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Editorial

Tailoring nutrient sequence and content to improve glucose tolerance: Why and how to do it

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At present, there is cogent evidence that postprandial hyperglycaemia is the key component of glycaemic disorders in type 2 diabetes (T2D) patients when they maintain "residual" dysglycaemia with HbA1c levels ranging from 6.5% to 7% [1,2]. Consequently, one of the ultimate targets for achieving near-normal, stable glucose homoeostasis is to eradicate abnormal post-meal glucose surges, even in those patients who exhibit near-normal pre-meal glucose levels and whose diabetes appears to be fairly well controlled [3]. More generally and irrespective of the degree of glycaemic control, it has been demonstrated that the absolute impact of postprandial glucose excursions on HbA1c is approximately 1% across the HbA1c spectrum in people with non-insulin-treated T2D as soon as HbA1c levels are > 6.5% [2,4]. Bringing all these observations together, it appears that, in any situation, the control of postprandial hyperglycaemia should never be neglected because this glycaemic disorder, when sustained, contributes significantly to overall glucose exposure, now recognized as one of the main causative risk factors for the development and progression of diabetic complications that not only involve microvascular disease, but also atherosclerotic lesions, both in type 1 diabetes (T1D) and T2D [5–10].

In normal healthy subjects, postprandial glucose homoeostasis is maintained within physiological limits through an immediate insulin secretory response and the normal tissue responsiveness to released insulin. Therefore, in situations where the ongoing antidiabetic treatment is failing to achieve postprandial glycaemic goals, it is reasonable to consider adding either a pharmacological treatment or dietary measures that specifically target postprandial glucose [11].

These goals can be achieved by either stimulating insulin secretion, suppressing glucagon release or delaying gastric-emptying [12]. It is now well established that glucagon-like peptide-1 (GLP-1), a gut-derived incretin hormone secreted throughout pre-meal periods, combines all these effects, albeit to different degrees [13]. However, as GLP-1 has a too-short half-life (only a few minutes) for use in clinical practice, pharmaceutical companies have been driven to develop new classes of hypoglycaemic agents, such as incretin mimetics (GLP-1 receptor agonists) and enhancers [dipeptidyl peptidase (DPP)-4 inhibitors]. All of these incretin-based therapies have the same basic mechanisms of action and exert their glucose-lowering effects with a mean decrement in HbA1c that can be set at approximately 0.7–1%. However, these drugs differ in their effectiveness against the two main components of the glycaemic disorders observed in T2D: basal and postprandial hyperglycaemia [14]. For instance, it has been demonstrated that prandial short-acting GLP-1 receptor agonists (such as exenatide and lixisenatide) primarily lower postprandial glucose via inhibition of gastric-emptying, whereas non-prandial long-acting compounds (including liraglutide, dulaglutide, extended-release exenatide) have stronger effects on fasting plasma glucose through their ability to enhance endogenous insulin and to suppress glucagon [15]. DPP-4 inhibitors are an alternative option for controlling postprandial glucose excursions. However, the effectiveness of this class of agents on post-meal glucose is less marked that that of short-acting GLP-1 receptor agonists, as DPP-4 inhibitors are generally not associated with slowing of gastric-emptying [13], even though DPP-4 inhibition is accompanied by a rise in postprandial levels of intact GLP-1 in plasma [16].

Thus, it appears that, while considerable progress has been made with the introduction into the market of drugs that target post-meal hyperglycaemia, the fact remains that all pharmacological approaches still need be complemented by dietary measures, which are considered crucial in cases where healthcare professionals wish to achieve maximum efficacy against post-meal glucose excursions [17].

In this issue of *Diabetes & Metabolism*, Trico et al. [18] report that, in patients with T2D, a dietary load supplying 23 g

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of protein and 17 g of fat prior to a 75-g oral glucose tolerance test (OGTT) improved glucose tolerance and insulin responses throughout the entire test period and at 120 min after administration of the glucose load, respectively. In this study [18], additional interesting observations were also made. Plasma GLP-1 concentrations were increased in a sustained manner, and the appearance of exogenous glucose in the bloodstream was blunted when the glucose challenge was preceded by a protein and lipid preload. Bearing in mind that, as already stated, postprandial glucose homoeostasis is mainly regulated by the insulin secretory response, the results observed by Trico et al. [18] offer further insights into the mechanisms that might be involved in the improvement of glucose tolerance after a carbohydrate-containing meal. These include, for example, the idea that the restoration of a more physiological GLP-1 release with its two consequences – a stimulatory effect on insulin secretion and a slowing-down action on gastric-emptying – seems to play a key role in improving glucose tolerance, as was observed after preloading with relatively small, but consistent, amounts of proteins and fats [19–21].

From a practical point of view, such observations raise the question of whether more consideration should be given to the nutrient feeding sequence during the time course of a meal [22,23] and, more generally, to the quality and quantity of nutrients given at meal times [17]. Considering the latter point, it is not really a novelty to say that the glycaemic response to a carbohydrate-containing meal is affected by several factors. Indeed, there is an abundant literature indicating that the ingestion of starchy foods with a low glycaemic index (GI) produces smaller postprandial blood glucose increments from baseline than do simple sugars [17,24–26]. These differences are mainly due to the fact that starch, a complex carbohydrate, requires progressive hydrolysis through sequential enzymatic actions [27], the most important of which is pancreatic α-amylase, whereas sucrose, a disaccharide, is rapidly hydrolysed through the action of intestinal α-glucosidase, located in the brush border of enterocytes in the small intestine.

Nevertheless, it remains difficult to establish equivalences between chemical structures of carbohydrates and their bioavailability. For example, fructose, a monosaccharide that is naturally present in fruit, but which can be artificially added as a sweetener to beverages and processed snacks, has a lower GI than either starch or sucrose. Another example is the lactose that is naturally present in milk. Hydrolysis of this disaccharide by β-glucosidase, located in brush-border enterocytes, and its subsequent cleavage into glucose and galactose are poorly efficient, thereby explaining why lactose has a low GI. In addition, even though the GI of any individual sugar is dependent on the nature of its carbohydrate-containing food, it should be noted that these sugars are also subject to significant changes when taken as part of a mixed meal [24].

In fact, it has long been known, for at least several decades, that proteins and fats decrease blood glucose responses and enhance insulin secretion when added to a carbohydrate meal [28]. This observation has been further confirmed by a number of investigators [17,29–31]. However, the evidence is inconclusive regarding the ideal amount of either protein or fat that should be added to the mixed meal. Here again, the study by Trico et al. [18] appears to suggest that such effects may be obtained with a dietary intake of 23 g of protein and 17 g of fat, amounts that can be supplied as 50 g of parmesan cheese and one boiled egg, and correspond to a total energy intake of ∼1000 kJ (239 kcal). Such a quantity of calories cannot be ignored because it can affect energy balance, and lead to an overconsumption of calories if used as a complementary intake rather than a substitute for other energy-containing foodstuffs. Indeed, healthcare professionals should always bear in mind that the dietary measures recommended in T2D should be consistent with goals to lose body weight or at least maintain it within reasonable limits, especially in patients who are already obese or prone to becoming overweight [17].

By demonstrating that a protein and lipid preload with no carbohydrate content can produce an improvement in metabolic tolerance of a glucose load given 30 min later, Trico et al. [18] have expanded an old concept first developed by Staub and Traugott approximately 100 years ago [32,33]. Those authors demonstrated that the administration of a carbohydrate load can influence glucose tolerance of the subsequent meal, provided that the meal is consumed within a reasonable time interval of less than a few hours. As well as adding a protein and lipid preload to this early concept, the findings of Trico et al. [18,19] are in parallel with and in addition to those of other investigators [22,23,34,35], thus allowing us to gain further insights into the mechanism underlying the Staub–Traugott effect, and to revisit it via the incretin system and endogenous GLP-1 secretion. Indeed, it was recently demonstrated that, in people with metformin-treated diabetes, a protein preload enhances the efficacy of vildagliptin, a DPP-4 inhibitor, and results in better postprandial glucose control by both slowing gastric-emptying and increasing plasma intact incretins [35].

One of the main conclusions that can be drawn from the Trico et al. study is that due consideration should be given to meal and nutrient sequential distributions to improve glucose tolerance in T2D, particularly at breakfast, the time when hepatic glucose production and insulin resistance are both at their maximum levels [36]. These two pathophysiological situations, especially when associated with a breakfast containing high-GI foods, can have several consequences, including the large and delayed post-breakfast glucose excursions referred to as the "extended dawn phenomenon" [1,3,37]. Substituting low-GI foods for higher-GI foods at this time of day, and structuring breakfast in a hierarchical manner such that intakes of protein- and fat-containing foods precede carbohydrate-containing foodstuffs, should be recommended in those patients for whom the extended dawn phenomenon is particularly marked. When it comes to lunch and dinner, the recommendations should include a sequential order where slow-release (low-GI) carbohydrates are consumed at the beginning of the meal, while those of faster release are consumed last as dessert.

Thus, for T2D patients, pastries, cookies and miscellaneous sweets can be permitted at the end of a meal, provided that their consumption is limited in both quantity and frequency to special occasions, such as weekly/monthly festive meals with relatives and/or friends. According to the data obtained by Trico