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Cystic fibrosis related diabetes - a new perspective on the optimal management of postprandial glycemia

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ABSTRACT

As the average life expectancy of patients with cystic fibrosis (CF) improves, the long term co-morbidities assume increasing importance. CF related diabetes (CFRD) has adverse effects on both nutrition and pulmonary function, and is associated with increased mortality. Abnormalities of glucose metabolism in CF represent a continuum; however the predominant abnormality is postprandial, not pre-prandial, glycaemia. Insulin is currently recommended as the treatment of choice for CFRD, but its use is associated with a number of limitations, including hypoglycaemia. Both the rate of gastric emptying and the consequent release of the 'incretin' hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like-peptide-1 (GLP-1), from the gut are important determinants of overall glycaemic control, particularly postprandial glycaemia. Both are abnormal in conditions associated with exocrine pancreatic insufficiency. Incretin based therapies that have the capacity to slow gastric emptying and/or modulate the release of 'incretin' hormones, are now used widely in type 2 diabetes (T2D). This paper explores the determinants of glycaemic control in CF, with a particular focus on the roles of gastric emptying and 'incretin' hormones, providing a rationale for the use of therapies that delay gastric emptying, including incretin mimetics, to minimise postprandial glycaemia and improve nutritional status.

INTRODUCTION

The establishment of specialised CF centres, and substantial nutritional and pharmaceutical advances during the last 60 years, have improved mean life expectancy for CF by more than 38 years, with the consequent clinical challenge of prevention and management of long-term co-morbidities, of which CFRD has increasing prominence [1]. The abnormalities of glucose metabolism in CF represent a continuum from normal, through pre-diabetes, to overt diabetes with the pathogenesis characterised by postprandial, rather than pre-prandial, hyperglycaemia. Insulin is currently the treatment of choice for CFRD although the acceptance and compliance with this therapy is challenging due to the already high burden of care in the CF population. Newer therapies are available that specifically modify postprandial glycaemia, such as those based on the incretin system, which are widely utilised in the management of T2D. These therapies may represent a logical treatment for CFRD, as monotherapy or in combination with basal insulin, as they specifically address postprandial hyperglycaemia.

CFRD Prevalence and Significance

The prevalence of CFRD increases with age, such that more than 50% of patients over 40 years are affected [2]. The mortality rate for CFRD has been estimated at 3.5 per 100 person years, from a peak 20 years ago of 6.2 per 100 person years, but remains substantially higher than in CF patients without diabetes [2]. This improvement is largely due to increased awareness and detection in the pre-diabetic state, which is imperative in light of persuasive evidence that the optimal management and long-term prognosis of CF, is affected greatly by the presence of carbohydrate intolerance. The long term implications of CFRD for pulmonary health

and body mass index (BMI) are considered of greater relevance than the microvascular and macrovascular complications classically associated with type 1 diabetes (T1D) and T2D, although with increased survival microvascular complications have now become apparent, as will be discussed. CFRD with fasting hyperglycaemia is associated with a decline in pulmonary function and nutrition, an increase in the incidence of *Pseudomonas aeruginosa* and *Burkholdaria cepacia* infection, doubling of hospitalisation rates, and an increase in the prevalence of liver disease [3]. CFRD also adversely affects prognosis after lung transplantation [4]. Whether these associations are a direct effect of CFRD, or reflect more severe disease is uncertain; however the degree of clinical decline, particularly in respiratory function, correlates directly with glycaemic control. Moreover, there is now persuasive evidence that the decline in nutritional and pulmonary status occurs 2- 6 years before the diagnosis of CFRD, when postprandial hyperglycaemia is less marked [5, 6]. This suggests that even 'early' carbohydrate intolerance, with relatively modest postprandial glycaemic excursions, is metabolically detrimental to pulmonary function. Upper airway glucose concentrations are higher in CF when compared with healthy subjects, and those with T1D or T2D, with the potential to facilitate bacterial growth and subsequent lung damage [7]. Direct toxic effects of hyperglycaemia on airway function remain to be established.

Microvascular complications occur in CFRD, albeit with a lower prevalence than in T1D or T2D, and are related both to the duration of diabetes and glycaemic control. Ten years from the diagnosis of CFRD, 50% of patients are reported to have peripheral neuropathy, 16% retinopathy and 14% microalbuminuria [8]. Macrovascular complications in CFRD have not featured in the literature, possibly

reflecting both the shorter life expectancy and beneficial effect conferred by the genetic mutation and fat malabsorption.

CFRD Pathogenesis

The pathogenesis of CFRD is multifactorial, with both the CF genotype and innate and adaptive immunity contributing to ß cell destruction [9, 10]. CFRD is characterised by predominantly postprandial, rather than pre-prandial, hyperglycaemia. This contrasts with T1D, and the proportional elevation of postprandial glucose in CF, relative to fasting glucose, is greater than in T2D. The primary defect has been regarded as insulin deficiency, with a variable contribution from insulin resistance, dependent on clinical state, infection, inflammation and concurrent steroid medication. There is, however, a poor correlation between clinical diabetes and the degree of islet cell damage, suggesting that other factors, such as autoimmunity, may be involved. However, the prevalence of islet antibodies and T1D susceptibility alleles in CFRD appear to be comparable to the general population, although CFRD and T1D co-exist in a minority [11]. It has been suggested that CFRD may be more closely related to T2D, with islet amyloid deposits, as seen in T2D, being evident in 69% at autopsy [12]. It is not clear whether amyloid deposits play a direct role in the pathogenesis of ß cell death or are simply a marker of increasing ß cell stress [13, 14]. Susceptibility genes that increase the risk of T2D in the general population have been found in CFRD, strongly suggesting these genes may increase the propensity to diabetes in CF, and a family history of T2D increases the risk of CFRD substantially [11].

The cystic fibrosis transmembrane conductance regulator (CFTR) protein may play a direct role in insulin secretion. Ivacaftor, a CFTR potentiator, is a new therapy

which improves chloride transport through the dysfunctional CFTR protein in individuals with the G551D mutation. The implications for glycaemic control are uncertain; however in a pilot study of 5 CF patients Ivancafor improved insulin secretion, albeit without affecting glycaemic control [15].

CFRD Diagnosis

Carbohydrate intolerance in CF represents a continuum on which patients fluctuate, depending on clinical variables including infection, energy requirement, nutritional state, gastrointestinal absorption and steroid therapy. The diagnosis of CFRD is challenging, not just because of this intra-individual variability, but also because of the lack of a 'gold standard' diagnostic test. In practice, carbohydrate intolerance in CF is commonly classified into categories of normal glucose tolerance, indeterminate glucose tolerance, impaired glucose tolerance, CFRD without fasting hyperglycaemia, and CFRD with fasting hyperglycaemia (Table 1*)* based on an oral glucose tolerance test (OGTT, 1.75g/kg body weight, maximum 75g) using fasting and 120 minute glucose levels [2].

Categories	**Fasting plasma glucose (mmol/L)**	**2hr plasma glucose (mmol/L)**
Normal glucose tolerance	<7.0	<7.8
Indeterminate glucose tolerance	<7.0	<7.8 with levels during 2 hours ≥11.1
Impaired glucose tolerance	<7.0	7.8-11.1
CFRD without fasting hyperglycaemia	<7.0	≥11.1
CFRD with fasting hyperglycaemia	≥ 7.0	OGTT not necessary

Table 1. Categories of carbohydrate intolerance in CF by OGTT.

Previously, the OGTT was regarded as the diagnostic gold standard with high sensitivity [16]; however more recent evidence indicates that many patients experience large glycaemic excursions at 30, 60 and 90 minutes after oral glucose, which may be clinically significant, but have normal blood glucose levels at baseline and 2 hours [17]. While there is a relationship between the 2 hour OGTT blood glucose value and glycaemic excursions following a mixed meal in healthy subjects, and those with impaired glucose tolerance or overt diabetes [18], the absolute blood glucose concentrations vary substantially between the two tests. The OGTT tends to elicit greater glycaemic excursions, while a mixed meal more accurately represents the glycaemic variations occurring in everyday life. In CF, this is particularly important, since exocrine pancreatic insufficiency may influence the response to a mixed meal, but not to oral glucose. Moreover, unless blood glucose is measured more frequently than at 2 hours (eg. every 30 min), the OGTT may miss an early glycaemic peak. The OGTT also has poor specificity, with up to 58% of patients with impaired glucose tolerance being shown to revert to normal glucose tolerance and only 14% progressing to CFRD over the following 5 years [19]. Measurement of insulin and C-peptide responses to an OGTT may aid in detecting abnormalities in carbohydrate metabolism and progression. A delayed and reduced insulin peak and first phase insulin response to oral and intravenous glucose tolerance tests are evident in CF subjects with impaired, compared with those with normal glucose tolerance [20]. This information may facilitate identification of those at high risk of progressing to CFRD however more studies are required. HbA1c cannot be used to

screen for CFRD, as levels are often falsely normal in CF and do not reliably correlate with glycaemic control.

CFRD Current Management

The 2009 International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice guidelines for the management of CFRD recommend a combination of basal (long-acting) and bolus (rapid-acting) insulin [21]. Pump insulin therapy offers the greatest flexibility and a reduction in the number of injections required [22]; however insulin regimens need to take into consideration the patients' individual needs and current treatment burden. Basal insulin doses start around 0.25u/kg/24h and are titrated to fasting blood glucose levels with suggested pre-meal insulin doses of 0.5-1u per 15g of carbohydrate and 'correction' doses added as required [21].

While a basal-bolus insulin regimen is recommended, a 2013 Cochrane review was unable to identify sufficient evidence to inform on the optimal management of hyperglycaemia in CF [23]. The relative benefits of postprandial, versus pre-prandial, glycaemic control have not been evaluated in CF; however in T2D it is now recognised that postprandial glycaemic excursions are a major determinant of 'overall' glycaemic control, particularly in the lower range of HbA1c.

The best management of CFRD without fasting hyperglycaemia and impaired or indeterminate glucose tolerance also remains unclear, and determining the optimal therapy for pre-diabetes is regarded as an urgent priority by the CF Foundation, American Diabetes Association and Pediatric Endocrine Society [24]. The outcomes of several studies indicate insulin therapy can ameliorate the decline in pulmonary function and BMI seen in the early stages of impaired glucose tolerance [5, 6]. In adults, an 8% increase in FEV1 and 42% decline in pulmonary

exacerbations were evident during 12 months of basal insulin (Glargine) therapy [6], with reversal of chronic weight loss [5]. These effects are attributable to insulin's anabolic role, increasing protein synthesis and BMI with enhanced respiratory muscle strength, rather than a direct effect of improved glycaemic control.

It is well recognised that it can be difficult to achieve satisfactory glycaemic control in CF subjects using insulin therapy. Not infrequently, the therapeutic emphasis has been on pre- rather than postprandial glycaemic control. In determining the optimal insulin regimen and maximising compliance, current therapies and social supports, need to be taken into consideration. Because insulin therapy is invasive, requires regular injections, and is associated with a high risk of hypoglycaemia, acceptability of this therapy in the early stages of carbohydrate intolerance, or indeed even in overt CFRD, is likely to be limited. There are few established alternative therapeutic options, given traditional oral hypoglycaemic agents are not currently recommended in CF due to limited data and the risk of adverse effects [23]. Metformin is associated with gastrointestinal side effects, has a theoretical risk of lactic acidosis, and is better suited to obese patients with insulin resistance. Sulphonylureas increase insulin secretion, but bind to the CF transmembrane conductance regulator, raising concerns they may interfere with other CF therapies. Thiazolidinediones primarily target peripheral insulin resistance, which is not the dominant feature in CFRD.

Glycaemic control in this population is further challenged by states of increased insulin resistance such as acute pulmonary infection and pregnancy, and following lung transplantation. Medications, such as corticosteroids, given during an acute pulmonary exacerbation, combined with increased insulin resistance can result in a temporary requirement for exogenous insulin. In those with CFRD acute

infection may increase insulin requirements 4 fold [21]. With resolution of the infection requirements typically return to previous levels.

During pregnancy, insulin resistance increases, putting women with CF at greater risk of developing gestational diabetes when compared to healthy females. Monitoring of blood glucose at routine appointments, an OGTT on confirmation of pregnancy (if one has not occurred the prior 6 months), and at the end of the 1st and 2nd trimester, is recommended [24].

Lung transplantation does not appear to increase the risk of diabetes in CF patients compared with non-CF transplant patients [25]; however glycaemic control deteriorates in the majority of CFRD patients following transplantation [26].

Hypoglycaemia can occur in CFRD in the context of insulin therapy, although normal hypoglycaemic awareness is generally maintained. Education is paramount in reducing the risk. The non-diabetic CF population may have a greater tendency to fasting hypoglycaemia than the healthy population [27].

DETERMINANTS OF GLYCAEMIA IN CF

Key determinants of postprandial glycaemic control in CF include gastric emptying, gut hormone secretion (particularly the incretins, GIP and GLP-1, but also cholecystokinin (CCK) and peptide tyrosine tyrosine (PYY)), the insulin and glucagon response, pancreatic enzyme supplementation and the high fat/ high energy diet recommended for these patients. Gastric emptying and incretin hormone secretion are central to postprandial glycaemic control [28]; but have received little attention in CF.

Gastric emptying in health and CF

In health, individual gastric emptying rates vary substantially between 1-4 kcal/min [29], with regulation predominantly arising through inhibitory feedback triggered by carbohydrate, protein and fat digestion in the small intestine. The presence of lipolytic products in the intestinal lumen contributes substantially to the neurohumoral feedback mechanisms that slow gastric emptying. The use of the lipase inhibitor, orlistat, in T2D is associated with accelerated gastric emptying and accentuation of postprandial hyperglycaemia [30]. The rate of gastric emptying is in turn a fundamental determinant of the release of gut peptides and the rate of carbohydrate absorption, both of which are central to postprandial glycaemic control. Gastric emptying accounts for around one third of the variation in peak glucose response after an oral glucose load in health or T2D [31]. Relatively more rapid gastric emptying (3-4kcal/min) is associated with a greater initial rise in blood glucose, while slower emptying (<1.5kcal/min) provides a more controlled rise [32].

Multiple variables may influence the rate of gastric emptying, including meal composition and volume, posture, illness, glycaemia and medications. Variables of particular relevance to CF are pancreatic enzyme supplementation, glycaemia and the high fat/ high energy diet prescribed for these patients. Exocrine pancreatic insufficiency affects around 80% of CF patients and requires pancreatic enzyme supplementation; however, the latter fails to normalise fat absorption in around 20% [33]. The relationship between gastric emptying of nutrients and supplemental enzymes is complex, and co-ordination of both to optimise nutrient absorption is therapeutically challenging, particularly when gastric emptying is disordered (either abnormally fast or slow) [33, 34]. It is recognised that there is substantial inter-individual variation in gastric emptying of food and enzymes respectively, with enzymes empting on average 60 minutes before food when given together [35].

Meal composition and the size of spheres in enzyme formulations are important. Mixing of enzymes with the liquid component of a meal can result in rapid non-parallel emptying, given that liquids empty more rapidly than solids. There is inconsistent information in relation to the impact of the size of the enzyme sphere on the rate of emptying; however, smaller spheres (≤1mm) generally empty more rapidly, and emptying of spheres ≥1.6mm may be delayed up to 3 hours after a meal [34]. Pancreatic enzyme efficacy is further impaired in CF by a lower intestinal pH, due to impaired HCO3 secretion, resulting in delayed dissolution of the enteric coating on enzyme formulations [36].

Gastric emptying is itself influenced by acute changes in blood glucose concentrations, with hyperglycaemia delaying gastric emptying, which in turn slows the absorption of ingested carbohydrate and reduces the propensity for further hyperglycaemia [37]. Conversely, in health and T1D, insulin-induced hypoglycaemia accelerates emptying, increasing the delivery of nutrients to the small intestine, and again providing an adaptive response [38].

The high fat diet prescribed in CF would be expected to favour slow gastric emptying, since fat is a potent inhibitor of emptying. However, ingestion of a diet high in fat in healthy subjects is associated with relatively more rapid emptying of fat, presumably reflecting a reduction in small intestinal inhibitory feedback [39]. In patients with CF, the majority of whom have pancreatic exocrine insufficiency, the emptying of high fat meals is further complicated by fat maldigestion, an issue which is discussed in detail subsequently. Protein, such as whey, has been shown to slow gastric emptying through enhanced gut hormone secretion [40]. Digestion of protein is also impaired in pancreatic insufficient CF, although to a lesser degree than fat, which may contribute to rapid gastric emptying in CF.

Despite the potential importance of abnormal gastric emptying in CF patients, only a limited number of studies have evaluated gastric emptying in this population [33, 41-45], with inconsistent results, attributable to differences in subject characteristics, meal composition, use of pancreatic enzymes and the method used to measure gastric emptying. Studies have reported abnormally rapid [41, 42] or delayed [44] emptying, or no difference from controls [33, 43, 45]. A bimodal pattern of gastric emptying has also been proposed, with more rapid emptying 'early' in the disease reflecting gut adaptations to the high energy diet, and delayed emptying 'later', when malnutrition is more likely to be present [42]. Rapid gastric emptying has been shown in exocrine pancreatic insufficiency from other causes, such as chronic alcoholism [46].

There is no consistent evidence of abnormal gastric musculature or innervation altering gastric emptying in CF; therefore it may be reasonable to conclude that gastric emptying in CF with exocrine pancreatic insufficiency, in the absence of enzyme replacement, will be more rapid due to fat malabsorption, since fat is crucial in regulating gastric emptying. In a small study of adults with CF we demonstrated rapid emptying of a high fat/ carbohydrate meal, associated with marked postprandial hyperglycaemia. Pancreatic enzyme supplementation slowed gastric emptying and markedly decreased the postprandial glycaemic excursion (Fig.1-2) [41]. We recently reported the same phenomenon in a study of 14 paediatric CF patients (Fig.3) [45].

Gut hormone secretion

The "incretin" hormones, GLP-1 and GIP, are secreted from intestinal L and K cells respectively in response to nutrient digestion and exposure [47] and are rapidly

degraded by the enzyme dipeptidyl peptidase-4 (DDP-4) to form ‘inactive’ metabolites. Up to 70% of the total insulin response to oral glucose can be attributed to the actions of GLP-1 and GIP, making these peptides critical to postprandial glycaemic control [47]. GLP-1 improves postprandial glycaemia through slowing gastric emptying and its glucose-dependent insulinotropic and glucagonostatic properties. GIP is insulinotropic, and can stimulate, rather than suppress, glucagon secretion, but appears not to affect gastric emptying [48]. Both the nutrient load and the rate at which nutrients empty to the small intestine are fundamental determinants of GLP-1 and GIP secretion. With increasing rates of small intestinal glucose exposure, there is a linear increase in GIP secretion. By contrast, GLP-1 secretion is minimal at low rates (<2kcal/min) of glucose exposure, but increases substantially at higher rates (3-4kcal/min) in both health and T2D [32].

CCK and PYY may also influence postprandial glycaemic control through inhibition of gastric emptying, with their release also being dependent on nutrient digestion. CCK is released from I-cells in the duodenum and PYY predominantly by the L cells in the distal small intestine and colon, both in response to fatty acids, amino acids and glucose.

Based on the above, it may be anticipated in CF, associated with untreated pancreatic insufficiency, that meal induced secretion of GLP-1, GIP, CCK and PYY would be impaired. No studies have evaluated CCK or PPY in CF, and evidence relating to GLP-1 and GIP secretion is limited and conflicting, probably reflecting methodological inconsistencies [41, 49]. Our recent work, in both adult and paediatric CF patients, has provided persuasive evidence of a marked reduction in GLP-1 and GIP secretion in response to a high fat/high carbohydrate meal [41, 45]. Pancreatic enzyme supplementation restored GLP-1 and GIP secretion, though the

latter was still not normalised in the adult group (Fig.2), perhaps suggesting suboptimal mixing of enzymes and nutrients in the most proximal small intestine, from which most of GIP is derived.

Insulin secretion and action

That CFRD represents a state of insulin deficiency is evidenced by the loss of 1st phase insulin secretion, characterised by a delay of at least 60 minutes in the insulin response to a meal when compared to health, together with a reduction in peak insulin levels [49, 50]. 1st phase insulin secretion is critical to the regulation of postprandial glycaemia, and in CF, impairment is evident in early stages of abnormal carbohydrate metabolism including some with a normal OGTT [50]. Insulin resistance as assessed by homeostatic model assessment (HOMA-IR), is also evident in CFRD, but probably plays a lesser role in postprandial glycaemic control, and assumes greater importance during infection, or treatment with corticosteroids. Dysregulation of glucagon secretion may occur in CF, as a result of damage to pancreatic α cells [49, 50]. A diminished glucagon response to insulin-induced hypoglycaemia is evident in pancreatic insufficient CF subjects [50]; conversely, an impaired capacity to suppress glucagon in response to oral glucose is increasingly evident as carbohydrate tolerance worsens [49]. Increases in insulin clearance, hepatic gluconeogenesis and glucose absorption may also contribute to glycaemic dysregulation in CF.

MANAGEMENT OF CFRD AND THE ROLE OF GASTRIC EMPTYING AND INCRETIN HORMONES

Many of the current recommendations for the management of CFRD are based on expert consensus, due to the lack of higher levels of evidence and the limited therapeutic options available [51]. The pathogenesis of abnormal carbohydrate metabolism in CFRD, particularly in the early stages, is dominated by postprandial, not pre-prandial hyperglycaemia, so the former should logically be the dominant therapeutic focus. Therapies that target postprandial hyperglycaemia may act by modifying gastric emptying and/or incretin hormone secretion; in particular, pancreatic enzyme supplementation, the use of macronutrient 'pre-loads', and incretin-based therapies, particularly GLP-1 agonists, may be of relevance in CF. There may also be additional benefit in combining these therapies with basal insulin to target postprandial and pre-prandial hyperglycaemia respectively. The combination of basal insulin with a GLP-1 agonist represents an approach attracting increasing attention in the management of T2D [52].

Pancreatic Enzyme Supplementation

Optimising pancreatic enzyme supplementation, through adequate dosing and timing of administration, is an important first step in achieving postprandial glycaemic control, with improved fat digestion stimulating gut hormone secretion and attenuating any tendency for rapid gastric emptying [41]. In the early stages of carbohydrate intolerance, this alone may be an effective management strategy. Pancreatic enzymes given prior to a meal at a dose appropriate for the fat content (500-4000IU lipase/gram of dietary fibre, mean 1800IU lipase/gram of fat/meal, maximum 10,000u lipase/kg/day [53]) would be a reasonable starting point, with efficacy assessed by postprandial blood glucose concentrations, particularly at 30 and 60 minutes. Dosing based on body weight alone is simpler; however dosing

based on the meal fat content is more likely to replicate the body's normal response. Combination therapy with a proton pump inhibitor, reducing duodenal acidity, may further optimise pancreatic enzyme efficacy. Additional information is required particularly regarding further therapeutic benefits of increased doses, and optimal timing in relation to the meal.

Potential Future Research

Macronutrient 'pre-load'.

The novel 'pre-load' concept is currently being explored in T2D for the management of postprandial hyperglycaemia. A macronutrient pre-load is consumed 30-60 minutes prior to a meal to prime neurohumoral feedback, resulting in pre-emptive slowing of gastric emptying and increased incretin hormone secretion. A fat pre-load, known to be potent in slowing gastric emptying, appears to have only a limited effect on overall postprandial glycaemia in T2D [54]. In contrast, acute administration of a whey protein preload slows gastric emptying, stimulates incretin hormones, and markedly increases insulin secretion, probably predominantly via amino acids, thereby markedly reducing postprandial glycaemia [40]. The increase in calorie consumption with a 'pre-load', a potential disadvantage in T2D, would not be an issue in CF; however the current CF dietary prescription of 3 meals and 3 snacks per day make a 'pre-load' less feasible. Further studies assessing the optimal quantity, timing and long term benefits, in particular the effect of a protein pre-load before the main meals in CF is required.

Incretin-based therapies.

Incretin-based therapies, particularly GLP-1 agonists, are effective in the management of T2D [52]. The half-life of subcutaneously administered GLP-1

agonists appears to dictate whether efficacy is primarily preprandial ('non-prandial') or postprandial ('prandial'). 'Prandial' agonists (exenatide, lixisenatide) have a short duration of action, exerting a greater effect on postprandial glycaemia, predominantly through potent slowing of gastric emptying and postprandial insulin suppression [55]. 'Non-prandial' agonists (liraglutide and exenatide LAR), are longer acting and better suited for pre-prandial glycaemic control, since their predominant mode of action is to stimulate insulin and suppress glucagon secretion [56]. The mechanisms underlying glucose-lowering induced by 'prandial' GLP-1 agonists suggest potential benefits even in the early stages of the continuum of abnormal carbohydrate metabolism in CF; however this remains uninvestigated. The combination of a GLP-1 agonist for control of postprandial glycaemia, in conjunction with basal insulin for pre-prandial glycaemic control, is being used to good effect in T2D [57] .This therapeutic combination may provide more effective pre- and postprandial glycaemic control in CFRD with fasting hyperglycaemia than insulin therapy alone, and should be explored further.

Adverse effects associated with GLP-1 agonists, include gastrointestinal symptoms and modest weight loss, both of which would of concern in the CF population. In T2D however, only a minority of patients cannot tolerate therapy due to nausea, particularly if the dosage is increased gradually [58]. It is not known whether GLP1 agonists affect body weight in those with a normal or low BMI. Furthermore rates of obesity (BMI>30kg/m2 in adults), previously not considered an issue in CF, are now increasing in CF centres in Europe, the USA and Australia [59-61]. Recent concerns relating to the potential association of incretin-based therapies with pancreatitis and pancreatic cancer have diminished [62] but need to be recognised, particularly in this patient group with pancreatic exocrine insufficiency.

CONCLUSION

The pivotal roles of pancreatic enzyme therapy, gastric emptying and incretin hormones in the pathophysiology of CFRD, characterised by postprandial hyperglycaemia, has largely been ignored. New therapies that act on gastric emptying and the incretin axis should be of considerable interest in the management of postprandial glycaemia in CF. With a high priority being given to finding appropriate and acceptable therapies for pre-diabetes and CFRD, the optimisation of pancreatic enzyme supplementation, which is fundamental in the management of carbohydrate intolerance in CF, should not be overlooked. The benefit of a macro-nutrient 'pre-load', and efficacy, tolerability and long term safety of incretin-based therapies should be further explored in this population.

Fig 1. Gastric emptying of a meal in healthy subjects (n= 6) and CF patients (with and without pancreatic enzyme replacement therapy (PERT), n=5). Results represent means ± SE. Emptying was faster in CF with placebo than in healthy subjects (P<0.001, group-by-time interaction; ^, points of significant difference). PERT normalised gastric emptying compared with placebo in CF patients (P<0.001, treatment-by-time interaction; #, points of significant difference). Reprinted from Kuo et al [41], with permission.

Fig 2. A. Plasma blood glucose, B. insulin, C. insulin-to glucose ratio, D. glucagon, E. GLP-1, and F. GIP concentrations in CF patients with and without pancreatic enzyme replacement therapy (PERT) and in healthy subjects after a mashed potato meal. Results represent mean ± SE. A, Blood glucose was higher in CF with placebo than in healthy subjects (P<0.001, group-by-time interaction; ^, points of significant difference). In CF patients PERT lowered blood glucose (P<0.001, treatment-by-time interaction; #, points of significant difference). B, Insulin concentrations did not differ between the groups. C, Insulin-to-glucose ratio was lower in CF patients than healthy subjects (P <0.05, group effect), and this did not improve with PERT. D, Glucagon concentrations did not differ between CF patients and healthy subjects but tended in CF patients to be higher after PERT (P=0.08, treatment effect). E, GLP-1 was lower in CF patients than healthy subjects (P<0.01, group effect), and this deficiency was completely reversed with PERT. F, GIP concentrations were lower in CF patients than in healthy subjects (P<0.001, group-by-time interaction; ^, points of significant difference). PERT increased plasma GIP secretion in CF patients (P<0.001, treatment-by-time interaction; # points of significant difference), but GIP remained lower than in healthy subjects (P<0.01, group-by-time interaction; *, points of significant difference). Reprinted from Kuo et al [41], with permission.

Fig 3. A. Plasma blood glucose, B. GLP-1, C. GIP, D. insulin, E. insulin-to- glucose ratio, F. and glucagon concentrations in CF patients with placebo and PERT and in healthy controls after a high fat pancake meal. Results represent mean ± SE. A, Blood glucose was higher in CF with placebo than controls (P < 0.0001). PERT partially normalised blood glucose levels (P = 0.0002). B, iAUC GLP-1 was lower in CF than controls (P = 0.04), and normalised with PERT. C, iAUC GIP was lower in CF than controls (P 0.003), and normalised with PERT. D, Insulin concentrations were lower in CF than controls (P = 0.02) and did not normalise with PERT (P = 0.4). D, Insulin-to-glucose ratio was lower in CF than controls and did not normalise with PERT (P = 0.3). E, Glucagon concentrations were similar between CF and controls (P = 0.3) and increased with PERT (P < 0.0001). Reprinted from Perano et al [45], with permission.

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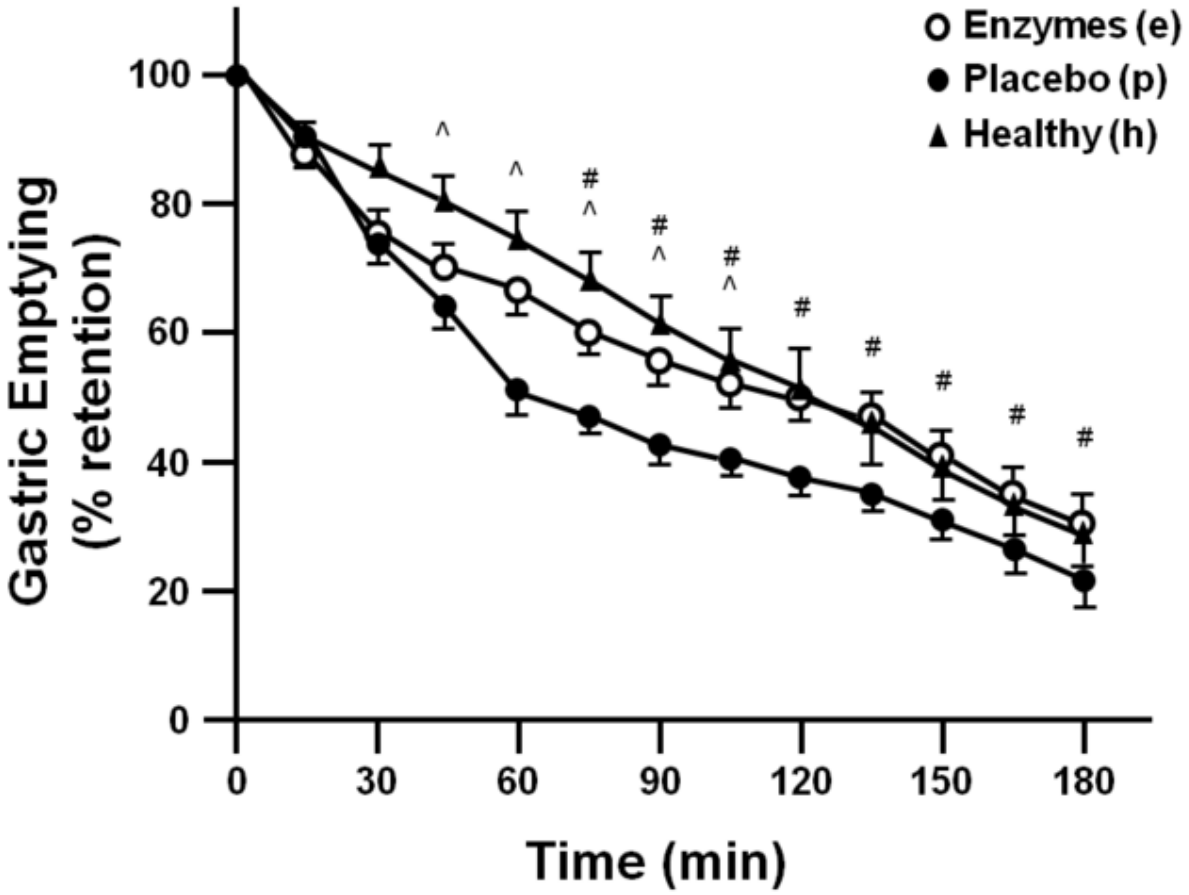

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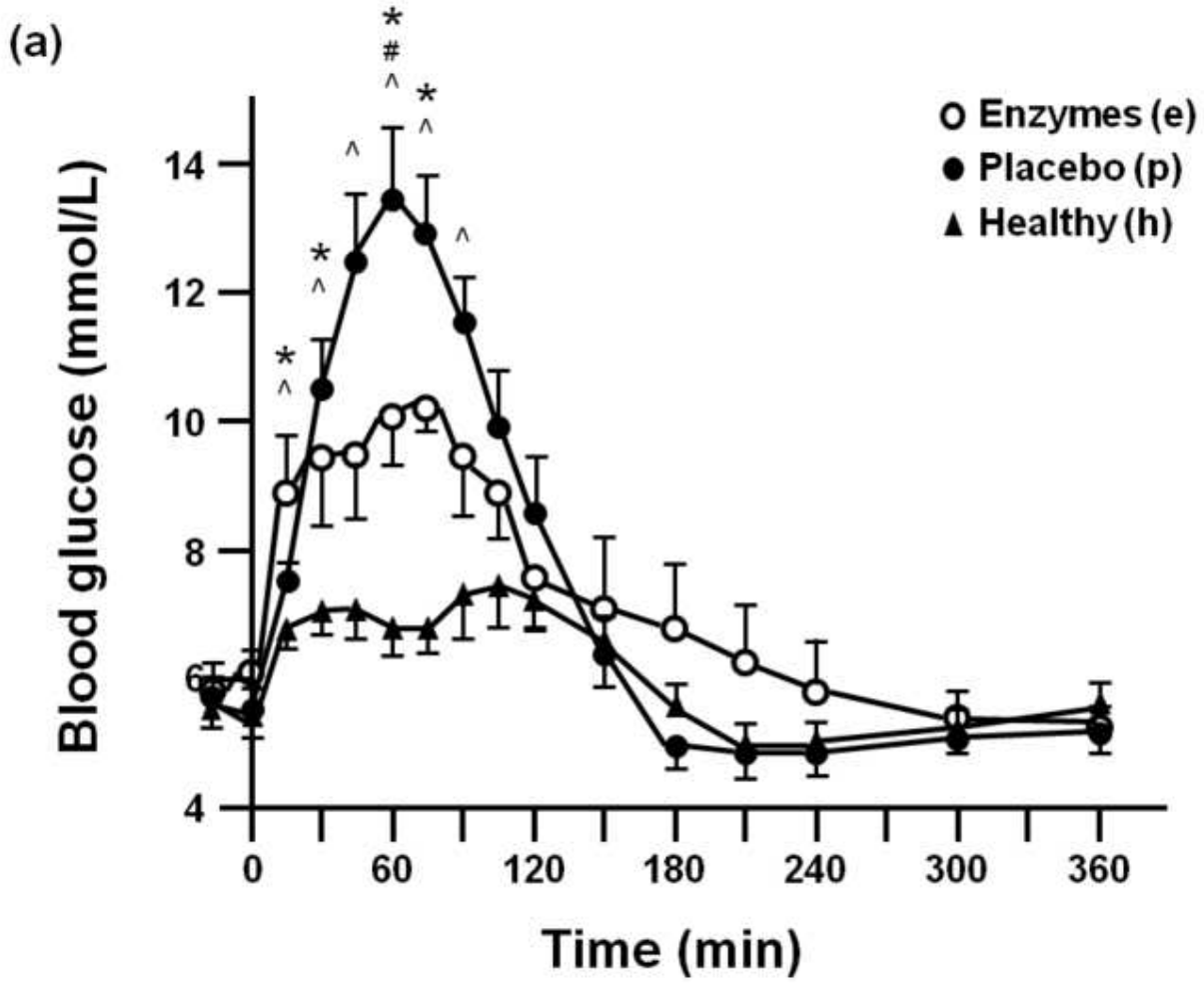

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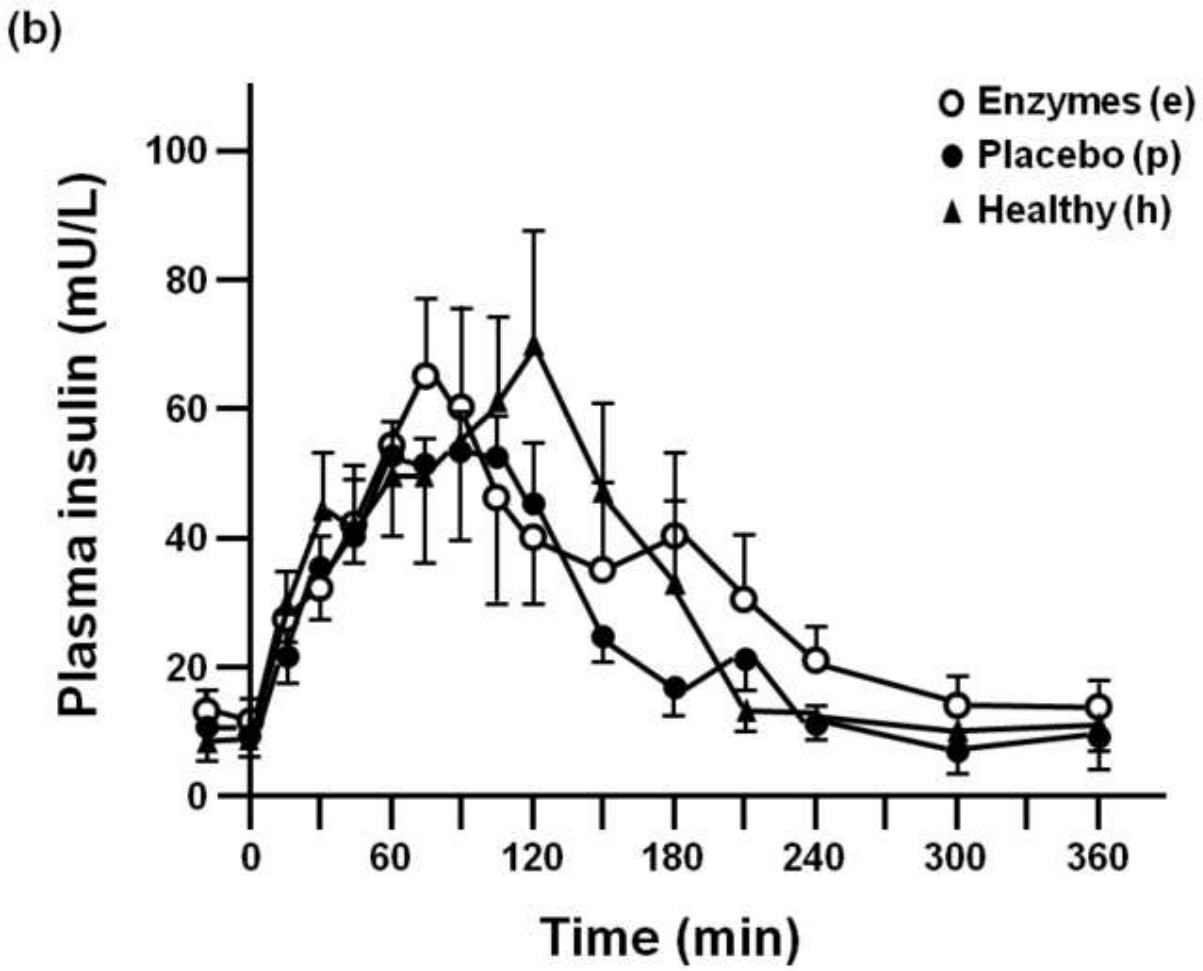

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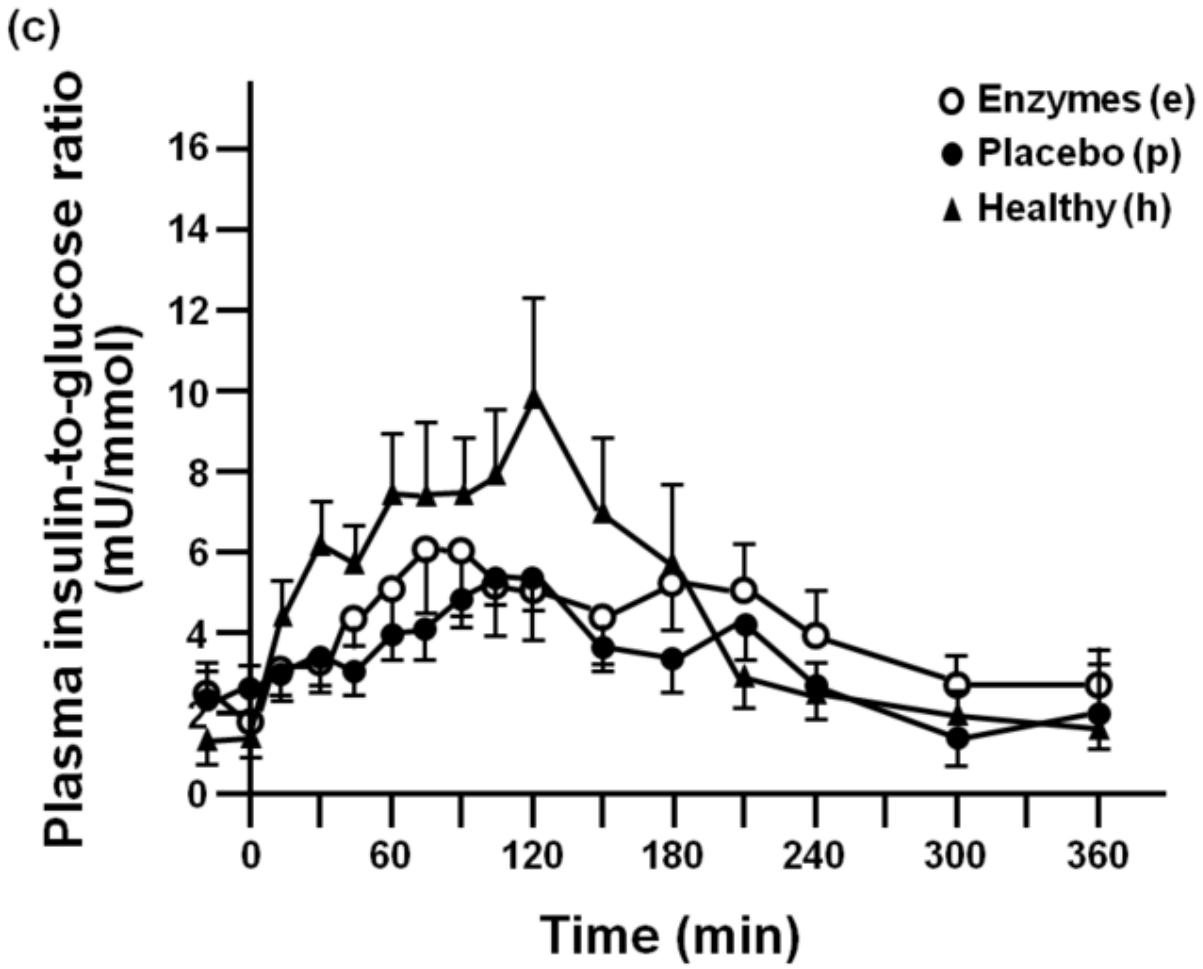

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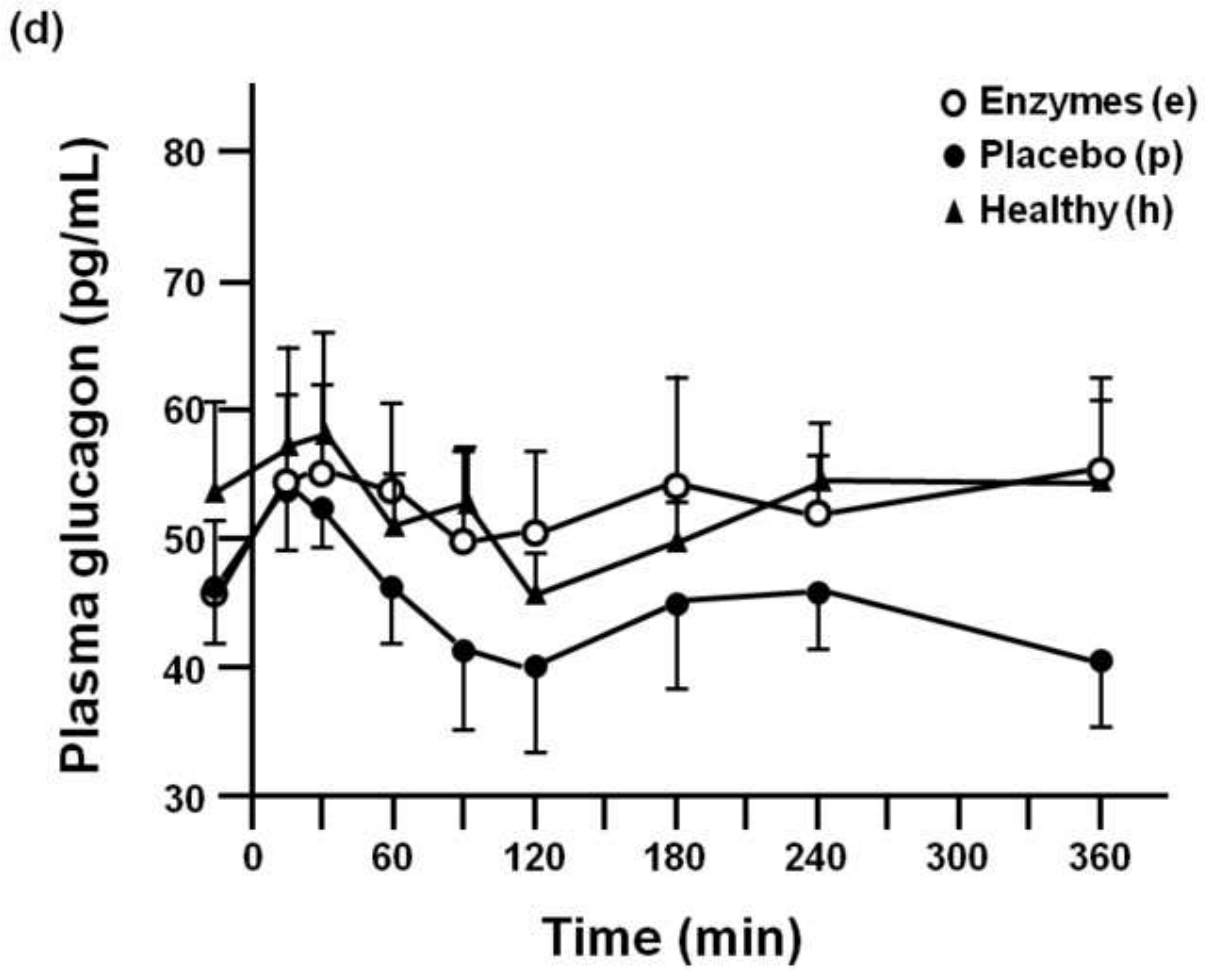

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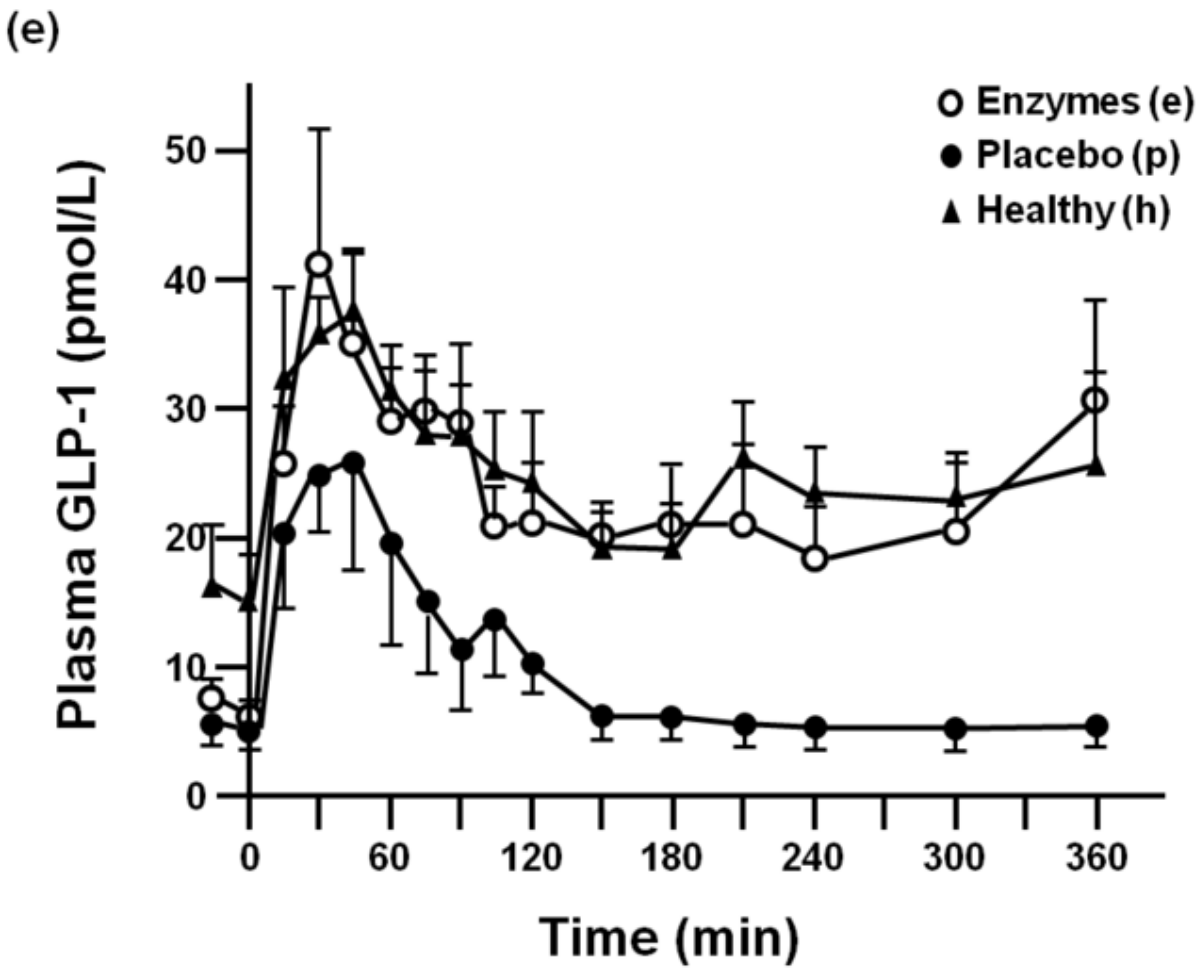

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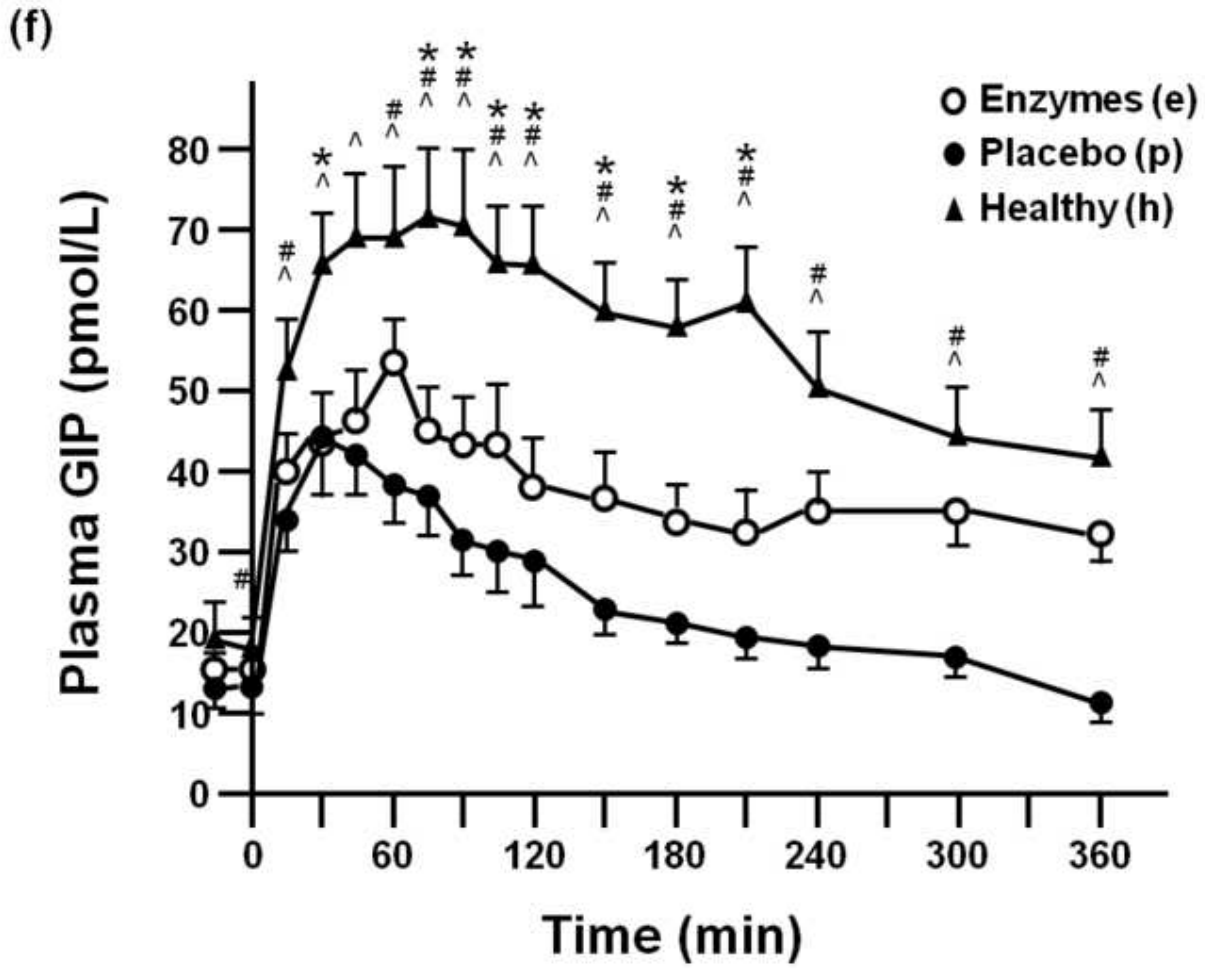

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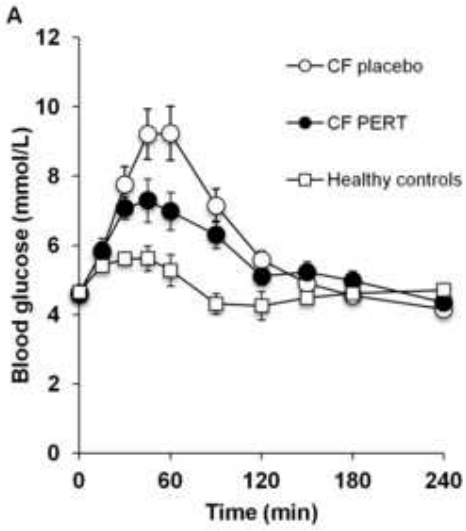

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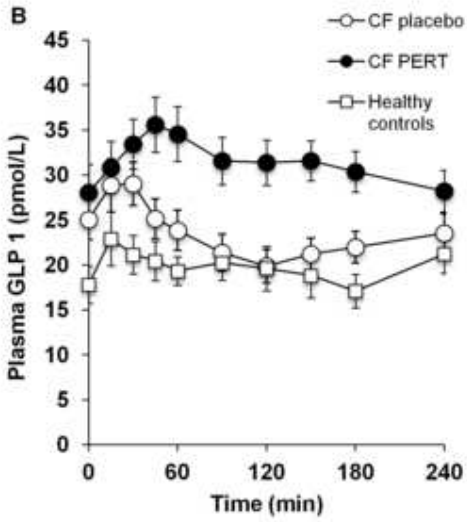

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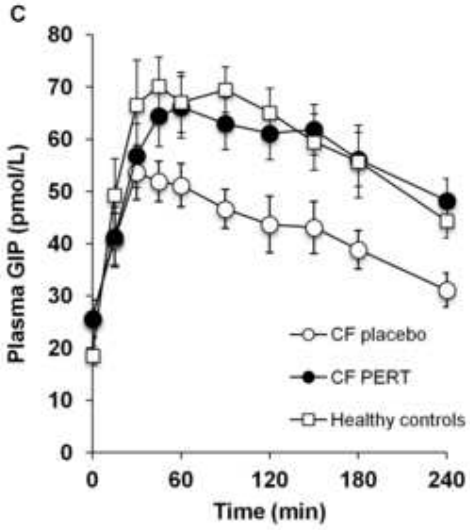

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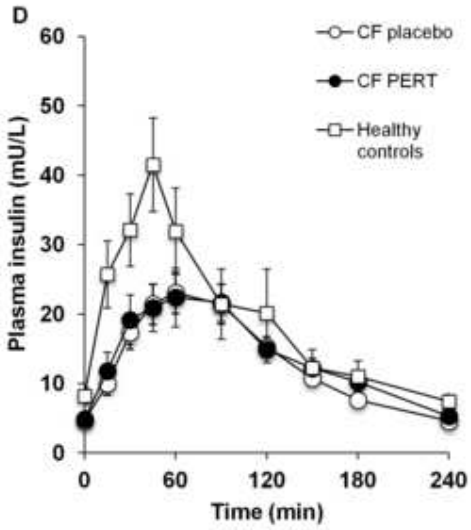

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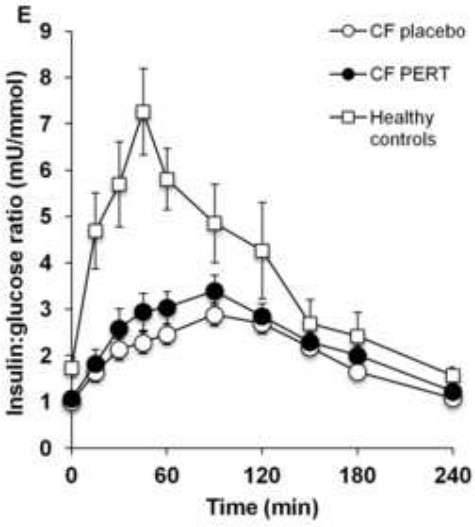

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