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CLINICAL UPDATE

Prandial Glucose Regulation in the Glucose Triad

Emerging Evidence and Insights

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While it is well established that overall glycemic control reduces the complications of diabetes, the role of fasting glycemia versus postprandial glycemia in the pathophysiology of diabetes and its complications, and the relative importance of these parameters as specific targets of therapy, remain controversial. Evidence that postprandial glucose (PPG) plays an independent, modifiable role in cardiovascular disease is accumulating, largely from epidemiological studies. A large number of epidemiological studies show that high postprandial glucose is an independent risk factor for cardiovascular disease: indeed, a more powerful risk factor than fasting glucose or HbA_{1c}. Pathophysiological hypotheses that support these observations include the contribution of postprandial glucose to HbA_{1c}; postprandial glucose as a surrogate marker for other cardiovascular risk factors, serum lipids and triglycerides in particular; and direct toxicity of elevated glucose levels attributed to "spikes" in glucose concentration following caloric ingestion. Early interventional data suggest that therapy targeted at postprandial glucose can have a favorable impact on cardiovascular events. While more interventional studies clearly are needed, the growing weight of evidence supports a therapeutic approach more directed at excessive prandial glycemic excursions that are characteristic of both type 1 and type 2 diabetes.

Key Words: Diabetes; type 2 diabetes; postprandial glucose; postprandial hyperglycemia; hyperlipidemia; hyper-triglyceridemia; cardiovascular risk.

Learning Objectives

- To review the evidence that glycemic control is an important part of diabetes management.
- To become familiar with evidence that postprandial glucose is associated with increased mortality and morbidity in non-diabetic people and patients with diabetes
- To appreciate arguments both for and against an independent role for postprandial glucose in glycemic monitoring and management

Introduction

The epidemic of diabetes is becoming increasingly apparent to physicians and the general public, both from the attention drawn to it in the lay press and the increasing number of individuals suffering its consequences. Diabetes mellitus affects at least 12% of all adults in the United States, and is now one of the most common chronic diseases in North America *(1)*. The probability of developing diabetes during a lifetime is now 35–50% in most populations *(2,3)*. Recent data emphasize that the prevalence of diabetes is increasing rapidly and, in particular, the age-at-onset of type 2 diabetes indicates that the disease is disproportionally affecting younger individuals. The importance of glycemic control for the prevention of the complications of diabetes is no longer debated. However, the best means to achieve adequate glycemic control remains controversial. Until the arrival of therapeutic tools targeted at specific components of the circadian variation in glucose levels, there was little choice, or debate, about potential treatments. The goal of management was to reduce HbA_{1c}, and therapies were directed toward lowering of fasting glucose levels, which were monitored as an indication of the effectiveness of treatment. Thus, fasting glucose and HbA_{1c} were the dominant components of glycemic monitoring, or the "base" of the therapeutic approach. The third cornerstone of the "glucose triad"—postprandial glucose—was largely ignored. The last decade has brought therapeutic tools capable of specifically lowering postprandial glucose. In the wake of

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these new therapies has come vigorous scientific debate about the validity and utility of targeting postprandial glucose excursion as an important component of the glucose triad.

What do we know? It is clear from DCCT and UKPDS that improved glycemic control reduces microvascular and neuropathic complications *(4,5)*. In addition, epidemiological and limited interventional studies in impaired glucose tolerance (IGT) support a probable beneficial effect of improved glycemic control on macrovascular complications *(6–11)*. It also is clear that IGT, a precursor of overt diabetes that is characterized by postprandial hyperglycemia, is associated with increased cardiovascular risk *(6,7)*. Furthermore, postprandial glucose makes a greater contribution to overall glycemia than fasting glucose at lower levels of HbA_{1c} *(12)*. However, we do not yet know for certain whether interventions directed at postprandial glucose excursions reduce the morbidity and mortality of diabetes. A recent publication by Esposito and colleagues raised the hope that targeting postprandial glucose with short-acting insulin secretagogues such as repaglinide actually can improve markers of cardiovascular risk *(13)*. It also remains unclear whether it is possible to balance safety with effectiveness in developing specific therapeutic strategies directed against postprandial hyperglycemia.

As in all scientific discussions, the arguments evolve as more data become available. Although it has been understood for a long time that improved glycemic control reduces the complications of diabetes, this was scientifically proven only a decade ago. While the clinical significance of the relationship is still being defined, compelling evidence is increasing that hyperglycemia and other metabolic abnormalities in the postprandial state have a role in the devastating cardiovascular sequelae of diabetes. This review summarizes the current state of an intriguing, and potentially very important, clinical debate.

The Epidemiology of Postprandial Hyperglycemia: Evidence For its Importance

Coronary heart disease and stroke remain the primary cause of death for people with diabetes, despite better treatment of diabetes and other established cardiovascular risk factors such as hypercholesterolemia and hypertension. Cardiovascular disease risk is increased two to five times for men and women, respectively, compared to people without diabetes *(14,15)*. It has been shown that the 7-yr incidence of cardiovascular events in type 2 diabetes is equal to that of post-MI patients without diabetes *(16)*. It is evident that either we are not modifying known risk factors sufficiently, or that we are not treating all risk factors, or both. The following is a summary of the evidence that postprandial hyperglycemia is an independent, modifiable risk factor for cardiovascular disease.

Many epidemiological studies have demonstrated that postprandial glucose levels have a more robust relationship with cardiovascular events than does fasting glucose (see Table 1). For example, a large metaregression analysis by Coutinho and colleagues from the University of McMaster, Canada, pooled aggregate data from 20 studies involving 95,783 adults *(17)*. Over 12 yr there were 3707 cardiovascular events. People with 2-h blood glucose values >7.8 mmol/L had a relative risk for cardiovascular events of 1.58, whereas elevated fasting glucose (>6.1 mmol/L) carried an elevated but lower risk (1.33).

Table 1
Studies That Associate Mealtime Glucose Spikes With Risk of Cardiovascular Disease and Mortality

DECODE, 1999 (*6*)	High 2-h post-load blood glucose is associated with increased risk of death, independent of fasting plasma glucose.
Pacific and Indian Ocean, 1999 (*48*)	Isolated 2-h hyperglycemia doubles the risk of mortality.
Funagata Diabetes Study, 1999 (*7*)	IGT, but not impaired fasting glucose, is risk factor for cardiovascular disease.
Whitehall, Paris, Helsinki Study, 1998 (*8*)	Men in upper 2.5% of 2-h postmeal glucose distribution had significantly higher coronary heart disease mortality.
The Rancho-Bernardo Study, 1998 (*9*)	2-h post-challenge hyperglycemia more than doubles the risk of fatal cardiovascular disease and heart disease in older adults.
Diabetes Intervention Study, 1996 (*10*)	Postmeal, but not fasting glucose, is associated with coronary heart disease.

The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), which examined data from 18,048 men and 7316 women, demonstrated that post-challenge glucose, not fasting glucose, predicted mortality in people with diabetes or IGT *(6)*. As post-challenge glucose levels increased, the risk increased, even after correction for fasting glucose levels. By contrast, increases in fasting glucose alone did not have a significant effect on mortality, once corrected for post-challenge glucose levels (see Fig. 1). The implications of DECODE are discussed more fully below.

The Diabetes Intervention Study (DIS), a prospective, population-based multicenter study from the University of Dresden involving 1139 patients with newly detected type 2 diabetes, examined the risk factors for coronary heart disease and all-cause death over 11 yr *(10)*. DIS found that baseline fasting glucose measurements and HbA_{1c} did not predict mortality risk, but 2-h plasma glucose values were significantly predictive ($p < 0.05$). Similarly, the Funagata Diabetes Study demonstrated that impaired fasting glucose did not significantly increase cardiovascular risk over 7 yr,

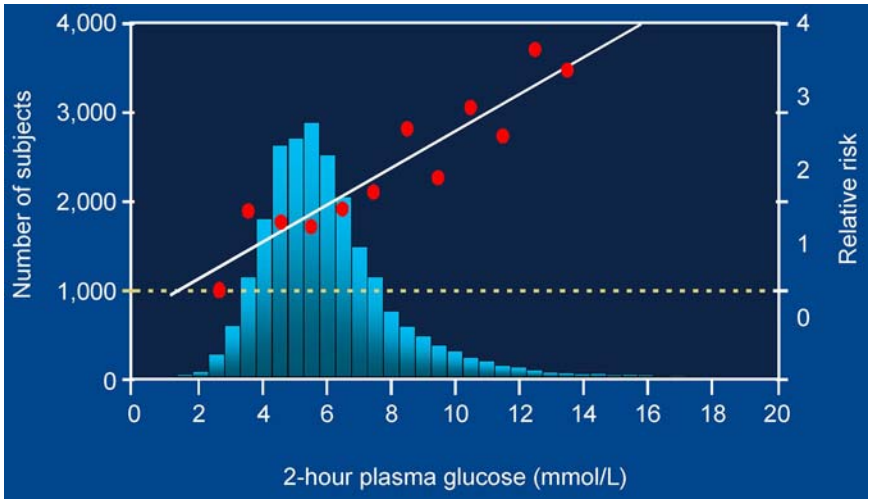

Fig. 1. The DECODE study: mortality risk within 7 yr increased with 2-h post-challenge glucose, not fasting glucose. (Adapted from ref. *3*. Reproduced courtesy of the American Diabetes Association.)

while IGT more than doubled the risk, compared to individuals with normal glucose tolerance (hazard ratio 2.219) *(7)*.

At the level of gross morphology, several studies have attempted to demonstrate a correlation between postprandial glucose levels and cardiovascular remodeling. The Risk Factors in Impaired Glucose Tolerance for Atherosclerosis and Diabetes (RIAD) study measured carotid intima-media thickness, a well-established marker of atherosclerosis, in 119 people with asymptomatic diabetes and correlated it to a variety of glycemic parameters *(18)*. The authors found that 2-h plasma glucose levels correlated more closely to intima-media thickness ($r = 0.23$, $p < 0.001$) than did fasting glucose ($r = 0.14$, $p < 0.004$).

Thus, the current body of data are suggestive for postprandial hyperglycemia being a risk factor for cardiovascular disease and, in many studies, this risk is independent of fasting glucose or HbA_{1c}. Although still in the early stages of investigation, the evidence is growing that postprandial hyperglycemia also is a *modifiable* risk factor.

Obstetrical studies clearly have demonstrated that utilizing postprandial glucose levels as a guide to glycemic management improves overall glycemic control (HbA_{1c}) and obstetrical outcomes. A study of gestational diabetes by de Veciana and colleagues demonstrated that women managed by postprandial blood monitoring compared to those using preprandial monitoring had significantly lower mean HbA_{1c} and a lower risk of cesarean section ($n = 66$) *(19)*. In addition, their newborns were less likely to be hypoglycemic or overweight. Similar results were achieved in a recent study of 61 pregnant women with type 1 diabetes: women guided by postprandial self-monitoring had significantly less preeclampsia (3% vs 21%, $p < 0.048$) and more success in achieving glycemic control targets (55% vs 30%, $p < 0.001$) than those assigned to preprandial monitoring *(20)*.

Recently the STOP-Noninsulin Dependent Diabetes Mellitus (STOP-NIDDM) trial provided the first demonstration of cardiovascular risk reduction by targeting postprandial glucose *(11)*. Although this study was designed primarily to assess the ability of alpha-glucosidase inhibitors to reduce the risk of developing diabetes, the study also evaluated the effect of this intervention on cardiovascular endpoints. This multicenter, double-blind, placebo-controlled study randomized 1429 patients with IGT to either placebo or 100 mg of acarbose, three times daily for approx 3 yr. After adjusting for other major cardiovascular risk factors, acarbose was associated with a 53% relative risk reduction in cardiovascular events ($p = 0.02$) and a 38% relative risk reduction in the incidence of new hypertension ($p = 0.004$). The number needed to treat to prevent one cardiovascular event was calculated as 40 patients with IGT over 3 yr. Alpha-glucosidase inhibitors reduce the levels of prandial glucose excursions and do not greatly affect fasting glucose levels; thus, this study provides the first trial evidence that lowering postprandial glucose may reduce the risk of cardiovascular disease.

Thus, there is consistent epidemiological evidence from many prospective studies that post-challenge and postprandial hyperglycemia are strong predictors of cardiovascular morbidity and mortality, as well as all-cause mortality. Early data from intervention trials indicate that better control of postprandial hyperglycemia is associated with a reduced incidence of cardiovascular disease.

The Pathobiology of Postprandial Hyperglycemia

As the epidemiological evidence has increased that postprandial glucose is a more powerful risk factor for cardiovascular disease than either fasting glucose or HbA_{1c}, many

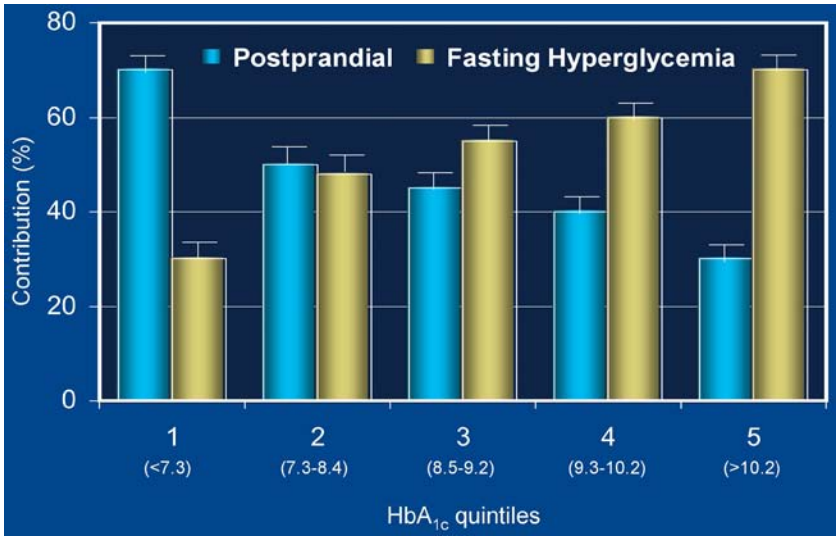

Fig. 2. Relative contributions of postprandial and fasting hyperglycemia to overall diurnal hyperglycemia, by quintiles of HbA_{1c}. (Adapted from ref. *12*. Reproduced courtesy of the American Diabetes Association.)

researchers have tried to elucidate the pathophysiological mechanisms that subserve this effect.

Three potential explanations have been put forward: first, that postprandial hyperglycemia is exerting its toxicity by its contribution to total tissue glycemic exposure (i.e., HbA_{1c}); second, that postprandial hyperglycemia is simply a marker for the metabolic syndrome, which is powerfully associated with cardiovascular risk; third, that postprandial glucose excursions could be having a direct, toxic effect on vascular tissues.

Postprandial Hyperglycemia as a Contributor to HbA_{1c}

Several trials have revealed a correlation between overall glycemic load (HbA_{1c}) and cardiovascular outcomes, including the UKPDS *(21)* and a Finnish study in elderly patients by Kuusisto and colleagues *(22)*. In the Finnish study, coronary heart disease (CHD) mortality was four times higher in patients with an HbA_{1c} >7.0%, compared to those with lower HbA_{1c} values.

Postprandial glucose contributes substantially to mean glycemia as measured by HbA_{1c}. Recent data indicate that postprandial glucose can contribute up to 70% of HbA_{1c}, and that the size of the contribution depends on the degree of glycemic control *(12)*. Postprandial glucose contributes most when the HbA_{1c} is closest to normal values. This indicates that, in patients with mildly or moderately elevated HbA_{1c}, targeting postprandial glucose can have a great effect. The significant contribution of postprandial glucose to HbA_{1c}, especially in milder disease, may also explain why HbA_{1c} gradually rose during the UKPDS *(5)*, but not during the10-yr DCCT *(23)* or the Kumamoto study *(24)*. In the latter two studies, interventions were targeted at both fasting and postprandial glucose levels; in the UKPDS there was no postprandial target.

The considerable contribution of postprandial glucose excursions to HbA_{1c} is logical, given that most people are in the postprandial, not fasting, state for the majority of the day. Avignon et al have confirmed that HbA_{1c} is better correlated with postprandial glucose levels than fasting glucose levels *(25)*.

Thus, it is reasonable to assume that the damaging effects of postprandial hyperglycemia are mediated, at least in part, by the substantial contribution of postprandial glucose excursions to overall glycemic load.

Postprandial Hyperglycemia as a Surrogate Marker for the Metabolic Syndrome

The argument that postprandial hyperglycemia is a surrogate marker for the metabolic syndrome is based on the fact that postprandial hyperglycemia and other well-established cardiac risk factors, such as serum lipids and hypertension, share a common link to insulin resistance. This raises the possibility that the link between cardiovascular risk and post-load glucose is confounded by other factors; i.e., that the risk attributed to postprandial glucose may actually be the result of other pathophysiological "mediators" associated with increased glucose (see Fig. 3).

Evidence indicates that both triglycerides and non-HDL cholesterol do indeed share many of the epidemiological, physiological, and pathophysiological characteristics of postprandial glucose. Levels of both triglycerides and non-HDL cholesterol have predictive power for 10-yr risk of cardiovascular disease in patients with diabetes (see Fig. 4) *(26,27)*. Triglycerides rise excessively after meals in people with type 2 diabetes, showing a steady increase during the day *(28)*. Moreover, these elevations in triglycerides appear to have physiological consequences. High-fat meals reduce flow-mediated vasodilation of arteries *(29)* and this appears to be mediated by oxidative stress (see Fig. 5) *(30)*.

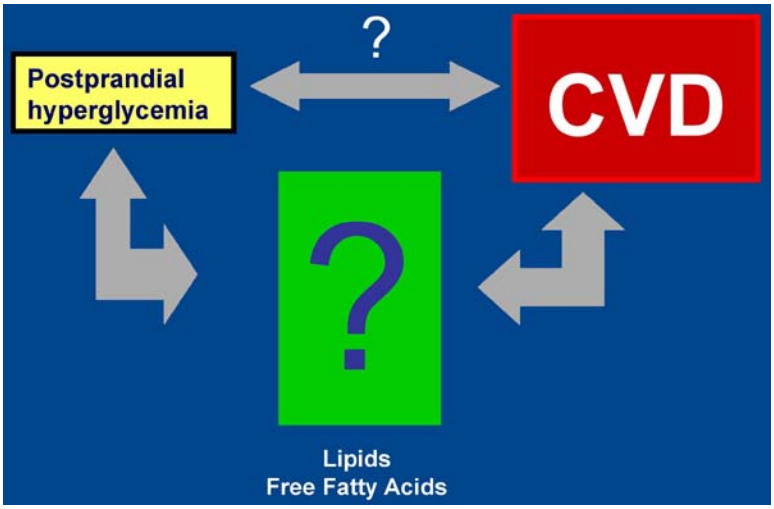

Fig. 3. Prandial glucose and CV disease: an association or a causal relationship?

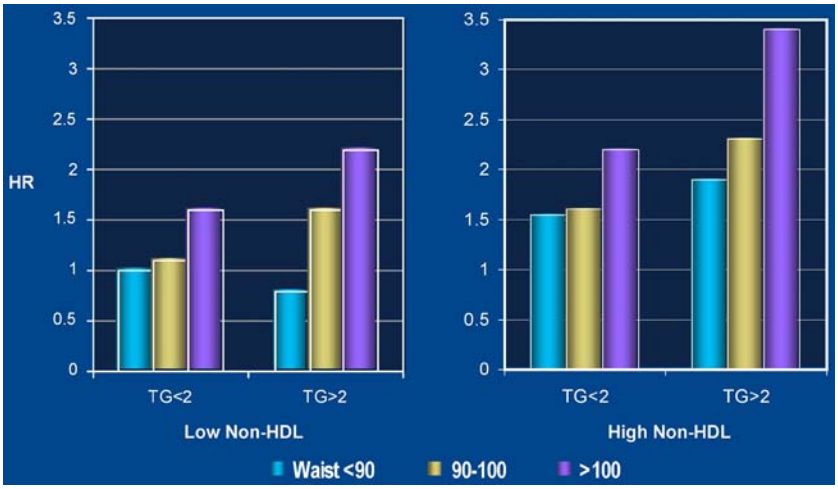

Fig. 4. Hazard ratio of CVD for combined categories of triglycerides and waist circumference, stratified for non-HDL cholesterol. (Adapted from ref. *27*. Reproduced courtesy of the American Diabetes Association.)

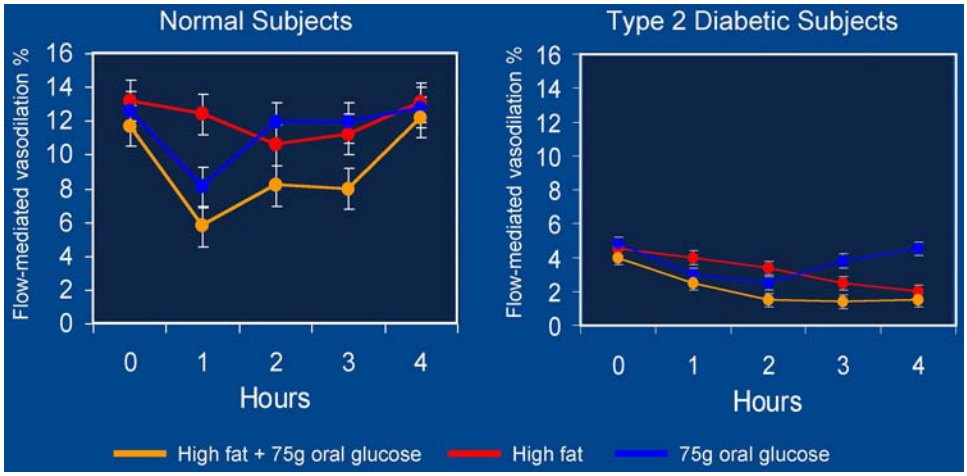

Fig. 5. Effect of high-fat load plus 75 g oral glucose on arterial function (flow-mediated vasodilation) in normal subjects and those with type 2 diabetes. (Adapted from ref. *30*. Reproduced courtesy of Lippincott, Williams & Wilkins.)

At least one epidemiologic study supports the notion that factors other than glucose play an important role in cardiovascular risk. The Hoorn Study demonstrated that increased cardiovascular risk with increased post-load glucose becomes insignificant if adjusted for other cardiovascular risk factors *(26,31)*. It is interesting to note that the large DECODE meta-analysis, which demonstrated an increased risk of cardiovascular disease based on 2-h post-challenge glucose levels, did not adjust for waist circumference or for relevant lipid concentrations *(6)*.

Taken together, these data strongly indicate that waist circumference, non-HDL cholesterol, and high triglycerides have at least an additive effect on cardiovascular risk (see Fig. 4) *(27)*. In patients with high waist circumference, triglycerides, and non-HDL cholesterol, the hazard ratio for cardiovascular disease was increased threefold. Thus, these data indicate that triglycerides and HDL cholesterol are major components of the metabolic syndrome leading to atherosclerotic damage. Postprandial glucose may, on the basis of epidemiological evidence, have an effect that is additive to those of the other risk factors.

Postprandial Glucose Excursions Exert a Direct, Toxic Effect on Vasculature

Evidence for a direct toxic effect of transient postprandial glucose excursions is accumulating, supporting the hypothesis put forward by the DCCT research group in 1995, that HbA_{1c} "is not the most complete expression of …glycemia." The group suggested that, "other features of diabetic glucose control, which are not reflected by A_{1c}, may add to, or modify, the risk of complications. For example …the extent of postprandial glycemic excursion" *(23)*. This idea finds circumstantial support from an Italian study that demonstrated fasting glucose variability (which is heavily influenced by the size of postprandial glucose spikes) was an independent predictor of cardiovascular mortality over 10 yr, and those people with the greatest variability had the worst outcome *(32)*.

Although the exact mechanisms are still not well defined, hyperglycemia is known to stimulate the production of reactive oxygen species through a variety of pathways, both direct and indirect, to increase levels of advanced glycation end products (AGEs) that are produced when intracellular dicarbonyls react with proteins. It now is well established that AGEs, highly damaging inflammatory mediators that raise levels of C-reactive protein and TNF-α are associated with diabetic vascular and neuropathic complications *(33,34)*.

In the conventional paradigm of direct glucose toxicity, glucose reacts rapidly with lysine to form glucoselysine, an unstable Schiff base, which then slowly converts to fructoselysine, the Amadori product. Both the unstable Schiff base and fructoselysine are highly reactive, and have the potential to lead to AGEs and thus, potentially to contribute to diabetes complications. Recent data suggest that the enzyme fructosamine-3-kinase (FN3K) may partially reverse the glycation process at an early stage by destabilizing fructoselysine *(35)*, thus providing a natural brake on AGE production.

There are data to suggest that glucose toxicity also occurs indirectly, through the increased production of α-dicarbonyls such as 3-deoxyglycosone (3-DG) and methylglyoxal (MG). These toxic sugars are up to 10,000 times more reactive than glucose. They are highly damaging to cells in culture, inhibiting cell growth, enzymatic activity, and DNA synthesis; promoting protein cross-linking and fragmentation; and producing protein precursors for AGE formation *(34)*. Levels of MG and 3-DG correlate with the severity of diabetes complications *(36)* and with levels of postprandial glucose *(37)*, but show no correlation with HbA_{1c} *(37)*.

Recently, a clinical study tested the hypothesis that reducing postprandial glucose levels and stabilizing glycemic fluctuations would reduce the formation of reactive α-dicarbonyls *(37)*. The double-blind crossover study, involving 21 people with type 1 diabetes, found that insulin lispro therapy over 2 mo significantly reduced mean postprandial glucose excursions compared to treatment with regular insulin therapy (mean difference: 142.3 mg/dL; $p = 0.0005$). Following standard test meals, levels of MG and 3-DG rose significantly. Linear regression analysis demonstrated that there was a highly significant correlation between postprandial glucose excursion and both postprandial MG excursions ($p = 0.0002$) and postprandial 3-DG excursions ($p = 0.0004$). These relationships remained highly significant on multiple regression analysis after correcting for factors such as age and duration of diabetes. Importantly, HbA_{1c} was not significantly different between the two treatment groups and was not correlated with MG or 3-DG excursions, indicating that HbA_{1c} does not always reflect the degree of glucose toxicity to which the patient may be exposed.

Cellular toxicity during the postprandial period also may be mediated through oxidative products. When exposed to hyperglycemia, the mitrochondrial electron-transport chain produces superoxide *(38)*. Dandona and colleagues demonstrated postprandial oxidative stress in obese patients, showing that generation of reactive oxygen species by mononuclear cells and polymorphonuclear leukocytes increased within 1 h of a 75 g glucose challenge in these patients *(39)*. This study and others also have demonstrated that high-carbohydrate meals reduce antioxidant capacity, as well as increasing oxidation. After 4 wk on a low-calorie diet, patients in the Dandona study showed significantly less postprandial oxidative stress. Ceriello and colleagues evaluated the effects of two standard meals designed to produce different degrees of hyperglycemia. They demonstrated that the meal that produced a greater degree of hyperglycemia both significantly increased lipid oxidation and reduced antioxidant capacity (as assessed by plasma total radical-trapping antioxidant parameter, TRAP) in 10 patients with type 2 diabetes *(40)*.

In conclusion, although much of the pathophysiological data on postprandial glucose elevation involves surrogate

markers, the accumulating data are highly suggestive that postprandial hyperglycemia is capable of causing direct vascular damage by the activation of multiple vascular toxins.

Are Current Data Sufficient to Justify Targeting Postprandial Glucose for Management?

Given the epidemiological, pathophysiological, and interventional observations suggesting that postprandial hyperglycemia is a risk factor for cardiovascular disease in diabetes, it is not unreasonable to ask whether postprandial glucose should now become a more central focus in diabetes management. Should we now use postprandial glucose levels to diagnose and monitor diabetes, and specifically target postprandial hyperglycemia with therapy?

Most treatment guidelines currently establish fasting glucose and HbA_{1c} in the pre-eminent role in the diagnosis and monitoring of diabetes, with postprandial (post-load) glucose measurements as supportive. The ADA currently defines impaired fasting glucose as >100 mg/dL and diabetes as >126 mg/dL *(41)*. Treating to postprandial glucose targets is recommended only if other measures fail *(41)*.

These glucose "cut points" are based on the risk of microvascular disease, retinopathy in particular. NHANES demonstrated that the incidence of retinopathy increases sharply above a fasting glucose of 110 mg/dL. Because most patients with diabetes die from cardiovascular disease, perhaps it is appropriate to consider basing therapeutic targets on the risk for macrovascular disease. This was not possible until recently because the relationship between glucose levels and cardiovascular disease was unclear. This situation is changing rapidly, and it is important to inform physicians treating patients with type 2 diabetes or people with IGT about the risks, and possible benefits in preventing, excessive postprandial glucose excursions.

The DECODE study *(42)*, in particular, has several important implications for diabetes management. DECODE was powered to overcome the limitations of many previous studies in which the relationship between hyperglycemia and cardiovascular disease was obscured by small sample size.

DECODE demonstrated that postprandial hyperglycemia has no "cut point." Postprandial glucose levels appear to be a continuous risk marker for mortality, just like other cardiovascular risk factors such as blood pressure and serum cholesterol. When adjusted for fasting glucose, IGT was associated with a 40% increased risk of cardiovascular disease and a 73% increased risk of all-cause mortality. Thus, patients with IGT have a 10-yr risk of death only 8% lower than patients with frank diabetes. By contrast, abnormal fasting glucose levels (>7.0 mmol/L) did not significantly increase the risk of cardiovascular disease or all-cause mortality when adjusted for post-load glucose.

DECODE also revealed that over half of all people with abnormal 2-h plasma glucose (≥7.8 mmol/L) had normal fasting glucose (<6.1 mmol/L) *(42)*. Thus, if fasting glucose remains the primary diagnostic criterion for the initiation of intervention, many patients with postprandial hyperglycemia will remain undiagnosed and untreated, despite having a substantially increased risk of cardiovascular disease.

Finally, fasting glucose levels did not increase with age in DECODE, in contrast to post-load glucose levels, which rose with age in a manner similar to that of blood pressure *(6)*. Thus, physicians monitoring their aging patients with fasting glucose measurements alone may entirely miss the onset of IGT and the associated increased risk of cardiovascular disease.

Similar findings were seen in DECODA, the companion study to DECODE that analysed data from five Asian studies *(43)*. In the Asian population, in which obesity is less common than in Caucasian populations, hyperglycemia was more characteristically postprandial than fasting. As in DECODE, mortality in the DECODA population was two to three times higher with elevations of 2-h post-load glucose, even when fasting glucose was adjusted to normal.

Conclusion

Although more interventional data clearly are needed, the accumulating body of evidence on a role for postprandial glucose in diabetic complications has important clinical implications that should not be ignored. It is time to seriously debate how we diagnose and monitor patients. Fasting glucose measurements alone will not identify all patients at high risk, and if used for serial monitoring as a patient ages, might never identify clinically significant postprandial hyperglycemia. Moreover, the data now suggest that therapies targeted at reducing postprandial hyperglycemia also should be considered by practitioners. This is becoming increasingly relevant with the development of drugs that specifically work through mechanisms that target beta-cell insulin secretion in an attempt to limit the extent of postprandial glycemic excursions. Drugs such as GLP-1 analogs, DPP-IV inhibitors, and short-acting insulin secretagogues may assume an increasingly important role in diabetes management, at least at stages of the disease when the beta cell is capable of responding *(44,45)*. Not only does lifestyle intervention in IGT prevent the progression to diabetes *(46,47)*, but the STOP-NIDDM trial provides tantalizing evidence that agents targeted at postprandial hyperglycemia can reduce cardiovascular sequelae *(11)*. Unfortunately, the weight of evidence supporting an important role for postprandial hyperglycemia in the genesis of cardiovascular complications rests primarily with observational studies. While it will be important to design further prospective interventional trials to directly test the specific impact of targeting postprandial hyperglycemia, it is useful to remind ourselves of the predictive value of observational studies on blood pressure and serum cholesterol. Historically, these studies started to change management long before

interventional data clinched the argument, to the benefit of millions of patients worldwide.

Based on available data, multiple interacting factors contribute to the risk for cardiovascular disease in diabetes. While the data supporting the roles of hypertension and hyperlipidemia are irrefutable, increasing data are beginning to suggest that postprandial glycemic excursion is an independent and treatable risk factor for cardiovascular disease. At the very least, reducing postprandial glucose excursion can improve mean glycemia (HbA_{1c}) and may well directly limit vascular injury. The remaining challenge is to document the importance of postprandial hyperglycemia through prospective interventional trials and to develop simple and effective treatment strategies.

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