either placebo or PERT.

lent than in participants with normal FE-1. While early satiation was more common in participants with low FE-1, this outcome should be regarded as exploratory and requires further confirmation. The only fat-soluble vitamin deficiency in those with low FE-1 was for vitamin D, but the prevalence of 37.5% was only marginally higher than in the general Australian adult population (31%) [34]. The abnormal MRCP findings are consistent with previous reports that pancreatic volume is decreased in T2DM [40] and individuals with low FE-1 [41]; further interpretation is compromised by the absence of control data and the presence of confounding factors, specifically age and obesity [40,42].

PERT did not lead to a reduction in the postprandial glycaemic excursion in participants with low FE-1, nor did it have any effect on the rate of gastric emptying or postprandial C-peptide concentrations. This is consistent with two previous studies on the impact of PERT in T1DM patients with low FE-1 [28], and in patients with chronic pancreatitis [27]. However, we previously reported a marked reduction in postprandial glycaemia with PERT in patients with cystic fibrosis and known PEI [24,25]. It therefore appears likely that the lack of effect of PERT in the current study reflects the absence of true PEI. While FE-1 is well validated for the diagnosis of PEI in severe chronic pancreatitis [43], this is not the case in diabetes. Hahn et al evaluated FE-1 against the gold standard secretin-cholecystokinin test in people with T1DM and reported a sensitivity, specificity and positive predictive value of only 55%, 59% and 40% respectively, indicating poor diagnostic reliability [44]. The significance of FE-1 in T2DM has been further questioned by the recent finding that low FE-1 was not predictive of reduced uptake of esterified omega-3 fatty acids in subjects with T2DM, a process which is dependent on pancreatic lipase [45].

Limitations of our study include the lack of assessment of fat-soluble vitamin concentrations and MRCP acquisition in participants with normal FE-1. Also, we did not exclude participants with potential secondary causes of PEI such as previous excessive alcohol consumption or a history of gallbladder disease. However, inclusion of such patients would, if anything, have raised the prevalence of low FE-1 in our cohort and increased the likelihood that PERT would lower postprandial glycaemia, so we do not believe these limitations had a substantial impact on the outcomes.

This is the first study, to our knowledge, to evaluate the impact of PERT in people with T2DM and low FE-1. The double-blind, randomised, cross-over design was a major strength, as was the recruitment of volunteers from the community in order to evaluate the benefit of PERT in 'typical' patients with T2DM. The study outcomes indicate that the clinical indications for PERT to improve glycaemic control should not be broadened. Moreover, the significance of low FE-1 concentrations in T2DM remains unclear. While associated with early satiation, there were no other clinical or biochemical findings that clearly linked low FE-1 to overt PEI. Our study establishes that low FE-1 is likely to be less prevalent than previously reported in T2DM and that acute administration of PERT is ineffective for reducing postprandial glycaemia in these patients. It therefore appears that while the measurement of FE-1 in T2DM warrants further exploration, it is currently of limited clinical relevance.

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Disclosure summary

KLJ has received research funding from Sanofi and drug supplies from Merck Sharp & Dohme. MH has participated in the advisory boards and/or symposia for Novo Nordisk, Sanofi, Novartis, Eli Lilly, Merck Sharp & Dohme, Boehringer Ingelheim and AstraZeneca, and has received honoraria for this activity. CKR has received research funding from AstraZeneca, Merck Sharp & Dohme, Eli Lilly, Novartis, and Sanofi. LKP has received research funding from Glaxo Smith Kline and has participated in symposia for Novo Nordisk, Merck Sharp and Dohme and Novartis and has received honoraria for this activity.

Declaration of Competing Interest

None of the other authors have any personal or financial conflict of interest to declare.

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