Postprandial hyperglycemia: a new frontier in diabetes management?

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ABSTRACT

Postprandial hyperglycemia is one of the earliest abnormalities of glucose homeostasis associated with type-2 diabetes and it is markedly exaggerated in diabetic patients with fasting hyperglycemia. An extensive body of data demonstrates a strong association between postprandial glucose levels and cardiovascular risk factors. Our article will focus on the concept of postprandial hyperglycemia, its physiopathology, its role on cardiovascular risk factors and the effects of new devices and a new faster insulin analog on postprandial hyperglycemia.

Introduction

Postprandial hyperglycemia is one of the earliest abnormalities of glucose homeostasis associated with type-2 diabetes and it is markedly exaggerated in diabetic patients with fasting hyperglycemia. An extensive body of data demonstrates a strong association between postprandial glucose levels and cardiovascular risk factors. In recent years postprandial hyperglycemia aroused the interest of various scientists: new glucose measuring devices and new insulin analogs are to be launched on the market configuring new ways of detecting and treating postprandial hyperglycemia. Our article will focus on the concept of postprandial hyperglycemia, its physiopathology, its role on cardiovascular risk factors and the effects of new devices and a new faster insulin analog on postprandial hyperglycemia.

What is postprandial hyperglycemia?

Postprandial hyperglycemia (PPG) is defined as a plasma glucose level exceeding 140 mg/dL.[1] Development of postprandial hyperglycemia coincides with an impairment or absence of the first-phase insulin response, a decrease in insulin sensitivity in the peripheral tissues and decreased suppression of hepatic glucose output after meals due to insulin deficiency.[2]

Many factors determine the postprandial hyperglycemia profile. In non-diabetic individuals, fasting plasma glucose concentrations (*i.e.*, following an overnight 8- to 10-h fast) generally range from 70 to 110 mg/dL. Glucose concentrations begin to rise ~10 min after the start of a meal with a peak of ~60 min (as a result of the absorption of dietary carbohydrates) and rarely exceed 140 mg/dL, returning to preprandial levels within 2-3 h. The postprandial hyperglycemia profile is determined by carbohydrate absorption, insulin and glucagon secretion and their coordinated effects on glucose metabolism in the liver and peripheral tissues (Figure 1).[3]

Even though glucose concentrations have returned to preprandial levels by 3 h, absorption of the ingested carbohydrate continues for at least 5-6 h after a meal.

Since people with type-1 diabetes (T1DM) have no endogenous insulin secretion, the time and height of peak of insulin concentrations and resultant glucose levels depend on the amount, type, and route of insulin administration.

In type 2 diabetic patients (T2DM), peak insulin levels are delayed and are insufficient to control PPG excursions adequately. In both type 1 and type 2 diabetic individuals, abnormalities in insulin and glucagon secretion, hepatic glucose uptake, suppression of hepatic glucose production and peripheral glucose uptake contribute to higher and more prolonged PPG excursions than in non-diabetic individuals.

Recently, considerable attention has been focused on the postprandial state, because isolated postprandial hyperglycemia, as occurs in people with impaired glucose tolerance, has been shown to double the risk for death from cardiovascular diseases[4] and because postprandial hyperglycemia appears to be the rate-limiting factor for achieving optimal glycemic control in patients with type 2 diabetes.[5] Furthermore, postprandial hyperglycemia is one of the earliest abnormalities of glucose homeostasis associated with type 2 diabetes and worsens - progressing to fasting hyperglycemia - as the condition progresses.[6]

Usually, the assessment of the metabolic homeostasis in diabetic patients depends on three parameters: fasting blood glucose, PPG and glycosylated hemoglobin (HbA1c). In many recent epidemiological studies, PPG assessment is related to the risk of micro and macrovascular complications. As a rule, the PPG at 2 h from the meal is less than 140 mg/dL, while determinations above 200 mg/dL allow diagnosing diabetes mellitus. The pathophysiologic mechanisms involved in regulating the rate of postprandial blood glucose are numerous, rather complex and interdependent. They involve insulin secretion, glucagon suppression and also the intervention of some intestinal hormones as glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1; they all contribute to the rapid physiological response to meal which leads to normoglycemia (Figure 1).[7] The key factor in determining the lowering of postprandial hyperglycemic peak is the first phase of insulin secretion.

During a meal, insulin is released in 2 phases. In the first phase there is a release of a small amount of insulin, over approximately a 10-min period, which preempts and blunts the postprandial glucose excursions. As plasma glucose levels increase, a more sustained second phase of insulin release occurs, which is proportional to the glycemic load of the meal. One of the earliest manifestations of T1DM and T2DM is
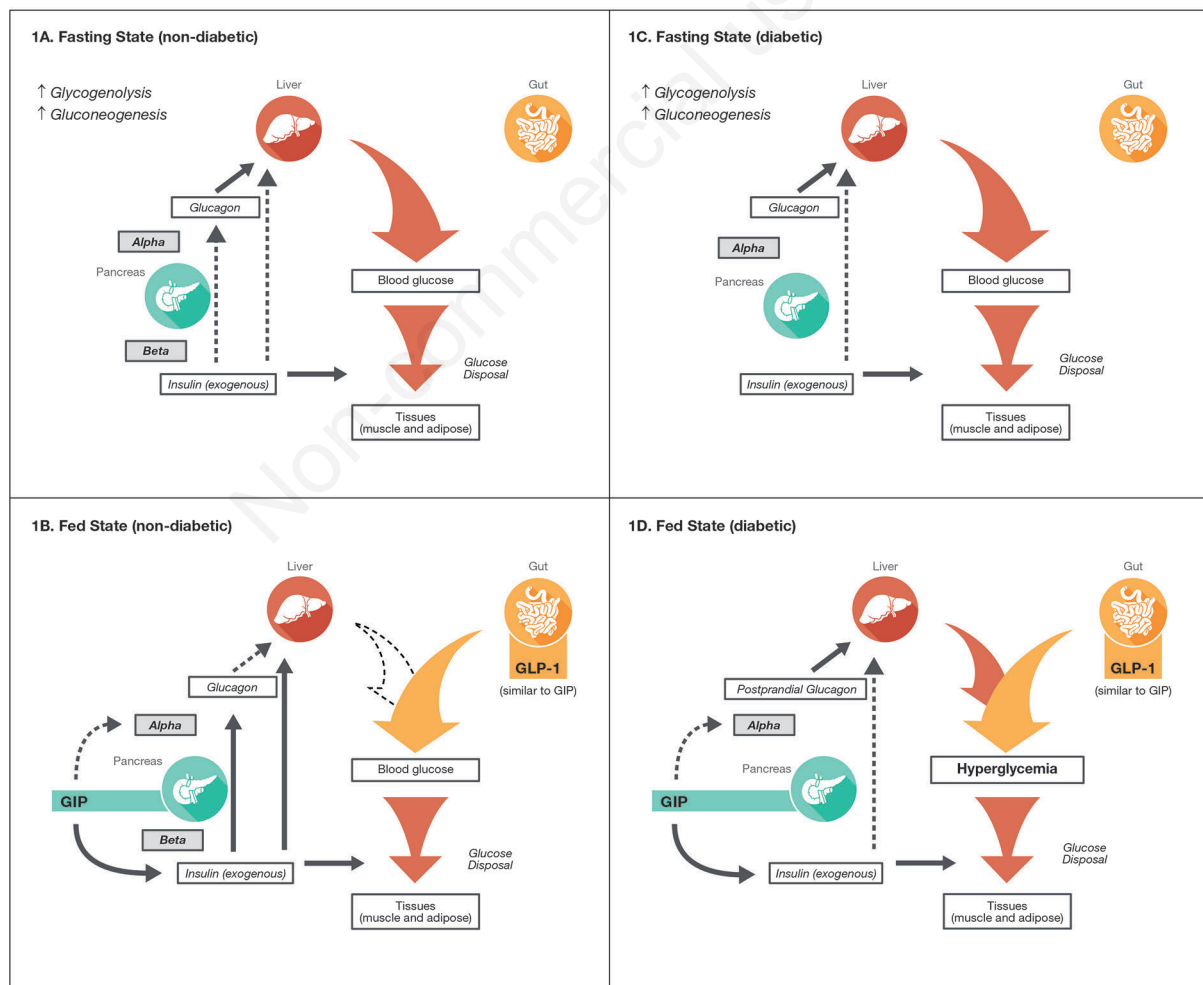

Figure 1. Glucose homeostasis and metabolism in non-diabetic and diabetic subjects. GIP, glucose-dependent insulino tropic homeostasis; GLP-1, glucagon-like peptide-1. *Adapted from Aronoff et al., 2004[3] and Provenzano and Scorsone, 2016.*[7]

the loss of first-phase insulin release.[6] When first-phase insulin response is lost, post meal glucose and free fatty acid levels increase rapidly, stimulating a delayed and excessive second-phase insulin response.

A consistent amount of data demonstrate a strong association between postprandial glucose levels and cardiovascular risk (Tables 1 and 2).[8,9] Large epidemiological studies have shown a continuous direct correlation between the level of postmeal glucose challenge glycemia and the risk for events, including coronary heart disease death, stroke, sudden cardiac death, and peripheral arterial disease.[10] In real life, the PPG state leads also to increased lipids levels: elevated triglycerides and their remnant lipoprotein particles. This contemporary elevation of carbohydrates and lipids after meals is named *postprandial dysmetabolism*. Postprandial dysmetabolism is a new parameter for the assessment of carbohydrates and lipids homeostasis. While the conventional risk factors defining cardiovascular diseases are evaluated in a fasting state, postprandial dysmetabolism is a postprandial state distinguished by abnormally increased circulating levels of glucose and lipids; therefore, it represents an independent risk factor for the onset of cardiovascular events. In Tables 1 and 2 several studies correlating PPG with cardiovascular events, development of atherosclerosis and microvascular diabetes complications are summed up.[8]

The main pathophysiologic mechanisms leading to cardiovascular damage are endothelial dysfunction and oxidative stress, activation of inflammation and coagulation mechanisms thus facilitating the penetration of lipoprotein particles into the arterial wall (Figure 2).[8]

How detecting postprandial hyperglycemia?

The conventional methods for the detection of postprandial hyperglycemia are the 75 g oral glucose tolerance test (OGTT) and self-monitoring of blood glucose (SMBG). Impaired GT is defined as plasma glucose levels 140-199 mg/dL after a 75g OGTT, while levels ≥200 mg/dL are a criterion for the diagnosis of diabetes.[11] Guidelines for management of postmeal glucose in diabetes currently recommend SMBG as the optimal method for assessing plasma glucose levels in insulin and non-insulin treated type 2 diabetic patients and they propose that the timing and frequency of SMBG should be individualized to each person's treatment regimen and level of glycemic

Table 1. Association of postprandial hyperglycemia with cardiovascular morbidity and mortality.

		Postprandial hyperglycemia and mortality/cardiovasular disease						
Study	**Participants**	**Results**						
		All cause mortality	**CVD mortality**	**CHD mortality**	**Stroke mortality**	**Cancer mortality**	**CVD events/ morbidity**	**MI/ACS**
Shaw *et al.*, 1999	9179 subjects	X	X			X		
Saydah *et al.*, 2001	3092 US adults	X						
DECODE Study Gorup, 2001	15,388 men and 7126 women	X	X	X	X			
Cavalot *et al.*, 2006	529 type 2 diabetics						X	
Barzin *et al.*, 2013	3794 subjects						(-)	
Strojek *et al.*, 2016	1115 patients		X				X	X
Saely *et al.*, 2008	1040 patients			X				

CVD, cardiovascular disease; CHD, coronary heart disease; MI, myocardial infarction; ACS, acute coronary syndrome. *Adapted from Pappas* et al.*, 2016.*[8]

Table 2. Association of postprandial hyperglycemia with microvascular complications.

		Postprandial hyperglycemia and microvascular complications		
Study	**Participants**		**Results**	
		Retinopathy	**Neuropathy**	**Nephropathy**
Shiraiwa *et al.*, 2005	232 type 2 diabetics	X	X	X
Sartore *et al.*, 2013	68 type 1 and 2 diabetics	X		
Sun *et al.*, 2015	650 subjects with hyperfiltration			X

Adapted from Pappas et al.*, 2016*[8] *and Sun* et al.*, 2016.*[9]

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control.[12] Emerging technologies for the evaluation of postprandial glucose levels include continuous glucose monitoring (CGM) and plasma 1.5-anhydroglucitol (1.5-AG).[8] CGM employs a sensor measuring interstitial glucose every 1-10 min, which then transmits this reading to a data storage device. 1.5-AG is a natural dietary polyol and it has been proposed as a marker for postmeal hyperglycemia but it is not readily available at the moment.[13,14] HbA1c values, too, can give many indications on PPG condition. Indeed, a study by Monnier *et al.* in 2003 demonstrated that the contribution of PPG to glycemic load varies according to the degree of glycemic control: in poorly controlled patients (HbA1c >10.2%) it was only 30% of the 24 h AUC, in the better controlled patients (HbA1c <7.3% to 8%) the contribution of PPG was from 70% to 50%.[15]

A barrier in diabetes management and in glucose variability (GV) and postprandial hyperglycemia study is glucose monitoring, mainly related to intensive insulin regimens, which require multiple invasive SMBG measurements, often painful and inconvenient. A new *flash glucose monitoring* has been recently launched on the market by Abbott; it is a non-invasive glucose monitoring using a discrete sensor applied on the backside of the arm, measuring and storing the glucose values for 14 days. A clinical trial in T2DM subjects, on intensive insulin treatment, showed that - in comparison with SMBG - flash glucose-sensing technology reduced hypoglycemia with no difference in HbA1c. Therefore, this new system for glucose monitoring seems safe, effective and a preferred alternative to the classic SMBG using lancets and strips to monitoring GV and PPG.[16,17]

In the management of diabetes, PPG is usually targeted 2 h after the start of meal. The management of PPG in diabetes is usually targeted 2 h after the start of the meal; it must be considered, indeed, that even the 1st hour post meal glycemia might be more dangerous than that at 2 h, since glycemia at 1 h both during OGTT or post meal is higher and it is a sufficient stimulus for increasing several cardiovascular risk factors such as inflammation, thrombosis and endothelial dysfunction, all having the oxidative stress generation as a possible pathogenetic factor.

Cumulative evidence reveals that 1-h post challenge glycemia may be related to an increased risk for cardiovascular disease (CVD). People with elevated 1-h post challenge glycemia present a worse risk profile in terms of lipid alterations, increased blood pressure, inflammatory markers and increased uric acid.[18]

Carotid intima-media thickness (CIMT) is a risk factor for CVD. One-hour post challenge glycemia has been found to be correlated with increased arterial stiffness and CIMT in several studies. Increased arterial stiffness in non-diabetic subjects, has also been associated with PPG at 1 h. Interestingly, CIMT has been associated not only with 1 and 2 h post challenge glycemia, but also with *glucose spike*, defined as the difference between basal glycemia and glycemic peak during OGTT.[19-22] These data are consistent with those reported in T2DM in relation to glucose peak during meals. One-hour post challenge glycemia is also correlated to increased left ventricular mass and left ventricular diastolic dysfunction.[19-22] The data are consistent with those reported in T2DM in relation to glucose peak during meals. One-hour post challenge glycemia is also correlated to increased left ventricular
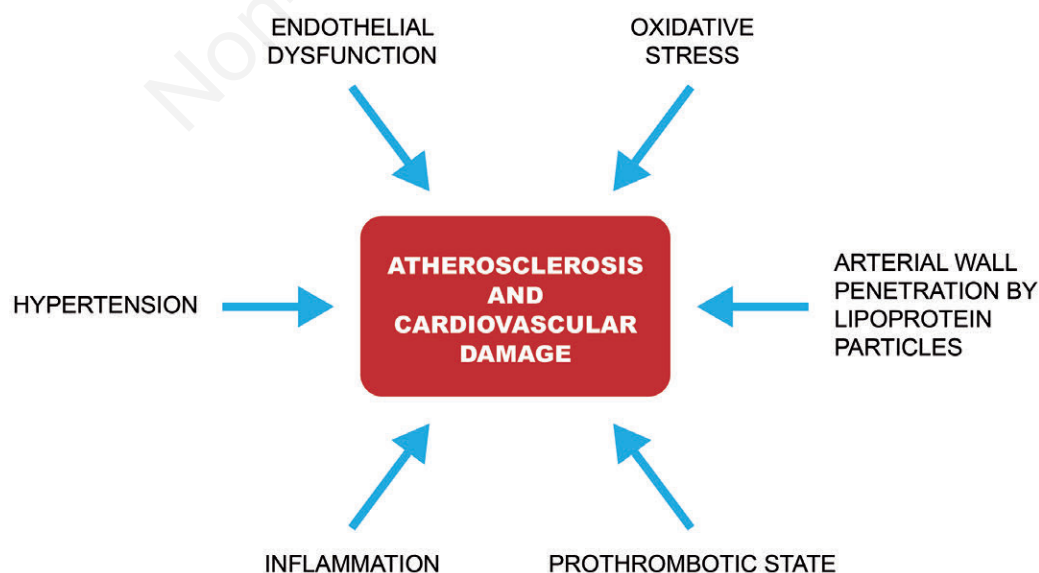

Figure 2. The main pathophysiologic mechanisms leading to cardiovascular damage. *Adapted from Pappas* et al.*, 2016*[8] *and Sciacqua* et al.*, 2011.*[23]

mass and left ventricular diastolic dysfunction (LVDD).[23]

This evidence may certainly help explain why 1-h post challenge glycemia has been found correlated to increased mortality and, more specifically, to cardiovascular mortality.[24,25]

Both cardiovascular events and all-cause mortality were assessed in the 14-year follow-up of the San Luigi Gonzaga Diabetes Study.[26] When all glycemic parameters, categorized according to the American Diabetes Association (ADA) targets were evaluated simultaneously in a Cox model (including the main non glycemic cardiovascular risk factors), the glycemic variables that remained significant for both cardiovascular events and overall mortality were HbA1c and PPG after lunch [hazard ratio (HR) for cardiovascular events: 1.7 and 1.5, respectively; HR for overall mortality: 1.8 for both variables]. It can be concluded that HbA1c and PPG after lunch (both 1st and 2nd hour) have similar and independent predictive power for cardiovascular events and all-cause mortality. Therefore, PPG is not only a key determinant of HbA1c but also an independent parameter in the risk stratification of cardiovascular events and total mortality. Indeed, the 1st hour postprandial glycemia better correlates to subclinical organ damages such as CIMT and LVDD. Also, GV simply defined as the degree to which a patient's blood glucose level fluctuates between high (peaks) and low (nadir) levels is a risk factor of cardiovascular events.[27] There is no general agreement on the method of evaluation of GV.[28,29] PPG is certainly one of the main determinants of glycemic variability.

In 2005, Scognamiglio[30] evaluated the impact of PPG on myocardial perfusion by myocardial contrast echocardiography. Conclusions were that PPG determines myocardial perfusions defects in T2DM without micro-macrovascular complications; postprandial myocardial perfusion defect may represent an early marker of the atherogenic process in the coronary circulation; hence, its reversal constitutes a potential goal of treatment.

Postprandial glycemia and in-patients

In 2013, Mendez *et al.* published a retrospective study on 4262 admissions to general medicine and surgery wards in a period of 2 years. Patients with point of care glucose monitoring and a minimum of two-glucose value per day on average were selected; GV was assessed by standard deviation (SD) and coefficient of variation (CV). Results of adjusted analysis indicate that for every 10-mg/dL increase in SD and 10-percentage point increase in CV, length of stay (LOS) increased by 4.4 and 9.7% respectively. Relative risk of death at 90 days also increased by 8% for every 10 mg/dL increase in SD. Authors concluded

that increased GV during hospitalization is independently associated with longer LOS and increased mortality in non-critically ill patients.[31]

It is known that for diabetic in-patients insulin therapy is the therapy of choice and the most flexible one: in-patients usually do not always eat on time, often present gastrointestinal disturbances like vomiting, often need to be radiologically examined with contrast medium exams; all these situations lead physicians to opt for insulin therapy in the basal bolus scheme; some hypoglycemic oral drugs have a long half-life and often they cannot be administered in case of contrast examinations (metformin). Insulin analogs are usually recommended for in-patients, they lead to less hypoglycemia and they adapt better to hospital needs.

Other aspects to be considered, for in-patients, are some specific situations like sepsis, hyperthermia, steroid therapy, organ failure (kidney, hepatic or heart failure); in these situations in-patients need a rapid correction of hyperglycemic peaks that the current insulin rapid analogues often are not able to achieve; they still do not perfectly mimic the physiological secretion of insulin: they have a later onset and a longer duration of action. Consequently, there is still a need for an ultrafast acting insulin analog in order to better mimic the physiopathology of insulin secretion after a meal.[32] EU has recently approved the launch on the market of a new *faster* insulin analog: the ultrafast acting insulin analog FIASP, by Novo Nordisk. It is a recombinant ultrafast insulin analog (aspart) with arginine as stabilizer and combined with nicotinamide (vitamin B3) with faster onset (5 minutes earlier) than aspart. In addition, it has a shorter duration of action (3-5 h) *versus* aspart, thus it is able to better control postprandial hyperglycemia.[33,34] In a randomized double-blind study on 52 patients with type 1 diabetes, faster acting insulin aspart had a faster onset of exposure compared with insulin aspart, shown by a 57% earlier onset of appearance [4.9 *vs* 11.2 min; ratio 0.43, 95% confidence interval (CI)], about 6 min of difference, a 35% earlier time to reach 50% maximum concentration (20.7 *vs* 31.6 min; ratio 0.65, 95% CI) and a greater early exposure within 90 min after dosing. The greatest difference occurred during the first 15 min, when the area under the serum insulin aspart curve was 4.5-fold greater with faster-acting insulin aspart than with insulin aspart. Faster acting insulin aspart had a significantly greater glucose-lowering affect within 90 min after dosing (Figures 3[35] and 4[33]).

Two multicenter phase-3 trials evaluated the efficacy and safety of fast-acting insulin aspart (faster aspart) *versus* insulin aspart (IAsp) in adults with T1DM and T2DM patients: respectively the ONSET 1 and ONSET 2 trial; they both aimed at evaluating HbA1c at baseline and after 26 weeks of double blinded treatments.[36,37] In both studies Fast Aspart
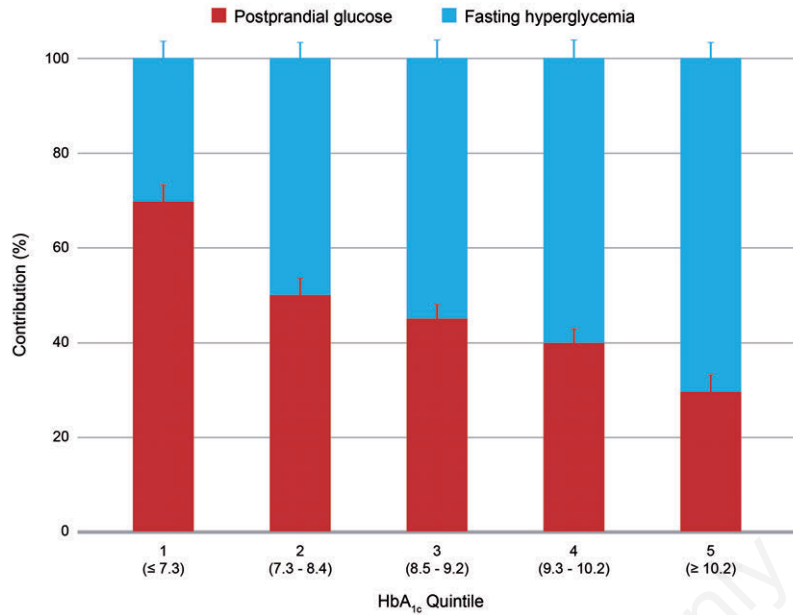
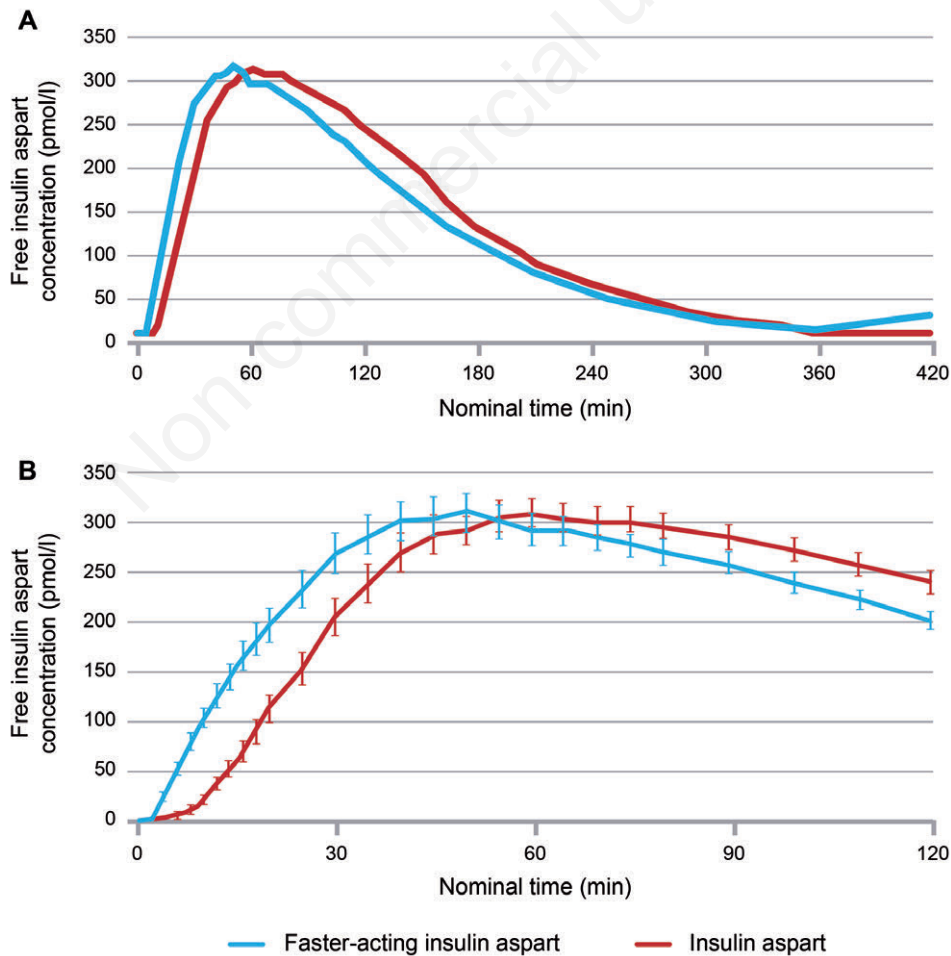**Figure 3. Postprandial glucose new implications regulation.** *Adapted from Leiter* et al*., 2005.*[35]

Figure 4. Mean (± standard error of the mean) concentration-time profiles for faster-acting insulin aspart and insulin aspart from (A) 0-7 hours and (B) 0-2 hours (early phase). *Adapted from Heise* et al*., 2016.*[33]

showed no inferiority to IAsp in reducing HbA1c values. In the ONSET 1 trial, the reduction (–0.15%) was statistically significant, but the most interesting datum was that Fast Aspart obtained a better reduction of PPG at 1 h post meal *versus* IAsp, inducing a reduction of glycemic peak in both studies. On the basis of this datum, it can be hypothesized that Faster Aspart insulin will become a new efficient insulin in controlling the PPG leading to a reduction of PPG, an emergent dangerous cardiovascular risk factor.

Conclusions

Postprandial glycemia and GV are two important targets of diabetes therapy since they represent the two main risk factors of diabetes vascular complications. Recent tools such as the new flash glucose monitoring and the new faster aspart insulin are able to study, manage and control GV and PPG. Particularly for the in-patients, the use of faster aspart might lead to a better post prandial control, an improved glucose profile and, last but not least, to a shorter LOS, with an important economic impact for the national health system.

In conclusion, the emerging new therapies for blood glucose control will hopefully contribute to better understand both postprandial hyperglycemia and glucose variability, thus leading to a better glucose control and to improved outcomes.

References

1. International Diabetes Federation (IDF). Clinical Guidelines Task Force. Guideline for management of postmeal glucose in diabetes. Brussels: International Diabetes Federation; 2007. Available from: https://www.idf.org/our-activities/advocacy-awareness/resources-and-tools/82:management-of-postmeal-glucose.html
2. Pratley RE, Weyer C. The role of impaired early insulin secretion in the pathogenesis of type II diabetes mellitus. Diabetologia 2001;44:929-45.
3. Aronoff SL, Berkowitz K, Shreiner B, Want L. Glucose metabolism and regulation: beyond insulin and glucagon. Diabet Spectr 2004;17:183-90.
4. Gerich JE. Clinical significance, pathogenesis, and management of postprandial hyperglycemia. Arch Intern Med 2003;163:1306-16.
5. Woerle HJ, Pimenta W, Meyer C, et al. Diagnostic and therapeutic implications of relationships between fasting, 2 hour postchallenge plasma glucose and HbA1c values. Arch Intern Med 2004;164:1627-32.
6. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. Diabet Care 2007;30:263-9.
7. Provenzano V, Scorsone A. Importanza della glicemia postprandiale e intensificazione della terapia insulinica. Media 2016;16:193-200.
8. Pappas C, Kandaraki EA, Tsirona S, et al. Postprandial dysmetabolism: too early or too late? Hormones 2016;15:321-44.
9. Sun ZJ, Yang YC, Wu JS, et al. Increased risk of glomerular hyperfiltration in subjects with impaired glucose tolerance and newly diagnosed diabetes. Nephrol Dial Transplant 2016;31:1295-301.
10. Keefe JOK, Bell DSH. Postprandial hyperglicemia/hyperlipidemia (postprandial dysmetabolism) is a cardiovascular risk factor. Am J Cardiology 2007;100:899-904.
11. American Diabetes Association (ADA). Standards of medical care in diabetes. Diabetes Care 2016;38:1-94.
12. International Diabetes Federation (IDF). Guideline for management of postmeal glucose in diabetes. Diabetes Res Clin Pract 2014;103:256-68.
13. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for management of dyslipidemia and prevention of atherosclerosis: executive summary. Endocr Pract 2012;18:269-93.
14. Seok H, Huh JH, Kim HM, et al. 1,5-anhydroglucitol as a useful marker for assessing short-term glycemic excursions in type 1 diabetes. Diabetes Metab J 2015;39:164-70C.
15. Monnier L, Lapinski H, Colette C. Contribution of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA1c. Diabetes Care 2003;26:881-5.
16. Ceriello A. Targeting one-hour postprandial glucose: Is it time for a paradigm swich in diabetes managment?. Diabet Technol Ther 2017;19:1-5.
17. Abdul-Ghani, Wiliams K, De Fronzo RA, et al. What is the best predictor of future type 2 diabetes? Diabetes Care 2007;30:1544-8.
18. Oh TJ, Lim S, Kim KM, et al. One hour post load plasma glucose concentration in people with normal glucose homeostasis predicts future diabetes mellitus: a 12 year community based cohort study. Clin Endocrin (Oxf) 2017;86:513-9.
19. Wu X, Chen H, Wang Y, et al. The relation between coronary risk factor and elevated 1-h post load plasma glucose levels in patients with established coronary heart disease. Clin Endocrinol (Oxf) 2013;78:67-72.
20. O' Leary DH, Polak JF, Kronmal RA, et al. Cardiovascular Health Study Collaborative Reasearch Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999;340:14-22.
21. Tsuboi A, Ito C, Fujiukawa R, et al. Association between the postprandial glucose levels and arterial stiffness measured according to the cardio-ankle vascular index in non diabetic subjects. Intern Med 2015;54:1961-9.
22. Esposito K, Ciotola M, Carleo D, et al. Post meal glucose peaks at home associate with carotid intima-media thickness in type 2 diabetes. J Clin Endocrinol Metab 2008;93:1345-50.
23. Sciacqua A, Miceli S, Carullo G, et al. One hour post load plasma glucose levels and left ventricular mass in hypertensive patients. Diabetes Care 2011;34:1406-11.
24. Vaccaro O, Ruth KJ, Stamler J. Relationship of postload plasma glucose to mortality with 19-yr follow up: comparison of one versus two plasma glucose measurements

in the Chicago People's Gas Company Study. Diabetes Care 1992;15:1328-34.

25. Yu PC, Bosnyaak Z, Ceriello A. Review The importance of glycated haemoglobin (HbA1c) and post prandial glucose (PPG) control on cardiovascular outcomes in patients with type 2 diabetes. Diabet Res Clin Pract 2010;89:1-9.

26. Cavalot F, Pagliano A, Valle M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus particularly in women: lesson from the San Luigi Gonzaga Diabetes Study. Diabetes Care 2011;34:2237-43.

27. Cavalot F. Do data in literature indicate that glycaemic variabilility is a clinical problem? Glycaemic variability and vascular complications of diabetes. Diabet Obesity Metab 2013;15:3-8.

28. Ceriello A, Inhat MA. Glycaemic variability a new therapeutic challenge in diabetes and the critical care setting. Diabet Med 2010;27:862-7.

29. Bergenstal RM. Glycemic variability and diabetes complications does it matter? Simply put, the better glycemic markers. Diabetes Care 2015;38:1615-21.

30. Scognamiglio R, Negut C, Avogaro A, et al. Postprandial myocardial perfusion in healthy subjects and Type 2 diabetes patients. Circulation 2005;112:179-84.

31. Mendez CE, Tannenber RJ, Mok KT, Umpierrez GE. Increased glycemic variability is independently associated with length of stay and mortality in non-critically ill hospitalized patients. Diabetes Care 2013;36:4091-7.

32. Ceriello A. Trattare la glicemia post prandiale a 1° 2 ore? Media 2017;17:53-7.

33. Heise T, Hövelmann U, Brøndsted L, et al. Faster-acting insulin aspart: earlier onset of appearance and greater early pharmacokinetic and pharmacodynamic effects than insulin aspart. Diabetes Obes Metab 2015;17:682-8.

34. Heise T, Pieber RT, Danne T, et al. A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and phamacodynamic characteristics of fast-acting Insulin in adults with type 1. Clin Pharmacokinet 2017;56:551-9.

35. Leiter LA, Ceriello A, Davidson JA, et al. Postprandial glucose regulation: new data and new implications. Clin Ther 2005;27:S42-S56.

36. Russell-Jones D, Bode BW, De Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus trwatment for type 2 diabetes: results of a 26-week multicenter, active controlled treat to target, randomized, parallel-group trial (Onset 1). Diabetes Care 2017 [Epub ahead of print].

37. Bowering K, Case C, Harvey J, et al. Faster aspart versus insulin aspart of a basal-bolus regimen in inadequately controlled Type 2 diabetes: The Onset 2 Trial. Diabetes Care 2017 [Epub ahead of print].