Association of Hyperglycemia and Insulin with Diabetic Cardiovascular Complications

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Abstract

Patients with diabetes and/or insulin resistance syndrome are at increased risk for developing cardiovascular disease. The UKPDS raised a great debate about the relative importance of hyperglycemia in the development of cardiovascular disease. Recently, several epidemiologic studies have suggested that high postprandial blood glucose levels are associated with a significant risk for the development of cardiovascular disease as well as a grave prognosis for these patients during acute coronary events. In addition, a number of reports reinforce the thesis that postprandial hyperglycemia is a risk factor for mortality. Our review summarizes the current knowledge on the relation between blood glucose, insulin levels, and cardiovascular morbidity and mortality, relating these data to the new World Health Organization and American Diabetes Association classification of disturbed glucose metabolism.

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The relationship between hyperglycemia and macrovascular disease is complex, and it is often difficult to isolate the effect of hyperglycemia on the cardiovascular system from other risk factors. Studies done in the 1970s and 1980s with the aim of defining the relationship between hyperglycemia and vascular events yielded conflicting or controversial results [1–3]. One problem associated with these studies was their cross-sectional study design and the parameters used for determining the existence of hyperglycemia, such as factoring in the level of blood glucose just prior to the acute myocardial infarction event. In addition, as a result of the methodologic problems associated with these studies, it was unclear whether the severity of the MI was caused by pronounced hyperglycemia or vice versa. However, these studies did demonstrate the existence of a link between hyperglycemia and macrovascular disease in both non-diabetic and diabetic patients. Some reports of patients with acute MI indicated that plasma glucose levels at admission to the coronary care unit correlated strongly with mortality regardless of whether the patient had diabetes or not [4]. In addition, Van Den Berghe et al. [5] have shown that intensive insulin therapy to maintain blood glucose below 6.1 mmol/L reduces morbidity and mortality. Two other studies suggested that hospital fatality rates are improved in patients with optimal control, as judged by blood glucose levels measured just before the infarct [6,7].

Recent studies provide a stronger indication that hyperglycemia is an important and independent risk factor for cardiovascular disease in patients with type 2 diabetes [8–14]. In addition, epidemiologic studies suggest that in people with type 2 diabetes, cardiovascular mortality is related to the degree of hyperglycemia [15].

The recently reported United Kingdom Prospective Diabetes Study (UKPDS) on the results of a large prospective observational study, which included 4,585 patients who were randomized to either intensive glycemic control interventions or conventional treatment, showed that for every 1% decrease in HbA1C, there was 14% reduction in risk for myocardial infarction [16].

Type 2 diabetes is a multisystem disorder that is often categorized as a syndrome that encompasses a wide range of problems, including insulin resistance, obesity, dyslipidemia, hypertension, altered coagulation, and accelerated atherosclerosis. Many of these problems often predate the overt diabetic state by many years, and the insulin resistance syndrome is seen as a developmental process that is initiated by both genetic and environmental factors. This raises the issue of early diagnosis of the conditions leading to type 2 diabetes, as a means of facilitating intervention in advance of overt diabetes.

It has been shown in many, but not all, reports that the concordance between the fasting glucose criterion of the ADA and the oral glucose tolerance test definition still utilized by the WHO is often low and that different subsets of subjects are diagnosed as diabetic by the two sets of criteria. The Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study provides some insight into this problem [17]. The DECODE report compared the prevalence of diabetes based on either the ADA criterion of a fasting plasma glucose $\geqslant$ 7 mmol/L or the WHO criterion of a 2 hour postprandial plasma glucose of >11.1 mmol/L. If fasting glucose alone were used as a diagnostic criterion, then 31% of diabetic subjects with a non-diabetic fasting glucose but a diabetic 2 hour glucose would not be diagnosed. In this context, it is important to emphasize that although diabetes is clearly a strong independent risk factor for CVD, the various diagnostic thresholds

MI = myocardial infarction

ADA = American Diabetes Association
WHO = World Health Organization

for diabetes were not based on any analysis of the glucose-CVD risk relationship [18].

Large prospective epidemiologic studies, by including comprehensive multivariate analyses of all major risk factors, have provided a much more accurate evaluation of cardiovascular risk associated with increased blood glucose concentrations. Based on observations from these studies, it has become clear that there are many temporal aspects to hyperglycemia, and that to truly understand the relationship between hyperglycemia and cardiovascular disease it is necessary to analyze the sub-components of hyperglycemia independently. Specifically, the pathogenic effects of fasting, postprandial, and total glycemic exposure have to be assessed separately.

Similarly, the different forms of coronary artery disease that were previously lumped together as "diabetic cardiovascular complications" need to be broken down into subgroups that include chronic progressive atherosclerotic disease, acute MI, and sudden cardiovascular death so as to better define the causative role of hyperglycemia. Refining the definitions of hyperglycemia and cardiovascular disease has allowed for a detailed analysis of the relationship between the two, and has facilitated the development of more optimal and rational treatment strategies for diabetic patients.

Postprandial hyperglycemia, development of CVD, and mortality

The role of postprandial hyperglycemia has recently come under scrutiny in terms of being a significant factor in the development of diabetic CVD [19]. Early studies such as the Whitehall Study had shown that impaired glucose tolerance in non-diabetics was associated with increased cardiovascular and coronary artery disease mortality [20]. The Diabetes Intervention Study, a multicenter trial conducted in East Germany, showed that patients with better controlled postprandial glucose levels (< 8 mmol/L) had a lower incidence of MI and cardiovascular death [21]. The DECODE study presented a systematic evaluation of the predictive value of hyperglycemia with regard to mortality in non-diabetics, those with borderline abnormalities in blood sugar, or those with diabetes based on the ADA's criteria for the diagnosis of diabetes mellitus [17].

The results of this study showed that fluctuation in the elevated postprandial blood glucose levels after 75 g glucose challenge is an independent predictor of mortality. The Funagata Diabetes Study investigators evaluated risk for overall mortality and cardiovascular mortality in a cohort of individuals from Funagata, Japan, with various categories of abnormal carbohydrate metabolism, including IGT, impaired fasting glucose, and overt diabetes [22]. Individuals with either IGT or frank diabetes were at significantly higher risk for death from cardiovascular causes than non-diabetics and those with IFG. As expected, the highest risk was found among those with fully expressed diabetes. Those with IFG did not differ from non-diabetics in terms of mortality. With regard to those with IGT, the survival rate was lower among individuals with IGT beginning 6 years after diagnosis, and the cardiovascular mortality for individuals with IGT was significantly higher beginning 4 years after the diagnosis. The increase in mortality, especially cardiovascular, underscores the importance of postprandial hyperglycemia as a risk factor, and lends credence to the claim that elevated postprandial blood glucose, as determined by OGTT, has important prognostic significance. It has also been noted that individuals with IGT tend to have a certain phenotype that is not necessarily found in those with abnormalities in fasting glucose only. Results from the DECODE study showed that patients with IGT have an increased prevalence of obesity. Others have also observed that IGT patients are more obese, more insulin-resistant, and have higher insulin levels as compared to normal individuals [23].

A number of other epidemiologic reports reinforce the thesis that postprandial glucose is a risk factor for mortality. In the Chicago Heart Study, investigators reported that cardiovascular mortality was significantly increased in men with asymptomatic post-challenge hyperglycemia (>11.1 mmol/L, 1 hour after a 50 g OGTT) [24]. Data from the Rancho Bernardo cohort suggest that older women with isolated post-challenge hyperglycemia, i.e., 2 hour post-challenge glucose >11.1 mmol/L but fasting plasma glucose <7.0 mmol/L, have a cardiovascular mortality rate that is 2.6 times that of age-matched euglycemic control subjects [25]. Meta-analyses of the association between glycemia and cardiovascular disease also indicate higher cardiovascular risk with increases in the level of 1 hour, 2 hour, and fasting glycemia [26,27]. Again, the strongest predictors are fasting and 2 hour postprandial blood glucose levels, suggesting that even mild blood glucose elevation is a major variable in the development of macrovascular disease. Several possible mechanisms that affect cardiovascular risk have been proposed as operating in patients with postprandial blood glucose oscillations, including QT interval prolongation, hypercoagulability, sympathetic overactivity, increased blood pressure, and postprandial elevations in lipid concentration [28].

Association of insulin levels and CVD

During the past decade, ample evidence has been presented on the association between the insulin level and a cluster of cardiovascular risk factors. However, the epidemiologic evidence from prospective studies on the relation between the insulin level and heart disease has not been convincing [29]. In some studies, fasting insulin, and in others stimulated insulin, has been associated with coronary heart disease. The relation has been found in men but not in women, and sometimes early in the study but not in later follow-up data [30]. Perhaps there are natural explanations for these inconsistent results, which are based on the differences between studies in terms of sample size, population, and methodology. Another possible explanation may be that it is not the elevated plasma insulin level *per se*, but an increase in its precursors, pro-

CVD = cardiovascular disease
IGT = impaired glucose tolerance
IFG = impaired fasting glucose
OGTT = oral glucose tolerance test

insulin and split pro-insulin that constitutes the association with coronary heart disease. It has already been shown in both diabetics and non-diabetics that pro-insulin and split pro-insulin have a stronger association than insulin with dyslipidemia (high triglycerides and low high density lipoprotein-cholesterol), hypertension, and IGT [31]. It has been shown that pro-insulin increases plasminogen-activated inhibitor type 1 (PAI-1) activity and thereby decreases fibrinolytic activity. Furthermore, a clinical trial treating type 2 diabetic patients with human pro-insulin was terminated prematurely because of a cluster of myocardial infarctions in the treated group [32]. Recently, Lindahl et al. [33] established that pro-insulin is an independent risk factor for the first acute MI in a non-diabetic population [33].

The role of insulin as a factor in diabetic CVD is an important issue for type 2 diabetics who may be hyperinsulinemic as a result of insulin resistance, or receiving significant quantities of insulin as part of enhanced glycemic control protocols. Clearly, increasing dosages of insulin can cause obesity, which is a risk factor for cardiovascular disease [34,35]. A different issue is whether insulin, a growth factor, is atherogenic. Insulin resistance has also been associated with hyperlipidemia, and several studies have shown that carotid intimal-medial thickness, a marker for atherosclerotic disease, is increased in individuals with hyperinsulinism.

On the other hand, in several large epidemiologic studies, insulin as a treatment modality does not appear to confer additional risk for cardiovascular diseases. Savage and colleagues [36] did not find an increased incidence of CVD in patients receiving insulin in place of oral hypoglycemic agents. The same finding was also noted in the recently completed UKPDS [37]. Additional support for the lack of a relationship between insulin levels and atherosclerosis is based on a study of a large series of insulinoma patients in whom there were no signs of unusual progressive atherosclerosis, despite the very high levels of sustained hyperinsulinemia [38].

In conclusion, hyperglycemia (both fasting and postprandial) and possibly hyperinsulinemia appear to play a role in the development of cardiovascular complications in diabetic patients. There is a possibility that some additional, poorly defined, diabetic-specific risk factors contribute to the pathogenesis of vascular disease. Another important consideration, especially with regard to developing health initiatives to improve treatment of type 2 diabetes, relates to absolute reduction in risk. Absolute reduction in risk depends not only on the percentage reduction of a specific risk factor, but also on the prevalence of the risk factor. For instance, even if the intensive treatment of hypertension and dyslipidemia yield a greater reduction in the relative risk in those individuals with these specific risk factors, the total number of patients benefiting from therapy is lower compared with those benefitting from intensive treatment of hyperglycemia, even though the reduction of relative risk is less [39]. The glucose thresholds used to define diabetes were chosen to identify people at risk for eye and kidney diseases, without regard to the risk of cardiovascular disease. If there is a glucose threshold for CVD, it may therefore be lower than that for diabetes or even for IGT.

Future treatment strategies

Control of postprandial glucose levels may help prevent or delay the onset of microvascular or macrovascular complications caused by diabetes. Thus, it is important to evaluate non-fasting glucose levels in addition to fasting plasma glucose [40]. The role of glycemic control in lowering cardiovascular morbidity and mortality in IGT and type 2 diabetes needs to be further defined. One of the issues to be resolved, at both the basic science and clinical levels, is whether postprandial hyperglycemia and hyperinsulinemia contribute to cardiovascular mortality. If postprandial hyperglycemia is a risk factor for CVD, it is important to determine the pathophysiologic molecular mechanisms involved, as this will have an impact on therapeutic options.

Until this information is available, it seems prudent to maximize postprandial glycemic control both by reducing postprandial glucose levels and preventing large oscillations in glucose values. For individual patients, intensifying general treatment measures (education, diet, exercise, drug treatment), along with improved glucose self-monitoring, is appropriate. Both postprandial and fasting glucose levels should be followed with special attention to the post-lunch period, as there has been a tendency to ignore this part of the day. The goal should be to lower average blood glucose throughout the day.

New drugs with major effects on postprandial glucose are now available, and thus we believe that the role of reducing postprandial blood glucose in large vessel disease will soon be clarified.

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Capsule

Out of rhythm

Atrial fibrillation (AF), a common rhythm disturbance in the heart, is increasing in prevalence as the population ages, yet little is known about its molecular pathogenesis. Chen et al. studied a large family in China with hereditary AF and identified the culprit gene as *KCNQ1* on chromosome 11p15.5. *KCNQ1* encodes a potassium channel subunit that has been previously linked to the pathogenesis of familial ventricular fibrillation and long QT syndrome. Importantly, the KCNQ1 mutations in the latter disorders lead to loss of channel function, whereas the mutation in the AF family produces a gain of function. Thus, alterations in a single ion channel can evoke distinct heart arrhythmias, a finding that may have important implications for the pharmacologic treatment of these disorders.

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