

# Clinical Significance, Pathogenesis, and Management of Postprandial Hyperglycemia

John E. Gerich, MD

**I**t is well established that strict glycemic control (hemoglobin A<sub>1c</sub> <7.0%) can prevent the microvascular complications of diabetes mellitus. Recent studies indicate that elevated plasma glucose concentrations are an independent and clinically significant risk factor for cardiovascular disease in nondiabetic and diabetic individuals. Thus, isolated postprandial hyperglycemia (2-hour postprandial glucose level >140 mg/dL [ $>7.8$  mmol/L]) in the face of normal fasting plasma glucose (<110 mg/dL [ $<6.1$  mmol/L]) and normal hemoglobin A<sub>1c</sub> (<6.1%) values is associated with a 2-fold increased risk of death from cardiovascular disease. These observations imply that more strict glycemic control is required to prevent macrovascular disease than microvascular disease. This review summarizes epidemiologic and experimental studies linking postprandial hyperglycemia to cardiovascular disease and therapeutic approaches available and in development to treat this disorder.

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It is now well established that hyperglycemia is a treatable cause of the microvascular complications of diabetes mellitus. Controlled clinical trials have demonstrated unequivocally that maintenance of hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels below 7.0% can prevent the development and progression of neuropathy, nephropathy, and retinopathy in patients with either type 1 or type 2 diabetes mellitus.<sup>1-3</sup>

Although these microvascular complications are a major problem for patients with type 1 diabetes, macrovascular complications (eg, ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) are the major cause of morbidity in patients with type 2 diabetes.<sup>4</sup> Compared with a nondiabetic individual, a person with type 2 diabetes has a 2- to 4-fold increased risk of dying from a myocardial infarction<sup>5,6</sup> or a stroke,<sup>4,5</sup> and a 10- to 15-fold increased risk of a lower extremity amputation.<sup>7,8</sup>

Despite the importance of macrovascular complications for patients with type

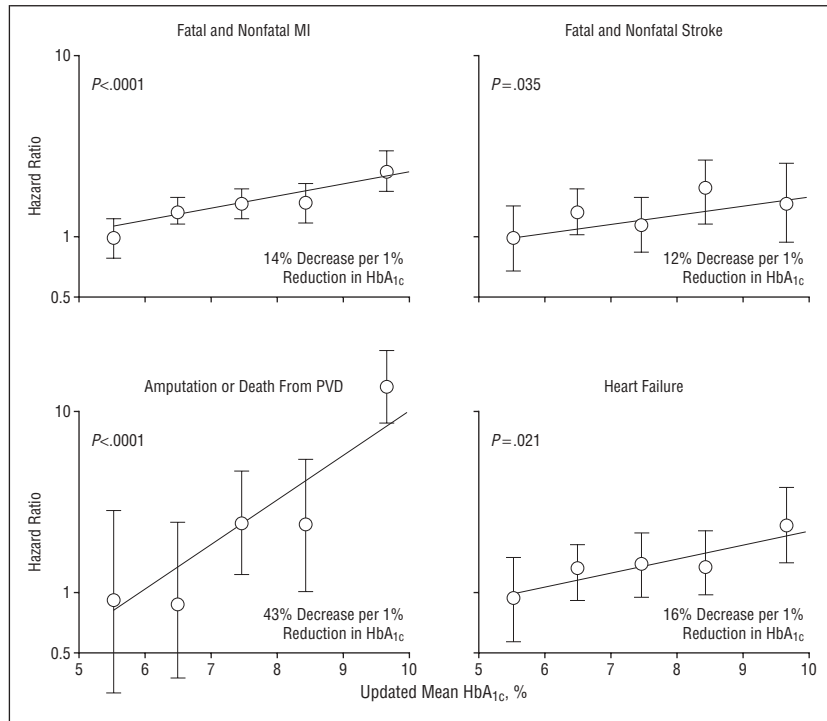
2 diabetes, current goals for glycemic control in these patients, such as those of the American Diabetes Association (ADA) (HbA<sub>1c</sub> <7.0%), have been based on epidemiologic data and clinical trials relevant to the prevention of microvascular complications. Recent evidence, however, strongly suggests that more aggressive glycemic control—in particular, that of postprandial hyperglycemia—may be necessary to reduce the risk for cardiovascular disease (CVD). Indeed, considerable data have accumulated over the past 5 years that indicate that elevated postprandial plasma glucose levels in the nondiabetic range increase the risk for CVD. It is the purpose of this review to summarize epidemiologic and experimental studies linking postprandial hyperglycemia to CVD and therapeutic approaches available and in development to treat this disorder.

## HYPERGLYCEMIA AND CVD

### General Considerations

The etiology of CVD is complex and multifactorial. Abnormalities in endothelial and vascular smooth muscle function, coagulation, and fibrinolysis pathways and

*From the Department of Medicine, University of Rochester Medical Center, Rochester, NY. Dr Gerich has served as consultant to or on advisory boards or speaker's bureaus for Novartis, Novo Nordisk, GlaxoSmithKline, Aventis, Bristol-Myers Squibb, Pfizer, and Emisphere Pharmaceuticals.*



**Figure 1.** Relationship between hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) and risk of myocardial infarction, stroke, heart failure, and amputation or death from peripheral vascular disease (PVD) in white men aged 50 to 54 years. Modified from Stratton et al,<sup>15</sup> with permission from the BMJ Publishing Group.

the production of growth factors, cytokines, adhesion molecules, as well as oxidative stress (free radical generation), all appear to play a role. Smoking, lipid abnormalities, hypertension, physical inactivity, and obesity are all well-established risk factors that affect these processes; hyperglycemia has now been added to these.<sup>4-6,9,10</sup> Obesity, hyperlipidemia, hypertension, and impaired glucose tolerance (IGT)/type 2 diabetes are frequently observed together, and the cluster of these risk factors (commonly referred to as the *metabolic syndrome* or the *insulin resistance syndrome*<sup>11-13</sup>) is associated with a 6-fold increase in cardiovascular mortality.<sup>14</sup>

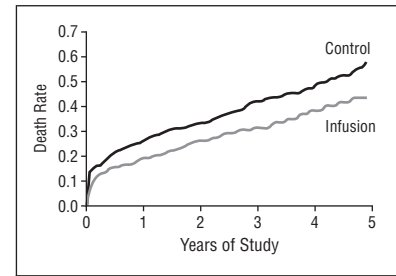
Three types of evidence link hyperglycemia to CVD: (1) controlled clinical trials demonstrating improved glycemic control reduces the risk for CVD; (2) epidemiologic studies elucidating a dose-response relationship between the risk for CVD and both fasting and postprandial glycemia; and (3) various in vivo and in vitro experiments demonstrating plausible mechanisms by which hyperglycemia may directly affect patho-

genetic mechanisms involved in CVD.

### Controlled Clinical Trials

Controlled clinical trials are generally regarded as the strongest type of evidence for demonstrating a cause-effect relationship between a risk factor and a particular complication. Two controlled clinical trials assessing the effects of intensive glycemic control have demonstrated beneficial effects on cardiovascular end points in people with type 2 diabetes.

The United Kingdom Prospective Diabetes Study (UKPDS), a trial using various regimens in approximately 5000 newly diagnosed patients with a median follow-up of 10 years, found that those in the intensively treated group (HbA<sub>1c</sub>, 7.0%) had a 16% reduced risk for myocardial infarction ( $P = .052$ ) compared with those in the conventional group (HbA<sub>1c</sub>, 7.9%) when data were analyzed using the conservative intent-to-treat approach.<sup>1</sup> A subsequent analysis of the data using updated HbA<sub>1c</sub> levels and multivariate regression (Cox proportional hazards



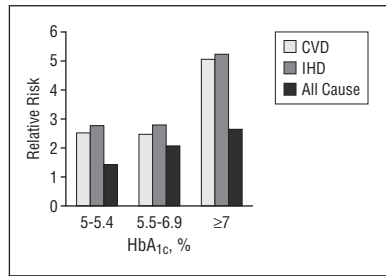
**Figure 2.** Actuarial mortality curves during long-term follow-up in patients receiving insulin-glucose infusion and in control patients in the Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction Study (death rate = number of deaths/number originally in the group;  $N = 620$ ). Absolute reduction in risk was 11%; relative risk, 0.72 (95% confidence interval, 0.55-0.92);  $P = .011$ . From Malmberg,<sup>16</sup> with permission from the BMJ Publishing Group.

models),<sup>15</sup> which corrected for concomitant lipid abnormalities, hypertension, smoking, and age, demonstrated that hyperglycemia (as reflected by HbA<sub>1c</sub> levels) was an independent risk factor for CVD with no apparent threshold (ie, the lower the HbA<sub>1c</sub> level, the lower the risk). Furthermore, the data showed that for every 1% reduction in HbA<sub>1c</sub> level from levels less than 6% to those greater than 10%, there were significant reductions in risk for myocardial infarction (14%,  $P < .0001$ ), stroke (12%,  $P = .035$ ), heart failure (16%,  $P = .021$ ), and amputation or death from peripheral vascular disease (43%,  $P < .0001$ ) (**Figure 1**).

The Diabetes and Insulin Glucose Infusion in Acute Myocardial Infarction Study (DIGAMI)<sup>16</sup> was a prospective trial of 620 diabetic patients with acute myocardial infarction who were randomized to either an intensive insulin regimen aimed at achieving near normoglycemia or conventional treatment, with a mean follow-up of 3.4 years; the intensively treated group had a 28% reduction in mortality ( $P = .011$ ) (**Figure 2**). Parenthetically, the results of this study thus provide strong evidence against atherogenic or deleterious cardiovascular effects of insulin and hyperinsulinemia.

### Epidemiologic Studies

Numerous prospective epidemiologic studies have demonstrated a correlation between the risk for CVD and either plasma glucose levels or



**Figure 3.** Relative risk of dying from cardiovascular disease (CVD), ischemic heart disease (IHD), and all-cause mortality relative to individuals with hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels below 5.0% in men aged 45 to 79 years. From Khaw et al.<sup>34</sup>

HbA<sub>1c</sub> values.<sup>17-31</sup> The reader is referred to an excellent summary and meta-analysis of these data as of 1999 by Coutinho et al.<sup>32</sup>

Although such studies cannot demonstrate a cause-effect relationship, they can elucidate a potential dose effect. What has become apparent over the last few years is that plasma glucose and HbA<sub>1c</sub> levels in the upper range of normal but still in the nondiabetic range (ie, fasting: <126 mg/dL [ $<7.0$  mmol/L]; 2-hour postprandial: <200 mg/dL [ $<11.1$  mmol/L]; and HbA<sub>1c</sub> <6.1%, respectively) are associated with an increased independent risk for CVD. The results of some key studies published within the last 3 years are summarized below to illustrate this point.

The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study<sup>33</sup> evaluated the relative risk of death from CVD, coronary heart disease, stroke, and all-cause mortality in 22 514 individuals followed up for a median of 8.8 years. Using a Cox proportional hazards model, it was found that the risks for death from CVD, coronary heart disease, stroke, and all causes were increased by 32%, 27%, 21%, and 37%, respectively, in people with IGT (2-hour plasma glucose concentrations of 140-198 mg/dL [ $7.8$ - $11.0$  mmol/L]) and by 40%, 56%, 29%, and 73%, respectively, in people with type 2 diabetes.

The results of the DECODE study were corroborated in a different ethnic population by the Funagata Diabetes Study, which showed a 2-fold increased risk of dying from CVD in Japanese with IGT.<sup>23</sup> Parenthetically, in this study there was no

increased risk in individuals with impaired fasting plasma glucose concentrations, ie, those between 110 and 126 mg/dL ( $6.1$ - $7.0$  mmol/L).

The Norfolk cohort of the European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk) Study<sup>34</sup> determined at the end of 1999 the fate of 4662 men aged 45 to 79 years who had their HbA<sub>1c</sub> measured between 1995 and 1997. The group was subdivided into those with HbA<sub>1c</sub> levels below 5.0%, those with values between 5.0% and 5.4%, those with values between 5.5% and 6.9%, those with values above 7.0%, and those with self-reported diabetes. Risk for death from CVD, coronary artery disease, and all-cause mortality was assessed using the Cox proportional hazards model after correcting for age, blood pressure, serum cholesterol, body mass index, cigarette smoking, and prior myocardial infarction or stroke. Relative to individuals with HbA<sub>1c</sub> levels below 5.0%, those with values between 5.0% and 5.4% had an increased risk for CVD, coronary artery disease, and all-cause mortality of 2.5, 2.7, and 1.4, respectively, and for those with HbA<sub>1c</sub> levels above 7.0%, the respective relative risks were 5.0, 5.2, and 2.6 (**Figure 3**). Of interest, the presence or absence of diabetes was not a risk factor independent of HbA<sub>1c</sub> levels. This observation strongly suggests that hyperglycemia per se was the key factor.

The Cardiovascular Health Study,<sup>35</sup> a prospective study of 4515 individuals 65 years or older followed up for 8 years, found that individuals with IGT had an increased risk for CVD of 22% after correction for age, ethnicity, and other known cardiovascular risks relative to that of individuals with normal glucose tolerance.

The above results are virtually identical with those from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study.<sup>36</sup> This was a 12- to 16-year follow-up of a representative sample of the US population who underwent oral glucose tolerance testing between 1979 and 1980. It was found that relative risk for death from CVD was increased by 20% in individuals with IGT and by

nearly 70% in individuals with previously undiagnosed diabetes.

The Hoorn Study,<sup>27</sup> a population-based 8-year follow-up of 2363 individuals aged 50 to 70 years without known diabetes found that, using conventional Cox proportional hazards model statistical evaluation, an elevated 2-hour postprandial plasma glucose level 2 SDs above the population mean (but still nondiabetic) increased the risk for death from CVD by 62% even after excluding individuals with preexisting CVD and correcting for other known risk factors.

Finally, further support is found in a longitudinal population-based study in Polynesia<sup>22</sup> in which nearly 10 000 individuals were followed up after 5 to 12 years. This study indicated that those with isolated postprandial hyperglycemia (fasting glucose levels <126 mg/dL [ $<7.0$  mmol/L] but 2-hour levels >200 mg/dL [ $>11.1$  mmol/L]) had an increased cardiovascular mortality of 2.3- (men) to 2.6- (women) fold.

In summary, current epidemiologic evidence indicates that plasma glucose (both fasting and postprandial values) is a continuous variable with respect to risk for CVD with no apparent threshold.<sup>37</sup> Moreover, it appears that increased postprandial glycemia in nondiabetic individuals carries a greater risk than increased fasting glycemia. Since postprandial plasma glucose levels increase before fasting levels, many experts in the field have emphasized the need for early detection and treatment of postprandial hyperglycemia.<sup>38-42</sup>

### Mechanisms for Adverse Cardiovascular Effects of Hyperglycemia

Putative cause-effect relationships inferred from epidemiologic studies are enhanced if plausible mechanisms are available. Information from both in vivo and in vitro experiments have provided biochemical-biophysiological mechanisms by which increases in plasma glucose levels may produce cardiovascular damage.<sup>43</sup> These include interactions between increased glucose fluxes through the polyol and glu-

cosamine pathways, increases in nonenzymatic glycation products and glycosylation of certain proteins, activation of diacylglycerol (DAG) and protein kinase C (PKC), decreased production of nitric oxide, and increases in generation of free radicals (oxidative stress).

**Figure 4** summarizes this complex situation. Hyperglycemia by its mass action will lead to increased tissue glucose uptake and metabolism by ordinarily minor pathways such as the polyol and glucosamine pathways. In addition, hyperglycemia will lead to glycosylation of extracellular proteins (such as low-density lipoprotein, which renders it more oxidizable and more atherogenic) and generation of free radicals (increased oxidative stress) and advanced glycation end products. Binding of advanced glycation end products to receptors on endothelial, smooth muscle, and fibroblast cells has been shown to lead to increased vascular permeability, increased coagulability, decreased thrombolysis, cell proliferation, and increased production of extracellular matrix proteins such as fibronectin, type IV collagen, laminin, and proteoglycans.<sup>44</sup> Generation of free radicals by hyperglycemia may promote atherogenesis (1) through peroxidation of low-density lipoprotein leading to a more atherogenic molecule, (2) by oxidation of fibrinogen leading to products that enhance coagulation, (3) by increasing platelet activation by collagen,<sup>45,46</sup> and (4) by decreasing production of nitric oxide.<sup>47</sup>

Endothelium-derived nitric oxide causes vasodilation and also inhibits platelet aggregation and adhesion of inflammatory cells to endothelium.<sup>48</sup> It has been shown that endothelium-dependent vasodilation is reduced in healthy volunteers after 6 hours of a hyperglycemic clamp.<sup>49</sup> A similar impairment in endothelium-dependent vasodilation is seen in healthy individuals after oral glucose intake.<sup>50</sup> Endothelium-dependent vasodilation is impaired in people with diabetes and is improved by vitamin C intake, thus implicating inactivation of nitric oxide by oxygen-derived free radicals.<sup>51,52</sup>

Many of the above processes are thought to be mediated to a large extent by activation of PKC and generation of DAG.<sup>43,53,54</sup> Hyperglycemia itself may directly increase PKC and DAG, since tissues incubated with high glucose concentrations have increased levels of DAG and PKC.<sup>46,54</sup>

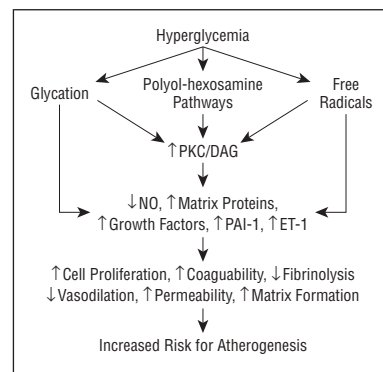
Activation of PKC and increased DAG promotes expression, formation, and enhanced activity of transforming growth factor B, type IV collagen, fibronectin, vascular endothelial growth factor, endothelin-1, caldesmon, plasminogen activator inhibitor-1, phospholipase A<sub>2</sub>, prostaglandin E<sub>2</sub>, and intercellular adhesion molecules. These have been identified to play a role in basement membrane thickness, extracellular matrix formation, angiogenesis, increased vascular permeability, smooth muscle cell proliferation, increased inflammatory cell adhesion, and decreased fibrinolysis.<sup>53</sup>

In summary, there are now several plausible mechanisms by which hyperglycemia occurring postprandially may directly or indirectly promote atherogenesis and thus predispose both nondiabetic and diabetic individuals to CVD.

## PATHOPHYSIOLOGY OF TYPE 2 DIABETES AND IGT

### General Considerations

Type 2 diabetes is a heterogeneous disorder involving variable combinations of impaired insulin secretion and insulin resistance, both of which can be influenced by genetic and acquired factors. Much controversy has surrounded the relative contribution of insulin resistance and impaired insulin secretion to the development of diabetes. Until a few years ago, it was generally thought that insulin resistance, rather than impaired  $\beta$ -cell function, was the major genetic factor. However, although insulin resistance is clearly an important contributing factor, current evidence indicates that it is neither essential nor the major genetic component.<sup>55</sup> Most of the insulin resistance found in patients with type 2 diabetes can be accounted for by obesity (especially increased visceral fat), physical inactivity, high-



**Figure 4.** Mechanisms by which hyperglycemia may increase risk for macrovascular disease. DAG indicates diacylglycerol; ET-1, endothelin 1; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; and PKC, protein kinase C.

fat diets, and the adverse effects of hyperglycemia (glucose toxicity), and increased circulating levels of free fatty acids (lipotoxicity).

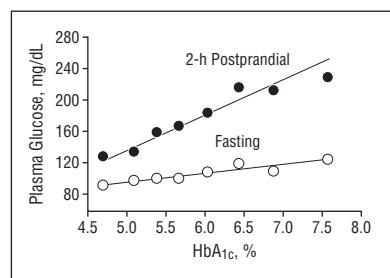
At the present time, therefore, the fundamental underlying genetic abnormality appears to be an impairment of  $\beta$ -cell function.<sup>55-60</sup> The evidence for this may be summarized briefly as follows: (1) genetically predisposed individuals such as the normal glucose-tolerant monozygotic twin or first-degree relative of someone with type 2 diabetes has reduced  $\beta$ -cell function but is not insulin resistant when compared with an appropriately matched control,<sup>55</sup> ie,  $\beta$ -cell dysfunction is detectable earlier than insulin resistance; (2) type 2 diabetes can occur in the absence of insulin resistance but not in the absence of impaired insulin secretion<sup>55</sup>; (3) weight loss in obese patients with type 2 diabetes can normalize insulin sensitivity but not  $\beta$ -cell function<sup>55</sup>; and (4) reduced  $\beta$ -cell function in normal glucose-tolerant individuals predicts subsequent development of type 2 diabetes.<sup>55</sup>

Impaired  $\beta$ -cell function is manifested most commonly by decreased early insulin release and the inability of the  $\beta$  cell to compensate appropriately for insulin resistance. In insulin-resistant individuals who are not genetically predisposed to diabetes (eg, obese and physically inactive individuals and women during the third trimester of pregnancy),  $\beta$  cells compensate for insulin resistance by increasing insulin release to maintain appropriate glucose production and

utilization. In individuals with IGT or type 2 diabetes, the capacity to secrete additional amounts of insulin to compensate for insulin resistance is reduced.<sup>60</sup> Thus, in a person with normal  $\beta$ -cell function, diabetes cannot develop solely as a result of insulin resistance.<sup>55,58,61</sup> The important contribution of underlying  $\beta$ -cell dysfunction has been confirmed by the UKPDS,<sup>62</sup> which found that at the time of diagnosis of diabetes, subjects exhibited a 50% reduction of  $\beta$ -cell function whose progressive deterioration was linked to poor glycemic regulation.

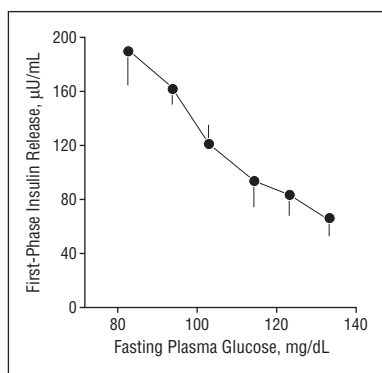
### Type 2 Diabetes

Type 2 diabetes (fasting plasma glucose >126 mg/dL or 2-hour postprandial value >200 mg/dL) is generally preceded by a period of lesser

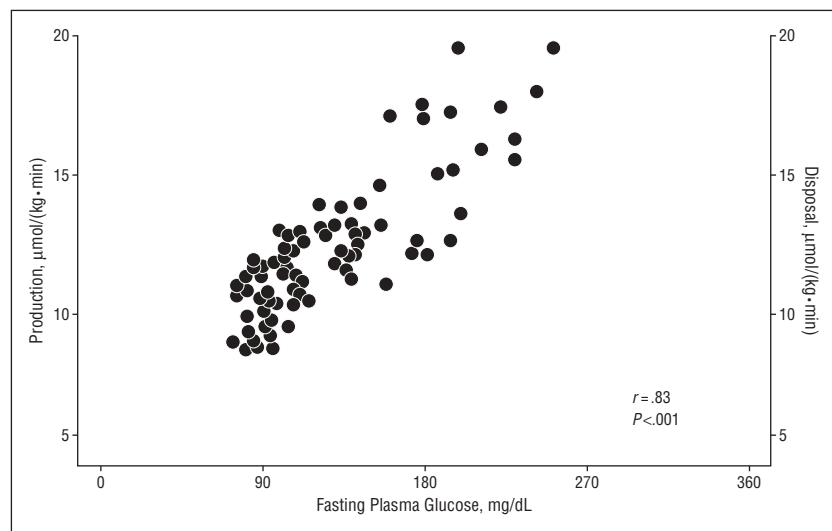


**Figure 5.** Relationship between increases in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels and increases in fasting and postprandial (2-hour) plasma glucose levels in 175 healthy volunteers with normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes mellitus. Data from Van Haeften et al.<sup>68</sup> To convert glucose to millimoles per liter, multiply by 0.05551.

fasting and postprandial hyperglycemia whose duration can vary considerably. In most instances, postprandial plasma glucose level increases first. This is illustrated in **Figure 5** from our database of volunteers for experiments who had undergone glucose tolerance tests and had their HbA<sub>1c</sub> levels measured. As HbA<sub>1c</sub> levels increase from less than 5.0% to over 7.5%, fasting plasma glucose levels increase from approximately 90 mg/dL (5.0 mmol/L) to approximately 125 mg/dL (6.9 mmol/L) (40%), whereas 2-hour postprandial values increase from approximately 130 mg/dL (7.2 mmol/L) to 230 mg/dL (12.8 mmol/L) ( $\approx$ 80%). This can be explained readily by 2 reasons. First, more insulin is needed after meals



**Figure 6.** Relationship between early (first-phase insulin release during hyperglycemic clamp studies) and fasting plasma glucose levels. Data from Van Haeften et al.<sup>68</sup> To convert glucose to millimoles per liter, multiply by 0.05551.



**Figure 7.** Glucose production and disposal in the postabsorptive state in nondiabetic and type 2 diabetic individuals as a function of their fasting plasma glucose levels. From Dinneen et al.<sup>63</sup> To convert glucose to millimoles per liter, multiply by 0.05551.

to maintain normoglycemia than in the fasting state. Second, the deleterious effect of insulin resistance would be more manifest since most postprandial glucose disposal occurs via insulin-sensitive pathways, whereas in the postabsorptive state most glucose disposal is not dependent on insulin. Although isolated increases in fasting plasma glucose levels above normal (110 mg/dL [6.1 mmol/L]) may occur, these are distinctly uncommon and the fasting plasma glucose level generally increases after the 2-hour value increase above normal (140 mg/dL [7.8 mmol/L]). By this time substantial decreases in early insulin release have already occurred and adversely affected postprandial glucose tolerance. Thus, as shown in **Figure 6**, early insulin release has decreased by about 50% by the time diabetes is diagnosed (on the basis of fasting plasma glucose levels). This is consistent with data of the UKPDS using HOMA modeling, which showed a 50% reduction in  $\beta$ -cell function at time of diagnosis.<sup>62</sup>

It is well established that fasting hyperglycemia occurs predominantly as the result of increased rates of glucose release by the liver and kidneys via gluconeogenesis<sup>63,64</sup> and is strongly correlated with increased rates of glucose release (**Figure 7**). Rates of tissue glucose uptake are generally also increased in people with fasting hyperglycemia, mainly because of mass action effects of the hyperglycemia. These rates, however, are lower than what would be observed in nondiabetic individuals with comparable hyperglycemia and hyperinsulinemia, indicating the presence of insulin resistance. Since, as indicated earlier, most glucose utilization in the fasting state is not insulin mediated, the major metabolic consequence of this insulin resistance is overproduction of glucose by the liver and kidneys. Fasting plasma insulin levels may be normal or increased relative to normoglycemic individuals but are clearly inappropriate for the degree of hyperglycemia, indicating  $\beta$ -cell malfunction.

It should be pointed out that to a certain extent fasting hyperglycemia may also be the result of antecedent postprandial hyperglycemia,

eg, the greater the hyperglycemia after an evening meal, the greater the hyperglycemia in the morning. The mechanisms responsible for postprandial hyperglycemia in patients with type 2 diabetes and in individuals with IGT are basically the same, but the abnormalities are more severe in patients with type 2 diabetes.<sup>63,65</sup>

### Impaired Glucose Tolerance

As shown earlier in Figure 5, postprandial glucose levels increase earlier than fasting levels as individuals progress toward diabetes. It is therefore not surprising that IGT precedes the development of type 2 diabetes.<sup>66</sup> Impaired glucose tolerance is defined as a condition in which fasting plasma glucose levels are below 126 mg/dL (7.0 mmol/L) and 2-hour postprandial values are between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L).<sup>66</sup> Impaired  $\beta$ -cell function, in particular poor early insulin secretion, has been found in individuals genetically predisposed to develop type 2 diabetes with normal glucose tolerance.<sup>67,68</sup> In individuals with IGT, early insulin release has further deteriorated (**Figure 8**) and is the major factor responsible for postprandial hyperglycemia.<sup>65</sup> Evidence for this may be summarized as follows: (1) impaired postprandial suppression of glucose release is strongly and negatively correlated with early insulin release<sup>65</sup>; (2) experimental reduction of early insulin release with somatostatin leads to IGT<sup>69</sup>; and (3) restoration of early insulin release by insulin administration<sup>70</sup> or by use of insulin secretagogues that improve early insulin release<sup>71</sup> or can improve or normalize glucose tolerance.

### POSTPRANDIAL HYPERGLYCEMIA

#### Monitoring

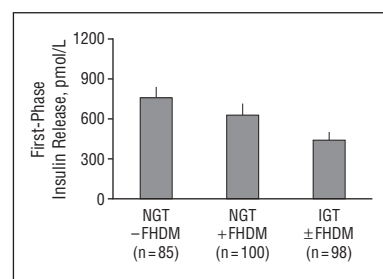
As summarized earlier, considerable epidemiologic evidence indicates that plasma glucose concentrations and HbA<sub>1c</sub> levels are independent continuous risk factors for CVD with no apparent

threshold. Likewise there is also considerable epidemiologic evidence indicating that postprandial hyperglycemia even in the absence of fasting hyperglycemia substantially increases the risk for CVD.

Glycosylated hemoglobin (HbA<sub>1c</sub>), a product of nonenzymatic glycosylation of the  $\beta$ -chain of hemoglobin by plasma glucose, is formed in proportion to increases in plasma glucose levels.<sup>72</sup> Measurement of HbA<sub>1c</sub> provides information on the average plasma glucose control over the preceding 3 months. It has therefore been used in many recent clinical trials and epidemiologic studies as an index of overall glycemic control. In most assays the stated upper limit of the nondiabetic range is 6.1%. Individuals with IGT can have HbA<sub>1c</sub> levels as low as 5.4% (Figure 5). Therefore, HbA<sub>1c</sub> is a relatively insensitive indicator of postprandial hyperglycemia.

Data from NHANES III<sup>73</sup> further illustrate this point. It was found that of patients with type 2 diabetes treated with diet and/or oral antihyperglycemic agents who were considered to have good glycemic control according to criteria of the ADA, ie, HbA<sub>1c</sub> <7.0%, 40% had postprandial hyperglycemia (ie, values >200 mg/dL [ $>11.1$  mmol/L]) while their fasting plasma glucose concentrations averaged less than 120 mg/dL (6.7 mmol/L). This is consistent with other data showing that patients with type 2 diabetes can have elevated HbA<sub>1c</sub> levels mainly attributable to postprandial hyperglycemia.<sup>74</sup> Furthermore, in NHANES III, it was found that all patients with HbA<sub>1c</sub> levels between 7.0% and 7.9% (below the value of 8.0% at which the ADA recommends action needs to be taken) had postprandial glucose levels above 200 mg/dL.

The seemingly inescapable conclusions of these studies are (1) that normal HbA<sub>1c</sub> levels can be associated with postprandial hyperglycemia of a magnitude associated with a substantially increased risk of death from CVD; and (2) that abnormal HbA<sub>1c</sub> levels may be mainly due to postprandial hyperglycemia. Thus, considering the epidemiologic data cited earlier, one can make an argument regarding the risk for CVD and postprandial hyperglycemia, that



**Figure 8.** First-phase insulin release determined during hyperglycemic clamp experiments in individuals with normal glucose tolerance (NGT) without a first-degree relative with type 2 diabetes mellitus (-FHDM), in individuals with NGT having a first-degree relative with type 2 diabetes (+FHDM), and in individuals with impaired glucose tolerance (IGT) with or without a first-degree relative with type 2 diabetes ( $\pm$ FHDM). From Van Haeften et al.<sup>68</sup>

postprandial plasma glucose levels should be monitored in diabetic patients, in addition to their HbA<sub>1c</sub>. Moreover, it may be advisable to check postprandial glucose levels in nondiabetic individuals with known cardiovascular risk factors (obesity, hyperlipidemia, hypertension, positive family history).

### ADA Consensus Panel

The above conclusions are at a variance with the published report of an ADA consensus panel of experts.<sup>75</sup> The panel concluded that there was insufficient evidence to determine accurately the relative contributions of fasting hyperglycemia and postprandial hyperglycemia to HbA<sub>1c</sub> levels. Second, it was pointed out that no clinical trials have assessed whether postprandial hyperglycemia, independent of other measures of glycemic control, plays a unique role in the pathogenesis of diabetes-specific complications; and third, that no prospective clinical trials have examined whether treatments that primarily lower postprandial hyperglycemia decrease cardiovascular events. Accordingly, the panel concluded that whether postprandial hyperglycemia is an independent risk factor for CVD is controversial and requires further study.

In all fairness to the panel, their conclusions were based on data available prior to the year 2000 and emphasized the lack of specific intervention trials while minimizing the importance of epidemiologic

data. Their conclusions have been challenged by more recent data.<sup>76,77</sup> It is my opinion that data from clinical trials, epidemiologic studies, and in vitro and in vivo experiments demonstrate clearly (1) that hyperglycemia, whether it be fasting or postprandial, is an independent risk factor for CVD; (2) that the risk is continuous without an apparent threshold; (3) that better glycemic control is needed to prevent macrovascular disease than the glycemic control for prevention of microvascular disease; (4) the goal of treatment for people with diabetes should be the lowest HbA<sub>1c</sub> level possible without unacceptable side effects; and (5) since HbA<sub>1c</sub> levels may miss postprandial hyperglycemia, postprandial glucose levels should be checked and if found to be in the range associated with increased CVD risk, should be treated.

### Management

**General Considerations.** Fasting and postprandial plasma glucose concentrations, although due to different pathologic mechanisms, are interrelated. The higher the plasma glucose level with which a patient goes to bed as a result of postprandial hyperglycemia, the higher will be the fasting hyperglycemia in the morning. Similarly, the higher the fasting hyperglycemia in the morning, the higher postprandial hyperglycemia will be during the day. Thus, maneuvers that primarily target fasting hyperglycemia might not be successful in normalizing fasting plasma glucose levels and achieving satisfactory HbA<sub>1c</sub> levels if postprandial hyperglycemia persists. Conversely, interventions that primarily target postprandial hyperglycemia might fail to achieve satisfactory HbA<sub>1c</sub> levels if fasting hyperglycemia persists. Regardless, one can certainly make the argument that for patients with normal or near-normal fasting plasma glucose levels but elevated HbA<sub>1c</sub> levels, maneuvers that target postprandial hyperglycemia should deserve strong consideration as the initial choice.

**Nonpharmacologic Interventions.** In individuals with IGT and in those with type 2 diabetes with

suboptimal, but not awful, glycemic control (eg, HbA<sub>1c</sub> 7.0%-8.0%), simple lifestyle modifications such as exercise, weight reduction, or change in diet composition can be particularly helpful. For example, several studies have demonstrated that weight-reducing diets and exercise can normalize glucose tolerance in individuals with IGT and reduce the risk of their developing type 2 diabetes.<sup>78-80</sup> Similarly, reducing the consumption of meals containing high glycemic index items (eg, rice and potatoes vs pasta) can lower postprandial plasma glucose increments as well as the average 24-hour plasma glucose concentration.<sup>81</sup>

**Pharmacologic Interventions.** If attempts with simple lifestyle changes have not produced a satisfactory response, pharmacologic intervention is indicated. Of all antidiabetic agents available in the United States, only the new nonsulfonylurea secretagogues (the meglitinides, repaglinide, and nateglinide), the  $\alpha$ -glucosidase inhibitors (acarbose and miglitol), and rapid-acting insulins specifically target postprandial hyperglycemia.<sup>82,83</sup>

The insulin secretagogue sulfonylureas in their immediate-release form and the insulin sensitizers (metformin and thiazolidinediones) primarily affect fasting plasma glucose concentrations. To the extent that fasting plasma glucose concentrations are reduced, so are postprandial plasma glucose levels. However, increments in postprandial glucose concentrations are largely unaffected.<sup>84-86</sup> These results can be explained at least in part because sulfonylureas primarily improve late, not early, insulin release,<sup>83</sup> because metformin primarily acts by decreasing overproduction of glucose in the fasting state<sup>85,87</sup> and because thiazolidinediones primarily improve peripheral glucose utilization,<sup>88</sup> which is not the major factor involved in postprandial hyperglycemia.<sup>65</sup> However, it should be pointed out that recent studies of a combination of metformin and glyburide have shown a reduction in postprandial glucose excursions.<sup>89</sup>

**Meglitinides.** The meglitinides (repaglinide and nateglinide) are

nonsulfonylurea insulin secretagogues that specifically affect early insulin release. Both these agents bind to islet  $\beta$  cells at different sites than sulfonylureas and with different kinetics. Although the result is the same, ie, inhibition of potassium channels that causes release of insulin secretion,<sup>83,90</sup> these agents only affect early insulin release. Because of this and their short half-life, they must be given just prior to meals.

Repaglinide, the first of this new class of nonsulfonylurea secretagogues, binds to the same receptor as sulfonylureas and to its own distinct site on the  $\beta$  cell.<sup>91</sup> Following oral administration with meals, it has a rapid and short-lived insulinotropic action.<sup>91</sup> It has been shown to be at least as effective as glyburide and glipizide in the treatment of patients with type 2 diabetes,<sup>92-94</sup> as reflected by HbA<sub>1c</sub> levels. There is evidence that this agent may result in less weight gain and hypoglycemia than most sulfonylureas.<sup>83</sup> It may be used as monotherapy or in combination with metformin, thiazolidinediones, and long-acting insulin.

Nateglinide, the second meglitinide to reach the market, is a phenylalanine derivative that has a similar mechanism of action to repaglinide. However, nateglinide has a lower affinity than repaglinide for the adenosine triphosphate-dependent potassium ion channels in the  $\beta$  cell; consequently, it dissociates more rapidly from the sulfonylurea receptor.<sup>95</sup> Nateglinide appears to have a more rapid onset and shorter duration of action than repaglinide,<sup>92</sup> but the clinical significance of this is unclear. Nateglinide appears to be less effective than glyburide, repaglinide, and metformin in lowering fasting plasma glucose and HbA<sub>1c</sub> levels,<sup>92,96,97</sup> but its use is associated with less hypoglycemia than glyburide. In contrast to repaglinide, no dose titration adjustment is necessary.<sup>83</sup> In general, as monotherapy in drug-naive patients, repaglinide would be expected to lower HbA<sub>1c</sub> levels by 1.0% to 1.5%. Although nateglinide might lower HbA<sub>1c</sub> levels somewhat less, it would be expected to result in less hypoglycemia than repaglinide.<sup>92</sup>

***α-Glucosidase Inhibitors.*** The  $\alpha$ -glucosidase inhibitors (acarbose and miglitol) delay carbohydrate digestion by selectively inhibiting glucosidase enzymes in the brush border of the small intestine. The slower digestion and absorption of carbohydrates reduces the postprandial rise in plasma glucose. Acarbose has also been shown to increase the secretion of glucagon-like peptide (GLP)-1, although the relative contribution of this effect to the reduction in postprandial hyperglycemia is unknown.<sup>98</sup> Both acarbose and miglitol are similarly effective in reducing postprandial hyperglycemia.<sup>99</sup> In general, this class of drugs lowers HbA<sub>1c</sub> levels by about 0.5%. Many patients do not tolerate these agents due to flatulence, abdominal pain, and diarrhea.<sup>99,100</sup>

***Insulin and Insulin Analogues.*** Preprandial administration of regular insulin or mixtures of regular insulin and a longer-acting insulin will decrease postprandial hyperglycemia. However, to obtain the optimal effects of regular insulin, it needs to be administered 20 to 40 minutes prior to meal ingestion.<sup>101</sup> This is inconvenient and usually not done by patients. Furthermore, the 4- to 6-hour duration of action of regular insulin often results in later hyperinsulinemia and hypoglycemia prior to the next meal. Consequently, the introduction of insulin analogues with a more rapid onset and shorter duration of action has been of considerable benefit to patients.<sup>102</sup>

Insulin lispro, the first human insulin analogue to be approved for the treatment of diabetes, is the result of exchange in the positions of the amino acids B28 proline and B29 lysine.<sup>103</sup> Insulin aspart is the result of exchange of aspartic acid for proline at position 28 of the B chain.<sup>104</sup> These alterations prevent formation of hexamers and result in a more rapid absorption leading to a faster onset of action, higher initial plasma concentrations and shorter duration of action compared with human regular insulin.<sup>103,105,106</sup> Both insulins have quite similar time-action profiles, generally providing peak plasma levels 40 to 50 minutes after injection (vs 60-90 minutes for regular insulin) with a duration of action of 2 to 4 hours (vs 4-6 hours for regular insulin).<sup>107</sup>

Use of these insulin analogues permits insulin injection immediately before—or even 5 minutes after—beginning meals, with at least similar and often better glycemic control than regular insulin and with less risk for hypoglycemia than regular insulin.<sup>102,108</sup>

Insulin treatment in type 2 diabetes has generally been initiated only after patients fail to achieve adequate glycemic control on maximal doses of 2 or 3 oral agents. However, a recent study comparing glyburide plus premeal lispro insulin, glyburide plus bedtime NPH (neutral protamine Hagedorn) insulin, and glyburide plus metformin twice daily found that the combination of glyburide plus premeal lispro insulin was best in reducing postprandial hyperglycemia and HbA<sub>1c</sub> levels without causing more hypoglycemia than the other regimens.<sup>109</sup> These results suggest that earlier use of insulin than in the past may be advantageous.

***Agents in Development.*** These include the synthetic human amylin analogue pramlintide, the insulinotropic hormone GLP-1,<sup>110</sup> a homologue of GLP-1-exendin, and inhalable formulations of insulin. Amylin is a pancreatic hormone co-secreted from islet  $\beta$  cells with insulin.<sup>82</sup> When administered to humans, it delays gastric emptying and reduces postprandial plasma glucose levels but has an impractically short half-life. Pramlintide, an amylin analogue, has a longer half-life and does not have a tendency to self-aggregate as does amylin.<sup>82</sup> Subcutaneous injection or intravenous infusion of pramlintide reduces postprandial glucose excursions in patients with type 1 or type 2 diabetes.<sup>111,112</sup> However, the necessity for injection and its relatively weak efficacy (approximately 0.5% HbA<sub>1c</sub> lowering) will probably limit use of this agent.

GLP-1 is a hormone released from intestinal L cells into the circulation after meals.<sup>113,114</sup> It is not an insulin secretagogue but enhances glucose-dependent insulin secretion through the activation of cyclic adenosine monophosphate-dependent protein kinase in pancreatic  $\beta$  cells.<sup>98,110</sup> Like pramlintide, a subcutaneous injection of

GLP-1 is effective in reducing postprandial hyperglycemia in patients with type 2 diabetes.<sup>113</sup> There is also evidence that GLP-1 may have beneficial effects on reducing insulin resistance and preserving  $\beta$ -cell function.<sup>110,115</sup> Work is under way to develop more effective analogues and agents that promote GLP-1 release or prolong its half-life. One such agent currently in clinical trials is exendin-4, a 39-amino acid peptide originally isolated from Gila monster saliva; this peptide has 53% homology with GLP-1, and acts as a GLP-1 receptor agonist, but with a much longer duration of action.<sup>114</sup> When infused in healthy volunteers, it reduces fasting and postprandial glucose levels, appetite, and gastric emptying, as does GLP-1.<sup>116</sup>

***Inhaled Insulin.*** Of all agents under development, inhalable insulin formulations are probably closest to being introduced into clinical practice. The potential for insulin to be absorbed via the human alveolar epithelium has been known for some time.<sup>117-119</sup>

Dosing and pharmacokinetic studies with liquid and powder formulations indicate that plasma insulin increments using inhaled insulin occur more rapidly and to higher peaks than with subcutaneous regular insulin, but are similar to parameters obtained with lispro insulin.<sup>120-123</sup> With an overall bioavailability in the range of 10% to 15%, administered doses result in plasma insulin profiles as reproducible as those observed after subcutaneous regular or lispro insulin with durations of action intermediate between regular and lispro insulin.

Clinical development of the powder formulation appears to be in a more advanced stage of development than the liquid formulation. Short- and long-term clinical trials of the powder formulation in patients with type 1 or type 2 diabetes have demonstrated that this preparation is as effective and well tolerated as regular subcutaneous insulin.<sup>124-126</sup> Long-term safety studies are ongoing. Moreover, assessment of patient satisfaction in these studies has shown preference of inhaled over subcutaneous regular insulin.<sup>125-127</sup>



## CONCLUSIONS

Hyperglycemia is an important risk factor for both microvascular and macrovascular complications of diabetes. Considerable recent evidence has accumulated, indicating that isolated postprandial hyperglycemia (ie, 2-hour postprandial levels >140 mg/dL and fasting levels <110 mg/dL) is common and is an independent clinically significant risk factor for CVD. The key factor responsible for postprandial hyperglycemia is impaired early insulin secretion.<sup>55-59,62,128</sup> Fortunately, treatment modalities are now available that specifically target postprandial hyperglycemia by improving early postprandial plasma insulin levels (eg, meglitinides, rapid-acting insulin analogues) and several new ones are in development (eg, inhaled insulin and GLP-1 agonists).

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Corresponding author and reprints: John E. Gerich, MD, University of Rochester Medical Center, 601 Elmwood Ave, Box MED/CRC, Rochester, NY 14642 (e-mail: mary\_little@urmc.rochester.edu).

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