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REVIEW

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Nutritional strategies to attenuate postprandial glycemic response

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Summary

Maintaining good glycemic control to prevent complications is crucial in people with type 2 diabetes and in people with prediabetes and in the general population. Different strategies to improve glycemic control involve the prescription of blood glucose-lowering drugs and the modulation of physical activity and diet. Interestingly, lifestyle intervention may be more effective in lowering hyperglycemia than pharmaceutical intervention. Regulation of postprandial glycemia is complex, but specific nutritional strategies can be applied to attenuate postprandial hyperglycemia. These strategies include reducing total carbohydrate intake, consuming carbohydrates with a lower glycemic index, the addition of or substitution by sweeteners and fibers, using food compounds which delay or inhibit gastric emptying or carbohydrate digestion, and using food compounds which inhibit intestinal glucose absorption. Nevertheless, it must be noted that every individual may respond differently to certain nutritional interventions. Therefore, a personalized approach is of importance to choose the optimal nutritional strategy to improve postprandial glycemia for each individual, but this requires a better understanding of the mechanisms explaining the differential responses between individuals.

KEYWORDS
dietary fiber, postprandial hyperglycemia, type 2 diabetes, α-glucosidase inhibitor

1 | INTRODUCTION

Glycemic variability is a predictor of premature mortality in the general population, in people with prediabetes, and in people with type 2 diabetes (T2D).[1,2] It is crucial to maintain good glycemic control in order to prevent the development of cardiometabolic diseases.[3] There are different strategies that can be applied to improve glycemic control. Besides dietary and lifestyle advices, the majority of patients with T2D are treated with blood glucose-lowering drugs. This includes drugs that improve insulin sensitivity in liver, adipose tissue, and skeletal muscle; drugs that increase insulin secretion of the pancreas; drugs that extend the duration of activity of the so-called satiety hormones gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1); and drugs that inhibit glucose reabsorption from the kidneys, thereby resulting in excretion of glucose via urine.

In the case of hyperglycemia in the absence of diabetes, lifestyle intervention, focused on diet and physical activity to improve glycemic control, was associated with a ±50% reduced risk of developing

Abbreviations: BMI, body mass index; CHO, carbohydrate; GI, glycemic index; GIP, gastric inhibitory polypeptide; GL, glycemic load; GLP-1, glucagon-like peptide-1; GLUT2, glucose transporter 2; HbA_{1C}, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; SGLT1, sodium-glucose cotransporter 1; T2D, type 2 diabetes.

diabetes.[4,5] Indeed, modulation of diet and exercise may improve whole-body insulin sensitivity, and some studies actually report that lifestyle intervention can be more effective in lowering hyperglycemia than the use of drugs.[6,7] As dietary carbohydrate (CHO) is the main dietary component affecting glycemia, many intervention studies that are described involve the effects of CHOs, including concepts like glycemic index (GI) and glycemic load (GL),[3] as described more extensively below. Nutritional strategies aimed at inhibiting CHO digestion and glucose absorption in the small intestine have been developed. Inhibition of CHO digestion and absorption leads to a delayed glucose appearance in the circulation, thereby decreasing postprandial hyperglycemia. The aim of this review is to give an overview of the determinants of postprandial glycemia related to diet composition, digestion, and absorption. We will discuss nutritional strategies that can be applied to inhibit the pace of digestion and absorption in order to ameliorate the postprandial glycemic response.

2 | REGULATION OF POSTPRANDIAL GLYCEMIA

The blood glucose concentration reflects the balance between glucose appearance and glucose disposal. In the fasted condition, no exogenous glucose enters the circulation and so glucose appearance is only influenced by metabolic processes in the body. The pancreas secretes glucagon and reduces insulin secretion when blood glucose concentrations are low, which promotes gluconeogenesis and glycogenolysis in the liver. In the postprandial state, glucose appearance is heavily influenced by the amount and composition of the food consumed, in particular dietary CHOs, and by the pace of food digestion and absorption. Blood glucose disposal, on the other hand, is strongly affected by whole-body insulin sensitivity and insulin secretion. Stimulation of insulin secretion, for instance by protein or amino acid ingestion, can also be considered to improve glycemic control.[8,9] However, such strategies to increase glucose disposal fall outside the scope of this review. Interestingly, stable isotope methodologies have made it possible to calculate how much exogenous glucose appearance contributes to postprandial glycemia in addition to endogenous glucose production.[10] These studies provide useful insight into the effects of specific CHO-containing products on postprandial glucose metabolism. For instance, the oral glucose tolerance test, which is used to measure the state of glucose tolerance of individuals, can be enriched with ^{13}C-glucose or [6,6-$^{2}H_2$]-glucose tracers to obtain information on postprandial glucose handling in different metabolic subgroups, such as people with normal glucose tolerance, impaired glucose tolerance, and impaired fasting glucose. Such a study revealed that the blood glucose pool in people with normal glucose tolerance consists of 90% exogenous glucose and 10% endogenous glucose 120 min after ingestion of the 75-g glucose load.[11] Additionally, people with impaired fasting glucose showed a similar postprandial glucose handling as compared to people with normal glucose tolerance, whereas people with impaired glucose tolerance showed substantially higher absolute exogenous glucose concentrations.[11] Similar tests may be performed to measure the rate of exogenous glucose appearance, endogenous glucose production, and glucose disposal rate after ingestion of numerous other food and drink products, such as bread or a sucrose drink, or mixed meals.[12,13]

2.1 | Glycemic index and glycemic load

The UK Scientific Advisory Committee on Nutrition recommends a reference intake of 50 E% of CHOs for the population on average.[14] This makes CHOs quantitatively the most important energy source for the body. CHOs are composed of one or more saccharide molecules, and depending on their structure, digestible CHOs can be divided into four main categories, namely, monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Importantly, digestible polysaccharides such as starches can influence postprandial glycemia directly, whereas nondigestible polysaccharides such as dietary fibers can influence postprandial glycemia more indirectly via interference with macronutrient absorption or microbial composition.

The concept of GI has been introduced to obtain a better classification of the health effects of CHOs beyond their chemical structure. GI is a numerical index on a scale of 0 to 100 and is used to indicate the potential of CHO-containing foods to increase blood glucose concentrations. For reference purposes, glucose is assigned the maximum value of 100. High-GI foods, which have a GI ≥ 70, can raise blood glucose concentrations more than low-GI foods, which have a GI ≤ 55.[15] Apart from GI, also GL is used to indicate the potential of food to increase blood glucose concentrations. However, in contrast to GI, GL also takes the total available CHO content of a certain amount of food into account.[15] It is therefore evident that the quantity of glycemic CHOs consumed, together with the relative ease by which those CHOs can be digested, both have a direct effect on postprandial glycemia. An enormous amount of research has been performed on elucidating the connection between CHO intake and numerous health outcomes. A series of systematic reviews and meta-analyses of studies in the general population showed that low-GI diets were associated with a reduced stroke mortality compared with high-GI diets.[16] In addition, it was found that low-GI diets effectively reduced glycated hemoglobin (HbA_{1C}), fasting glucose, body mass index (BMI), total cholesterol, and low-density lipoprotein in people with type 1 diabetes, T2D, and impaired glucose tolerance.[17] In line with this, a recent meta-analysis which included prospective cohort studies with up to 26 years of follow-up found there was strong evidence for a causal effect of GI and GL on the risk of T2D.[18] Furthermore, consumption of low-GI foods and limiting the GL of meals improved glycemic control in patients with T2D, and possibly people with a normal glucose tolerance.[19] However, there was no effect on fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), high-density lipoprotein, triglycerides, and insulin requirements.[17] Communicating available information on GI and GL to the general public for health benefits has been stressed internationally,[15] but there are some limitations. Indeed, only a certain number of food items have officially tested GI values, most of which are for American and Australian food products. Furthermore, the number of participants used to test the GI of specific food items is often limited, and epidemiological nutritional studies estimate long-term intakes for individual participants by using dietary questionnaires which are not optimally designed and also not validated for dietary GI and GL.[20,21] In addition to this, it is also very difficult to tease out the effects of postprandial glucose per se, because it is accompanied by elevated fasting blood glucose concentrations, and postprandial hyperlipidemia and hyperinsulinemia.[22] Especially the magnitude of the reduction in acute postprandial glucose exposure needed to achieve long-term metabolic health effects is currently unknown. A recent systematic review and meta-analysis of dietary intervention studies in relation to postprandial hyperglycemia showed that only a small heterogeneous set of dietary intervention studies are available where postprandial glucose was measured, and that more dietary intervention studies are needed.[22] Additionally, the authors of a recent systematic review and meta-analysis describing the effects of α-glucosidase-inhibiting drugs on acute postprandial glucose and insulin responses, were able to quantify clinically relevant estimates for a reduction in postprandial glucose per se, also for individuals without diabetes.[5] This meta-analysis indicates that a relative reduction of acute incremental postprandial glucose of ±45–50% (0.5 mmol/L in people without diabetes and 1.5 mmol/L in people with diabetes) can be seen as a clinically relevant reference point for reducing postprandial glucose concentrations via pharmaceutical and lifestyle interventions in the long term.[5]

2.2 | Strategies to reduce glycemic index and glycemic load

There are several nutritional strategies that can be used to reduce the GI and GL of the diet, thereby attenuating postprandial hyperglycemia. It is possible to simply limit the amount of glycemic CHOs in the diet or specific food products, but that comes at the expense of sweetness. Sweeteners, on the other hand, work well as a replacement for glucose or sucrose to lower postprandial glycemia, without affecting the sweetness of the product. Fructose is considered to be a naturally occurring caloric sweetener. A replacement of 67% sucrose by fructose showed lower values for the incremental area under the curve of glucose from 0 to 120 min compared with a 50% replacement, a 33% replacement, or no replacement at all.[23] This has prompted the European Food Safety Authority and the European Commission to approve the health claim that the replacement of sucrose and/or glucose by fructose lowers postprandial glycemia. Apart from fructose, there is also a wide variety of non-nutritive, low-energy or otherwise alternative artificial and plant-derived sweeteners available to reduce postprandial glycemia, such as stevia, aspartame, trehalose, and isomaltulose. Studies in which several of these sweeteners have been investigated are reviewed elsewhere.[24,25] Trehalose is a less commonly occurring disaccharide consisting of two glucose molecules linked together in a different way compared with the disaccharide maltose. Trehalose and maltose both provide approximately 4 kcal/g consumed, but trehalose contains an α-1,1-glycosidic bond, whereas maltose contains an α-1,4-glycosidic bond. Isomaltulose is a less commonly occurring disaccharide consisting of one glucose molecule plus one fructose molecule linked together in a different way compared with the disaccharide sucrose. Isomaltulose and sucrose also provide 4 kcal/g consumed, but isomaltulose contains an α-1,6-glycosidic bond, whereas sucrose contains an α-1,2-glycosidic bond. Both trehalose and isomaltulose were found to reduce glycemic and insulinemic responses in individuals who were overweight and had glucose intolerance, as well as in healthy individuals.[26–30] Also other studies found beneficial effects for isomaltulose when compared with sucrose.[31–33] These results clearly show the possibility to reduce the dietary intake of glycemic CHOs by replacing them with sweeteners or other structurally manipulated CHOs, at least in the short term. Additionally, a meta-analysis of human intervention studies supports the use of low-energy sweeteners in weight management, constrained primarily by the amount of added sugar that those sweeteners can displace in the diet.[34] Notably, for artificial sweeteners, adverse health effects on microbial composition and glycemic control have also been reported, but data are not consistent,[24,25,35] and could not be confirmed in a meta-analysis of human studies.[36] More studies will be needed to investigate the possible impact of sweeteners on certain determinants of metabolic health.[25]

2.3 | Health effects of dietary fibers

Dietary fibers are indigestible CHOs, containing a heterogeneous group of compounds, which are an important component of a healthy diet. Systematic reviews and meta-analyses have shown that total fiber intake reduces T2D risk[37] and incidence in a dose–response dependent manner.[16] Additionally, a systematic review and meta-analyses to analyze the effects of total dietary fiber intake on glycemic control and cardiometabolic risk factors in people with prediabetes, type 1 diabetes, and T2D showed a dose–response relationship between fiber intake and reduction in HbA_{1C}, fasting plasma glucose, insulin, and HOMA-IR.[38] In line, a meta-analysis of randomized controlled trials showed that microbiota-accessible CHOs improved glycemic control, blood lipid, body weight, and inflammatory markers for people with T2D.[39] Due to their health effects, in many countries, it is recommended to increase total fiber intake to 25–35 g per day for adults. Current fiber intake is only ±20 g per day on average.[39] Overall, it is recommended to consume more whole grains as a way to increase fiber intake.[16,38,40]

Despite the above evidence, well-controlled long-term human intervention studies are not always consistent with respect to effects of specific fibers on T2D and cardiometabolic risk.[41] This emphasizes the heterogeneity of compounds which vastly differ in water solubility, viscosity, binding and bulking ability, and fermentability, and also vary in their effects on host metabolism and cardiometabolic health.[41,42] The properties of different fibers in relation to health effects are discussed extensively elsewhere.[39,41–47] Below, the effects of prebiotic fibers (fermented by gut microbiota), insoluble fibers, and viscous soluble fibers will be discussed; the latter in the context of nutritional strategies to reduce gastric emptying.

2.3.1 | Health effects of prebiotic fibers

Prebiotic fibers exert their health effects because they are fermented specifically by the gut microbiota, thereby allowing beneficial microorganisms to increase in number. In people with T2D, dietary fiber consumption in general has been shown to improve HbA_{1C} and BMI by modulating the gut microbiota composition.[48,49] Inulin-type fructans are nonviscous soluble fibers and have prebiotic properties, which are beneficial for blood glucose regulation.[50] A recent systematic review and meta-analysis revealed that longer-term supplementation with inulin-type fructans improves glycemic control in people with prediabetes and T2D.[51] Both inulin and oligofructose are examples of inulin-type fructans. Longer-term supplementation with inulin may increase the relative abundance of bifidobacteria, which is a possible underlying mechanism of the beneficial metabolic effects seen in such studies.[52] In addition to their prebiotic properties, the nonviscous soluble fibers fructans have an intrinsic sweetness, which may also make them suitable in an acute setting to partially replace glycemic CHOs in food. It was found that 20% replacement of sucrose by oligofructose in a yoghurt drink, as well as 30% replacement of sucrose by inulin in a fruit jelly both resulted in reduced glycemic and insulinemic responses in healthy adults compared with the full-sugar variants.[53]

2.3.2 | Health effects of insoluble fibers

Insoluble fibers, which include wheat bran and cellulose, do not dissolve in water, and mostly contribute to fecal bulking.[41,43] Foods containing whole grains are rich in insoluble fibers, and are associated with a decreased risk of developing T2D, as indicated by several meta-analyses.[16,40] The underlying mechanisms may relate to interference with nutrient absorption, alterations in gastrointestinal transit time, and effects on the gut microbiota composition.[41]

2.4 | Nutritional strategies to reduce gastric emptying

Gastric emptying has a major influence on glycemia by allowing further digestion of disaccharides and polysaccharides, as well as the absorption of glucose in the small intestine. Reducing the rate of gastric emptying will lead to reduced postprandial glucose concentrations, at least in the early postprandial phase for people without or with T2D.[54–56] In the early 1990s, it has been estimated that gastric emptying after the ingestion of 75 g of glucose dissolved in water accounts for approximately 34% of the variance in peak plasma glucose concentration.[57] The mechanisms that regulate gastric emptying rate are highly complex,[58] and involve control by multiple hormones, including ghrelin, cholecystokinin, GLP-1, and peptide YY.[59] Ghrelin stimulates gastric emptying, whereas cholecystokinin, GLP-1, and peptide YY inhibit gastric emptying. Furthermore, as a bidirectional feedback response to prevent excessive blood glucose fluctuations, gastric emptying is inhibited by hyperglycemia and stimulated by hypoglycemia.[60] In healthy participants, mean gastric emptying time after a meal was found to be approximately 3.5 h,[61] whereas in individuals with T2D, both a reduced gastric emptying rate and an increased gastric emptying rate have been found.[62,63] One of the explanations for the variation in gastric emptying in diabetes may relate to the fact that hyperglycemia and hypoglycemia are both common in individuals with T2D, thereby having opposite effects on gastric emptying rate via hormonal feedback. Another aspect of interest is that solid and liquid meals can also differentially affect gastric emptying rate.[64] It has been shown that consumption of CHOs as liquids leads to substantially higher postprandial glycemic responses than consumption of CHOs as solid food,[65] although it is the digestibility of CHOs that has the largest influence on postprandial glucose concentrations.[66]

Nutritional strategies to slow down the rate of gastric emptying, thereby attenuating the postprandial glycemic response, include co-ingestion of glycemic CHOs with other macronutrients such as fat and protein.[67–69] In a randomized crossover study, men with T2D ingested water before a mashed potato meal, oil before a mashed potato meal, or water before a mashed potato meal that contained oil. From that study, it was clear that fat—in this case the oil—slowed down gastric emptying and reduced postprandial glycemic and insulinemic responses compared with water.[70] In another study involving people with T2D, a whey protein preload slowed down gastric emptying and reduced postprandial glycemic response after a potato meal compared with the condition in which no whey protein was consumed with the meal, as well as compared with the condition where whey protein was ingested as part of the potato meal.[71]

In addition to fat and protein, consumption of (viscous) dietary fiber can also slow down the rate of gastric emptying.[72] Viscous soluble fibers, which include β-glucan, psyllium, pectin, and raw guar gum, have the characteristic that they can form gel-like structures, thereby influencing gastric emptying and further digestion of nutrients. Regarding acute effects on gastric emptying, one study measured the impact of guar gum and chickpea flour, which has a high fiber content, added to wheat-based flatbreads on postprandial glucose kinetics in healthy males, and found that these reduced postprandial glucose and insulin concentrations compared with the control flatbread.[73] It was also shown in men and women without diabetes that the ingestion of a meal containing β-glucan resulted in reduced glycemic and insulinemic responses as well as a delayed gastric-emptying half-time compared with a β-glucan-free control meal, which had the same macronutrient and energy content.[74] The conclusion of a recent systematic review and meta-analysis on oat β-glucan was that there is strong evidence that the addition of oat β-glucan to CHO-containing meals attenuates glycemic and insulinemic responses.[75] Psyllium was also shown to delay gastric emptying,[76] and to attenuate the glycemic response when added to a meal.[77] Longer-term supplementation with viscous soluble fiber psyllium has been shown to reduce fasting blood glucose and HbA_{1C}.[78] A systematic review and meta-analysis of viscous soluble fiber supplementation in patients with T2D showed that longer-term supplementation improves markers of glycemic control, such as HbA_{1C}, fasting glucose, and HOMA-IR.[79] The mechanisms linking the effects on acute postprandial glycemic response to longer-term improvements in glycemic control in people with T2D, are not fully elucidated.

2.5 | Rate of carbohydrate digestion in the small intestine

The rate of glucose appearance in plasma is directly dependent on the small intestinal transit time, on the amount of glucose that is present in the different segments of the small intestine at a given time, and on the affinity of the intestinal glucose transporter.[80] Several studies have shown that small intestinal transit in healthy participants is completed within a few hours after consuming a meal,[81] approximately 4.5 h in total on average.[61] Nevertheless, there are major inter-individual differences in whole-gut transit time, depending on sex, age, and the country of residence.[61] Increasing age was associated with a shorter gastric emptying time, but a longer small bowel transit time plus colonic transit time.[61] The female sex was associated with a longer gastric emptying time, and small bowel transit time plus colonic transit time.[61] In a recent study, researchers provided a labeled mixed meal to lean participants and participants with morbid obesity, and investigated the rate of gastric emptying and the small intestinal transit time. Whereas the gastric emptying and small intestinal transit were slower, and postprandial glucose absorption was reduced in the participants with obesity compared with the lean participants, overall postprandial glucose was higher.[82] These findings can be explained due to increased fasting glucose concentrations and decreased insulin sensitivity in the participants with obesity compared with the lean participants.[82]

One widely used approach to reduce postprandial glucose concentrations is by inhibiting digestion of CHOs, thereby inhibiting intestinal glucose uptake. CHO digestion is regulated by a number of enzymes at several locations across the digestive tract. Disaccharides, which are either ingested or produced during the digestion of polysaccharides, are hydrolyzed to monosaccharides by different disaccharidases.[83] These disaccharidases are brush-border enzymes located in the intestinal epithelium. Pharmacological α-glucosidase inhibitors are widely prescribed to patients with T2D to reduce postprandial hyperglycemia, either as a monotherapy or in combination with other anti-diabetic drugs,[84] and they are also used by people without diabetes in order to prevent the development of diabetes, generally attenuating an increase in acute postprandial glucose by ±45–50% in both groups.[5] The α-glucosidase inhibitor acarbose has been shown to be effective in reducing postprandial hyperglycemia in patients with T2D.[85] However, gastrointestinal side effects such as flatulence, soft stools, and abdominal discomfort have been reported,[85,86] and therefore, the search for additional synthetic α-glucosidase inhibitors is ongoing.[87] Numerous alternative compounds with possibly superior α-glucosidase inhibitory profiles isolated from plant sources have also been reported, many of which belong to the class of phenolic compounds, but these were mainly investigated in vitro.[88,89] Phenolic compounds are a class of organic molecules in which one or more hydroxyl groups are directly linked to an aromatic ring. Polyphenols are compounds which have multiple phenol units. Flavonoids form the largest class of compounds within the family of polyphenols, which also consists of the classes of phenolic acids and lignans. Anthocyanins are a well-known example within the class of flavonoids. Many plants produce phenolic or polyphenolic compounds, prompting numerous studies in which the effects of polyphenol-containing fruits and berries on intestinal CHO digestion are investigated.

Blackcurrants, apples, red grapes, cinnamon, and blueberries are examples of plant components found to contain anthocyanin and/or procyanidin.[90–92] When blackcurrant extract containing 600-mg anthocyanins was consumed by men and postmenopausal women immediately before a high-CHO meal, it resulted in lower glucose and insulin concentrations in the early postprandial period up to 30 min compared with the control without blackcurrant extract, and in lower GLP-1 and GIP concentrations in the later postprandial period up to 90 or 120 min.[92] This has been suggested to be caused, at least partly, by the inhibitory effects of the anthocyanins and other polyphenols in the drinks on pancreatic α-amylase and intestinal α-glucosidase activity. In a different study, apple, red grape, and cinnamon were found to inhibit α-glucosidase, α-amylase, and lipase in an in vitro model resembling the human gastrointestinal system.[91] In yet another study, an optimization process was investigated for the extraction of components from grape seeds, which led to a higher inhibition of α-glucosidase and α-amylase than acarbose in vitro.[93] Finally, a study in young adults showed a beneficial postprandial glycemic response after ingestion of blueberry powder rich in anthocyanins compared with a sugar-matched control without blueberry anthocyanins.[90] Importantly, it must be noted in the case of polyphenols that the mechanism of action in attenuating increases in postprandial glucose can extend much further than α-glucosidase inhibitory activity alone.

Besides the phenolic compounds described above, there are other compounds which can have similar inhibitory effects on CHO-digesting enzymes, such as L-arabinose, D-sorbose, a milk protein hydrolysate, and inulin-type fructans. L-arabinose is a low-calorie pentose, and therefore a monosaccharide, with sweetener properties. It is a substantial component of plant cell wall polysaccharides. In vitro studies showed that L-arabinose acts as a specific α-glucosidase inhibitor to target the activity of sucrase in an uncompetitive manner, but not the activity of other glycoside hydrolases.[94] L-arabinose can remain bound to the sucrase-sucrose complex for up to several hours,[95] preventing the hydrolysis of sucrose to glucose and fructose. In healthy participants[96,97] and people with T2D,[97] it was found that L-arabinose co-ingestion can limit sucrose beverage-induced increases in blood glucose concentrations acutely. Importantly though, excessive inhibition of sucrase can lead to an accumulation of undigested sugars in the small intestine, resulting in major clinical consequences such as diarrhea and abdominal pain.[98] One study reported gastrointestinal symptoms after ingestion of 75 g sucrose combined with either 1-, 2-, or 3-g L-arabinose,[96] whereas this was not the case in another study after ingestion of 50 g sucrose combined with 2-g L-arabinose.[97] A different compound, D-sorbose, an artificially created isomer of the naturally occurring monosaccharide L-sorbose, was also found to inhibit disaccharidases in rats, thereby attenuating postprandial increases in blood glucose and insulin concentrations.[99] The same authors also demonstrated that rat intestinal enzymes are a suitable substitute for human enzymes when testing the inhibitory effects of compounds on disaccharidases.[100] Furthermore, a milk protein hydrolysate with an inhibitory effect on α-glucosidase activity showed reduced postprandial glucose concentrations compared with placebo in participants with prediabetes, and decreased HbA_{1C}.[101] Finally, in a mouse model, it has also been shown that inulin-type fructans from chicory have a direct inhibitory effect on sucrase activity.[102] Those mice were fed a diet supplemented with an inulin extract for 3 weeks, after which the jejunal mucosa was taken and tested in vitro. The investigators observed that the ability to hydrolyze sucrose into glucose was significantly reduced in the mice that received the diet supplemented with inulin, compared with the group of mice fed a standard diet.[102] These studies show that reducing digestion of sucrose is a suitable strategy to target hyperglycemia, although the number of human studies is limited relative to the number of in vitro and rodent studies.

2.6 | Carbohydrate uptake in the small intestine

Glucose uptake over the intestinal membrane is regulated by several intestinal glucose transporters. At the apical membrane of the small intestinal epithelial cells, the sodium-glucose cotransporter 1 (SGLT1) uses the Na^+ gradient across the membrane to actively transport glucose and galactose into the epithelial cells, whereas fructose diffuses passively into epithelial cells via GLUT5. At the basolateral membrane, glucose, galactose, and fructose passively diffuse into the bloodstream via glucose transporter 2 (GLUT2). Influencing these processes can result in beneficial effects on postprandial glycemia. In lean participants, GLUT2 has not been found on the apical membrane.[103] In participants with morbid obesity and insulin resistance, however, GLUT2 has been shown to accumulate in the apical membrane of jejunal enterocytes and this allowed glucose to passively diffuse into the bloodstream.[103] The inhibitory effects of polyphenols on SGLT1 and GLUT2 have been investigated mainly in Caco-2 cells as an in vitro model of human enterocytes.[104] In vitro studies showed that sappanin-type homoisoflavonoids and the flavonoids quercetin and isoquercitrin noncompetitively inhibit GLUT2, thereby preventing the uptake of glucose.[105,106] In support of this, also an in vivo study in healthy men and women demonstrated that the flavonoid hesperidin decreased the postprandial glycemic response to orange juice via inhibition of GLUT2.[107] Apple and blackcurrant polyphenol-rich drinks lowered postprandial glucose concentrations in healthy men and postmenopausal women.[108] Both apple and blackcurrant polyphenols reduced total and GLUT-mediated glucose uptake in vitro in Caco-2 cells.[108] For other polyphenols and phenolic acids extracted from strawberries and apples, it was also found that they can inhibit SGLT1 and/or GLUT2 in vitro.[109] Interestingly, berry flavonoids may not only inhibit the glucose transporters, but they may also decrease the expression of those transporters in Caco-2 cells.[110] This additional characteristic may make phenolic compounds exceptionally beneficial for attenuating postprandial glycemic responses in humans. Available information and controversies about inhibition of glucose transporters by phenolic compounds have been reviewed elsewhere.[111] Overall, the beneficial effects of polyphenols on postprandial glycemic response may be a combination of the α-glucosidase inhibitory qualities described earlier, as well as the glucose transporter inhibitory qualities.[112] Interestingly, the effects of polyphenols are not limited to the two mechanisms which we have described. Other mechanisms may include effects on gut microbiota composition, mitochondrial function, substrate utilization, and lipolysis.[113,114]

3 | INTERINDIVIDUAL DIFFERENCES IN POSTPRANDIAL GLYCEMIC RESPONSE

It has become clear that there is a high interindividual variability in the glycemic response to certain foods. To elucidate individual differences in postprandial glycemic response, Zeevi et al. developed a model which predicts the response to certain types of food with the use of a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity status, and gut microbiota composition.[115] The model was initially developed for a heterogeneous Israeli population consisting of both men and women with a BMI ranging from normal to obese, and with a state of glucose tolerance ranging from normal to T2D.[115] Later on, it was also found to be applicable to a Midwestern American population without diabetes,[116,117] suggesting that the model might be valuable for other populations as well. Large interindividual variability in glycemic responses to standardized meals was also found by another study, which allowed the authors to identify so-called "glucotypes", which is a form of classification that can place individuals into clinically relevant subgroups based on absolute amount of glucose variability and the fraction of time spent in low, moderate, or high variability.[118] Yet another study, the PREDICT 1 study, also showed a high interindividual variability in postprandial glycemic response to identical meals, and this study is currently being followed-up in order to better understand individual responses to food.[119] Indeed, personalized approaches require an understanding of the mechanisms explaining differential responses in order to be reproducible and translated into treatment strategies and guidelines.

4 | CONCLUSION AND FUTURE DIRECTIONS

Good glycemic control is crucial to maintain health and to prevent disease.[3] This is the case in people with T2D, but large fluctuations in glycemia should also be avoided in healthy individuals and individuals with prediabetes. There are different strategies that can be applied to attenuate postprandial glycemia, including pharmacological and nutritional strategies as well as exercise. This review discussed the main determinants of postprandial glycemic response, and nutritional strategies to attenuate that response. Postprandial glycemic response is the combined result of several key aspects and processes, namely the total amount of ingested CHOs, the structural properties of the ingested CHOs, the rate of gastric emptying, the rate of CHO digestion, and the rate of glucose absorption in the small intestine. Nutritional strategies to attenuate postprandial glycemic response include reducing the amount of ingested CHOs, consuming CHOs with a lower GI, the addition of or substitution by sweeteners and fibers, using food compounds which delay or inhibit gastric emptying or CHO digestion, and using food compounds which inhibit intestinal glucose absorption.

Apart from nutritional and physical determinants, there also seem to be additional factors that influence glycemia. In general, the timing of food intake and how that may affect glycemic and metabolic responses has become a hot topic, with studies demonstrating that both high-GI and low-GI meals increase postprandial glucose concentrations more at dinner than at breakfast.[120,121] This points towards a possible role for the circadian rhythm in the regulation of glycemia. The complex process of regulation of glucose metabolism by the circadian functions falls outside the scope of this review and has been reviewed elsewhere.[122]

Overall, it can be concluded that there are several nutritional strategies available to achieve an attenuation in postprandial glycemia. Despite the availability of such strategies, it must be noted that there are individual or subgroup-based responses to certain types of food, so a personalized approach is of importance to choose the optimal nutritional strategy to improve postprandial glycemia for every individual.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

KP wrote the manuscript. RM and EB conceptualized the manuscript. KP, RM, and EB discussed the content. RM, LvL, and EB reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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