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Impact of postprandial glucose control on diabetes-related complications: How is the evidence evolving?

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ABSTRACT

Conflicting findings in the literature and lack of long-term definitive outcome studies have led to difficulty in drawing conclusions about the role of postprandial hyperglycemia in diabetes and its complications. Recent scientific publications support the role of postprandial glucose (PPG) as a key contributor to overall glucose control and a predictor of microvascular and macrovascular events. However, the need remains for definitive evidence to support the precise relationship between PPG excursions and the development and progression of cardiovascular complications of diabetes. Drawing firm conclusions on the relationship between PPG and microvascular and macrovascular complications is challenged by the absence of antidiabetic agents that can specifically exert their action on PPG alone, without a basal glucose-lowering effect. Areas under investigation include interventions that more closely approximate 'normal' physiological postprandial responses, as well as technologies that advance the mode of insulin delivery or optimize methods to sense glycemic levels and variation. In conclusion, the precise role of postprandial hyperglycemia in relation to development of diabetic complications is unclarified and is one of the remaining unanswered questions in diabetes. Nevertheless, current evidence supports PPG control as an important strategy to consider in the comprehensive management plan of individuals with diabetes.

1. Diabetes and its complications

Diabetes, with its associated complications, imposes a growing health burden worldwide (Seaquist, 2014). Cardiovascular disease (CVD) is a major complication of both type 1 and type 2 diabetes (Duca, Sippl, & Snell-Bergeon, 2013). Individuals with diabetes have a two- to four-fold increased risk of developing CVD, and it is the leading cause of mortality in this patient population (Duca et al., 2013; Lorber, 2014). As such, the management of cardiovascular risk remains an important goal of treatment in individuals with diabetes. Microvascular complications of diabetes, including retinopathy, nephropathy and neuropathy, have a significant impact on morbidity and mortality, and represent the leading causes of blindness, renal failure and nerve injuries associated with non-healing ulcers and non-traumatic amputation (Kitada, Zhang, Mima, & King, 2010).

Significant progress has already been made in reducing the risk of cardiovascular complications through prevention strategies such as early identification of individuals at risk, lifestyle modifications and management of cardiovascular risk factors associated with the development of complications, including hyperglycemia, hypertension, dyslipidemia, obesity, cigarette smoking, physical inactivity and prothrombotic factors (Lorber, 2014). Additional steps must, however, be taken to reduce the residual risk.

A primary focus in the management of hyperglycemia has been on lowering glycosylated hemoglobin (HbA_{1c}), largely based on outcome trials to date which suggest that HbA_{1c} is the primary glycemic predictor of diabetes complications (American Diabetes Association, 2015). Landmark studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), have demonstrated the association between HbA_{1c} and microvascular complications (Stratton, Adler, Neil, et al., 2000). While strategies aimed at lowering HbA_{1c} have led to reductions in cardiovascular risk, it is tempting to postulate that postprandial glucose (PPG) may have a role to play beyond its contribution to HbA_{1c} (Ceriello, 2010; Ceriello, Hanefeld, Leiter, et al., 2004; Monnier, Lapinski, & Colette, 2003).

This article aims to review the role of postprandial hyperglycemia, both in terms of its contribution to overall glucose control and also in

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relation to the risk of diabetes complications. It explores the scientific literature, including ongoing studies, and provides recommendations for the design of future studies. Finally, it discusses interventions, both existing and emerging, that have the potential to improve fluctuations in PPG levels and, therefore, impact on the heavy burden of complications in individuals with diabetes.

2. Contribution of postprandial glycemic excursions to overall glucose control

PPG is a key contributor to overall glycemic control, and represents a primary target to improve HbA_{1c} levels and, in turn, to reduce the vascular complications of diabetes (Ceriello, 2010; Ceriello, Hanefeld, Leiter, et al., 2004; American Diabetes Association, 2015; Monnier et al., 2003; Stratton et al., 2000). Thus, a reduction in postprandial glycemic excursions contributes both to the maintenance of glucose homeostasis and the longer-term development and progression of the complications of diabetes.

2.1. Physiological responses following a meal

In people without diabetes, postprandial hyperglycemia appears as a transient and modest surge in glycemia after the ingestion of food (Moore, Coate, Winnick, An, & Cherrington, 2012; Rizza, 2010). The resulting postprandial rise in glucose is restrained through physiological processes that involve the rapid secretion of insulin and the inhibition of glucagon to suppress hepatic glucose production (Bansal & Wang, 2008; Rizza, 2010). In addition, glucose uptake is stimulated in hepatic and peripheral tissues (Moore et al., 2012).

A key determinant of postprandial hyperglycemia is the rate of gastric emptying after ingesting a meal, which varies according to extrinsic and intrinsic factors (Tambascia, Malerbi, & Eliaschewitz, 2014). Extrinsic factors that affect gastric emptying include the caloric content and macrocomposition of a meal (Tambascia et al., 2014). After a meal is ingested, food in the intestine leads to the release of incretin hormones such as glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) from the gut (Leech, Dzhura, Chepurny, et al., 2011; Yabe & Seino, 2011). One of the main effects of GIP is to stimulate insulin secretion (Yabe & Seino, 2011). The effects of GLP-1 are several: (1) it stimulates the hypothalamus to decrease appetite and, through neural connections to the vagus, inhibits gastric emptying; (2) it increases insulin and reduces glucagon secretion; and (3) it triggers the release of insulin from the pancreatic β-cells along with the hormone amylin which, like incretins, acts on the vagus to reduce gastric emptying (Marathe, Rayner, Jones, & Horowitz, 2013; Tambascia et al., 2014). In addition to extrinsic regulation of gastric emptying, the process is regulated intrinsically via parasympathetic signals in response to, for example, hyperglycemia (Tambascia et al., 2014).

In individuals with diabetes, food intake and a rise in PPG elicit a delayed and blunted insulin response, accompanied by impaired inhibition of glucagon secretion and decreased hepatic and peripheral glucose uptake (Rizza, 2010). This leads to pronounced hyperglycemia, which has been reported to be associated with increased risk of microvascular and macrovascular complications (Authors/Task Force Members, Ryden, Grant, et al., 2013; American Diabetes Association, 2015; Handelsman, Bloomgarden, Grunberger, et al., 2015; International Diabetes Federation Guideline Development Group, 2014).

2.2. PPG excursions as a component of overall glucose control

The relative contributions of PPG and fasting plasma glucose (FPG) to hyperglycemia vary according to HbA_{1c} value, with PPG contributing more in well-controlled individuals and FPG in those with poor control (Monnier et al., 2003). Postprandial glucose increments are found to contribute approximately 70% to overall hyperglycemia, in patients with an HbA_{1c} <7.3% (Monnier et al., 2003).

Nevertheless, despite relative differences in the contribution of PPG versus FPG varying with deteriorating glycemic control, the absolute impact of PPG excursions on HbA_{1c} is approximately 1% (as a percentage point of HbA_{1c}), irrespective of the HbA_{1c} value, in individuals with non-insulin-treated type 2 diabetes and HbA_{1c} values ≥6.5% (Monnier, Colette, & Owens, 2011). Such findings suggest that, at least theoretically, an antidiabetic agent that specifically reduces PPG excursions, without any effect on basal glycemia, would decrease HbA_{1c} levels by about 1%.

3. Exploring the role of PPG in diabetes-related complications

Postprandial hyperglycemia has been associated with increased risk of diverse complications; in addition to CVD and microvascular events, elevated PPG has been associated with such conditions as cognitive dysfunction and cancer.

3.1. PPG and CVD risk

Several epidemiological studies have reported a link between cardiovascular risk and postprandial hyperglycemia, including the Framingham Offspring Study and the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study (DECODE Study Group EDEG, 1999; Decode Study Group EDEG, 2003; Decode Study Group tEDEG, 2001; Meigs, Nathan, D'Agostino, Wilson, & Framingham Offspring S., 2002). The association between postprandial hyperglycemia and risk of CVD was underscored in a meta-analysis including 95,783 subjects (Coutinho, Gerstein, Wang, & Yusuf, 1999). Notably, very few people with manifest type 2 diabetes were included in the studies. In addition, the statistical analysis did not adequately compensate for a greater proportion of patients with high postprandial hyperglycemia displaying metabolic syndrome or other cardiovascular risk factors compared with patients with lower PPG values, which may have confounded the conclusions.

In the 'Risk Factors in Impaired Glucose Tolerance (IGT) for Atherosclerosis and Diabetes (RIAD)' study the carotid intima-media thickness in individuals at risk for type 2 diabetes was found to be more closely related to 2-hour postload glucose than to HbA_{1c} or FPG (Temelkova-Kurktschiev et al., 2000). In two other studies, the level of postload glucose was associated with the number of coronary arteries with stenosis (Nakamura et al., 2003; Sasso, Carbonara, Nasti, et al., 2004). Esposito et al. (2004) compared the changes in carotid intima-media thickness during 1-year treatment with either the postprandial regulator, repaglinide, or the sulfonylurea, glyburide, and found a significant regression with repaglinide despite similar HbA_{1c} values between groups (Esposito, Giugliano, Nappo, & Marfella, 2004). The 'Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM)' in people with IGT receiving acarbose (an antidiabetic agent used to target PPG) found a 2.5% absolute risk reduction in CVD (number needed to treat (NNT) = 40; mean follow-up 3.3 years) and also a reduction in the progression of carotid intima-media thickness, compared with placebo treatment (Chiasson, et al., 2003; Hanefeld et al., 2004).

Further prospective evidence comes from the Diabetes Intervention Study, in which post-breakfast glucose levels, rather than fasting glucose, were found to be related to myocardial infarction (MI) and death over 11 years in patients with type 2 diabetes (Hanefeld, Fischer, Julius, et al., 1996). Additional evidence supporting the association comes from the San Luigi Gonzaga Diabetes Study, a prospective study involving over 500 individuals with type 2 diabetes. In this study, PPG was found to be a stronger predictor of cardiovascular events than fasting blood glucose (BG), particularly in women (Cavalot, Petrelli, Traversa, et al., 2006). A direct association between PPG levels and cardiovascular events/all-cause mortality was