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REVIEW

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

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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]

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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 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 modulants, 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 variability[41] 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

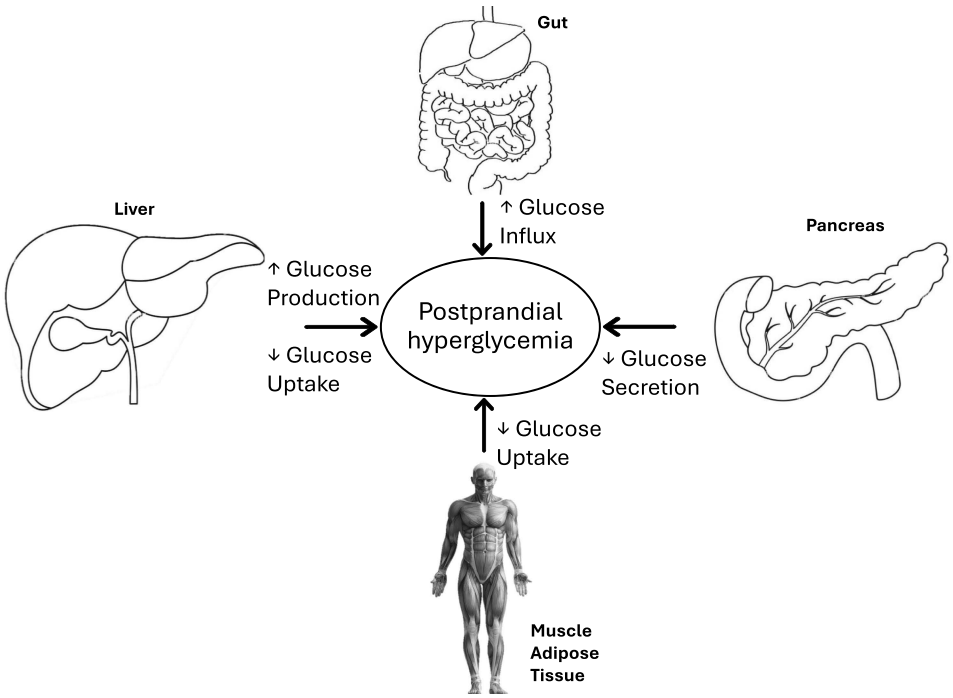

Figure 1 Pathophysiology of Post-prandial Hyperglycemia.

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), reproducedwith 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 modulants 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 modulants, 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 F2α (8-isoPGF2α).[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 diabetes[114] 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 glycemic 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 Study[133] 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 ± 0.07mm) was significantly attenuated in the acarbose group compared to controls on placebo (0.05 ± 0.06mm; $p = 0.027$). 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 >140/90mm 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 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 diabesity 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 diabesity and its cost to society makes closing this gap all the more relevant and urgent by the day.

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