

POST-PRANDIAL HYPERGLYCEMIA. POST-PRANDIAL HYPERGLYCEMIA AND DIABETES

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SUMMARY - Post-prandial hyperglycemia (PPHG) is an independent risk factor for the development of macrovascular complications. It is now recognized that normalizing post-prandial blood glucose is more difficult than normalizing fasting glucose. Many factors affect the post-prandial blood glucose excursion. The glycemic index of the meal depends on the nature of the ingested food and starch composition. Gastric emptying is influenced by various factors including gut hormones such as GIP and GLP1, which potentiate insulin secretion, especially in its acute first phase, now referred to as an incretin effect. They also modulate glucagon secretion. Post-prandial hyperglycemia is limited by uptake of glucose by the liver and by inhibition of endogenous glucose production in this organ. In healthy controls, hepatic glucose production is halved after a meal, whereas in glucose-intolerant individuals and type 2 diabetics this inhibition is impaired (20-30% versus 50%). The persistence of endogenous glucose production during the post-prandial phase appears to be the main culprit in the PPHG. This reduced decrease in endogenous glucose in glucose intolerant and type 2 diabetic patients depends not only on the first acute phase of insulin secretion, but above all on the non-suppressed glucagon level during the post-prandial phase. Glucagon levels fall in healthy control subjects during the post-prandial phase. Although peripheral glucose uptake by insulin-dependent tissues is altered in type 2 diabetic patients, it does not appear to be the major cause of the PPHG as there are patients with insulin resistance but without post-prandial hyperglycemia.


Key-words: post prandial hyperglycemia, gastro-intestinal hormones, hepatic glucose metabolism, insulin sensitivity.

RÉSUMÉ - Hyperglycémie post-prandiale. Hyperglycémie post-prandiale et diabète

L'hyperglycémie post-prandiale est un facteur de risque indépendant de complications macro-vasculaires. Il est admis qu'il est beaucoup plus difficile de normaliser la glycémie post-prandiale que la glycémie à jeun. De nombreux facteurs participent à l'excursion post-prandiale du glucose. La composition du repas lui-même, sa richesse en amidon participent à l'index glycémique. Ensuite, la vidange gastrique est modulée par différents facteurs et les hormones gastro-intestinales telles le GIP ou le GLP1 participent au phénomène « incretin » caractérisé par une potentialisation de l'insulino-sécrétion et particulièrement de son pic précoce quand le glucose est apporté par voie orale, par opposition à un apport par voie veineuse. Les hormones gastro-intestinales modulent aussi la sécrétion de glucagon. Ensuite, le flux de glucose provenant de la digestion gagne le courant portal et le foie est capable de minimiser l'excursion susceptible d'être engendrée par cette arrivée massive au cours de la digestion. Il peut d'une part extraire et stocker une partie du glucose provenant de la digestion, mais surtout il diminue la production endogène de glucose. Cette diminution au cours de la digestion est d'environ 50 % chez un sujet contrôle, mais n'est que de 25 à 30 % chez un intolérant au glucose ou un patient diabétique de type 2. Ainsi, cette moindre diminution semble le facteur principal de l'excursion glycémique post-prandiale. Cette moindre diminution de la production hépatique endogène dépend essentiellement du pic précoce de sécrétion insulinique et aussi de la non suppression du niveau de glucagon au cours de la digestion chez le patient intolérant au glucose et le patient diabétique de type 2, alors que chez le patient contrôle, le glucagon s'effondre régulièrement au cours de la digestion.

La captation de glucose par les tissus périphériques est bien sûr altérée en cas de diabète de type 2, mais ne semble pas être le facteur essentiel participant à l'hyperglycémie post-prandiale, dans la mesure où des patients insulino-résistants ont été décrits avec une insulino-résistance périphérique très certaine et sans hyperglycémie post-prandiale.

Mots-clés : hyperglycémie post prandiale, hormones gastro-intestinales, production hépatique de glucose, sensibilité à l'insuline.

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The main challenge in the management of patients with diabetes mellitus is to maintain blood glucose levels as close to normal as possible. In general, normalizing post-prandial blood glucose is more difficult than normalizing fasting hyperglycemia. In type 2 diabetic patients, non-fasting (post lunch and extended post lunch) plasma glucose levels are better correlated with HbA1c than are fasting levels [1]. In addition, epidemiological studies have indicated that post-prandial hyperglycemia (PPHG) or hyperinsulinemia are independent risk factors in the development of macrovascular complications of diabetes mellitus. The Paris prospective study [2] and the Helsinki policeman study [3] found a stronger association of fatal and non-fatal cardiovascular diseases with 1 and 2 hour post-prandial hyperinsulinism than with fasting hyperinsulinemia. The association between high but non-diabetic blood glucose levels and the risk of death was recently evaluated by Balkau [4]. Even a mild post-prandial increase of blood glucose was found to be a risk factor.

There are also theoretical reasons why PPHG may pose an added risk. PPHG in certain individuals may be associated with post-prandial hyperlipemia [5]; lipoproteins with enhanced atherogenic potential have been identified during post-prandial lipemia [6], and PPHG also enhances lipid peroxidability [7].

There is as yet no direct evidence that a strategy specifically designed to control post-prandial glucose would lower such risks in diabetics. Such studies would not be easy to conduct as the benefit from post-prandial control needs to be distinguished from the benefit from better overall glucose control.

The post-prandial glycemic excursion may be influenced by the composition of meals, gastric outflow, degradation of food within the intestinal lumen and the clearance of blood glucose: glucose is metabolized by insulin-dependent tissues (liver, muscle, adipocytes) as well as non-insulin dependant tissues, which all need to be taken into account.

■ FOOD COMPOSITION, GASTRIC EMPTYING, DIGESTIVE ENZYMES AND PPHG

Jenkins first described the variability in the blood glucose excursion after intake of the same carbohydrate amount. The nature of the starch was found to be an important determinant of the blood glucose and insulin responses to food giving rise to the concept of glycemic index. The fiber content of the food may also play a role as cooking modifies the composition of starch. It has also been shown that when different foods are consumed together the mean index of the meal is preserved. So the nature of the ingested food can influence the excursion in blood glucose levels [8].

Gastric emptying may promote a rapid increase in blood glucose if the nutrients rapidly pass into the intestinal lumen as observed in patients with gastrectomy. It is also recognized that the rate of gastric emptying is influenced by the immediate blood glucose concentration. In healthy subjects, experimentally induced hyperglycemia slows emptying [9-10] and in patients with type I diabetes mellitus, emptying was found to be slower during induced hyperglycemia than euglycemia [10-11]. Results were more ambiguous from investigations in diabetic patients with prolonged elevations in blood glucose and progressive improvement in blood glucose. Holzapfel *et al.* [12] demonstrated that gastric emptying was unaffected by the significantly lower pre and post-prandial blood glucose concentration resulting from a readjustment of the treatment regimen. They studied nine patients with type 2 diabetes on secondary failure to oral hypoglycemic therapy before and after an improvement of blood glucose level with insulin therapy. The rate of gastric emptying was the same in both situations. Although glucose levels exceeded 15 mmol/l during the second oral hypoglycemic failure, or were below 10 mmol during insulin therapy, this difference in PP blood glucose did not modify gastric emptying. Thus for the variation in blood glucose observed in clinical practice, blood glucose may have little influence on the rate of gastric emptying.

After leaving the stomach, the digestibility of food may also be reduced by the presence of enzyme inhibitors, such as pectin and phytate [13-14], while other substrates such as tannins may slow down the action of enzymes such as pancreatic α amylase and improve the post-prandial blood glucose excursion [15]. The inhibition of intestinal α amylase slows the passage of carbohydrates from the intestinal lumen to the blood portal system and so carbohydrate malabsorption resulting from a slow digestion may contribute to a lower post-prandial blood glucose level [16].

Meal composition, the nature of the starch, α amylase from the pancreas and α glucosidase from the gut wall all modify the rate of glucose passing from the intestinal lumen to the blood stream, and may all contribute to post-prandial hyperglycemia.

■ GASTRO-INTESTINAL HORMONES AND PPHG

The insulin response of β cell to a given increase in plasma glucose is greater when the glucose has been given orally rather than intravenously [17]. This is due in part to the secretion of gut hormones, also called incretins, which potentiate glucose-induced insulin secretion [18]. The definition of the incretin effect and incretin hormones by Creutzfeld [18] is now well documented: the incretin effect is the greater effect of oral than intravenous glucose on the insulin response [19], or an equivalent rise in glycemia from the

parenteral route [20-21]. In normal subjects up to 60% of the insulin secretory response after an oral glucose load is not caused by a direct interaction of glucose with the β cell, but by the secretion of insulinotropic peptides. Incretin hormones are gut factors released after oral nutrients intake; they stimulate insulin secretion in the post-prandial state and may well play a role in PPHG.

GLP1 and GIP are the major hormone mediators regulating post-prandial insulin release. Both peptides are released from endocrine cells in the intestinal mucosa after ingestion of nutrients and enhance post-prandial insulin release from the β cell. Both hormones fulfil criteria for incretins. GIP is thought to play an important role in the mediation of this signal and is now a good candidate for an incretin [19]. However, supra-physiological levels of GIP are needed to potentiate insulin secretion and amplification of the insulin response to oral glucose load, and an additional factor is now assumed to be required. This was borne out by the fact that an incretin effect was still observed when circulating GIP was inactivated by anti-GIP antibodies [22]. GLP1 could be another incretin factor [23]. Nauk compared the insulinotropic activity of exogenous incretin hormone GIP and GLP1 in nine type 2 diabetic patients. Synthetic human GIP or GLP1 were administered under hyperglycemic clamp conditions. Plasma GIP and GLP1 levels were comparable to that after oral load. Both GIP and GLP1 augmented insulin secretion in a dose-dependent manner. With GIP, the maximum effect in type 2 diabetics was significantly lower (-54%) than in normal subject, although the difference was not significant [24].

GLP1 is the major product from intestinal proglucagon processing and is secreted from the L cell of the jejunum and ileum. GLP 1 1-37 is cleaved after position 6 resulting in the bioactive molecule GLP1 7-37, which is at least partially further C-terminal-truncated and associated with GLP1 7-36. In man, approximately 80% of GLP1 circulates in the truncated aminated form. GLP1 is promptly released into the circulation after oral ingestion of both fat, amino acids and mixed meals. The glucose dependence of GLP1 secretion has been described [25]. GLP1 level increased 4-fold from basal levels after ingestion of 50 g of glucose, and increase 8-fold after 100 g of glucose. GLP1 peaked at 20 min and then sharply declined and basal levels were reached at 60 min. Once GLP1 is secreted, it acts on membrane receptors of pancreatic β cells. After internalization [26], it stimulates insulin secretion and enhances proinsulin biosyntheses. GLP1 also delays gastric emptying (50% emptying time increases from 16 ± 2 to 30 ± 5 min [27-28]). This action appears to be independent of the stimulation of insulin secretion. GLP1 also lowers glucagon levels in patients with type 2 diabetes [29]. GLP1 receptor gene expression has been detected in β cells, but also in

liver, muscle and adipose cells although no clear-cut effects had been demonstrated in those cells. In normal subjects, infusion of GLP1 lowers the meal-related increase in blood glucose concentration. The insuligenic index (ratio of insulin to glucose) increases 10-fold, suggesting that GLP1 has a significant insulinotropic effect in normal individuals [30]. When injected subcutaneously there is a small stimulation of basal insulin secretion, but secretion was found to be enhanced with increasing glucose levels, confirming the potential interaction between GLP1 and glucose in insulin secretion [30].

GLP1 was found to produce a marked increase in insulin secretion in diet-treated type 2 diabetic patients with mild hyperglycemia [31-32], and it has also been shown to be effective in poorly controlled type 2 diabetes patients on oral therapy [23]. However, the majority of studies report an exaggerated GIP response [33] and elevated GLP1 levels in patients with type 2 diabetes [24, 34], suggesting that the reduced incretin effect in patients with type 2 diabetes may be due to insensitivity of β cells to the hormones. Nevertheless, it has been shown that an inherited defect in the GLP receptor gene is not a major risk factor for the development of type 2 diabetes [35, 36]. So incretin factors may participate in the regulation of post-prandial blood glucose excursion, but they are probably not major contributors.

■ AMYLINE AND PPHG

Pancreatic β cells have been found to produce and cosecrete a second hormone, amyline, along with insulin [37]. In a study using supraphysiological concentrations of this hormone it has been implicated in the development of insulin resistance [38], but at physiological concentrations it appears to play a role in glucose homeostasis. It is a 37 amino acid peptide hormone that is copackaged with insulin in the secretory granules of the pancreatic β cells. The both hormones are secreted together. Studies in man have demonstrated that the plasma concentrations of insulin and amyline rise and fall in parallel following meals.

Amyline acts on glucose homeostasis via two mechanisms. First there is a good evidence that amyline delays the delivery of nutrients to the small intestine and thus modulates inflow of glucose from food into the circulation [39]. After subcutaneous injection of amyline in normal and diabetic rats, it was shown to inhibit gastric emptying in a dose-dependent manner and at doses that appeared to be within the physiological range. More recently, it has been shown that amyline suppresses post-prandial glucagon secretion [40].

Amyline deficiency in diabetics may result in an accelerated delivery of nutrients and loss of suppression of hepatic glucose production leading to excessive glucose inflow into the circulation in the post-

prandial state. It has been shown that injection of Pramilitide (amyline analogue) slows the delivery of nutrients to the small intestine. However, Pramilitide was not found to reduce the hyperglycemia following an intravenous glucose load, indicating that the effect is mediated in the gastrointestinal tract [41, 42]. So a deficiency of amyline may be associated with accelerated gastric emptying. Since amyline is secreted from β cells in response to glucose and incretins such as GLP1, it would be a good candidate for a role in a feedback loop controlling the transit of chyme from the stomach to the intestine and hence the subsequent absorption of glucose and post-prandial hyperglycemia.

■ HEPATIC GLUCOSE METABOLISM

In the post-absorptive state (on awakening in the morning) blood glucose is normal and stable, being derived from a constant production of endogenous glucose (mainly by the liver) matching the requirements of tissues. After breakfast, there is a new flux of glucose into the circulation, and gut transport and hepatic and extra-hepatic tissues maintain normal carbohydrate tolerance.

In a non-diabetic individual, the liver minimizes post-prandial hyperglycemia both by increasing glucose uptake and by suppressing endogenous glucose production [43]. Thirty percent of the glucose intake is cleared by the liver [44] and the rest reaches the peripheral circulation. Post-prandial suppression of endogenous glucose production can prevent 20-30 g of glucose from entering the systemic circulation [45].

Type 2 diabetic patients are generally hyperglycemic before and after meals, although the post-prandial glucose excursion will be determined by the prevailing fasting glycemia. However, post-challenge glycemic excursions in type 2 diabetic patients are usually about twofold those of normal controls [46-48]. Post-prandial factors thus appear to be important in these patients.

The normal metabolic response to the ingestion of glucose can be quantified by the doubly labelled OGTT technique: labelled glucose is infused to measure overall glucose appearance (RaT) and disappearance (RdT) rates, and a distinct labeling of the oral glucose load allows calculation of appearance (RaE) and disappearance (RdE) rates of exogenous glucose [49]. In normal individuals, about 25% of the oral glucose is taken up by splanchnic tissues (gut and liver), and endogenous glucose production is suppressed by 50% [50]. Muscle uptake represents 25-56% of the oral load [50], the remainder is cleared by non-insulin-sensitive peripheral tissues and adipose tissue [51]. Measurements by indirect calorimetry also indicate that 1/3 of the oral load is oxidized, while 2/3 are stored [51]. Post-prandial hyperglycemia may stem from reduced splanchnic glucose uptake, exces-

sive (inadequately suppressed) endogenous glucose production and reduced peripheral uptake due to defective oxidation or storage of glucose.

Doubly labelled OGTTs have been conducted to study post-challenge hyperglycemia in glucose-intolerant subjects and in type 2 diabetics [46-48, 52] as well as in experimental post-prandial hyperglycemia due to starvation [53] or induced by a lipid infusion [54, 55].

In a study of non-diabetic patients but with glucose intolerance, Mitrakou et al [56] examined whether post-prandial hyperglycemia was due to excessive glucose entry or to decreased glucose utilization. In the event of excessive glucose entry, the authors wished to find out whether it was due to a failure to suppress endogenous glucose production or to an enhanced systemic inflow of meal-derived glucose. The patients had near normal basal glucose levels (6.2 ± 0.6 mmol/l), but high post-load glucose (12 mmol at 60 min) and were compared with control subjects. Endogenous glucose production was monitored with ^6H glucose tracer, and each subject ingested 50 g of glucose labelled with ^{14}C glucose. They calculated the overall rate of appearance of glucose (endogenous and exogenous). In all groups, the rate of systemic appearance of ingested glucose peaked after 30 min and there was no significant difference between the two groups. Basal endogenous glucose production did not differ between the two groups, but in normal subjects it decreased significantly within 30 min and was suppressed by approximately 50% for up to five hours. In the glucose-intolerant patients, endogenous glucose production did not decrease until 60 min and was suppressed by less than 30%. Total endogenous glucose output over five hours was therefore significantly higher (181 ± 8 mmol \neq 133 ± 8 mmol) in the patients with glucose intolerance. As a consequence of the reduced suppression of endogenous glucose output, the rate of total systemic appearance of glucose was significantly higher in the glucose intolerant subjects. The ratio of total disappearance of glucose did not significantly differ between the groups. The higher increase in post-prandial plasma glucose concentration in these patients was due to a greater rate of total glucose appearance.

Thus in patients with near normal basal glucose level but high post-prandial glucose levels, the PPHG seems to be due to a defect in post-load suppression of hepatic glucose production without any impairment in total glucose disappearance.

In a similar study of 13 type 2 diabetic patients and 7 controls [47], the amount of meal-derived glucose reaching the systemic circulation was found to be slightly greater in diabetic patients ($622 \pm 19 \neq 521 \pm 15$) owing to a slight greater rate of entry during the first two hours. Endogenous glucose production decreased in the non-diabetics to a nadir of 0.9 ± 0.1 at 90 min; in contrast, the nadir in the type 2 diabetic

patients was observed around 300 min and was rather elevated (1.3 ± 0.1 mg/kg/min). Thus in type 2 diabetic patients there is excessive endogenous glucose production after carbohydrate ingestion, which is accompanied by a slight but significant increase in the amount of ingested glucose reaching the systemic circulation both directly and via de novo glucose formation from meal-derived three carbon precursors. Since the increased rate of glucose entry is not accompanied by an appropriate increase in glucose uptake, there is a post-prandial hyperglycemia attributed to a combination of hepatic insulin-resistance and impaired insulin secretion.

These observations indicate that post-prandial suppression of endogenous glucose production also occurs in type 2 diabetic patients, but the magnitude of this suppression is too small to account for the hyperglycemia. This leads to excess glucose for disposal in extra-hepatic tissues. The pattern of suppression of glucose production also differs, coinciding with a rapid increase in insulin secretion, whereas the suppression of endogenous is prompt and sustained in the non-diabetic controls. In contrast, in type 2 diabetic patients, glucose production after a meal declined slowly over five hours.

These two studies demonstrated that reduced suppression of endogenous glucose output is primarily responsible for the excessive post-prandial increase in plasma glucose levels. The liver thus plays a pivotal role in the regulation of post-prandial glycemia. It can minimize the amount of glucose entering the systemic circulation after a meal by extracting a portion of the ingested glucose [57] and by decreasing the rate of endogenous glucose release. The failure to adequately suppress hepatic glucose release appears to be a major deficit in patients with type 2 diabetes.

Decreased insulin secretion [56] and loss of first phase insulin release [58], persistence of preprandial glucagon levels [59-61] and high free fatty acids levels [54-55-62] leading to hepatic insulin resistance may contribute to this excessive glucose production. On the other hand, splanchnic uptake of glucose is normal [46, 52, 63] or very slightly reduced in type 2 diabetics [47-48], and does not seem to contribute to their impaired glucose tolerance [56].

The reduced suppression of endogenous glucose production could be due to hepatic insulin-resistance, abnormal insulin and glucagon suppression or both. A meal suppressed glucagon levels in normal controls by 20-30%, but had little effect in type 2 diabetic patients [64], while the transient increase in post-hepatic glucose cycling correlated with both glucagon and glucose levels [65]. In the study of Mitrakou *et al.*, plasma insulin was lower, glucagon level was unchanged and the molecular ratio of plasma insulin to glucagon was almost halved in type 2 diabetic patients.

Glucagon appears to be important. Dinneen [59] studied the effect of glucagon suppression in two situations: endogenous glucagon secretion was either inhibited by somatostatin, or glucagon was infused to either mimic the pattern of post-prandial suppression that is normally observed in normal individuals, or maintain a constant glucagon concentration as observed in type 2 diabetic patients. A test meal was served and 6^3H glucose and 6^{14}C glucose were used as tracers to follow glucose appearance from both digestion and endogenous glucose production. A higher post-prandial glucose concentration was observed on the constant glucagon regimen, which stemmed from an increased rate of glucose appearance rather than a decreased disappearance.

The reciprocal relation between glucose and glucagon is abolished in diabetic patients [60], and glucagon is not suppressed following carbohydrates ingestion. Failure to suppress glucagon in the post-prandial state impairs glucose tolerance by excessive post-prandial glucose production from splanchnic tissues.

An impaired suppression of hepatic glucose production may result from a direct insulin-resistance of the action of glucagon or may be due to a defect in suppression of NEFA. Kruszynska [66] studied glucose kinetics (IV 3^3H glucose oral C^{14} glucose) after a 75 oral glucose load in two conditions. In one set of experiments, plasma NEFA were maintained by infusion of 20% of liposyn and heparin: plasma glucose rose more rapidly, total glucose appearance was higher due to increased hepatic glucose output ($28.4 \pm 1 \neq 21.2 \pm 1.5$ g over 4 hours). Total glucose disposal was also higher. In summary, impaired suppression of NEFA after a glucose load impairs the ability of insulin to suppress hepatic glucose output. The role of NEFA has also been documented in both animal [62] and human studies [67].

Hepatic splanchnic glucose uptake therefore seems to be a major determinant in the PPHG (68). In glucose-intolerant individuals, basal endogenous glucose production does not differ from normal, but after an oral load it falls more slowly than in control subjects, despite an absence of any difference in total disappearance. In type 2 diabetic patients, the role of endogenous production is also important, but it is combined with a defect in peripheral glucose disappearance; the impaired action of glucagon and NEFA on endogenous glucose suppression seems to be important in these patients.

■ ROLE OF INSULIN SECRETION AND TISSUE INSULIN SENSITIVITY IN PPHG

The pancreatic insulin response is described as an early burst of insulin release, followed by a gradually increasing phase of insulin secretion lasting for several hours. A characteristic finding in the early stages

of glucose intolerance or diabetes is the loss of the first phase of insulin secretion. Cherington [69] demonstrated that in the absence of the first phase insulin secretion, the stimulatory effect of glucagon on gluconeogenesis is enhanced. Luzi and De Fronzo [58] confirmed that the loss of the first phase was associated with a marked impairment in the initial suppression of hepatic glucose production: in control subjects the combination of hyperinsulinemia plus hyperglycemia leads to a prompt and marked (75%) inhibition of hepatic glucose production within twenty minutes. When the same degree of hyperglycemia was created in the absence of the first phase, the suppression of hepatic glucose production was markedly impaired and remained almost double normal levels. So the loss of the first phase of insulin secretion may contribute to a reduced suppression of hepatic glucose production leading to a higher glucose appearance in the circulation and PPHG. However, it should be kept in mind that there may be a degree of insulin resistance and that insulin is not active on all tissues.

Bassu *et al.* [70] studied the change in the pattern of insulin delivery in the post-prandial state. It is not yet known whether defects in insulin secretion or action give rise to the same pattern and degree of hyperglycemia nor whether a combination of the two leads to any greater impairment in glucose tolerance. These authors first characterized the post-prandial insulin profile in control subjects and in typical type 2 diabetic patients after a standard meal. They then used a computer driver infusion to deliver insulin to mimic the "diabetic profile" in healthy lean controls whose endogenous insulin secretion was inhibited with somatostatin. Glucose was also infused to mimic the amount and pattern of glucose entering the systemic circulation following ingestion of 50 g of glucose. This procedure was conducted in lean non-diabetic subjects (normoglycemic non-insulino-resistant), obese non-diabetic subjects (normoglycemic low insulino-resistant subjects) and patients with type 2 diabetes (moderately hyperglycemic insulino-resistant). Thus they were able to observe the action of a non-diabetic and a diabetic insulin profile in individuals with different degrees of insulino-resistance. When the diabetic insulin pattern was reproduced in control subjects, blood plasma levels were not modified and endogenous glucose release was normally suppressed. When the normal insulin pattern was reproduced in type 2 diabetic patients, blood glucose levels remained high and hepatic glucose output was not suppressed. Thus hepatic insulino-resistance and endogenous hepatic glucose production were assumed to be major factors in hyperglycemia, while impairments in insulin secretion play a minor role in the PPHG.

In another study [61], they attempted to account for the hepatic insulino-resistance by a modification of hepatic sensitivity to glucagon or by a higher gluca-

gon level in the presence of insulin deficiency. This is of practical importance as a variety of agents that either inhibit glucagon secretion or antagonize glucagon action are under development. They studied non-diabetic subjects in which the suppression or absence of suppression of glucagon was induced by administration of somatostatin and appropriately timed glucagon infusions. A variable intravenous glucose infusion mimicked the systemic rate of glucose appearance normally observed after ingestion of 50 g glucose, and insulin was infused in a manner designed to mimic a normal non-diabetic or type 2 diabetic post-prandial insulin profile.

The rate of glucose disappearance above basal levels did not differ between individuals reproducing the non-diabetic or diabetic insulin profiles in the glucagon suppressed or non-suppressed study. The effect of the non-diabetic insulin profile combined with a rise in glucose concentration resulted in a prompt inhibition of endogenous glucose production in both glucagon-suppressed and glucagon non-suppressed conditions. But the diabetic insulin profile and the rise in glucose concentration led to a prompt decrease in endogenous glucose production in the glucagon-suppressed study, glucose production did not decrease and even increased in the glucagon non-suppressed condition. The overall result was a considerably lower inhibition of glucose production.

These findings indicate that the sole suppression of glucagon could inhibit endogenous glucose production and reduce the post-prandial glucose excursion even in patients with type 2 diabetes who have impaired insulin secretion.

In people with glucose intolerance or type 2 diabetes, carbohydrate ingestion fails to suppress plasma glucagon and may even increase it. The lack of suppression of glucagon leads to hepatic insulino-resistance in diabetics. However, the lack of suppression of glucagon had a minimal effect on glucose tolerance when insulin levels rose rapidly (non-diabetic insulin profile).

Although inhibition of endogenous glucose production effectively reduces the inflow of non-meal glucose into the blood stream, the liver also extracts glucose from the splanchnic stream. Taylor [71] using a non-invasive NMR technique showed that liver glycogen concentration fell overnight from 350 ± 18 ml/l four hours after evening meal to 207 ± 22 ml/l in the fasting state. After a test meal, net hepatic glycogen concentration rose at an average rate of 0.3 mmol/l/min for 260 min. This corresponded to a net hepatic glycogen synthesis of 28.3 ± 3.7 g, equivalent to 20% of meal carbohydrate.

Skeletal muscles are also insulin-sensitive tissues and many authors have studied their glucose uptake. Keley [72] estimated that muscle took up 26% of an oral glucose load, 15% of the oral glucose taken up by muscle was released as lactate, 50% was oxidized and

35% was metabolized for storage. So muscle and splanchnic tissues take up comparable percentages of an oral glucose load and both contribute to stabilize post-prandial blood glucose levels.

Reduction of peripheral glucose uptake also contributes to PPHG, as indicated by a lower glucose Rd after correction for glycosuria and glucose remaining in the glucose space [46], or expressed by lower glucose metabolic clearance rates [52]. Interestingly, in type 2 patients, the defect seems to concern both the oxidative and non-oxidative disposal of glucose [48, 52], whereas non-oxidative glucose disposal is increased in starvation or lipid-induced glucose intolerance [53, 55].

In a study of healthy controls, patients with type 2 diabetes, and first degree relatives of those patients with glucose intolerance (post-prandial hyperglycemia) and with normal glucose tolerance (normal post-prandial glycemia), Erikson [73] found that the relatives with an impaired oral glucose tolerance had the same degree of impairment in glucose storage as did those with normal metabolism. Impaired glucose storage is apparently common in relatives of type 2 diabetic patients, but is not associated with glucose intolerance as insulin secretion is normal. Therefore both insulin resistance and impaired insulin secretion appear to be required for development of impaired glucose tolerance and post-load hyperglycemia.

CONCLUSION

The postprandial blood glycemia excursion is a complex phenomena that depends on a variety of factors including the composition of food, gut hormones, digestive enzymes, hepatic glucose production and its inhibition, and peripheral glucose uptake. PPHG mainly stems from a reduced inhibition of hepatic glucose production via insulin resistance combined with a defect in glucagon suppression and an impairment in the action of gut hormones. Thus there is considerable scope for therapeutic strategies.

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