Should Postprandial Glucose Be Routinely Measured and Treated to a Particular Target? No!

JOHN B. BUSE, MD, PhD, CDE

Diabetes is a serious medical condition associated with disability, premature death, and enormous medical costs (1). Arguably more important is the insidious way in which the diagnosis of diabetes afflicts people with worry and despair over the loss of health as well as the burden of self-care. As health care professionals, our recommendations to patients regarding methods and targets of treatment can dramatically influence the quality of patients’ lives.

The issue at hand is this: Should postprandial glucose (PPG) be routinely measured and treated to a particular target? I will answer this from the perspective of guidelines generally applicable in the medical community, with the recognition that for particular patients, very different approaches could be appropriate. The problem with attempting to answer this question is that there is essentially no direct clinical trial evidence to inform the decision, leaving a great deal to opinion.

There are numerous epidemiological studies, such as DECODE (Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe), suggesting that 2-h glucose levels >140 mg/dl 2 h after meals in patients with diabetes. At face value, it seems illogical to base the care of people with diabetes eating several meals a day on single glucose measurements obtained during an oral glucose tolerance test in “normal” individuals. Furthermore, interpretation of these epidemiologic studies is confounded by the fact that postchallenge glucose is also a marker of insulin resistance and the metabolic syndrome (3). Since other components of the metabolic syndrome cosegregate with postchallenge glucose in these studies, it leaves unanswered the question of whether PPG is a contributor to CVD and therefore worthy of measurement and specific antihyperglycemic therapy or whether it is just an innocent bystander. Recent studies in which multivariate analysis has been used to examine the CVD risk associated with elevated postchallenge glucose independent of other CVD risk factors, as well as in the setting of elevated fasting glucose, suggest that the independent effect of PPG is minimal or nonexistent (4, 5). These more recent analyses seem more relevant to the situation of patients with diabetes than the earlier association studies. Overall, these epidemiologic studies are too confounded to be adequate justification for PPG monitoring or aggressive treatment.

There are novel pharmaceutical agents that specifically target PPG and, at the same time, reduce average glycemia, as reflected by HbA1c. These include the α-glucosidase inhibitors, monomeric insulin analogs, fast-acting insulin secretagogues, amylin analogs, and glucagon-like peptide 1 (GLP-1) receptor agonists. Many studies suggest that these agents reduce HbA1c, with a lesser risk of hypoglycemia and weight gain than agents that predominantly address fasting and/or preprandial glucose values. The argument as to whether PPG monitoring is useful is often confused with an argument regarding the utility of these diabetes drugs. It is incontrovertible that these treatments are valuable in the management of diabetes. That said, there are no strong data to suggest that monitoring PPG is in any way necessary to use these treatments effectively; in the package inserts of marketed agents, only those for acarbose and miglitol provide specific information that the 1-h PPG may be useful in dose titration (6–11).

In fact, at least in the setting of insulin therapy, monitoring fasting, premeal, bedtime, and mid-sleep glucose values has at least two functions—to ensure safety by allowing for early recognition of hypoglycemia as well as to direct treatment for reducing HbA1c. This approach has been validated in numerous outcomes studies to reduce microvascular risk (12–15). There are no outcomes studies of type 1 or type 2 diabetes in which postprandial treatment targets have been used to primarily drive treatment decisions. The study of Bastyr et al. (16), in which randomization to premeal lispro insulin versus bedtime NPH versus metformin in sulfonylurea-treated patients, demonstrated that the final HbA1c in those treated with lispro was lower than in the other two groups. There were several confounders, but in any case, these data are often cited as clinical trial evidence in support of the benefit of PPG monitoring. In fact, the Bastyr et al. study used only fasting and premeal glucose targets to drive dose titration, even in the lispro group. Similarly, a repaglinide study, in which subjects were randomized to fast-
ing or PPG monitoring to drive dose titration, documented better control when dosing of a repaglinide was adjusted in response to fasting glucose than PPG (17). So, the use of postprandially targeted drugs does not require and is not an adequate justification for the use of PPG monitoring.

Though glucose monitoring was an integral part of the Diabetes Control and Complications Trial (DCCT) and Kumamoto studies (13,14), there are very few if any randomized prospective studies in the setting of type 2 diabetes that demonstrate appreciable benefit of glucose monitoring vis-à-vis improvements in average glycemia as assessed by HbA1c (18,19). Nevertheless, the American Diabetes Association (ADA) (20,21) has recommended that there are specific clinical situations in which monitoring of PPG could be considered: 1) “Suspected postprandial hyperglycemia: in patients who achieve their premeal glucose targets, but whose overall glycemic control as determined by HbA1c is inappropriately high, PPG monitoring and therapy to minimize PPG excursions may be beneficial.” 2) “Monitoring treatment aimed specifically at lowering PPG: in patients with type 1 or type 2 diabetes who are treated with glucose-lowering agents expected primarily to reduce PPG, monitoring may be useful in titrating these treatments or in confirming that patients have responded to the intervention. It is also possible that PPG monitoring may be beneficial to evaluate the effect of changes in nutrition or exercise patterns.” 3) “Hypoglycemia: hypoglycemia in the postprandial period is rare except in response to exercise or rapid-acting insulin analogs.”

There are still no multicenter randomized trials to support the superiority of these approaches to the classic approach of monitoring premeal glycoses and pushing therapy as limited by hypoglycemia, despite over 5 years of expert opinion in this regard (22).

If PPG values are measured, what are reasonable targets by which to evaluate treatment efficacy? This is an exceptionally difficult question to answer because PPG levels are not only affected by overall glycemic control but also by the meal size, time of day, nutrient composition, physical activity, insulin sensitivity, insulin secretion, and pharmacodynamics of drug therapies. This year, the ADA has reinstated a “PPG target” in its recommenda-

tions: <180 mg/dl. This particular value was selected for several reasons. First, peak PPG levels in nondiabetic normal weight individuals (mean age 40 years) after a large supper (50% of total daily calories on a weight-maintenance diet comprised of 50% carbohydrates, 20% protein, and 30% fat) averages ~180 mg/dl (23). It seems that picking lower targets in typically overweight, older individuals with type 2 diabetes is unrealistic if higher levels occur in normal subjects on defined moderate diets. Second, if normal individuals experience such levels, albeit only transiently, perhaps there are not major pathophysiological consequences to similar (though perhaps longer) glycemic excursions in people with diabetes. Third, there is support from large prospective trials that average PPG levels of ~180 mg/dl would be associated with an HbA1c of ~7%. In the DCCT, the average postbreakfast glucose, at an HbA1c of 7%, was ~220 mg/dl, while the average postmeal glucose value after lunch and supper was 180 mg/dl (24). There are no published large-scale trials in which patients were treated with typical regimens (e.g., combination therapy) and PPG values recorded to allow a similar analysis in type 2 diabetes. Such data should be available in the near future.

Lower PPG targets (e.g., <140 mg/dl) are probably unachievable in the average patient with type 2 diabetes in the U.S., at least based on available resources and expertise. In the DCCT, such levels of PPG would have been associated with HbA1c values in the range of 4.9–5.9% (13). There are no prospective clinical trial data to suggest that PPG targets would be associated with better outcomes than premeal glucose targets, with the exception of a single study in gestational diabetes (25). Others believe that equivalent outcomes could have been attained using equivalently stringent premeal glucose targets and have criticized that study’s conclusions (26).

So, why not pursue lower targets of PPG if they could be associated with improvements of HbA1c? Well, foremost because such an effort would certainly be associated with potential harms. An increased risk of hypoglycemia would surely result from the reduction in average glycemia unless frequent monitoring of fasting, premeal, and bedtime glucose were also performed to avoid preprandial glucose values substantially <90 mg/dl. This may become feasible in the near future when continuous glucose monitoring technology becomes routinely available. Secondly, achieving postprandial control based on frequent PPG monitoring would require specific targeted therapy delivered with each meal and snack. Such intensive programs of glucose monitoring and treatment would certainly dramatically increase costs for patients and insurers, as well as increase the burden on patients and health care providers in obtaining, analyzing, and acting on a greater number of different kinds of values. There is even the potential that the increased effort on the part of patients and providers to achieve and maintain lower PPG targets would minimize the ability of both groups to pursue other health care targets that are better documented to reduce morbidity and mortality than postprandial glycemia but frequently forgotten, such as immunizations, cancer screening, and the treatment of dyslipidemia and hypertension. These kinds of concerns might be mitigated with new drug therapies that are easy to administer, improve insulin secretory dynamics, and have little risk of hypoglycemia; we hope this will be the case with depot injections of exenatide, a GLP-1–like drug under development (27). But at least for the next few years, there is clearly a potential risk, as well as definite cost implications, in recommending routine PPG monitoring, particularly when combined with low postprandial targets.

However, if lower PPG targets were recommended, is there not the potential that the benefits would outweigh the risks? That is certainly possible, but not assured. One factor that limits the potential benefit of such an approach is that end-stage microvascular end points (blindness, renal failure, and amputation) in people with diabetes and average levels of HbA1c of ~7% area pretty rare (15,28–30). Further lowering of HbA1c in such patients may require that hundreds of patients be treated for decades to prevent disabling microvascular end points. On the other hand, the annual risk of severe hypoglycemia at near normal levels of average glucose is more than an order of magnitude higher in patients with type 1 diabetes and several fold higher in those with type 2 diabetes. What is worse, the risk of severe hypoglycemia increases as-
ymptotically with further lowering of average glycemia. Thus, it is possible, even likely, that the risks of severe hypoglycemia could far outweigh potential benefits with further reduction of average glycemia, even using postprandial approaches. Reflecting that reality, no multicenter study has ever achieved average sustained levels of HbA1c substantially <7% independent of approach because of the limitation of hypoglycemia.

How about the potential that stringent PPG targeting could improve CVD outcomes? Again, this is possible but not particularly likely for many of the reasons listed thus far. It must be remembered that there is not robust evidence that glycemic control is associated with benefits with respect to cardiovascular risk reduction. The Veterans Affairs Cooperative Study of Diabetes Mellitus suggested a nonstatistically significant worsening of CVD outcomes associated with more intensive therapy with insulin in patients who had failed sulfonylurea therapy (31). The overall U.K. Prospective Diabetes Study (UKPDS) demonstrated a trend toward improved outcomes in the area of myocardial infarction, but worse outcomes with respect to stroke (15). In the overweight UKPDS cohort, there was a significant reduction associated with metformin therapy (32). Parenthetically, those randomized to insulin or sulfonylurea, despite better glycemic control, did not demonstrate significant reductions in CVD risk as compared with conventional treatment with diet. Arguably, a much stronger argument could be made that metformin and perhaps other insulin-sensitizing approaches, as well as treatment of traditional cardiovascular risk factors, would provide for a much greater probability of reducing CVD events in people with type 2 diabetes than targeting PPG. There already is a bias in the primary care, cardiology, and endocrinology communities that managing glucose is the most important intervention in people with diabetes, despite the fact that we have definitive proof that lipid-lowering therapy and blood pressure control can save lives and reduce the risk of both micro- and macrovascular complications (33). Greater focus on the hypothesized cardiovascular benefits of intensive PPG management in the absence of any clinical trial data to support the contention has the potential of increasing the misguided glucocentric version of diabetes management to the detriment of peoples’ health.

In summary, at first glance, PPG seems to provide an obvious opportunity to intervene for clinicians concerned about what we perceive as generally inadequate care and poor outcomes in people with diabetes. We must remember that more is not necessarily better, as recently discovered regarding combination hormone replacement therapy in the Women’s Health Initiative in which an intervention with substantial support from epidemiological studies was shown to be harmful (34). Just because we can use a new intervention, it will not necessarily provide benefit in patients with diabetes, as we learned in the BARI (Bypass Angioplasty Revascularization Investigation) trial in which angioplasty, though quite safe and effective in people without diabetes, was shown to be associated with substantially worse outcomes than bypass surgery in patients with diabetes and coronary artery disease (35).

Thinking hard about the potential impact of routine PPG monitoring and treatment to achieve stringent postprandial goals suggests that there exist the possibility of both harms and benefits. This does not deny the obvious efficacy of treatments that specifically target PPG, as they clearly lower HbA1c. The current ADA guidelines are prudent, allowing for considerable flexibility for clinicians to explore the utility of PPG monitoring in patients who are not achieving HbA1c treatment targets, in patients using postprandial-targeted therapies and in those with symptoms of hypoglycemia in the postprandial period. The target of <180 mg/dl 2 h after the beginning of the meal is an attempt to provide an average level of postprandial control that would be associated with an HbA1c ≤7%. There is insufficient evidence to recommend routine postprandial monitoring or application of more aggressive targets.

In the future, with improvements in continuous glucose monitoring technology and the availability of new pharmaceutical agents that restore β-cell function, it is likely that more aggressive postprandial management will be both safer and less burdensome. As those kinds of interventions will certainly be expensive, it is important that research studies be conducted in the near future to explore the dynamics of the postprandial state and the relevance of management of PPG to the development of complications.

Acknowledgments — Thanks to Laura Raftery for her helpful suggestions and editorial assistance, the faculty of the Division of General Medicine at the University of North Carolina for their continuing efforts to acculturate me in the world of evidence-based medicine, and Dr. Jaime Davidson and the audiences who have participated in our previous debates and have raised so many informative questions over the last 11 months.

References
Commentary


30. DCCT Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44:968–983, 1995


