



Manipulation of Post-Prandial Hyperglycaemia in Type 2 Diabetes: An Update for Practitioners

Lina Shibib ¹, Mo Al-Qaisi¹, Nicola Guess², Alexander D Miras³, Steve E Greenwald ⁴, Marc Pelling¹, Ahmed Ahmed¹

¹Department of Surgery and Cancer, Imperial College London, London, UK; ²Nuffield Department of Primary Care Health Sciences, Oxford University, Oxford, UK; ³School of Medicine, Ulster University, Coleraine, UK; ⁴Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Correspondence: Mo Al-Qaisi, Email mrcgp74@yahoo.co.uk

Abstract: This review paper explores post-prandial glycemia in type 2 diabetes. Post-prandial glycemia is defined as the period of blood glucose excursion from immediately after the ingestion of food or drink to 4 to 6 hours after the end of the meal. Post-prandial hyperglycemia is an independent risk factor for cardiovascular disease with glucose “excursions” being more strongly associated with markers of oxidative stress than the fasting or pre-prandial glucose level. High blood glucose is a major promoter of enhanced free radical production and is associated with the onset and progression of type 2 diabetes. Oxidative stress impairs insulin action creating a vicious cycle where repeated post-prandial glucose spikes are key drivers in the pathogenesis of the vascular complications of type 2 diabetes, both microvascular and macrovascular. Some authors suggest post-prandial hyperglycemia is the major cause of death in type 2 diabetes. Proper management of post-prandial hyperglycemia could yield up to a 35% cut in overall cardiovascular events, and a 64% cut in myocardial infarction. The benefits of managing post-prandial hyperglycemia are similar in magnitude to those seen in type 2 diabetes patients receiving secondary prevention with statins – prevention which today is regarded as fundamental by all practitioners. Given all the evidence surrounding the impact of post-prandial glycemia on overall outcome, it is imperative that any considered strategy for the management of type 2 diabetes should include optimum dietary, pharma, and lifestyle interventions that address glucose excursion. Achieving a low post-prandial glucose response is key to prevention and progression of type 2 diabetes and cardiometabolic diseases. Further, such therapeutic interventions should be sustainable and must benefit patients in the short and long term with the minimum of intrusion and side effects. This paper reviews the current literature around dietary manipulation of post-prandial hyperglycemia, including novel approaches. A great deal of further work is required to optimize and standardize the dietary management of post-prandial glycemia in type 2 diabetes, including consideration of novel approaches that show great promise.

Keywords: glycemic response, post-prandial, hyperglycemia, diabetes, acarbose, GLP-1, metformin, plant fibre, whey protein, gastric emptying, intestinal absorption, glycemic index, glucose excursion

Introduction

Diabetes was first recorded by the Ancient Egyptians, who managed to identify the condition some 3500 years ago. One of the first to detail the clinical condition was Aretaeus, an ancient Greek physician who lived in Cappadocia (in modern day Turkey) around 120 AD. Aretaeus noted that the disease was “fortunately rare” but added “short will be the life of the man in whom the disease is fully developed”.¹

Today, diabetes is anything but rare. In fact, it is a global pandemic which keeps growing, fuelled and moving in lockstep with the growth in numbers of the overweight and obese. In more modern times, amongst adults, the incidence of diabetes has doubled every 20 years since 1945.² In 1994, the worldwide prevalence of type 2 diabetes was 99 million (1.8% of the global population); by 2010, this figure had reached 285 million people (6.4% of the global population). The prevalence of diabetes increases unabated and is on course to reach a staggering 642 million people by 2030 (7.7% of the global population), assuming the prevalence does not grow at any faster than current rates.³

By contrast, the second observation by Aretaeus, concerning life expectancy in poorly managed diabetes, is still as true today as it was 2000 years ago. In the West, 44% of those with type 2 diabetes will die within 10 years of diagnosis if poorly managed,⁴ mostly from macrovascular disease. The incidence of cardiovascular disease (and mortality from it) is 2–3 times greater in people with type 2 diabetes than in the general population.⁵ As the majority of diabetes patients develop complications, this results in a significant burden on health services. Complications are present in up to 50% of diabetes patients at the time of diagnosis.⁶ Currently, some 10–12% of the entire NHS budget of the UK is spent on diabetes, an amount that will rise to 17% by 2035 if current trends continue.⁷ This devastating trend is unsustainable at a time of tremendous fiscal challenge in the West.

The therapeutic targets of anti-diabetic pharmacotherapy in type 2 diabetes have classically been fasting and pre-prandial glucose levels rather than any specific focus on post-prandial glucose levels.^{8,9} Whereas fasting glucose reflects the net effect of basal insulin and glucagon on endogenous glucose production and glucose disposal, post-prandial blood glucose levels are dependent on the rate of exogenous glucose absorption and associated changes in endogenous glucose production and glucose disposal.¹⁰

It has recently been appreciated that the rise in blood glucose after a meal can make the major contribution to HbA1c, and indeed predominates over fasting blood glucose, in patients with relatively good glycaemic control (ie, HbA1c is 8.0% or less).¹¹ Accordingly, minimisation of post-prandial glycaemic excursions represents a specific target for achieving optimal glycaemic control in otherwise well-controlled diabetes.¹²

Population studies have also found that a fasting glucose level as low as 5.0 mmol/L could still be associated with a 2-hour post-prandial level >11.1 mmol/L.^{13,14} Therefore, post-prandial hyperglycemia is frequently seen even in the setting of “good” diabetic control confirmed by HbA1c and fasting glucose levels.¹⁵

For example, in a 7-day study of 3284 patients with type 2 diabetes otherwise well-controlled on oral medications, when daily plasma glucose profiles were assessed, post-prandial plasma glucose values of greater than 8.9 mmol/L were recorded at least once in 84% of those studied, confirming that post-prandial hyperglycemia is frequently seen even in the setting of “good” diabetic control confirmed by HbA1c and fasting glucose levels.¹⁵ Population studies have found that a fasting glucose level as low as 5.0 mmol/L could still be associated with a 2-hour post-prandial level >11.1 mmol/L.^{13,14}

In patients with type 2 diabetes on oral antidiabetics, where HbA1c has fallen back to a satisfactory level, major post-prandial glucose peaks frequently persist, even in those on insulin. Mean post-prandial glucose values rarely reach their target levels and commonly remain above 7.8 mmol/L.^{16,17}

The main outcome measure tracked in type 2 diabetes has been the general control of fasting (chronic) glycaemia using HbA1c values, with a target of less than 6.5%.¹⁸ However, HbA1c is not able to track post-prandial hyperglycemia. Patients with post-prandial hyperglycemia sufficient for a label of impaired glucose tolerance or even frank diabetes may have HbA1c levels within the normal range, and so carry twice the cardiovascular mortality risk of healthy individuals, without being any wiser about their predicament from a reading of their HbA1c values. Indeed, in the 10-year prospective DIANA study, patients with impaired glucose tolerance who had early intervention targeting post-prandial glycemia saw significantly improved coronary risk outcomes.¹⁹

Controlling post-prandial glucose excursion appears important in both the management and prevention of type 2 diabetes^{20,21} whilst persistent lowering of post-prandial glucose levels can improve overall glycemic control and prevent diabetes-related complications.²² Some authors suggest that post-prandial hyperglycemia is the major cause of death in type 2 diabetes,²³ and also an independent risk factor for other lifestyle-related disease like cardiovascular disease,²⁴ hypertension,²⁵ and obesity.²⁰

Prevention of type 2 diabetes should be a priority for practitioners and society as a whole, but current preventative efforts are yet to yield significant impact on slowing down the rise of the condition or its mushrooming complications. It follows that there must be a gap in the preventative strategy, which necessitates a review of current theory and practice of diabetes management with the aim of highlighting any possible gaps that might yield improvements in both the prevention and the management, but in particular in the prevention. Controlling post-prandial hyperglycemia in the overweight and obese population appears to be key to preventing type 2 diabetes in these populations and should start when individuals are still healthy and lean.^{26,27}

Going Back to the Beginning: Understanding Prandial Glycemia and Hyperglycemia

Studies using digital continuous glucose monitors have provided a real-time window for observing the dynamics of prandial glycaemia in healthy and diabetic individuals.²⁸ In healthy individuals, the glycemic peak is seen 30 to 60 minutes after starting a meal, with maximum blood glucose levels usually dropping below 7.8 mmol/L within 2 hours. Blood glucose levels generally reset to pre-prandial levels after 2 to 3 hours, although digested carbohydrates can take up to 5 to 6 hours after a meal to absorb and register fully in the glycemic profile.^{29,30} Time-in-range is a new metric (3.9–10.0 mmol/L) made possible by continuous glucose monitors. There is strong correlation between time-in-range and HbA1c levels, with a time-in-range of 70% equating to a HbA1c level of 7%.^{31–33}

The post-prandial course of blood glucose levels is modulated by several rate-limiting factors, including gastric emptying; the intestinal absorption of glucose; pre-existing reduced insulin sensitivity in the peripheral tissues; the decrease in the suppression of hepatic glucose output (glycogenolysis) after meals; the rate of gluconeogenesis of the liver; the rate of insulin secretion after meals, and its converse, the glucagon suppression rate; any imbalance of autonomic nerve activity between sympathetic and parasympathetic; and the action of incretin hormones. Disturbances in these particular modulators, some of which are genetically primed, can cause an increase in post-prandial hyperglycemia.^{34–39} A summary of the main pathophysiological mechanisms is illustrated in Figure 1.⁴⁰

In normoglycemics, gastric emptying usually occurs at a constant caloric rate of between 1 and 4 kcal/min with low intra-individual variability⁴¹ with a mean gastric emptying time of 3.5 hours.⁴² Gastric emptying is controlled by the incretin system and influenced by the solid or liquid nature and the macronutrient composition of the meal.^{43–45} Gastric emptying is a major determinant of post-prandial glucose and accounts for some 35% of the variance in peak glucose in both healthy individuals and type 2 diabetes patients. Many practitioners fail to recognise that in patients with type 2 diabetes, including those who have little or no evidence of complications, gastric emptying can be abnormally rapid regardless of glycaemic control, which can result in exaggerated post-prandial hyperglycaemia. Paradoxically, and by contrast, 20–50% of patients with long-standing diabetes who have autonomic neuropathy frequently have delayed gastric emptying, or gastroparesis.^{45–57} These observations are not always consistent.⁵⁸ There is also some inter-ethnic variability in gastric emptying, with Asian populations having more rapid gastric emptying than Caucasian ones.⁵⁹ This is

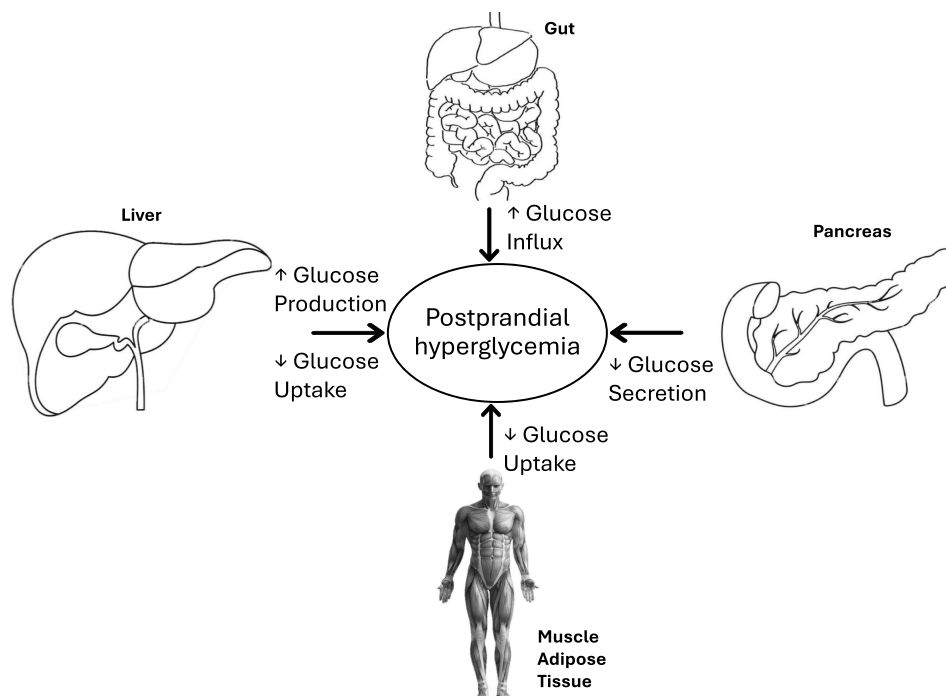


Figure 1 Pathophysiology of Post-prandial Hyperglycemia.

Notes: Re-created from Sudhir R, Mohan, V (2002). This figure was re-created to improve visual quality, maintaining all original data and content unchanged. Original source: Sudhir, R, Mohan, V, Postprandial Hyperglycemia in Patients with Type 2 Diabetes Mellitus. *Mol Diag Ther*, 1, 105–116 (2002), reproduced with permission from SNCSC.⁴⁰

also of note, given the dominance of rice and carbohydrate foods in the habitual Asian diet. Furthermore, there is bidirectional feedback control of gastric emptying, so that gastric emptying is inhibited by hyperglycemia and stimulated by hypoglycemia.⁶⁰ It has been suggested that rapid gastric emptying may precede frank type 2 diabetes.^{61,62}

An understanding of the dynamics of gastric emptying helps guide our understanding of the time course of the peak of glucose excursion after a meal. In individuals with impaired glucose tolerance and early type 2 diabetes, relatively more rapid gastric emptying is associated with a maximal glycaemic response between 30 and 60 minutes and recession at 120 minutes. By contrast, in individuals with long-standing type 2 diabetes, there can be further “shift to the right” so the peak is between 60 and 120 minutes. These results are not consistent and can vary.^{62,63}

Intestinal glucose absorption is a dynamic, complex process that tracks the delivery, digestion, and transport of glucose along the gastrointestinal tract. There is wide inter-individual variation in these factors, but relatively low intra-individual variation. Many practitioners may be unaware that patients with type 2 diabetes or obesity exhibit increased capacity of small intestinal absorption of glucose.^{64–66} Glucose absorption is dependent on a number of factors, principally the exposure of carbohydrate to the mucosa of the small bowel (which in turn is determined by the rate of gastric emptying and small bowel transit), the rate of digestion and breakdown of complex carbohydrates into smaller monosaccharides, and glucose sensing and transport by the small bowel mucosa.^{67–69} The absorption of glucose by the small intestine is the proximate determinant of the appearance and excursion of post-prandial glucose in the peripheral circulation, which is linked to the release of the incretin hormones of the gastrointestinal tract that in turn influence post-prandial glucose metabolism through modulating gastrointestinal motor function, insulin and glucagon release, and satiety.⁷⁰ In type 2 diabetes, increased glucose absorption in the proximal small intestine may reduce the availability of glucose in the distal small intestine, and hence the stimulation of GLP-1 release.⁷¹

The actions of incretin hormones have a major impact on the time course of the glucose excursion in this complicated cycle of interference. Studies have shown that the profile of post-prandial plasma glucose excursion is associated with deficiencies in the secretion of amylin, a glucoregulatory peptide that is normally co-secreted with insulin from the β -cells, as well as the secretion of incretin hormones by the gut, including glucagon-like peptide-1 (GLP-1) and glucose-dependent gastric inhibitory peptide (GIP).^{72–75} Released in response to nutrients from the digestion of food, the gut-derived incretin hormones GLP-1 and GIP act upon pancreatic β -cells to promote insulin secretion. It is estimated that the actions of GLP-1 and GIP drive some 50–70% of post-prandial insulin release.⁷⁶ In addition, GLP-1 suppresses inappropriate glucagon secretion from pancreatic α -cells, and at physiological doses, GLP-1 slows down gastric emptying by inhibiting gastroduodenal motility,⁷⁷ which thereby increases satiety and reduces food intake. Both GLP-1 and GIP are rapidly broken down by DPP-4.⁷⁸

The size, nutritional composition, and timing of meals, combined with the pre-prandial glucose level, duration and type of diabetes, and the presence of comorbidities, are all additional factors that will interact with all these modulators to give the final glycemic profile.^{79–83} Given that foods and beverages are not inert and contain active agents (both natural and as a result of processing) that can interfere with these modulators, it makes the glycemic profile a result of a truly complex interference. For example, common drinks like caffeine speed up gastric motility and interfere with gastric emptying.

Post-prandial hyperglycaemia is defined as having a plasma glucose level of more than 7.8 mmol/L when measured 2 hours after the start of a meal.^{84,85} The post-prandial rise of plasma glucose level and its persistence is a classical sign of diabetes and pre-diabetes. Analysis of the data from the Kumamoto study found a post-prandial glucose of 10 mmol/L to be a threshold for entering a high-risk group for developing diabetes-related complications.⁸⁶ This was also the threshold first accepted by the American Diabetes Association for high risk.⁸⁷ However, the American Association of Clinical Endocrinologists subsequently reduced the threshold for high risk to 7.8 mmol/L.⁸⁸ In 2001, an American Diabetes Association (ADA) consensus meeting accepted post-prandial glucose as a potentially distinct contributor to both HBA1c targets and diabetes-related complications.⁸⁹ Subsequent evidence suggested that reducing post-prandial glucose excursion is equal (or more important) in effect than reducing fasting plasma glucose in reaching overall target HBA1c goals and in reducing the risk of diabetes-related complications.^{12,89} A further important advance in consensus occurred in 2014, when the International Diabetes Federation issued specific guidelines for assessing and treating post-prandial glucose excursions in patients with diabetes, with a threshold of <9.0 mmol/L 1–2 hours after a meal.⁸⁴ In the UK, the National Institute for Health and Care Excellence (NICE) recommends that adults with type 1 diabetes who test post-prandial glucose levels should aim for 5–9 mmol/L at least 90 minutes after eating.⁹⁰ Interestingly, optimal windows for testing for post-prandial peak are associated

with glucose tolerance. In healthy individuals, relatively faster gastric emptying is associated with a peak at 30 minutes. In individuals with impaired glucose tolerance, slightly less fast gastric emptying sees the peak shift to between 30 and 60 minutes. In individuals with frank type 2 diabetes of long-standing duration, there is further rightward shift, so that the peak comes between 60 and 120 minutes. Individuals with early type 2 diabetes can have rapid gastric emptying and shift their peak to the left.^{45,62,63,91}

Most recently, the Endocrine Society convened in 2018 in Washington DC to look at novel self-management methods of addressing post-prandial hyperglycemia in insulin-dependent diabetics.⁹² Despite this concerted effort over two decades, managing post-prandial hyperglycemia remains challenging and poorly understood and/or addressed by practitioners and patients alike.

A Japanese study group has taken real-world data to look at thresholds for post-prandial hyperglycemia. Having first shown that post-prandial hyperglycemia at clinic visits is associated with increased risk of all-cause mortality in real-world patients with type 2 diabetes,^{93–95} they estimated a threshold of 13.8 mmol/L for 2-hour blood glucose to identify patients at high risk of mortality. In addition, from the same data, it followed that patients at high risk of mortality had readings >25% of the time above 10.0 mmol/L, or >5% of the time above 13.9 mmol/L.

Prior to clinical diabetes, there is a variable period of pre-diabetes, and the metabolic disturbance is first evidenced by increasingly elevated levels of post-prandial plasma glucose, which reach the threshold for impairment, followed by the threshold for frank diabetes, in a time-course that depends on genetics and lifestyle. The first glucose abnormality that is detected in pre-diabetes is therefore a subtle, perhaps intermittent, rise in the post-prandial glucose levels because of a reduction in first-phase insulin secretion. Much, much later in the time course of diabetes, only after significant decline in beta-cell function, do we see elevation of the fasting glucose levels.⁹⁶

This knowledge could be of great help to practitioners in giving patients the best chance of avoiding diabetes-related complications.⁹⁶

Post-Prandial Glucose Excursion and Accelerated Atherosclerosis

Post-prandial glucose excursion is a marker for metabolic abnormalities that are associated with early and progressive atherosclerosis. The underlying pathophysiology for this is being slowly unravelled.

Post-prandial hyperglycemia induces oxidative stress,⁹⁷ which in combination with soluble advanced glycation end products (AGEs) and lipid peroxidation products, act as key activators of upstream kinases, leading to endothelial dysfunction and expression of inflammatory genes.⁹⁸ Numerous studies have shown that hyperglycemic spikes are associated with endothelial dysfunction in normal volunteers and in patients who have type 2 diabetes.^{99,100}

In vitro studies confirm that the post-prandial glucose spike (especially if rapid) provokes endothelial cell apoptosis and induces endothelial cell damage.¹⁰¹

Williams et al showed that intra-arterial infusion of 50% dextrose to induce acute hyperglycemia in healthy subjects resulted in impaired endothelium-dependent vasodilation.¹⁰² This confirms that elevated glucose levels are likely a chronic cause of endothelial dysfunction.

Shige et al demonstrated endothelial function became impaired in type 2 diabetes after the intake of fat- and sucrose-rich meals, with the level and change in post-prandial endothelial function correlating closely with concurrent changes in blood glucose.¹⁰³ Others have shown that a rapid deterioration in endothelial function is seen in pre-diabetic patients undergoing an oral glucose tolerance test, and this deterioration correlates with the level of hyperglycemia measured at 2 hours.¹⁰⁰

Endothelial dysfunction marks the first stage of atherosclerosis.¹⁰⁴ There is a strong relationship between endothelial dysfunction and risk of atherosclerotic disease, whilst the degree of early endothelial dysfunction reflects the predisposition of an individual to develop further atherosclerotic disease. Therefore, the presence and degree of endothelial dysfunction is a proxy and early marker for the risk of diabetes-related complications.¹⁰⁵

Acute hyperglycemia in both normal and diabetic subjects increases circulating levels of ICAM1, which is an activating factor in the first stage of atherosclerosis.^{106,107} Atherosclerosis is essentially an inflammatory process, especially in diabetes,¹⁰⁸ and acute hyperglycemia during the post-prandial state increases production of plasma interleukin-6, tumor

necrosis factor- α and interleukin-18.¹⁰⁹ Given post-prandial peaks are higher and last for longer in type 2 diabetes and pre-diabetes, ICAM1 levels will also be greater in these conditions.

Neutrophil activation also plays a major part in the inflammatory process inducing atherosclerosis. Of the various types of leukocytes, the neutrophil count was shown to be the best predictor of future cardiovascular events in a large patient cohort with high risk of coronary artery and cerebrovascular disease.¹¹⁰ Acute increases in post-prandial plasma glucose are associated with activation of neutrophils in patients with impaired glucose tolerance.¹¹¹

Acute hyperglycemia promotes oxidative stress. The direct evidence for this is based on the effects of post-prandial hyperglycemia on markers of oxidative stress such as nitrotyrosine and 8-iso-prostaglandin F 2α (8-isoPGF 2α).¹¹¹

Early atherosclerosis is detectable in the carotid artery, especially in patients with type 2 diabetes, as well as those with prediabetes. The relationship between post-prandial hyperglycemia and atherosclerosis can be tracked against the carotid intima-media thickness (IMT). This variable, commonly measured with imaging ultrasound, is a reliable predictor of myocardial infarction and stroke.¹¹² Multivariate analysis shows that the 2-hour post-prandial glucose level is closely associated with increased IMT but there was no correlation between HbA1c nor fasting glucose levels and abnormal IMT values. When 2-hour prandial glucose was >7.8 mmol/L, the odds ratio for an increased IMT was 1.88.¹¹³ Post-prandial hyperglycaemia is a strong and independent marker of accelerated atherogenesis in IMT studies, whereas fasting glucose levels are not.

Post-Prandial Hyperglycemia and Diabetic-Related Complications

Diabetic cardiovascular disorders include microvascular and macrovascular disease. Microangiopathy typically manifests as diabetic retinopathy and diabetic nephropathy, while the macrovascular disorders frequently include occlusive vascular disorders leading to myocardial infarction, cerebral infarction and peripheral arterial disease of the lower limbs.

Cardiovascular complications account for 40–50% of deaths in patients with type 2 diabetes¹¹⁴ and reduce life expectancy by 5–10 years. The risk of complications is particularly pertinent for younger patients as they have longer to develop complications.¹¹⁵ Type 2 diabetes has been shown to be associated with a markedly increased risk for atherosclerotic coronary arteries and cerebrovascular diseases.^{116,117}

Even in the early stages of type 2 diabetes, when fasting glucose and HbA1c can be within normal limits, post-prandial hyperglycemia is a risk for macrovascular complications (such as myocardial infarction or stroke)^{118–122} as well as microvascular complications.^{51,113,123} Impaired glucose tolerance predisposes to the acceleration of atherosclerosis and therefore progression of cardiovascular events.¹²⁴

Diabetes-related complications, such as retinal disease, renal failure, and peripheral arterial disease, are also morbid and affect quality of life. Some 26 million patients in the West suffer with peripheral arterial disease alone, most of them asymptomatic until the disease has progressed significantly. On the other hand, it has been known for some time that almost two-thirds of patients with symptomatic cardiovascular disease have deranged glycaemic control.¹²³ A significant number of these patients would not be picked up by testing fasting glucose levels, but only when testing after a meal or through an oral glucose tolerance test.¹²⁴

It is post-prandial hyperglycemia, not fasting hyperglycemia, that can independently predict the occurrence of cardiovascular complications.¹²³ For example, the data from the Funagata Diabetes Study consistently showed that the 1-hour or 2-hour glucose level was a better predictor of cardiovascular risk than both the fasting glucose and the HbA1c level.¹³ Even a mild rise in post-prandial blood glucose is associated with an increased risk of cardiovascular mortality.¹³

Several epidemiological studies have shown a strong correlation between elevated post-prandial glucose levels and negative clinical outcomes.

Some of the most interesting data has been in studies of fetal health in gestational diabetes linking post-prandial hyperglycemia to fetal macrosomia.^{125,126}

Numerous studies have provided population data linking post-prandial glycemia and onset of cardiovascular disease. A large study tracking a novel proxy biomarker for post-prandial hyperglycemia (1,5-anhydroglucitol) found strong evidence to link post-prandial glucose to cardiovascular disease.¹²⁷ Studies, such as DECODE (Diabetic Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe), demonstrated that post-prandial levels of glucose are an independent risk factor for cardiovascular disease and that they have greater effect than the fasting glucose.^{128,129}

The DECODE study produced a continuous graded and direct relationship between 2-hour glucose and the risk of cardiovascular mortality.¹²⁹ Accelerated post-prandial excursion is strongly associated with the development of cardiovascular disease.^{129,130} Even in patients with normal glucose tolerance and with a post-prandial glucose <7.8 mmol/L, the level of peak post-prandial glycemia still correlates with the risk of cardiovascular mortality and all-cause mortality.¹³¹ The cardiovascular risk associated with post-prandial glycemia begins to increase at levels >4.4 mmol/L. Even at 7.8 mmol/L, the threshold at which patients are classified as only just having impaired glucose tolerance (IGT) or prediabetes, cardiovascular risk is already increased by 58%.

These findings concerning post-prandial glycemia are seen in populations of various ethnicities. The results of the DECODA Study in Asians showed that 2-hour blood glucose levels accurately predict total death and cardiovascular death.¹³²

The risk of cardiovascular disease and all-cause mortality increases with increasing levels of post-prandial glycemia.¹²⁰ The Honolulu Heart Study found an increased risk of death from coronary heart disease alone and in combination with non-fatal myocardial infarction that independently tracked increased levels of post-prandial glucose.¹²¹

The Diabetes Intervention Study¹³³ was the first study to investigate 1-hour post-prandial glucose levels after a meal (breakfast). Those with post-prandial glucose level >10 mmol/L at inclusion had a 40% greater risk of myocardial infarction than those with ≤8.05 mmol/L. Multivariate analysis confirmed that 1-hour post-prandial glucose levels (after breakfast) were an accurate predictor of mortality, whatever the cause. In newly diagnosed type 2 diabetes, the study additionally demonstrated that whilst post-prandial glucose is an independent risk factor for mortality, fasting blood glucose was not.¹³³

In another study in native Americans, independent of other risk factors, 2-hour post-prandial glucose was correlated with the onset of cardiovascular disease and diabetic complications, whilst the risk of death from both of these was increased by 20–30% for each 5.6 mmol/L increment in the 2-hour prandial glucose level.¹³⁴ In the Verona study, the predictive power of fasting glucose and post-prandial glucose levels (sampled twice, after breakfast and lunch) for cardiovascular events remained consistently accurate and equally predictive, even after accounting for various other risk factors.¹³⁵

The UK Prospective Diabetes Study (UKPDS) revealed a strong association between fasting hyperglycaemia and microvascular complications in type 2 diabetes. For each 1% improvement in HbA1c, there was a concomitant 37% reduction in the risk of retinal disease.¹³⁶ However, the UKPDS study did not interrogate post-prandial glucose values separately in its analyses and relied only on fasting glucose values to modulate treatment. By contrast, the prospective Kumamoto study used both variables (fasting and post-prandial glucose) for adjusting intensive insulin therapy and had data from 8 years of follow-up.⁸⁶ The Kumamoto study confirmed that post-prandial glucose values are strongly linked with the onset of retinal and kidney disease (similar to the association with fasting glucose and HbA1c levels).⁸⁷ In established diabetes, there is little room to doubt that both post-prandial hyperglycaemia and fasting hyperglycaemia are powerful promoters of diabetic microangiopathy and the consequent microvascular complications associated with diabetes. Further, the relative contribution to the risk of developing microvascular complications from post-prandial hyperglycemia increases substantially when the degree of fasting hyperglycaemia is still moderate or minor. In patients with type 2 diabetes on oral medications and with an HbA1c value of less than 7.3%, the post-prandial glucose level contributes some 70% to the residual excess of HbA1c.¹¹ In these patients, practitioners should consider treatment that specifically targets post-prandial glucose, such as adding acarbose or a glinide to the conventional treatment.

The data from all these studies suggest that post-prandial glycemia is a relevant and important factor for predicting cardiovascular risk in type 2 diabetes and cannot be completely ignored. In fact, post-prandial glucose is more important than fasting glucose in patients with pre-diabetes or early diabetes for microvascular complications. Then in established diabetes, post-prandial glucose excursion has a similar impact on risk to that of fasting blood glucose levels for microvascular complications. As far as diabetic macrovascular complications are concerned, post-prandial blood glucose excursion can be more specifically implicated than fasting hyperglycemia.

Whilst looking at relative contributions to risk, it is also important to put these results into an absolutist context. Addressing post-prandial hyperglycemia yields benefits of the same order of magnitude as those seen in diabetic patients receiving secondary prevention with statins, the advent of which is widely regarded as one of the top advances of modern medicine.¹³⁷ Despite this, to date, the relative value of the two variables (fasting glucose versus post-prandial glucose) is poorly understood or acted upon by practitioners, leading to poorer outcomes for patients.

Although there are relatively fewer of them within the output of diabetes research, several studies have confirmed that managing post-prandial glucose spikes significantly reduces diabetes-related complications. A large study of Australian adolescents, albeit type 1 diabetics, showed a significant reduction in diabetic retinopathy when insulin programmes were adjusted to address post-prandial glycemia.¹³⁸

Recently, the concept of glucose variability has been reported by various studies.¹³⁹ Rapid excursions in blood glucose – both up and down – are not specifically reflected in HbA1c,¹⁴⁰ and we frequently see type 2 diabetes patients with similar HbA1c results but markedly different daily glucose profiles when tracked on a continuous glucose monitor, where the frequency and duration of glucose peaks and troughs can be tracked.¹⁴¹ Post-prandial glucose is the major determinant of glucose variability in patients with type 2 diabetes or pre-diabetes.¹⁴²

There is mounting evidence that glucose variability is a more damaging accelerator of atherosclerosis than chronic hyperglycemia.¹⁴³ In particular, glucose variability is a marker for increased progression of coronary artery disease and plaque vulnerability.^{144–156} Glucose variability can predict early mortality in the general population as well as those with pre-diabetes or frank type 2 diabetes.^{157,158}

Targeting glucose variability in healthy volunteers with lifestyle interventions has been shown to be more effective than using drugs^{159,160} and netted up to some 50% reduced risk of developing type 2 diabetes.^{161,162}

Dietary Manipulation of Post-Prandial Hyperglycemia

Nutritional interventions represent the greatest opportunity to cost-effectively manipulate and optimise post-prandial glycemic excursions.¹⁶³ Any dietary intervention that slows down gastric emptying and/or gastric digestion/absorption of glucose stimulates enhanced natural secretion of GLP-1 (with associated improvements in insulin release and reduction of insulin resistance) and is therefore highly desirable and a focus for further scrutiny in this section.

A novel dietary intervention to limit post-prandial glucose excursion would be to eat carbohydrates last in a meal. Data from several studies^{164–166} in patients with pre-diabetes and type 2 diabetes suggested that nutrient order and consuming carbohydrates last could reduce post-prandial glucose and insulin peaks by more than 40%.

Macronutrient preloads of plant fibre and/or protein in advance of meals have been found to significantly reduce both glucose and incremental glucose peaks compared to eating carbohydrates ad libitum.^{164,166–172}

Dietary fibers are resistant carbohydrates, which do not undergo digestion, and appear to be an important anti-diabetic component of the diet. Systematic reviews and meta-analyses have shown that total fiber intake reduces T2D risk and incidence in a dose-dependent manner.^{173,174} Fibers vary widely in their water solubility, viscosity, binding, bulking ability, and fermentability, and consequent effect on health.^{175,176} Fermentable (pre-biotic), soluble, and highly viscous fibers have the most effect on cardiometabolic health.^{175–182} Consumption of viscous dietary fibre can slow down gastric emptying. Viscous soluble fibres slow down gastric emptying by forming gel-like structures after ingestion and can interfere with both digestion and absorption of sugars.¹⁸³ Increasing soluble fiber intake with a meal has a positive effect on post-prandial glucose in patients with type 2 diabetes.^{184–188}

Consuming whey protein in doses ranging from 9g to 60g up to 30 minutes prior to a meal as a preload has been shown to effectively regulate glucose excursions in type 2 diabetes by 30 to 50% of the post-prandial glucose areas under the curve.^{170,189–209} Consistent daily pre-meal shots of as little as 15g whey protein in patients with non-insulin dependent type 2 diabetes on ad libitum diets reduced time spent in hyperglycemia by an average of 9% or 2 hours per day, translating to a 16.4% reduction in the time-averaged area under curve, and accompanied by enhanced secretion of GIP, GLP-1, and glucagon, as well as a 2-fold increase in plasma insulin concentrations.^{210,211} Adding protein-rich sources to carbohydrate-based meals reduced post-prandial glucose peaks by 20 to 30%.²¹² Replacing breakfast with a liquid whey protein meal replacement appears to improve post-prandial glycemic and GLP-1 responses when compared to regular breakfasts in patients with type 2 diabetes.²¹³

These benefits of whey protein consumption prior to meals for reducing carbohydrate-induced post-prandial hyperglycemia appear to be retained in older adults.²¹⁴ Further, whey protein is likely to have other beneficial effects in older people that reduce risk of diabetes-related complications, like maintaining skeletal muscle mass and function, and reductions in blood pressure, blood triglyceride levels, inflammation and oxidative stress.²¹⁵

Lower doses of whey protein given 10min to 30min before meals lower glucose excursion principally by slowing gastric emptying without stimulating insulin secretion.^{26,203,205,216} By contrast, co-ingestion of whey protein with a meal is reported to blunt glucose excursion by increasing insulin secretion in a dose-dependent manner, requiring higher doses of protein.²¹⁷

Moreover, a second meal effect has been recently described, where food choice in one meal (good or bad) has an effect on the post-prandial glucose level of the second meal.²¹⁸ A second meal effect has been reported with protein, which usually suppresses the post-prandial glucose in the subsequent meal.^{219–222}

Food order therefore represents a novel and simple intervention to improve glucose and insulin peaks after food.

The Role of Pharmacotherapy in Dietary Manipulation

In frank diabetes, pharmacotherapy will be required in almost all cases as part of its management, although recent work has underscored the potential reversibility of type 2 diabetes. As many as 50% of overweight patients with type 2 diabetes who shed at least 10kg of body fat (through lifestyle interventions) can go into remission, an eye-opening statistic that reaches 90% in those who are able to shed 15kg of body fat.²²³

The gastrointestinal actions of metformin have been overlooked, which are highly relevant to its glucose lowering after meals. For example, metformin slows gastric emptying to reduce post-prandial glycaemia in type 2 diabetes.²²⁴ There is also recent evidence showing that metformin, when administered 30–60 min before a nutrient load, is more effective than administration with a meal, to reduce the subsequent glycaemic response in metformin-treated patients with type 2 diabetes.^{225,226}

Newer GLP-1 agonists have joined many other classes of medication that target post-prandial hyperglycemia. GLP-1 drugs potentiate B-cell activity and the release of insulin.

However, with respect to pharmacotherapy, it should be noted that repeated overstimulation of the B-cell may accelerate the loss of B-cell function and lead to a deterioration in glycemic control in the long run.²²⁷ Therefore, interventions that can modulate post-prandial glycemia without requiring or further stimulating artificial insulin release should be exhausted first before those that rely on intrusive pharmacotherapy.

Acarbose is a drug which is known to be dietary modulant and can positively impact post-prandial glucose excursion through regulating and/or inhibiting the activity of digestive enzymes, but which has negligible or no absorption into the human blood stream, acting in effect like a dietary supplement. This less intrusive drug is worthy of special consideration by practitioners. Interestingly, inhibition of carbohydrate digestion and absorption in the proximal small bowel would intuitively potentiate the possibility of increased interaction of nutrients with the distal small bowel and thereby increase the secretion of GLP-1.⁶⁵

Acarbose is particularly noteworthy due to its lower costs, and fewer side effects, not least because of its negligible systemic absorption. An experimental combination oral drug with long-acting acarbose and orlistat (which similarly has negligible systemic absorption) has given stellar results in research trials for glycemic control and weight loss and would therefore be an excellent candidate for long-term prevention and improved outcomes for type 2 diabetes, although there does not appear to be much reaction from the pharmaceutical industry or mainstream academia to this very important work.^{228–230}

Targeting Post-Prandial Glycemia to Reduce Risk

Only one study about preventing type 2 diabetes (STOP-NIDDM) has specifically included the treatment of post-prandial hyperglycaemia in its outcome measures. Its primary aim was to determine the reduction in the development of confirmed type 2 diabetes by early treatment of impaired glucose tolerance (IGT) within a moderate range (defined as 2h post-prandial glucose in the range of 7.8 mmol/L – 11.1 mmol/L, so long as fasting glucose was in the range of 5.6–7.7 mmol/L) with acarbose.

Using an average daily dose of 194mg acarbose for 3.3 years, the rate of conversion from IGT to diabetes was 25% less when compared to using placebo.²³¹ The STOP-NIDDM study also revealed a dramatic reduction in the onset of cardiovascular events, consistent with the findings of many other studies.¹³⁷ Patients using the acarbose had a 49% reduction in all types of cardiovascular events, as well as a 2.5% reduction in the absolute risk. This protective effect was

particularly pronounced for myocardial infarction, where the relative risk was reduced by a colossal 91% whilst the absolute risk improved by 2.9%.

Interestingly, the soft epidemiological data from using acarbose in the STOP-NIDDM study can be validated against harder imaging data in patients with impaired glucose tolerance and in those with confirmed diabetes. After 3.9 years of using acarbose, the progression of IMT ($0.02 \pm 0.07\text{mm}$) was significantly attenuated in the acarbose group compared to controls on placebo ($0.05 \pm 0.06\text{mm}$; $p = 0.027$). On further analysis, the annual progression of IMT was found to be approximately 50% slower on acarbose, and IMT even regressed and returned to the mean values seen in non-diabetic individuals for many of the patients treated with acarbose. The improvement seen in IMT with remained significant even after multivariate analysis adjusting for variations in sex, body mass index (BMI), heart rate, high-density lipoprotein-cholesterol, and total cholesterol.

Elsewhere, and in lockstep with these observations, it has been reported that, after just 3 months of treatment with acarbose, there are significant improvements in endothelial function (as serially assessed by flow-mediated dilatation, a proxy test for endothelial function) and a reduction in hsCRP and VCAM-1.¹¹¹

A meta-analysis of acarbose known as MeRIA (Meta-analysis of Risk Improvement under Acarbose) included a total 7 studies of patients with type 2 diabetes. MeRIA analysed results in patients who had been randomly assigned to double-blind treatment with acarbose (dose range 50–200mg, up to three times daily) versus treatment with placebo.¹⁰¹ There was a 35% reduction in cardiovascular events in patients treated with the acarbose compared to those receiving only the placebo ($p < 0.01$). The absolute risk of a cardiovascular event improved by 3.3% in the patients using acarbose. This translates to a benefit of preventing one cardiovascular event for every 30 patients treated with acarbose for the period of the study period (1.9 years). The analysis of data confirmed again that, in particular, the rate of myocardial infarction was reduced by no less than 64% in the patients treated with acarbose compared with those using only the placebo.¹³⁷

Several separate cardioprotective benefits have been reported from treating post-prandial hyperglycemia. There was an unexpected 34% reduction in the incidence of new cases of hypertension (defined as blood pressure $>140/90\text{mm Hg}$) in patients treated with acarbose compared with placebo during a prospective study (STOP-NIDDM).¹³⁷ Two mechanisms have been proposed for this unexpected finding: an improvement in endothelial function linked to the attenuation of post-prandial glucose levels and/or a reduction in post-prandial water and salt absorption induced by acarbose, an effect previously seen in healthy volunteers.²³²

Further, it is known that post-prandial increases in blood glucose levels are linked to increases in the level of triglycerides. In patients with type 2 diabetes with normal fasting triglycerides, serum triglyceride levels double or triple during the day, with peaks typically seen after meal times.²³³ This post-prandial hypertriglyceridemia in type 2 diabetes is a potent pro-atherogenic factor, correlating closely with carotid IMT values, and similar to post-prandial glucose and low-density lipoprotein (LDL) levels.²³⁴ Adequate control of post-prandial hypertriglyceridemia is therefore a high-value target (alongside post-prandial hyperglycemia) for preventing macrovascular complications in diabetic individuals.²³⁵ Acarbose is capable of inhibiting both these pro-atherogenic actors, inducing a significant reduction in post-prandial hypertriglyceridaemia, both in those with normal and those with elevated fasting triglyceride values.^{236,237} Interestingly, acarbose also reduces the levels of post-prandial remnants and chylomicrons.²³⁷

It is important to note that when one compares the results of acarbose treatment to those of the UKPDS study, the results with acarbose are vastly superior. This finding should be all the more noteworthy for practitioners to consider, given that the UKPDS study is the largest prospective type 2 diabetes study of its kind, where patients received “intensive” therapy – but little or none of that “intensity” was targeted at post-prandial hyperglycemia specifically. At the end of the treatment period in the UKPDS study, there was a 16% reduction in myocardial infarction compared to control subjects (which was of dubious significance, $p = 0.052$), whilst HbA1c was reduced by 0.9%.²³⁸ By contrast, in MeRIA, myocardial infarction was cut by 64% and HbA1c values by 0.6%.¹³⁷

During the UKPDS, the target for the therapeutic strategy was based almost exclusively on fasting glucose values, with a target fasting glucose of $<6\text{ mmol/L}$. Patients were treated with either a sulfonylurea or an injection of ultralente or isophane insulin.²³⁸ By contrast, the target in MeRIA was principally post-prandial glucose, with a mean reduction of 9.13 mmol/L , and only a slight reduction in fasting glucose values (-3.04 mmol/L). The huge reduction in the rate of coronary events with acarbose compared to “intensive” therapy in UKPDS is almost certainly due to the improvement in

post-prandial hyperglycemia and secondary improvement in post-prandial (hyper)triglyceridemia seen specifically with acarbose use. This dramatic improvement in outcome correlates with what has been demonstrated elsewhere from a reduction in pro-atherogenic factors (like oxidative stress, endothelial dysfunction, etc.) and sharper control of general cardiovascular risk factors (systolic blood pressure, body mass index, post-prandial hypertriglyceridemia, post-prandial pro-coagulant factors). This explains why very similar results were reported in the STOP-NIDDM study, which initially, only included patients with impaired glucose tolerance or patients with no or only slight fasting dysglycaemia. The final damnation of the therapeutic approach taken in UKPDS is that more than 50% of diabetic patients in UKPDS progressed to insulin within 9 years. This tells us that “best practice treatment” of the type in UKPDS, even when intensive, is poor therapy at best, or no therapy at worst, for the underlying pathophysiological condition.

The multi-source, independent evidence that attenuation of post-prandial dysmetabolism by acarbose results in improved endothelial function and inflammatory status, slowing down and reversing atherosclerosis, points strongly to what might be missing from the UKPDS therapeutic strategy. It should be made particularly clear to practitioners that acarbose appears not only to *prevent* but also *reverse* atherosclerosis, the latter aspect making post-prandial hyperglycemia an interesting topic for practitioners to explore further in the midst of a diabetes pandemic.

Significantly preventing or slowing down progression from impaired glucose tolerance to frank diabetes, and from frank diabetes without insulin to where insulin is required, is not only seen with acarbose therapy but also with dietary interventions and other therapeutic approaches that attenuate post-prandial hyperglycemia, including the thiazolidinediones and orlistat.²³⁹ With respect to orlistat, the XENDOS study was one of the largest of its kind.²⁴⁰ In the XENDOS study, there was an almost 30% reduction in the overall cumulative incidence of new type 2 diabetes over 4 years with orlistat treatment, and in those in whom pre-diabetes had already been diagnosed the reduction was close to 47%.²⁴¹

Given that post-prandial hyperglycemia, a preventable cause of morbid complications, is directly induced by the intake of food and drink and that dietary modifications are likely to enhance the effect of pharmacotherapy, education about diabetes should focus more on its control.

Towards More Effective Lifestyle Interventions

Interestingly, following a low calorie, low fat, low carbohydrate diet in addition to consistent physical exercise (a lifestyle with which it is not easy to ensure or maintain compliance) would probably suffice to control post-prandial hyperglycemia in pre-diabetes patients.²³⁰ As few are compliant with lifestyle advice in the long term, this section has been reserved for the end.

For those few who can be compliant, lifestyle changes that inhibit post-prandial hyperglycemia are additive and synergistic to pharmacotherapy in frank diabetes for preventing progression, even more so than in populations with pre-diabetes or normoglycemia.

It should be mentioned that recently structured psychological behavioural interventions aimed at dietary manipulation have shown traction, with up to 30% of patients maintaining the dietary adjustment and benefits at 2 years. Behavioural intervention is eminently deliverable via digital means, with digital behaviour change apps like Noom becoming a booming trend in the US.^{242,243}

Exercise is an adjunct to dietary modulation. The timing of exercise appears to be more important than its amount or vigour.²⁴⁴ As little as 10 minutes or more of post-prandial walking can lower the glycemic impact of meals, effectively blunting post-prandial sugar spikes.²⁴⁵ Other studies have shown benefits from moderate or high-intensity exercise some 30 to 60 minutes after eating.²⁴⁶

It has to be considered by practitioners that patients have very low compliance with lifestyle interventions in general. By contrast, lifestyle changes specifically addressing post-prandial hyperglycemia can be very focused and far less disruptive, and therefore more likely to achieve better compliance. For example, advising a brisk walk within 30 minutes of food is perhaps more easily accepted and implemented than the traditional “move more, eat less” advice. Very short high-intensity interval training routines of a type that can target post-prandial hyperglycemia (but which can be done seated, or standing, without breaking into a sweat, or leaving the office, and which take less than 5 minutes) can easily be designed by physical therapists. Of great promise and causing minimal disruption are Electrical Muscle Stimulation (EMS) belts that can be placed on the abdomen within 30 min of eating and require no voluntary movement on the part

Table 1 Attenuating Post-Prandial Glucose Excursion

Dietary	Pharmacology	Lifestyle
Calorie-restricted	Acarbose	Order of macronutrient intake (carbohydrates last)
Low fat	GLP-1 agonists	Post-prandial physical activity
Low carbohydrate	Metformin (pre-prandial)	Digital behaviour change
High fiber meal pre-load		
Whey protein meal pre-load		

of the patient;²⁴⁷ however, a great deal more research needs to go into the selection of frequencies and protocols for muscular stimulation to optimise the attenuation of post-prandial hyperglycemia. Practitioners need to give advice that fits in with lifestyles, if they want higher compliance. Similarly, a great deal of further research needs to be applied to lifestyle advice for improved compliance, bearing in mind that the population with type 2 diabetes is usually very sedentary in the first place.

Conclusion

Hyperglycemia after a meal induces endothelial dysfunction, inflammatory reactions and oxidative stress, which lead to the acceleration of atherosclerosis and increased risk of cardiovascular events. As pre-diabetes and frank diabetes have higher post-prandial peaks which last for longer, individuals who carry these burdens suffer more damage than normoglycemics from each and every episode of prandial glycemia.

This paper has cited numerous studies which have demonstrated the association of peak post-prandial glycemia and progressive atherosclerosis. Researchers from around the world have also demonstrated the link between post-prandial hyperglycemia and diabetic-related complications, especially cardiovascular morbidity and mortality. Not surprisingly, interventional studies in diabetes have shown the tremendous added value of a therapeutic strategy which includes the targeted control of post-prandial hyperglycemia. The benefit of controlling post-prandial hyperglycemia is comparable to equal to the benefit of using statins for secondary prevention in type 2 diabetes – surprisingly good for a therapeutic target that is largely not closely tracked by practitioners. Of course, all interventions for diabetes should include and start with lifestyle changes, but practitioners should bear in mind that patients have very low compliance with general lifestyle advice of the “move more, eat less” approach.

A great deal of further work is still required to standardise and optimise the methodology of lifestyle and dietary interventions. Dietary and lifestyle interventions should be combined with the most effective, least toxic pharmacotherapies to address post-prandial hyperglycemia in diabetes. [Table 1](#) gives an overview of areas of interest worthy of further research.

This review paper has attempted to give practitioners a solid background and context for understanding where there is a gap in best practice, and the further work required to fill this gap. The growing global pandemic of diabetes and its cost to society makes closing this gap all the more relevant and urgent by the day.

Disclosure

ADM has received research funding from the MRC, NIHR, Jon Moulton Charitable Foundation, Fractyl, Gila, Randox and Novo Nordisk. ADM is a shareholder in the Beyond BMI clinic, which provides clinical obesity care. ADM reports personal fees from Lilly, personal fees from Astra Zeneca, personal fees from Boehringer Ingelheim, personal fees from Currax, personal fees from Algorithm, during the conduct of the study. NG reports personal fees from Heartland Food Products Group, personal fees from Eli Lilly, personal fees from Boehringer Ingelheim, grants from Oviva, during the conduct of the study. Dr Mo Al-Qaisi reports being director and sole shareholder of Ziro Foods Ltd, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Reed JA. Aretaeus, the Cappadocian. *Diabetes*. 1954;3:419–421. doi:10.2337/diab.3.5.419
2. Barnett T. Epidemiology, complications and costs of diabetes mellitus. In: Tony B, editor. *The Insulin Treatment of Diabetes: A Practical Guide*. London: E-map healthcare; 1998:6–9.
3. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. 2013;380:2095–2128. doi:10.1016/S0140-6736(12)61728-0
4. Panzani G. Mortality and survival in type II (non-insulin dependent) diabetes mellitus. *Diabetologia*. 1987;30:123–131. doi:10.1007/BF00274216
5. Garcia MJ, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes*. 1974;23:105–111. doi:10.2337/diab.23.2.105
6. UK Prospective Diabetes Study (UKPDS) Group. UK prospective diabetes study VIII. study design, progress and performance. *Diabetologia*. 1991;34:877–890. doi:10.1007/BF00400195
7. Diabetes and the NHS - News and events, University of York. Available from: <https://www.york.ac.uk/news-and-events/features/diabetes-nhs/>. Accessed December 26, 2023.
8. Holman RR, Turner RC. Optimizing blood glucose control in type 2 diabetes: an approach based on fasting blood glucose measurements. *Diabetologia*. 1988;5:582–588.
9. Trovati M, Burzacca S, Mularoni E, et al. A comparison of the predictive power for overall blood glucose control of a ‘good’ fasting level in type 2 diabetic patients on diet alone or with oral agents. *Diabetologia*. 1992;9:134–137.
10. Wu T, Rayner CK, Horowitz M. Inter-regulation of gastric emptying and incretin hormone secretion: implications for postprandial glycemic control. *Biomarkers Med*. 2016;10(11):1167–1179. doi:10.2217/bmm-2016-0164
11. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care*. 2003;26(3):881–885. doi:10.2337/diacare.26.3.881
12. Riddle MC. Basal glucose can be controlled, but the prandial problem persists—it’s the next target. *Diabetes Care*. 2017;40(3):291–300. doi:10.2337/dc16-2380
13. Tomiyama M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata diabetes study. *Diabetes Care*. 1999;22:920–924. doi:10.2337/diacare.22.6.920
14. Miyazaki M, Kubo M, Kiyohara Y, et al. Comparison of diagnostic methods for diabetes mellitus based on presence of retinopathy in a Japanese population: the hisayama study. *Diabetologia*. 2004;47:1411–1415. doi:10.1007/s00125-004-1466-8
15. Bonora E, Corrao G, Bagnardi V, et al. Prevalence and correlates of post-prandial hyperglycaemia in a large sample of patients with type 2 diabetes mellitus. *Diabetologia*. 2006;49(5):846–854. doi:10.1007/s00125-006-0203-x
16. Riddle MC, Rosenstock J, Gerich J. Insulin Glargine 4002 study investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26(11):3080–3086. doi:10.2337/diacare.26.11.3080
17. Janka HU, Plewe G, Riddle MC, et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care*. 2005;28(2):254–259. doi:10.2337/diacare.28.2.254
18. National Agency for Health Accreditation. Strategies for care of the type 2 diabetic patient excluding care of complications: recommendations of ANAES (National Agency for Health Accreditation and Evaluation March 2000) [in French]. *Diabetes Metab*. 2000;26(5):10–96.
19. Kataoka Y, Yasuda S, Asaumi Y, et al. Long-term effects of lowering postprandial glucose level on cardiovascular outcomes in early-stage diabetic patients with coronary artery disease: 10-year post-trial follow-up analysis of the DIANA study. *J Diabetes Complications*. 2023;37(5):108469. doi:10.1016/j.jdiacomp.2023.108469
20. Blaak EE, Antoine J-M, Benton D, et al. Impact of postprandial glycaemia on health and prevention of disease. *Obes Rev*. 2012;13:923–984. doi:10.1111/j.1467-789X.2012.01011.x
21. Riddle M, Umpierrez G, DiGenio A, Zhou R, Rosenstock J. Contributions of basal and postprandial hyperglycemia over a wide range of A1C levels before and after treatment intensification in type 2 diabetes. *Diabetes Care*. 2011;34:2508–2514. doi:10.2337/dc11-0632
22. Blevins T. Control of postprandial glucose levels with insulin in type 2 diabetes. *Postgrad Med*. 2011;123(4):135–147. doi:10.3810/pgm.2011.07.2313
23. Jakubowicz D, Wainstein J, Tsameret S, Landau Z. Role of high energy breakfast “Big Breakfast Diet” in clock gene regulation of postprandial hyperglycemia and weight loss in type 2 diabetes. *Nutrients*. 2021;13:1558. doi:10.3390/nu13051558
24. De Veegt F, Dekker JM, Ruhé HG, et al. Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn study. *Diabetologia*. 1999;42:926–931. doi:10.1007/s001250051249
25. Grinnan D, Farr G, Fox A, Sweeney L. The role of hyperglycemia and insulin resistance in the development and progression of pulmonary arterial hypertension. *J Diabetes Res*. 2016;2016:2481659. doi:10.1155/2016/2481659
26. Gheldof N, Francey C, Rytz A, et al. Effect of different nutritional supplements on glucose response of complete meals in two crossover studies. *Nutrients*. 2022;14(13):2674. doi:10.3390/nu14132674
27. Mainous AGI, Tanner RJ, Baker RE, Zayas C, Harle AC. Prevalence of prediabetes in England from 2003 to 2011: population-based, cross-sectional study. *BMJ Open*. 2014;4:e005002.
28. Akturk HK, Rewers A, Joseph H, et al. Possible ways to improve postprandial glucose control in type 1 diabetes. *Diabetes Technol Ther*. 2018;20(S2):S224–S232. doi:10.1089/dia.2018.0114
29. Mazze RS, Strock E, Wesley D, et al. Characterizing glucose exposure for individuals with normal glucose tolerance using continuous glucose monitoring and ambulatory glucose profile analysis. *Diabetes Technol Ther*. 2008;10(3):149–159. doi:10.1089/dia.2007.0293
30. Fox LA, Beck RW, Xing D; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. *Diabetes Care*. 2010;33(6):1297–1299. doi:10.2337/dc10-0006
31. American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43(Suppl. 1):S66–S76. doi:10.2337/dc20-S006
32. Beck RW, Bergenstal RM, Cheng P, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. *J Diabetes Sci Technol*. 2019;13:614–626. doi:10.1177/1932296818822496

33. Vigersky RA, McMahon C. The relationship of hemoglobin A1C to time-in-range in patients with diabetes. *Diabetes Technol Ther.* 2019;21:81–85. doi:10.1089/dia.2018.0310
34. Basu A, Caumo A, Bettini F, et al. Impaired basal glucose effectiveness in NIDDM: contribution of defects in glucose disappearance and production, measured using an optimized minimal model independent protocol. *Diabetes.* 1997;46(3):421–432. doi:10.2337/diab.46.3.421
35. Shah P, Basu A, Basu R, Rizza R. Impact of lack of suppression of glucagon on glucose tolerance in humans. *Am J Physiol.* 1999;277(2):E283–E290. doi:10.1152/ajpendo.1999.277.2.E283
36. Sharma A, Varghese RT, Shah M, et al. Impaired insulin action is associated with increased glucagon concentrations in nondiabetic humans. *J Clin Endocrinol Metab.* 2018;103(1):314–319. doi:10.1210/jc.2017-01197
37. Delgado-Aros S, Kim DY, Burton DD, et al. Effect of GLP-1 on gastric volume, emptying, maximum volume ingested, and postprandial symptoms in humans. *Am J Physiol Gastrointest Liver Physiol.* 2002;282(3):G424–G431. doi:10.1152/ajpgi.2002.282.3.G424
38. Vella A, Reed AS, Charkoudian N, et al. Glucose-induced suppression of endogenous glucose production: dynamic response to differing glucose profiles. *Am J Physiol Endocrinol Metab.* 2003;285(1):E25–E30. doi:10.1152/ajpendo.00530.2002
39. Halawi H, Khemani D, Eckert D, et al. Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. *Lancet Gastroen Hepatol.* 2017;2(12):890–899. doi:10.1016/S2468-1253(17)30285-6
40. Sudhir R, Mohan V. Postprandial hyperglycemia in patients with type 2 diabetes mellitus. *Mol Diag Ther.* 2002;1:105–116.
41. Bharucha AE, Batey-Schaefer B, Cleary PA, et al. Delayed gastric emptying is associated with early and long-term hyperglycemia in type 1 diabetes mellitus. *Gastroenterology.* 2015;149:330–339. doi:10.1053/j.gastro.2015.05.007
42. Wang YT, Mohammed SD, Farmer AD, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. *Aliment Pharmacol Ther.* 2015;42(6):761–772. doi:10.1111/apt.13329
43. Marathe CS, Rayner CK, Jones KL, Horowitz M. Relationships between gastric emptying, postprandial glycemia, and incretin hormones. *Diabetes Care.* 2013;36(5):1396–1405. doi:10.2337/dc12-1609
44. Stevens JE, Jones KL, Rayner CK, Horowitz M. Pathophysiology and pharmacotherapy of gastroparesis: current and future perspectives. *Expert Opin Pharma.* 2013;14(9):1171–1186. doi:10.1517/14656566.2013.795948
45. Phillips LK, Deane AM, Jones KL, Rayner CK, Horowitz M. Gastric emptying and glycaemia in health and diabetes mellitus. *Nat Rev Endocrinol.* 2015;11(2):112–128. doi:10.1038/nrendo.2014.202
46. Bharucha AE, Camilleri M, Forstrom LA, Zinsmeister AR. Relationship between clinical features and gastric emptying disturbances in diabetes mellitus. *Clin Endocrinol (Oxf).* 2009;70:415–420. doi:10.1111/j.1365-2265.2008.03351.x
47. Horowitz M, Harding PE, Maddox AF, et al. Gastric and oesophageal emptying in patients with type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 1989;32(3):151–159. doi:10.1007/BF00265086
48. Phillips WT, Schwartz JG, McMahan CA. Rapid gastric emptying of an oral glucose solution in type 2 diabetic patients. *J Nucl Med.* 1992;33(8):1496–1500.
49. Schwartz JG, Green GM, Guan D, McMahan CA, Phillips WT. Rapid gastric emptying of a solid pancake meal in type II diabetic patients. *Diabetes Care.* 1996;19(5):468–471. doi:10.2337/diacare.19.5.468
50. Watson LE, Xie C, Wang X, et al. Gastric emptying in patients with well-controlled type 2 diabetes compared with young and older control subjects without diabetes. *J Clin Endocrinol Metab.* 2019;104(8):3311–3319. doi:10.1210/jc.2018-02736
51. Goyal RK, Cristofaro V, Sullivan MP. Rapid gastric emptying in diabetes mellitus: pathophysiology and clinical importance. *J Diabetes Complications.* 2019;33(11):107414. doi:10.1016/j.jdiacomp.2019.107414
52. Horowitz M, Dent J. Disordered gastric emptying: mechanical basis, assessment and treatment. *Baillière's Clin Gastroen.* 1991;5(2):371–407. doi:10.1016/0950-3528(91)90034-X
53. Russo A, Stevens JE, Chen R, et al. Insulin-induced hypoglycemia accelerates gastric emptying of solids and liquids in long-standing type 1 diabetes. *J Clin Endocrinol Metab.* 2005;90(8):4489–4495. doi:10.1210/jc.2005-0513
54. Horowitz M, Maddox AF, Wishart JM, Harding PE, Chatterton BE, Shearman DJ. Relationships between oesophageal transit and solid and liquid gastric emptying in diabetes mellitus. *Eur J Nucl Med.* 1991;18(4):229–234. doi:10.1007/BF00186645
55. Rayner CK, Jones KL, Horowitz M. Chapter 18 - Diabetic gastroparesis. In: McCallum RW, Parkman HP editors. *Gastroparesis.* Academic Press; 2021:237–253. doi:10.1016/B978-0-12-818586-5.00018-1
56. Xie C, Huang W, Wang X, et al. Gastric emptying in health and type 2 diabetes: an evaluation using a 75 g oral glucose drink. *Diabet Res Clin Pract.* 2021;171:108610. doi:10.1016/j.diabres.2020.108610
57. Perano SJ, Rayner CK, Kritas S, et al. Gastric emptying is more rapid in adolescents with type 1 diabetes and impacts on postprandial glycemia. *J Clin Endocrinol Metab.* 2015;100(6):2248–2253. doi:10.1210/jc.2015-1055
58. Jones KL, Horowitz M, Wishart MJ, Maddox AF, Harding PE, Chatterton BE. Relationships between gastric emptying, intragastric meal distribution and blood glucose concentrations in diabetes mellitus. *J Nucl Med.* 1995;36(12):2220–2228.
59. Wang X, Xie C, Marathe CS, et al. Disparities in gastric emptying and postprandial glycaemia between Han Chinese and Caucasians with type 2 diabetes. *Diabet Res Clin Pract.* 2020;159:107951. PMID: 31790715. doi:10.1016/j.diabres.2019.107951
60. Mihai BM, Mihai C, Cijevschi-Prelipcean C, et al. Bidirectional relationship between gastric emptying and plasma glucose control in normoglycemic individuals and diabetic patients. *J Diabetes Res.* 2018;2018:1736959. doi:10.1155/2018/1736959
61. Cremonini F, Mullan BP, Camilleri M, Burton DD, Rank MR. Performance characteristics of scintigraphic transit measurements for studies of experimental therapies. *Aliment Pharmacol Ther.* 2002;16(10):1781–1790. doi:10.1046/j.1365-2036.2002.01344.x
62. Marathe CS, Horowitz M, Trahair LG, et al. Relationships of early and late glycaemic responses with gastric emptying during an oral glucose tolerance test. *J Clin Endocrinol Metab.* 2015;100(9):3565–3571. doi:10.1210/JC.2015-2482
63. Jalleh RJ, Wu T, Jones KL, Rayner CK, Horowitz M, Marathe CS. Relationships of glucose, GLP-1 and insulin secretion with gastric emptying after a 75g glucose load in type 2 diabetes. *J Clin Endocrinol Metab.* 2022;107:10. doi:10.1210/clinem/dgab672
64. Thazhath SS, Marathe CS, Wu T, et al. The glucagon-like peptide 1 receptor agonist exenatide inhibits small intestinal motility, flow, transit, and absorption of glucose in healthy subjects and patients with type 2 diabetes: a randomized controlled trial. *Diabetes.* 2016;65(1):269–275. doi:10.2337/db15-0893

65. Zhang X, Young RL, Bound M, et al. Comparative effects of proximal and distal small intestinal glucose exposure on glycemia, incretin hormone secretion, and the incretin effect in health and type 2 diabetes. *Diabetes Care*. 2019;42(4):520–528. doi:10.2337/dc18-2156
66. Young RL, Chia B, Isaacs NJ, et al. Disordered control of intestinal sweet taste receptor expression and glucose absorption in type 2 diabetes. *Diabetes*. 2013;62(10):3532–3541. doi:10.2337/db13-0581
67. Dyer J, Wood IS, Palejwala A, Ellis A, Shirazi-Beechey SP. Expression of monosaccharide transporters in intestine of diabetic humans. *Am J Physiol Gastrointest Liver Physiol*. 2002;282:G241–248.
68. Fiorentino TV, Suraci E, Arcidiacono GP, et al.: Duodenal sodium/glucose cotransporter 1 expression under fasting conditions is associated with postload hyperglycemia. *J Clin Endocrinol Metab*. 2017;102:3979–3989. doi:10.1210/jc.2017-00348
69. Ait-Omar A, Monteiro-Sepulveda M, Poitou C, et al. GLUT2 accumulation in enterocyte apical and intracellular membranes: a study in morbidly obese human subjects and ob/ob and high fat-fed mice. *Diabetes*. 2011;60:2598–2607. doi:10.2337/db10-1740
70. Wu T, Rayner CK, Jones KL, Xie C, Marathe C, Horowitz M. Role of intestinal glucose absorption in glucose tolerance. *Curr Opin Pharmacol*. 2020;55:116–124. PMID: 33227625. doi:10.1016/j.coph.2020.10.017
71. Xie C, Jones KL, Rayner CK, Wu T. Enteroendocrine hormone secretion and metabolic control: importance of the region of the gut stimulation. *Pharmacetics*. 2020;12(9):790. doi:10.3390/pharmaceutics12090790
72. Fineman MS, Koda JE, Shen LZ, et al. The human amylin analog, pramlintide, corrects postprandial hyperglucagonemia in patients with type 1 diabetes. *Metabolism*. 2002;51(5):636–641. doi:10.1053/meta.2002.32022
73. Koda JE, Fineman M, Rink TJ, et al. Amylin concentrations and glucose control. *Lancet*. 1992;339(8802):1179–1180. doi:10.1016/0140-6736(92)90785-2
74. Holst JJ, Gromada J. Role of incretin hormones in the regulation of insulin secretion in diabetic and nondiabetic humans. *Am J Physiol Endocrinol Metab*. 2004;287(2):E199–E206. doi:10.1152/ajpendo.00545.2003
75. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86(8):3717–3723. doi:10.1210/jcem.86.8.7750
76. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired beta-cell function? *Diabetes*. 2010;59(5):1117–1125. doi:10.2337/db09-1899
77. Little TJ, Pilichiewicz AN, Russo A, et al. Effects of intravenous glucagon-like peptide-1 on gastric emptying and intragastric distribution in healthy subjects: relationships with postprandial glycaemic and insulinemic responses. *J Clin Endocrinol Metab*. 2006;91(5):1916–1923. doi:10.1210/jc.2005-2220
78. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696–1705. doi:10.1016/S0140-6736(06)69705-5
79. Ceriello A. The glucose triad and its role in comprehensive glycaemic control: current status, future management. *Int J Clin Pract*. 2010;64(12):1705–1711. doi:10.1111/j.1742-1241.2010.02517.x
80. Alsahli M, Gerich JE. Hypoglycemia, chronic kidney disease, and diabetes mellitus. *Mayo Clin Proc*. 2014;89(11):1564–1571. doi:10.1016/j.mayocp.2014.07.013
81. Vella A, Camilleri M. The gastrointestinal tract as an integrator of mechanical and hormonal response to nutrient ingestion. *Diabetes*. 2017;66(11):2729–2737. doi:10.2337/db17-0021
82. Basu A, Alzaid A, Dinneen S, Caumo A, Cobelli C, Rizza RA. Effects of a change in the pattern of insulin delivery on carbohydrate tolerance in diabetic and nondiabetic humans in the presence of differing degrees of insulin resistance. *J Clin Invest*. 1996;97(10):2351–2361. doi:10.1172/JCI118678
83. Service FJ, Hall LD, Westland RE, et al. Effects of size, time of day and sequence of meal ingestion on carbohydrate tolerance in normal subjects. *Diabetologia*. 1983;25(4):316–321. doi:10.1007/BF00253193
84. International Diabetes Federation Guideline Development Group. Guideline for management of postmeal glucose in diabetes. *Diabet Res Clin Pract*. 2014;103(2):256–268. doi:10.1016/j.diabres.2012.08.002
85. Monnier L, Colette C, Dunseath GJ, et al. The loss of postprandial glycaemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care*. 2007;30(2):263–269. doi:10.2337/dc06-1612
86. Shichiri M, Kishikawa H, Ohkubo Y, et al. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care*. 2000;23 Suppl. 2:B21–9.
87. Association AD; American Diabetes Association. Postprandial blood glucose. American Diabetes Association. *Diabetes Care*. 2001;24(4):775–778. doi:10.2337/diacare.24.4.775
88. AACE. The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: the AACE system of intensive diabetes self-management 2002 update. *Endocr Pract*. 2002;8(1):41–82.
89. Ceriello A, Genovese S. Atherogenicity of postprandial hyperglycemia and lipotoxicity. *Rev Endocr Metab Disord*. 2016;17(1):111–116. doi:10.1007/s11154-016-9341-8
90. Type 1 diabetes in adults: diagnosis and management. National Institute for Health and Care Excellence; 2015. Available from: <https://www.nice.org.uk/guidance/ng17>. Accessed May 24, 2024.
91. Jalleh RJ, Jones KL, Rayner CK, Marathe CS, Wu T, Horowitz M. Normal and disordered gastric emptying in diabetes: recent insights into (patho)physiology, management and impact on glycaemic control. *Diabetologia*. 2022;65(12):1981–1993. doi:10.1007/s00125-022-05796-1
92. Garg SK, Rewers AH, Akturk HK. Ever-increasing insulin-requiring patients globally. *Diabetes Technol Ther*. 2018;20(S2):S21–S24. doi:10.1089/dia.2018.0101
93. Takao T, Suka M, Yanagisawa H, et al. Impact of postprandial hyperglycemia at clinic visits on the incidence of cardiovascular events and all-cause mortality in patients with type 2 diabetes. *J Diabetes Investig*. 2017;8:600–608. doi:10.1111/jdi.12610
94. Takao T, Takahashi K, Suka M, et al. Association between postprandial hyperglycemia at clinic visits and all-cause and cancer mortality in patients with type 2 diabetes: a long-term historical cohort study in Japan. *Diabet Res Clin Pract*. 2019;148:152–159. doi:10.1016/j.diabres.2019.01.006
95. Takao T, Suka M, Yanagisawa H, Kasuga M. Thresholds for postprandial hyperglycemia and hypertriglyceridemia associated with increased mortality risk in type 2 diabetes patients: a real-world longitudinal study. *J Diabetes Investig*. 2021;12(5):886–893. doi:10.1111/jdi.13403

96. Heine RJ, Balkau B, Ceriello A, et al. What does postprandial hyperglycaemia mean? *Diabet Med.* 2004;21(3):208–213. doi:10.1111/j.1464-5491.2004.01149.x
97. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. *Diabetes Care.* 1996;19:257–267. doi:10.2337/diacare.19.3.257
98. Schmidt AM, Yan SD, Wautier JL, Stern D. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. *Circ Res.* 1999;84:489–497. doi:10.1161/01.RES.84.5.489
99. Marfella R, Verrazzo G, Acampora R, et al. Glutathione reverses systemic hemodynamic changes by acute hyperglycemia in healthy subjects. *Am J Physiol.* 1995;268:E1167–E1173.
100. Kawano H, Motoyama T, Hirashima O, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. *J Am Coll Cardiol.* 1999;34:146–154. doi:10.1016/S0735-1097(99)00168-0
101. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. *Diabetes.* 2003;52:2795–2804,2003. doi:10.2337/diabetes.52.11.2795
102. Williams SB, Goldfine AB, Timimi FK, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation.* 1998;97:1695–1701. doi:10.1161/01.CIR.97.17.1695
103. Shige H, Ishikawa T, Suzukawa M, et al. Endothelium-dependent flow-mediated vasodilation in the postprandial state in type 2 diabetes mellitus. *Am J Cardiol.* 1999;84:1172–1174. doi:10.1016/S0002-9149(99)00548-2
104. De Caterina R. Endothelial dysfunctions: common denominators in vascular disease. *Curr Opin Lipidol.* 2000;11:9–23. doi:10.1097/00041433-200002000-00003
105. Al-Qaisi M, Kharbanda RK, Mittal TK, et al. Measurement of endothelial function and its clinical utility for cardiovascular risk. *Vascular Health and Risk Manag.* 2008;4(3):647–652. doi:10.2147/VHRM.S2769
106. Ceriello A, Falletti E, Motz E, et al. Hyperglycemia-induced circulating ICAM-1 increase in diabetes mellitus: the possible role of oxidative stress. *Horm Metab Res.* 1998;30:146–149. doi:10.1055/s-2007-978854
107. Marfella R, Esposito K, Giunta R, et al. Circulating adhesion molecules in humans: role of hyperglycemia and hyperinsulinemia. *Circulation.* 2000;101:2247–2251. doi:10.1161/01.CIR.101.19.2247
108. Plutzky J. Inflammation in atherosclerosis and diabetes mellitus. *Rev Endocr Metab Disord.* 2004;5:255–259. doi:10.1023/B:REMD.0000032414.17672.5c
109. Nappo F, Esposito K, Cioffi M, et al. Postprandial endothelial activation in healthy subjects and in type 2 diabetic patients: role of fat and carbohydrate meals. *J Am Coll Cardiol.* 2002;39:1145–1150. doi:10.1016/S0735-1097(02)01741-2
110. Hoffman M, Blum A, Baruch R, Kaplan E, Benjamin M. Leukocytes and coronary artery disease. *Atherosclerosis.* 2004;172:1–6. doi:10.1016/S0021-9150(03)00164-3
111. Node K, Inoue T. Postprandial hyperglycemia as an etiological factor in vascular failure. *Cardiovasc Diabetol.* 2009;8(23):23. doi:10.1186/1475-2840-8-23
112. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular health study col laborative research group. *N Engl J Med.* 1999;340(1):14–22.
113. Temelkova-Kurktschiev TS, Koehler C, Henkel E, et al. Postch allenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care.* 2000;23(12):1830–1834. doi:10.2337/diacare.23.12.1830
114. de Marco R, Locatelli F, Zoppini G, et al. Cause-specific mortality in type 2 diabetes: the Verona Diabetes Study. *Diabetes Care.* 1999;22(5):756–761. doi:10.2337/diacare.22.5.756
115. Schneider H, Lischinski M, Jutzi E. Survival time after onset of diabetes: 29-year follow-up mortality study in a diabetes cohort from a rural district. *Diabetes Metab.* 1993;19(1 Pt 2):152–158.
116. Krolewski A, Kosinski E, Warram JH, et al. Magnitude and determinants of coronary disease in juvenile-onset diabetes mellitus. *Am J Cardiol.* 1987;59:750–755. doi:10.1016/0002-9149(87)91086-1
117. Kannel W, McGee D. Diabetes and cardiovascular risk factors: the Framingham Study. *Circulation.* 1979;59:8–13. doi:10.1161/01.CIR.59.1.8
118. Ceriello A. The emerging role of post-prandial hyperglycemic spikes in the pathogenesis of diabetic complications. *Diabet Med.* 1998;15:188–193. doi:10.1002/(SICI)1096-9136(199803)15:3<188::AID-DIA545>3.0.CO;2-V
119. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes: diagnostic criteria and performance revisited. *Diabetes Care.* 1997;20:785–791. doi:10.2337/diacare.20.5.785
120. Lowe LP, Liu K, Greenland P, et al. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men: the Chicago Heart Association Detection Project in Industry Study. *Diabetes Care.* 1997;20:163–169. doi:10.2337/diacare.20.2.163
121. Donahue RP, Abbott RD, Reed DM, Yano K. Post challenge glucose concentration and coronary heart disease in men of Japanese ancestry: Honolulu Heart Program. *Diabetes.* 1987;36:689–692. doi:10.2337/diab.36.6.689
122. Balkau B, Shipley M, Jarrett J, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall study, the Paris prospective study, and the Helsinki policemen study. *Diabetes Care.* 1998;21:360–367. doi:10.2337/diacare.21.3.360
123. Cavalot F, Petrelli A, Traversa M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2006;91:813–819. doi:10.1210/jc.2005-1005
124. Leiter LA, Ceriello A, Davidson JA, et al. International Prandial Glucose Regulation (PGR) study group: postprandial glucose regulation: new data and new implications. *Clin Ther.* 2005;27(suppl):S42–S56. doi:10.1016/j.clinthera.2005.11.020
125. Wright LA, Hirsch IB, Gooley TA, Brown Z. 1,5-Anhydroglucitol and neonatal complications in pregnancy complicated by diabetes. *Endocr Pract.* 2015;21(7):725–733. doi:10.4158/EPI14437.OR
126. Jovanovic-Peterson L, Peterson CM, Reed GF, et al. National institute of child health and human development—diabetes in early pregnancy study. maternal postprandial glucose levels and infant birth weight: the diabetes in early pregnancy study. *Am J Obstet Gynecol.* 1991;164(1):103–111. doi:10.1016/0002-9378(91)90637-7
127. Selvin E, Rawlings A, Lutsey P, et al. Association of 1,5-anhydroglucitol with cardiovascular disease and mortality. *Diabetes.* 2016;65(1):201–208. doi:10.2337/db15-0607

128. Levitan EB, Song Y, Ford ES, et al. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? *Arch Intern Med.* 2004;164(19):2147–2155. doi:10.1001/archinte.164.19.2147
129. DECODE Study Group, and the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med.* 2001;161(3):397–405. doi:10.1001/archinte.161.3.397
130. DECODE Study Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care.* 2003;26(3):688–696. doi:10.2337/diacare.26.3.688
131. Sasso FC, Carbonara O, Nasti R, et al. Glucose metabolism and coronary heart disease in patients with normal glucose tolerance. *JAMA.* 2004;291:1857–1863. doi:10.1001/jama.291.15.1857
132. Nakagami T, Qiao Q, Tuomilehto J, et al. Screen-detected diabetes, hypertension and hypercholesterolemia as predictors of cardiovascular mortality in five populations of Asian origin: the DECODA study. *Eur J Cardiovasc Prev Rehabil.* 2006;13(4):555–561. doi:10.1097/01.hjr.0000183916.28354.69
133. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia.* 1996;39:1577–1583. doi:10.1007/s001250050617
134. Sievers ML, Bennett PH, Nelson RG. Effect of glycemia on mortality in Pima Indians with type 2 diabetes. *Diabetes.* 1999;48(4):896–902. doi:10.2337/diabetes.48.4.896
135. Leese B. Economic evaluations of Type II diabetes. In: The social and cost implications of Type II diabetes. In: Bengt Jönsson H, Krans MJ, editors. *Pharmaco Economics 8.* Springer; 1995:23–27.
136. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258):405–412. doi:10.1136/bmj.321.7258.405
137. Hanefeld M, Cagatay M, Petrowsch T, et al. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J.* 2004;25(1):10–16. doi:10.1016/S0195-668X(03)00468-8
138. Downie E, Craig ME, Hing S, Cusumano J, Chan AK, Donaghue KC. Continued reduction in the prevalence of retinopathy in adolescents with type 1 diabetes: role of insulin therapy and glycemic control. *Diabetes Care.* 2011;34(11):2368–2373. doi:10.2337/dc11-0102
139. Farkouh ME. Blood glucose variability: a new metric for interventional cardiology? *JACC.* 2015;8:812. doi:10.1016/j.jcin.2015.01.021
140. Ceriello A, Ilnat MA. 'Glycaemic variability': a new therapeutic challenge in diabetes and the critical care setting. *Diabet Med.* 2010;26:222–225.
141. Siegelar SE, Holleman F, Hoekstra JB, DeVries JH. Glucose variability; does it matter? *Endocr Rev.* 2010;31:171. doi:10.1210/er.2009-0021
142. Monnier L, Colette C. Postprandial and basal hyperglycaemia in type 2 diabetes: contributions to overall glucose exposure and diabetic complications. *Diabetes Metab.* 2015;41(S1):6S9–6S15. doi:10.1016/S1262-3636(16)30003-9
143. Kuroda M, Shinke T, Sakaguchi K, et al. Effect of daily glucose fluctuation on coronary plaque vulnerability in patients pre-treated with lipid-lowering therapy: a prospective observational study. *JACC.* 2015;8:800. doi:10.1016/j.jcin.2014.11.025
144. Tang X, Li S, Wang Y, et al. Glycemic variability evaluated by continuous glucose monitoring system is associated with the 10-y cardiovascular risk of diabetic patients with well-controlled HbA1c. *Clin Chim Acta.* 2016;461:146–150. doi:10.1016/j.cca.2016.08.004
145. Mita T, Otsuka A, Azuma K, et al. Swings in blood glucose levels accelerate atherogenesis in apolipoprotein E-deficient mice. *Biochem Biophys Res Commun.* 2007;358(3):679–685. doi:10.1016/j.bbrc.2007.04.118
146. Kuroda M, Shinke T, Sakaguchi K, et al. Association between daily glucose fluctuation and coronary plaque properties in patients receiving adequate lipid-lowering therapy assessed by continuous glucose monitoring and optical coherence tomography. *Cardiovasc Diabetol.* 2015;14:78. doi:10.1186/s12933-015-0236-x
147. Kuroda M, Shinke T, Otake H, et al. Effects of daily glucose fluctuations on the healing response to everolimus-eluting stent implantation as assessed using continuous glucose monitoring and optical coherence tomography. *Cardiovascular Diab.* 2016;15:1–4. doi:10.1186/s12933-016-0395-4
148. Xia J, Qu Y, Yin C, Xu D. Optical coherence tomography assessment of glucose fluctuation impact on the neointimal proliferation after stent implantation in a diabetic/hypercholesterolemic swine model. *Int Heart J.* 2017;59:58. doi:10.1536/ihj.16-520
149. Okada K, Hibi K, Gohbara M, et al. Association between blood glucose variability and coronary plaque instability in patients with acute coronary syndromes. *Cardiovasc Diabetol.* 2015;14:111. doi:10.1186/s12933-015-0275-3
150. Gohbara M, Hibi K, Mitsuhashi T, et al. Glycemic variability on continuous glucose monitoring system correlates with non-culprit vessel coronary plaque vulnerability in patients with first-episode acute coronary syndrome- optical coherence tomography study. *Circ J.* 2015;80:111–125.
151. Nusca A, Lauria Pantano A, Melfi R, et al. Glycemic variability assessed by continuous glucose monitoring and short-term outcome in diabetic patients undergoing percutaneous coronary intervention: an observational pilot study. *J Diabetes Res.* 2015;2015:250201. doi:10.1155/2015/250201
152. Teraguchi I, Imanishi T, Ozaki Y, et al. Acute-phase glucose fluctuation is negatively correlated with myocardial salvage after acute myocardial infarction. *Circ J.* 2014;78(1):170–179. doi:10.1253/circj.CJ-13-0723
153. Gohbara M, Iwahashi N, Kataoka S, et al. Glycemic variability determined by continuous glucose monitoring system predicts left ventricular remodeling in patients with a first ST-segment elevation myocardial infarction. *Circ J.* 2015;79(5):1092–1099. doi:10.1253/circj.CJ-14-1226
154. Xia J, Xu J, Hu S, et al. Impact of glycemic variability on the occurrence of periprocedural myocardial infarction and major adverse cardiovascular events (MACE) after coronary intervention in patients with stable angina pectoris at 6months follow-up. *Clin Chim Acta.* 2017;471:196–200. doi:10.1016/j.cca.2017.06.014
155. Tokue M, Iijima R, Imamura T, et al. Impact of glycemic variability in patients with ST-elevated myocardial infarction. *Int J Cardiol.* 2015;187:660–662. PMID: 25880405. doi:10.1016/j.ijcard.2015.03.365
156. Xia J, Xu J, Li B, et al. Association between glycemic variability and major adverse cardiovascular and cerebrovascular events (MACCE) in patients with acute coronary syndrome during 30-day follow-up. *Clin Chim Acta.* 2017;466:162–166. doi:10.1016/j.cca.2017.01.022
157. Kim MK, Han K, Park YM, et al. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation.* 2018;138(23):2627–2637. doi:10.1161/CIRCULATIONAHA.118.034978
158. Jang JY, Moon S, Cho S, Cho KH, Oh CM. Visit-to-visit HbA1c and glucose variability and the risks of macrovascular and microvascular events in the general population. *Sci Rep.* 2019;9(1):1374. doi:10.1038/s41598-018-37834-7

159. Goldberg RB, Temprosa M, Haffner S, et al. Effect of progression from impaired glucose tolerance to diabetes on cardiovascular risk factors and its amelioration by lifestyle and metformin intervention: the Diabetes Prevention Program randomized trial by the Diabetes Prevention Program Research Group. *Diabetes Care*. 2009;32(4):726-732. doi:10.2337/dc08-0494
160. Kitabchi AE, Temprosa M, Knowler WC; The Diabetes Prevention Program Research Group. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. *Diabetes*. 2005;54(8):2404-2414. doi:10.2337/diabetes.54.8.2404
161. Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. *Lancet*. 2012;379:9833;2243-2251. doi:10.1016/S0140-6736(12)60525-X
162. Alsema M, Ruijgrok C, Blaak EE, et al. Effects of alpha-glucosidase-inhibiting drugs on acute postprandial glucose and insulin responses: a systematic review and meta-analysis. *Nutr Diabetes*. 2021;11(1):11. doi:10.1038/s41387-021-00152-5
163. Xin Y, Davies A, Briggs A, et al. Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the diabetes remission clinical trial (DiRECT)/counterweight-plus weight management programme. *Diabetologia*. 2020;63(10):2112-2122. doi:10.1007/s00125-020-05224-2
164. Shukla AP, Dickison M, Coughlin N, et al. The impact of food order on postprandial glycaemic excursions in prediabetes. *Diabetes Obes Metab*. 2019;21(2):377-381. doi:10.1111/dom.13503
165. Shukla AP, Iliescu RG, Thomas CE, Aronne LJ. Food order has a significant impact on postprandial glucose and insulin levels. *Diabetes Care*. 2015;38(7):e98-e99. doi:10.2337/dc15-0429
166. Shukla AP, Andono J, Touhamy SH, et al. Carbohydrate-last meal pattern lowers postprandial glucose and insulin excursions in type 2 diabetes. *BMJ Open Diabetes Res Care*. 2017;5(1):e000440. doi:10.1136/bmjdr-2017-000440
167. Imai S, Fukui M, Ozasa N, et al. Eating vegetables before carbohydrates improves postprandial glucose excursions. *Diabet Med*. 2013;30(3):370-372. doi:10.1111/dme.12073
168. Faber EM, van Kampen PM, Clement-de Boers A, et al. The influence of food order on postprandial glucose levels in children with type 1 diabetes. *Pediatr Diabetes*. 2018;19(4):809-815. doi:10.1111/pedi.12640
169. Russell WR, Baka A, Björck I, et al. Impact of diet composition on blood glucose regulation. *Crit Rev Food Sci Nutr*. 2016;56(4):541-590. doi:10.1080/10408398.2013.792772
170. Wu T, Little TJ, Bound MJ, et al. A protein preload enhances the glucose-lowering efficacy of vildagliptin in type 2 diabetes. *Diabetes Care*. 2016;39:511-517. doi:10.2337/dc15-2298
171. Trico D, Baldi S, Tulipani A, et al. Mechanisms through which a small protein and lipid preload improves glucose tolerance. *Diabetologia*. 2015;58:2503-2512. doi:10.1007/s00125-015-3710-9
172. Wu T, Bound MJ, Zhao BR, et al. Effects of a d-xylose preload with or without sitagliptin on gastric emptying, glucagon-like Peptide-1, and postprandial glycaemia in type 2 diabetes. *Diabetes Care*. 2013;36:1913-1918. doi:10.2337/dc12-2294
173. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet*. 2019;393(10170):434-445. doi:10.1016/S0140-6736(18)31809-9
174. Hardy DS, Garvin JT, Xu H. Carbohydrate quality, glycemic index, glycemic load and cardiometabolic risks in the US, Europe and Asia: a dose-response meta-analysis. *Nutr Metab Cardiovasc Dis*. 2020;30(6):853-871. doi:10.1016/j.numecd.2019.12.050
175. Blaak EE, Riccardi G, Cho L. Carbohydrates: separating fact from fiction. *Atherosclerosis*. 2021;328:114-123. doi:10.1016/j.atherosclerosis.2021.03.025
176. Chutkan R, Fahey G, Wright WL, McRorie J. Viscous versus nonviscous soluble fiber supplements: mechanisms and evidence for fiber-specific health benefits. *J Am Acad Nurse Pract*. 2012;24(8):476-487. doi:10.1111/j.1745-7599.2012.00758.x
177. Stephen AM, Champ MM, Cloran SJ, et al. Dietary fibre in Europe: current state of knowledge on definitions, sources, recommendations, intakes and relationships to health. *Nutr Res Rev*. 2017;30(2):149-190. doi:10.1017/S095442241700004X
178. McRorie JW, McKeown NM. Understanding the physics of functional fibers in the gastrointestinal tract: an evidence-based approach to resolving enduring misconceptions about insoluble and soluble fiber. *J Acad Nutr Diet*. 2017;117(2):251-264. doi:10.1016/j.jand.2016.09.021
179. Xie Y, Gou L, Peng M, Zheng J, Chen L. Effects of soluble fiber supplementation on glycemic control in adults with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Clin Nutr*. 2021;40(4):1800-1810. doi:10.1016/j.clnu.2020.10.032
180. Weickert MO, Pfeiffer AFH. Impact of dietary fiber consumption on insulin resistance and the prevention of type 2 diabetes. *J Nutr*. 2018;148(1):7-12. doi:10.1093/jn/nxx008
181. The InterAct Consortium. Dietary fibre and incidence of type 2 diabetes in eight European countries: the EPIC-InterAct Study and a meta-analysis of prospective studies. *Diabetologia*. 2015;58(7):1394-1408. doi:10.1007/s00125-015-3585-9
182. Cassidy YM, McSorley EM, Allsopp PJ. Effect of soluble dietary fibre on postprandial blood glucose response and its potential as a functional food ingredient. *J Funct Foods*. 2018;46:423-439. doi:10.1016/j.jff.2018.05.019
183. Yu K, Ke MY, Li WH, Zhang SQ, Fang XC. The impact of soluble dietary fibre on gastric emptying, postprandial blood glucose and insulin in patients with type 2 diabetes. *Asia Pac J Clin Nutr*. 2014;23(2):210-218. doi:10.6133/apjcn.2014.23.2.01
184. Nisak MB, Ruzita A, Norimah A, Azmi KN, Fatimah A. Acute effect of low and high glycemic index meals on post-prandial glycaemia and insulin responses in patients with type 2 diabetes mellitus. *Malays J Med Health Sci*. 2009;5:10.
185. Kamalpour M, Ghalandari H, Nasrollahzadeh J. Short-term supplementation of a moderate carbohydrate diet with psyllium reduces fasting plasma insulin and tumor necrosis factor- α in patients with type 2 diabetes mellitus. *J Diet Suppl*. 2018;15:507-515. doi:10.1080/19390211.2017.1358791
186. Silva FM, Kramer CK, Crispim D, Azevedo MJ. A high-glycemic index, low-fiber breakfast affects the postprandial plasma glucose, insulin, and ghrelin responses of patients with type 2 diabetes in a randomized clinical trial. *J Nutr*. 2015;145:736-741. doi:10.3945/jn.114.195339
187. Lobos DR, Vicuña IA, Novik V, Vega CA. Effect of high and low glycemic index breakfast on postprandial metabolic parameters and satiety in subjects with type 2 diabetes mellitus under intensive insulin therapy: controlled clinical trial. *Clin Nutr ESPEN*. 2017;20:12-16. doi:10.1016/j.clnesp.2017.04.082
188. De Carvalho CM, de Paula TP, Viana LV, Machado VM, de Almeida JC, Azevedo MJ. Plasma glucose and insulin responses after consumption of breakfasts with different sources of soluble fiber in type 2 diabetes patients: a randomized crossover clinical trial. *Am J Clin Nutr*. 2017;106:ajcn157263.
189. Smith K, Bowden Davies KA, Stevenson EJ, 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. doi:10.3389/fnut.2020.587843

190. King DG, Walker M, Campbell MD, Breen L, Stevenson EJ, West DJ. A small dose of whey protein co-ingested with mixed-macronutrient breakfast and lunch meals improves postprandial glycemia and suppresses appetite in men with type 2 diabetes: a randomized controlled trial. *Am J Clin Nutr*. 2018;107(4):550-557. doi:10.1093/ajcn/nqy019
191. Watson LE, Phillips LK, Wu T, et al. Differentiating the effects of whey protein and guar gum preloads on postprandial glycemia in type 2 diabetes. *Clin Nutr*. 2019;38(6):2827-2832. doi:10.1016/j.clnu.2018.12.014
192. Pallotta JA, Kennedy PJ. Response of plasma insulin and growth hormone to carbohydrate and protein feeding. *Metabolism*. 1968;17:901-908. doi:10.1016/0026-0495(68)90156-X
193. Gannon MC, Nuttall FQ, Lane JT, Burmeister LA. Metabolic response to cottage cheese or egg white protein, with or without glucose, in type II diabetic subjects. *Metabolism*. 1992;41:1137-1145. doi:10.1016/0026-0495(92)90300-Y
194. Gannon MC, Nuttall FQ, Grant CT, Ercan-Fang S, Ercan-Fang N. Stimulation of insulin secretion by fructose ingested with protein in people with untreated type 2 diabetes. *Diabetes Care*. 1998;21:16-22. doi:10.2337/diacare.21.1.16
195. Nuttall FQ, Gannon MC, Wald JL, Ahmed M. Plasma glucose and insulin profiles in normal subjects ingesting diets of varying carbohydrate, fat, and protein content. *J Am Coll Nutr*. 1985;4:437-450. doi:10.1080/07315724.1985.10720086
196. Gunnerud U, Östman E, Björck I. Effects of whey proteins on glycaemia and insulinaemia to an oral glucose load in healthy adults; a dose-response study. *Eur J Clin Nutr*. 2013;67:749-753. doi:10.1038/ejcn.2013.88
197. Ma J, Stevens JE, Cukier K, et al. Effects of a protein preload on gastric emptying, glycemia, and gut hormones after a carbohydrate meal in diet-controlled type 2 diabetes. *Diabetes Care*. 2009;32:1600-1602. doi:10.2337/dc09-0723
198. Nilsson M, Stenberg M, Frid AH, Holst JJ, Björck IM. Glycemia and insulinemia in healthy subjects after lactose-equivalent meals of milk and other food proteins: the role of plasma amino acids and incretins. *Am J Clin Nutr*. 2004;80:1246-1253. doi:10.1093/ajcn/80.5.1246
199. Kung B, Anderson GH, Paré S, et al. Effect of milk protein intake and casein-to-whey ratio in breakfast meals on postprandial glucose, satiety ratings, and subsequent meal intake. *J Dairy Sci*. 2018;101:8688-8701. doi:10.3168/jds.2018-14419
200. Adams RL, Broughton KS. Insulinotropic effects of whey: mechanisms of action, recent clinical trials, and clinical applications. *Ann Nutr Metab*. 2016;69:56-63. doi:10.1159/000448665
201. McGregor RA, Poppitt SD. Milk protein for improved metabolic health: a review of the evidence. *Nutr Metab*. 2013;10:46. doi:10.1186/1743-7075-10-46
202. Pal S, Ellis V, Dhaliwal S. Effects of whey protein isolate on body composition, lipids, insulin and glucose in overweight and obese individuals. *Br J Nutr*. 2010;104:716-723. doi:10.1017/S0007114510000991
203. Akhavan T, Luhovyy BL, Brown PH, Cho CE, Anderson GH. Effect of premeal consumption of whey protein and its hydrolysate on food intake and postmeal glycemia and insulin responses in young adults. *Am J Clin Nutr*. 2010;91:966-975. doi:10.3945/ajcn.2009.28406
204. Watson LE, Phillips LK, Wu T. A whey/guar "preload" improves postprandial glycaemia and glycated haemoglobin levels in type 2 diabetes: a 12-week, single-blind, randomized, placebo-controlled trial. *Diabetes Obes Metab*. 2019;21:930-938. doi:10.1111/dom.13604
205. Akhavan T, Luhovyy BL, Panahi S, Kubant R, Brown PH, Anderson GH. Mechanism of action of pre-meal consumption of whey protein on glycemic control in young adults. *J Nutr Biochem*. 2014;25:36-43. doi:10.1016/j.jnutbio.2013.08.012
206. Jakubowicz D, Froy O, Ahrén B, et al. Incretin, insulinotropic and glucose-lowering effects of whey protein pre-load in type 2 diabetes: a randomised clinical trial. *Diabetologia*. 2014;57:1807-1811. doi:10.1007/s00125-014-3305-x
207. Ma J, Jesudason DR, Stevens JE, et al. Sustained effects of a protein 'preload' on glycaemia and gastric emptying over 4 weeks in patients with type 2 diabetes: a randomized clinical trial. *Diabet Res Clin Pract*. 2015;108:e31-e34. doi:10.1016/j.diabres.2015.02.019
208. Anderson GH, Tecimer SN, Shah D, et al. Protein source, quantity, and time of consumption determine the effect of proteins on short-term food intake in young men. *J Nutr*. 2004;134:3011-3015. doi:10.1093/jn/134.11.3011
209. Hall WL, Millward DJ, Long SJ, et al. Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. *Br J Nutr*. 2003;89:239-248. doi:10.1079/BJN2002760
210. Smith K, Taylor GS, Walker M, et al. Pre-meal whey protein alters postprandial insulinemia by enhancing β -cell function and reducing insulin clearance in T2D. *J Clin Endocrinol Metab*. 2023;108(8):e603-e612. doi:10.1210/clinem/dgad069
211. Smith K, Taylor GS, Brunsgaard LH, et al. Thrice daily consumption of a novel, premeal shot containing a low dose of whey protein increases time in euglycemia during 7 days of free-living in individuals with type 2 diabetes. *BMJ Open Diabetes Res Care*. 2022;10(3):e002820. doi:10.1136/bmjdr-2022-002820
212. Gannon MC, Nuttall FQ. Amino acid ingestion and glucose metabolism – a review. *IUBMB Life*. 2010;62(9):660-668. doi:10.1002/iub.375
213. Sridonpai P, Prachansuwan A, Praengam K, et al. Postprandial effects of a whey protein-based multi-ingredient nutritional drink compared with a normal breakfast on glucose, insulin, and active GLP-1 response among type 2 diabetic subjects: a crossover randomised controlled trial. *J Nutr Sci*. 2021;10:e49. doi:10.1017/jns.2021.41
214. Oberoi A, Giezenaar C, Rigda RS, et al. Comparative effects of co-ingesting whey protein and glucose alone and combined on blood glucose, plasma insulin and glucagon concentrations in younger and older men. *Nutrients*. 2022;14(15):3111. doi:10.3390/nu14153111
215. Sousa GTD, Lira FS, Rosa JC, et al. Dietary whey protein lessens several risk factors for metabolic diseases: a review. *Lipids Health Dis*. 2012;11:67. doi:10.1186/1476-511X-11-67
216. Gheldof N, Francey C, Rytz A, et al. Effect of different nutritional supplements on glucose response of complete meals in two crossover studies. *Nutrients*. 2022;14(13):2674.
217. Frid AH, Nilsson M, Holst JJ, Björck IM. Effect of whey on blood glucose and insulin responses to composite breakfast and lunch meals in type 2 diabetic subjects. *Am J Clin Nutr*. 2005;82:69-75. doi:10.1093/ajcn/82.1.69
218. Jenkins DJ, Thorne MJ, Camelon K, et al. Effect of processing on digestibility and the blood glucose response: a study of lentils. *Am J Clin Nutr*. 1982;36:1093-1101. doi:10.1093/ajcn/36.6.1093
219. Chen MJ, Jovanovic A, Taylor R. Utilizing the second-meal effect in type 2 diabetes: practical use of a soya-yogurt snack. *Diabetes Care*. 2010;33:2552-2554. doi:10.2337/dc10-0552
220. Meng H, Matthan NR, Ausman LM, Lichtenstein AH. Effect of prior meal macronutrient composition on postprandial glycemic responses and glycemic index and glycemic load value determinations. *Am J Clin Nutr*. 2017;106:ajcn162727.
221. Kuwahara M, Kim H-K, Furutani A, Mineshita Y, Nakaoka T, Shibata S. Effect of lunch with different calorie and nutrient balances on dinner-induced postprandial glucose variability. *Nutr Metab*. 2022;19:65. doi:10.1186/s12986-022-00704-1

222. Xiao K, Furutani A, Sasaki H, Takahashi M, Shibata S. Effect of a high protein diet at breakfast on postprandial glucose level at dinner time in healthy adults. *Nutrients*. 2022;15(1):85. doi:10.3390/nu15010085
223. Reversing type 2 diabetes - Newcastle magnetic resonance centre - Newcastle University. Available from: <https://www.ncl.ac.uk/magres/research/diabetes/reversal/#publicinformation>. Accessed December 28, 2023.
224. Borg MJ, Rayner CK, Jones KL, Horowitz M, Xie C, Wu T. Gastrointestinal mechanisms underlying the cardiovascular effect of metformin. *Pharmaceuticals*. 2020;13(11):410. doi:10.3390/ph13110410
225. Xie C, Iroga P, Bound MJ, et al. Impact of the timing of metformin administration on glycaemic and glucagon-like peptide-1 responses to intraduodenal glucose infusion in type 2 diabetes: a double-blind, randomised, placebo-controlled, crossover study. *Diabetologia*. 2024;67(7):1260–1270. doi:10.1007/s00125-024-06131-6
226. Hashimoto Y, Tanaka M, Okada H, et al. Postprandial hyperglycemia was ameliorated by taking metformin 30 min before a meal than taking metformin with a meal; a randomized, open-label, crossover pilot study. *Endocrine*. 2016;52(2):271–276. doi:10.1007/s12020-015-0786-4
227. Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on beta-cell function and insulin sensitivity in ADOPT. *Diabetes*. 2011;60(5):1552–1560. doi:10.2337/db10-1392
228. Holmbäck U, Forslund A, Grudén S, et al. Effects of a novel combination of orlistat and acarbose on tolerability, appetite, and glucose metabolism in persons with obesity. *Obes Sci Pract*. 2020;6(3):313–323. doi:10.1002/osp4.405
229. Holmbäck U, Grudén S, Litorp H, et al. Effects of a novel weight-loss combination product containing orlistat and acarbose on obesity: a randomized, placebo-controlled trial. *Obesity*. 2022;30(11):2222–2232. doi:10.1002/oby.23557
230. Petersen JL, McGuire DK. Impaired glucose tolerance and impaired fasting glucose--a review of diagnosis, clinical implications and management. *Diab Vasc Dis Res*. 2005;2(1):9–15. doi:10.3132/dvdr.2005.007
231. Chiasson JL, Josse RG, Gomis R, et al.; STOP-NIDDM Trial Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet*. 2002;359(9323):2072–2077. doi:10.1016/S0140-6736(02)08905-5
232. Langsted A, Nordestgaard BG. Nonfasting Lipid Profiles: the Way of the Future. *Clin Chem*. 2015;61(9):11231125. doi:10.1373/clinchem.2015.243139
233. Syväne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet*. 1997;350(Suppl):S120–S123. doi:10.1016/S0140-6736(97)90024-6
234. Adiels M, Boren J, Caslake MJ, et al. Overproduction of VLDL1 driven by hyperglycemia is a dominant feature of diabetic dyslipidemia. *Arterioscler Thromb Vasc Biol*. 2005;25(8):1697–1703. doi:10.1161/01.ATV.0000172689.53992.25
235. Bansal S, Buring JE, Rifai N, et al. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA*. 2007;298(3):309–316. doi:10.1001/jama.298.3.309
236. Harchaoui KEL, Visser ME, Kastelein JJP, et al. Triglycerides and cardiovascular risk. *Curr Cardiol Rev*. 2009;5(3):216222. doi:10.2174/157340309788970315
237. Eberly LE, Stamler J, Neaton JD. Relation of triglyceride levels, fasting and nonfasting, to fatal and nonfatal coronary heart disease. *Arch Intern Med*. 2003;163(9):1077–1083. doi:10.1001/archinte.163.9.1077
238. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837853.
239. Younis N, Soran H, Farook S. The prevention of type 2 diabetes mellitus: recent advances. *QJM*. 2004;97(7):451–455. doi:10.1093/qjmed/hch077
240. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. 2004;27(1):155–161. doi:10.2337/diacare.27.1.155
241. Sjöström L. Analysis of the XENDOS study (Xenical in the Prevention of Diabetes in Obese Subjects). *Endocr Pract*. 2006;12 Suppl 1:31–33. doi:10.4158/EP.12.S1.31
242. Spahn JM, Reeves RS, Keim KS, et al. State of the evidence regarding behavior change theories and strategies in nutrition counseling to facilitate health and food behavior change. *J Am Diet Assoc*. 2010;110(6):879–891. doi:10.1016/j.jada.2010.03.021
243. Novo Nordisk. Novo Nordisk and Noom to partner around digital health solutions to help people with obesity lose weight and keep it off; 2019. Available from: <https://ml-eu.globenewswire.com/Resource/Download/353ec32a-cdea-4f9e-ba9>. Accessed June 11, 2024.
244. Chacko E. Exercising tactically for taming postmeal glucose surges. *Scientifica*. 2016;2016:4045717. doi:10.1155/2016/4045717
245. Colberg SR, Zarrabi L, Bennington L, et al. Postprandial walking is better for lowering the glycemic effect of dinner than pre-dinner exercise in type 2 diabetic individuals. *J Am Med Dir Assoc*. 2009;10(6):394–397. doi:10.1016/j.jamda.2009.03.015
246. Li Z, Hu Y, Yan R, et al. Twenty minute moderate-intensity post dinner exercise reduces the postprandial glucose response in Chinese Patients with type 2 diabetes. *Med Sci Monit*. 2018;24:7170–7177. doi:10.12659/MSM.910827
247. Sanchez MJ, Mossayebi A, Sigaroodi S, et al. Effects of neuromuscular electrical stimulation on glycemic control: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2023;14:1222532. doi:10.3389/fendo.2023.1222532

Diabetes, Metabolic Syndrome and Obesity

Dovepress

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal>