

Is Hyperglycemia a Causal Factor in Cardiovascular Disease?

Does proving this relationship really matter? Yes

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Given that cardiovascular disease is a common complication of diabetes (1) and the leading cause of death among people with diabetes (2,3), it is important that we use the most effective therapies to manage lipids, blood pressure, and glycemia to reduce the risk, progression, and impact of macrovascular disease. Recent studies by Gaede et al. (4) clearly demonstrated that intensive management of all risk factors, including lipids, blood pressure, and glycemia, had significant beneficial effects on cardiovascular-related deaths. This intensive therapy was also found to be cost-effective (5).

Nevertheless, questions are now being raised regarding the importance of glycemia relevant to the prevention and/or progression of cardiovascular disease. To begin answering these questions, we first need to ask: Is there any reason *not* to believe there is a link between hyperglycemia and cardiovascular disease?

PLENTY OF AVAILABLE EVIDENCE

— We have strong evidence from large randomized controlled trials that clearly establish a causal relationship between poor glycemic control and the development of microvascular disease (6,7). Why should we assume that large blood vessels are immune to the same damaging effect of hyperglycemia? We should not: there is plenty of evidence linking hyperglycemia to macrovascular risk.

Analysis of data from 3,642 U.K. Prospective Diabetes Study subjects (for whom complete data for potential confounders were available) showed a signif-

icant 14% ($P < 0.0001$) reduction in myocardial infarction for each 1% reduction in mean A1C (8).

An early meta-regression analysis by Coutinho et al. (9) showed that the progressive relationship between glucose levels and cardiovascular risk extends below the diabetic threshold. Analyzed studies comprised 95,783 people who had 3,707 cardiovascular events over 12.4 years.

More recently, Levitan et al. (10) confirmed that hyperglycemia in the nondiabetic range was associated with increased risk of fatal and nonfatal cardiovascular disease, with a similar relationship between events and fasting or 2-h plasma glucose. In the meta-analysis of 38 studies, cardiovascular events increased in a linear fashion without a threshold for 2-h postprandial plasma glucose, whereas fasting plasma glucose showed a possible threshold effect at 99 mg/dl.

Hanefeld et al. (11) found significant positive trends in risk reduction for all selected cardiovascular event categories with treatment with acarbose, an α -glucosidase inhibitor that specifically reduces postprandial plasma glucose excursions by delaying the breakdown of disaccharides and polysaccharides (starches) into glucose in the upper small intestine. In all of the seven studies with at least 1 year's duration, people treated with acarbose not only showed reduced 2-h postprandial levels compared with control subjects, but treatment with acarbose was significantly associated with a reduced risk for myocardial infarction and other cardiovascular events. Similar findings have been reported in subjects

with impaired glucose tolerance who were treated with acarbose (12).

A 2006 meta-analysis by Stettler et al. (13) showed that efforts to improve glycemia yield significant reductions in macrovascular disease in type 1 and type 2 diabetes. The benefit was particularly strong in younger patients with shorter duration of the disease. A more recent report from the Euro Heart Survey on Diabetes and the Heart (14) showed a pronounced decrease in cardiovascular events in subjects with newly diagnosed diabetes treated with glucose-lowering agents.

The International Diabetes Federation recently published its guideline for managing postprandial glucose (15), providing strong evidence regarding the role of postprandial hyperglycemia as an independent risk factor for macrovascular disease. Among the several studies cited in the guideline is a report by Esposito et al. (16), who demonstrated a reduction in carotid intima-media thickening by reducing postprandial glucose excursions. Carotid intima-media thickening is directly related to clinical manifest cardiovascular disease and is associated with increased risk for myocardial infarction and stroke (17,18).

Although the exact mechanism by which vascular damage occurs is not fully understood, numerous studies support the hypothesis of a causal relationship between hyperglycemia and oxidative stress (19–24). Oxidative stress has been implicated as the underlying cause of both the macrovascular and microvascular complications associated with type 2 diabetes (25–27).

Some propose that hyperglycemia, free fatty acids, and insulin resistance feed into oxidative stress, protein kinase C activation, and advanced glycated end product receptor activation, leading to vasoconstriction, inflammation, and thrombosis (28). Acute hyperglycemia and glycemic variability appear to play important roles in this mechanism. For example, some studies (29–31) have shown that variability in glucose levels may be

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more damaging than a constant high concentration of glucose.

Regardless of the mechanism(s) behind vascular damage, or whether you even believe there is a relationship between hyperglycemia and cardiovascular disease, perhaps the bigger question is, "Does it really matter?"

FROM EVIDENCE-BASED TO SOUND CLINICAL JUDGMENT

— Of course it is important to understand as much as we can about diabetes, its causes, and its complications. However, to debate whether hyperglycemia is a causal factor in the development of cardiovascular disease serves little purpose. Almost everyone agrees that hyperglycemia drives the development and progression of microvascular complications. Therefore, we should continue to treat hyperglycemia aggressively, even though some believe that we lack randomized control trials (the alleged "holy grail" of research) to prove a relationship between hyperglycemia and macrovascular disease.

It is important to note, however, that although the Diabetes Control and Complications Trial (DCCT) (6) failed to show a statistically significant causal relationship between hyperglycemia and cardiovascular disease because of the low rate of macrovascular events, the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) (32) study, which followed 1,341 of the original DCCT cohort for an additional 12 years, showed that intensive management of glycemia does have significant long-term effects on the risk of cardiovascular disease in type 1 diabetes. Whereas some may argue that the EDIC study was not randomized, and thus not substantive, it can also be argued that EDIC was simply an extension of DCCT, with long enough duration to actually detect the impact of glycemic control on macrovascular disease.

If the question at hand is whether we should stop treating the other risk factors, lipids and high blood pressure, and focus only on glucose control, then a serious debate would be warranted. To our knowledge, no such therapeutic approach has been proposed.

In summary, our position is that there is strong evidence supporting the causal relationship between hyperglycemia and cardiovascular disease. It is also our position that diabetes and all of its associated risk factors should be managed aggres-

sively, regardless of whether one believes in the current strength of the evidence relationship between hyperglycemia and cardiovascular disease.

Clearly, sound clinical judgment is needed to set safe and reasonable goals for diabetes management, especially in elderly patients and those with known cardiovascular disease or other high-risk factors; however, in our younger patients, aggressive treatment of *all* metabolic abnormalities with persistent titration of medication until all goals are met is needed.

Regarding the significance of this particular debate, we find it somewhat concerning that both the American Diabetes Association and the American Heart Association has actually spent time researching and reviewing this issue (33). We propose that more time and effort be spent on finding ways to improve our delivery of care rather than focus on academic issues that have no real clinical bearing on the way we manage diabetes.

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