

Inflammation and Cardiovascular Disease in Patients With Diabetes

Lessons From the Diabetes Control and Complications Trial

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Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with diabetes; in type 1 diabetes, CVD typically is related to diabetic nephropathy.¹ In both type 1 (DCCT, the Diabetes Control and Complications Trial) and type 2 diabetes (UKPDS, the United Kingdom Prospective Diabetes Study), intensive glucose control affects macrovascular disease less than microvascular disease.^{2,3} The pathophysiology of CVD in patients with diabetes is complex. Insulin-resistance syndrome risk factors rather than hyperglycemia per se seem to affect the risk of CVD in patients with both type 1⁴ and type 2 diabetes.⁵

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Elevated levels of C-reactive protein (CRP) have been related to CVD risk mainly in nondiabetic populations⁶; data in diabetic populations are scarce. Much less is known about the relationship of adhesion molecules to insulin resistance, diabetes, and CVD, respectively. This commentary, therefore, focuses on CRP as a marker of chronic, subclinical inflammation related to CVD.

CRP levels are elevated in nondiabetic individuals with increased insulin resistance and the metabolic syndrome,⁷ in patients with type 2 diabetes,⁸ and less consistently so in patients with type 1 diabetes.⁹ Components of the insulin-resistance syndrome, including obesity, rather than hyperglycemia contribute significantly to elevated CRP levels.^{7,8} A proinflammatory state prevails also in prediabetic individuals 5 years before the actual onset of (type 2) diabetes.¹⁰ In prediabetic individuals, increased insulin resistance rather than impaired insulin secretion defines the proatherogenic state, as exemplified by elevated blood pressure and dyslipidemia,¹¹ as well as inflammation.¹²

Given the strong correlation of inflammation with measures of body weight and insulin resistance (and changes thereof), and the fact that insulin therapy quite consistently has been associated with weight gain, it would be expected that insulin therapy may increase circulating levels of inflammatory markers, including CRP. Alternatively, intensive insulin therapy may improve CVD risk; in the DCCT, the estimated relative risk reduction for macrovascular events

was 42%.¹³ Although the risk reduction in the DCCT was statistically nonsignificant, the low number of events (52 patients experienced a total of 108 major macrovascular events, corresponding to 0.84 and 0.49 events per 100 patient years in the conventional and intensive treatment groups, respectively) and the ensuing limited power of the study to detect a significant difference need to be taken into account. Thus, one may speculate that an intensive insulin regimen would be beneficial with respect to (ie, lowering) circulating CRP levels.

In a report from the DCCT in this issue of *Circulation*, Schaumberg et al demonstrate findings that confirm these seemingly contradictory hypotheses.¹⁴ In this study, there was no overall treatment effect of intensive insulin treatment (versus conventional insulin therapy) on the change in CRP levels during the 3-year study period; however, intensive treatment maintained the levels of CRP over time (no change versus baseline). In contrast, in the conventional treatment group, CRP levels increased slightly during the course of the study (see their Table 2), possibly reflecting the natural, progressive course of the disease, in particular in those patients with type 1 diabetes characterized by features of the insulin-resistance syndrome.¹⁵ In the Insulin Resistance Atherosclerosis Study (IRAS), accordingly, plasminogen activator inhibitor-1 levels increased over time in prediabetic individuals with rising glucose levels and the development of diabetes.¹⁶ Based on the results of the study by Schaumberg et al (see their Figure 1), it can be concluded that patients in the intensive treatment group who gained the most weight (upper tertile of weight gain) may be at high risk of CVD (increase in CRP), whereas in patients who gained less weight (lowest tertile of weight gain), CVD risk may in fact be reduced (decrease in CRP). This finding suggests that dynamics in body weight influence the effect of intensive insulin treatment on inflammation and possibly CVD risk.

Subjects with type 1 diabetes who gain weight develop characteristics of the metabolic syndrome: hypertension, dyslipidemia (high triglycerides, low HDL cholesterol, small dense LDL), and high levels of CRP and plasminogen activator inhibitor-1.^{14,15} At least in subjects with type 2 diabetes, the metabolic syndrome markedly increases the risk of cardiovascular mortality, especially in women.¹⁷

Hyperglycemia as a risk factor for CVD (as represented by CRP levels) may be overwhelmed by the insulin-resistance syndrome (as represented by weight), in that the insulin-resistance syndrome may be relatively more important to CVD than hyperglycemia. This would imply that hyperglycemia is a more important risk factor for CVD in patients with type 1 diabetes, for whom the lack of insulin secretion is the core

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defect, relative to patients with type 2 diabetes, for whom insulin resistance is a core defect in addition to impaired insulin secretion. Accordingly, in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), for every 1% increase in HbA_{1c}, the hazard ratio for ischemic heart disease was 1.18 in young-onset diabetes versus 1.10 in older-onset diabetes.¹⁸

It is interesting to note that in the study by Schaumberg et al statistical adjustment for average HbA_{1c} during the trial did not affect the weight gain—treatment interaction on CRP levels. This suggests that intensive treatment may be beneficial to patients who gain less weight as a result of intensive treatment per se and independent of its overall glucose- (ie, HbA_{1c}-) lowering effect. One explanation for this interesting finding could be the fact that intensive treatment affects postprandial glycemia more than does conventional treatment. Inflammatory markers have been related to the postprandial state¹⁹; therefore, better postprandial control in an intensive, relative to a conventional, insulin regimen may explain a potential benefit of intensive treatment. In line with this, we have shown recently that nondiabetic individuals with isolated postchallenge hyperglycemia (impaired glucose tolerance with normal fasting glucose) are more insulin resistant and have an unfavorable cardiovascular risk profile, including increased CRP levels, as compared with those with isolated fasting hyperglycemia (normal glucose tolerance with impaired fasting glucose).²⁰ The role of glucose spikes in relationship to oxidative stress and endothelial dysfunction has been highlighted by some investigators.²¹ This hypothesis, however, awaits confirmation from a randomized controlled trial with clinical end points that specifically target postprandial hyperglycemia.

In the DCCT, a low number of CVD events along with a nonsignificant reduction in CVD risk were found.¹³ Accordingly, after the end of the DCCT, in the ongoing Epidemiology of Diabetes Interventions and Complications (EDIC) study, a high proportion of the long-term differences between the treatment groups in the intima-media thickness of the common carotid artery at year 6 of the observational extension study was explained by differences in HbA_{1c} during the original randomized study period.²² These data suggest that a beneficial effect of intensive insulin therapy on the progression of atherosclerosis and possibly CVD may indeed be achieved in the long-term.

The conclusions from these new analyses from the DCCT by Schaumberg et al could be straightforward; intensive insulin therapy aiming at decreasing HbA_{1c} levels to the nondiabetic range is likely to improve CVD, but attention needs to be paid to limiting weight gain. Admittedly, this goal is not an easy one to achieve from a clinical standpoint. During the DCCT, weight gain was substantial (≈ 2 kg/year in the intensive treatment group in the present cohort), encompassing a magnitude that is likely to confer adverse CVD risk. Therefore, from an individual patient point of view, as well as from a public healthcare perspective, any intensive treatment regimen aiming at strict glycometabolic control needs to be balanced and measured against any potential adverse effect on weight. It is likely that patients with diabetes, both type 1 and type 2, will benefit most from intensive treatment, if at the same time they can avoid weight gain or even lose weight as a result of the treatment.

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