Shifting the Disease Management Paradigm From Glucose

What are the pros?

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With the worldwide growing prevalence of obesity and type 2 diabetes, cardiovascular disease (CVD), diabetic nephropathy, retinopathy, and neuropathy as principal complications of diabetes are expected to become a major public health challenge. Diabetes accounts for at least double the number of death rates compared with otherwise healthy individuals. Hyperglycemia represents the hallmark of diabetic metabolic changes, but whether antihyperglycemic treatment alone is sufficient to prevent cardiovascular and other organic complications in type 2 diabetes is a matter of debate.

A recent meta-analysis of epidemiological studies reported an 18% increase in CVD risk for every 1% increase in A1C (1). Two major studies have underlined the importance of optimal glycemic control in reducing diabetes-related complications. The U.K. Prospective Diabetes Study (UKPDS) showed that intensive glycemic control (mean A1C below 7%) by means of insulin or oral agents in type 2 diabetic patients reduces the relative risk for microvascular outcomes by 25% over a period of 10 years (relative risk reduction). The reduction in macrovascular end points (myocardial infarction) was of borderline significance (16% relative risk reduction, $P = 0.052$) (2). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) trial reported a 50% reduction in CVD outcomes in type 1 diabetic patients treated intensively over a period of 6.5 years and followed for a further 12 years (3). In contrast to these data, the intensive glucose-lowering arm of the Action to Control Cardiovascular Risk (ACCORD) trial—a major trial in type 2 diabetic patients—has been recently stopped because of increased mortality in this group (4). The ACCORD trial was set up to test three complementary medical treatment strategies for type 2 diabetes to reduce CVD morbidity and mortality. Aggressive reduction of A1C below 6%, combined increase in HDL cholesterol, and reduction of LDL cholesterol and lowering of blood pressure (BP) were the main therapeutic targets. Because of safety concerns after concise review of the available data and recommendation by the safety monitoring board, the intensive blood glucose (BG)-lowering treatment arm was halted in February 2008. There was a higher death rate in the intensively treated group, although a lower rate of primary outcome events such as nonfatal myocardial infarction was detected. The BP- and lipid-lowering trials will be continued until June 2009.

The unexpected high mortality in the group undergoing a treatment targeting an A1C below 6% was attributed to hypoglycemic episodes in older and plurimorbid patients, or to the adverse effects of a particular drug or drug combination. These data are not isolated, since the 2-year feasibility phase of the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes Mellitus (VA-CSDM) found a nonsignificant increase in the risk for cardiovascular events in the intensively treated group (5).

Moreover, some combinations of drugs (such as metformin and sulfonylureas) have previously been considered to be responsible for increased mortality, suggesting that hyperglycemia should not be lowered at any price (6). Overall, at least three conclusions can be drawn from these data: *1*) lowering of BG in elderly and plurimorbid patients should be performed with caution, *2*) combination therapies should be rigorously considered, and *3*) there may be a certain threshold beyond which lowering of BG may be detrimental.

One further aspect that is under debate in diabetes treatment is which of the two aspects of hyperglycemia should be mainly addressed: the preprandial or the postprandial hyperglycemia? Several studies have found that postprandial BG correlates better with CV risk than does fasting BG (7). The possible mechanisms have been reviewed elsewhere (8). Consistent with these findings, treatment of postprandial hyperglycemia with acarbose in people with type 2 diabetes resulted, according to a meta-analysis of seven randomized studies, in a reduction of CVD development by 35% (9). Evidence from large interventional studies is still lacking and the results of ongoing trials are expected.

From all the aforementioned data, it is obvious that controversy still exists as to whether postprandial or fasting BG should be targeted, and it is not exactly known at which point the benefit of lowering BG stops and the harm begins.

However, there is also another factor beyond hyperglycemia that jeopardizes the cardiovascular system of diabetic patients during the postprandial phase. Recently, it has been shown that dietary toxins significantly impair endothelial function in the postabsorptive state in people with type 2 diabetes, an effect that went beyond hyperglycemia and hypertriglyceridemia (10). Food toxins generated by heating consist of advanced glycation end products (AGEs) and lipoxidation end products, as well as other

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substances with an increased oxidative potential. The above-mentioned effects were mostly reversible by changing the method of meal preparation. Repeated, even transient, impairment of endothelial function is believed to result in permanent changes, an important contributor to the development of atherosclerosis (11).

The role of AGEs in the development of endothelial dysfunction (ED), atherosclerosis, and complications of diabetes and aging has been emphasized (12). Therefore, exogenous AGEs are believed (but not yet conclusively demonstrated) to play a role in the development of diabetes complications in addition to the endogenously generated AGEs. The formation of the latter is also stimulated by conditions that occur in the postprandial state such as hyperglycemia, oxidative stress (13,14), or increase in AGE precursors such as methylglyoxal (10). Methylglyoxal is a highly reactive α-oxoaldehyde metabolite of glucose degradation pathways and a precursor of AGEs and is elevated in plasma of patients with type 2 diabetes (15). In vitro experiments revealed that AGEs as well as methylglyoxal increase tissue factor expression on the surface of monocytes. Methylglyoxal enhances platelet-neutrophil aggregation and the expression of MAC-1 on neutrophils and Apo2.7 on neutrophil mitochondria. These findings may contribute to the understanding of diabetic thrombosis and the associated high cardiovascular risk in diabetic patients (16). There is evidence that because of its reactivity, methylglyoxal might play a role in the etiology of type 2 diabetes–related heart failure. In rats, methylglyoxal levels are highest in the aorta and myocardium compared with other tissues (17); in addition, methylglyoxal reacts nonenzymatically with arginine residues of proteins to form the AGEs argpyrimidine and N-δ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (methylglyoxal-H1). In different cells, heat shock protein 27 (HSP27) was detected as a major argpyrimidine containing protein. Comparing human myocardial samples from patients with cardiomyopathy and those with cardiomyopathy plus type 2 diabetes, in relation to nonfailing donor hearts, we observed an increased argpyrimidine modification of HSP27 in left ventricular myocardial samples of explanted hearts from diabetic patients compared with individuals without type 2 diabetes. It was postulated that these modifications are consequences of the altered cardiac metabolism found in type 2 diabetes and are relevant for the stability of the myocardial cytoskeleton. The impact of type 2 diabetes on cardiomyopathy, termed "diabetic cardiomyopathy," is under debate (18).

We therefore believe that endogenously generated AGEs and precursors act synergistically with the exogenous AGEs to induce oxidative stress and lead to the long-term cardiovascular and diabetes complications. The reduction in endogenously generated AGEs goes beyond the treatment of hyperglycemia, since several treatments that reduce oxidative and carbonyl stress (e.g., angiotensin II receptor inhibitors, antioxidants, aminoguanidine) have proven their efficacy in decreasing AGE levels (19). Mitigating the exogenous AGE burden is also mostly independent from hyperglycemia (10,14).

Currently, it is widely believed that CVD and mortality could be reduced in diabetic patients, not only by reducing hyperglycemia, but also by reducing risk factors, such as dyslipoproteinemia and increased BP.

Dyslipoproteinemia in type 2 diabetes is characterized by at least three major features: moderately increased LDL cholesterol (women), increased triglycerides, and decreased HDL cholesterol (20). The importance of treating dyslipidemia in diabetes has been emphasized by the Adult Treatment Panel III Guideline of the National Cholesterol Education Program (21), wherein LDL targets have been set to below 100 mg/dl and even <70 mg/dl in patients with diabetes and CVD (22). The results of cholesterol-lowering trials in individuals with diabetes have been reviewed in detail elsewhere (20,23). The Cholesterol Treatment Trialists' Collaborators reported that in their study populations of patients with type 2 diabetes, they found a 9% proportional reduction in all-cause mortality and a 21% proportional reduction in major vascular events for each reduction of 1 mmol/l in LDL cholesterol (24).

Overall, there is strong evidence for the importance of LDL lowering to reduce CVD in diabetic patients. Although promising, the reduction in triglycerides and increase in HDL cholesterol with fibrates in these patients remain to be demonstrated (20).

Increased risk for CVD in parallel with increased systolic and diastolic BP has been suggested (25). In a subgroup of people with type 2 diabetes within the Systolic Hypertension in the Elderly Program (SHEP), a post hoc analysis revealed that BP reduction resulted in a reduction of major CVD events by 34% (26). There also seems to be an additional benefit if lower diastolic BP values are targeted, since a post hoc analysis of subjects with diabetes from the Hypertension Optimal Treatment (HOT) study showed that major CVD events could be reduced by 51% in those randomized to achieve a diastolic BP of ≤80 mmHg, compared with individuals with a BP goal of ≤90 mmHg (27). A recent meta-analysis emphasized the importance of reducing BP in CVD prevention in subjects with diabetes (28). The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) (29) recommended initiation of antihypertensive treatment at BP values of systolic ≥130 mmHg or diastolic ≥85 mmHg. The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, comprising 11,145 patients, addressed the tight regulation of BP as an important risk factor of macrovascular and microvascular complications in type 2 diabetes.

The use of an ACE inhibitor in combination with diuretic treatment for reducing severe vascular events in patients with diabetes, irrespective of initial BP levels, or the use of other BP-lowering drugs, was investigated. Compared with patients assigned to placebo after a mean of 4.3 years of follow-up, active therapy reduced systolic and diastolic BP by 5.6 and 2.2 mmHg, respectively. The relative risk of a major macrovascular or microvascular event was significantly reduced by 9% ($P = 0.04$). Reduction in macrovascular and microvascular events was comparable, but failed to reach statistical significance. The relative risk of death from CVD was reduced (relative risk reduction 18%; $P = 0.03$) and the risk of death from any cause was reduced (relative risk reduction 14%; $P = 0.03$) (30).

As recently shown in the STENO-2 study, an intensified multifactorial intervention using multiple drug combinations aiming at tight glucose control, renin angiotensin system blockade, anticoagulation, and lipid lowering, in addition to behavior modification, led to a sustained beneficial effect in reducing cardiovascular and microvascular events, as well as mortality rates from cardiovascular and other causes (31). A total of 160 patients with type 2 diabetes and persistent microalbuminuria were assigned to receive either intensive or conventional

therapy for a mean duration of 7.8 years, with time to death from any cause defined as a primary end point. The intensive therapy was associated with a lower risk of death from cardiovascular causes (hazard ratio 0.43, $P = 0.04$) and of cardiovascular events (hazard ratio 0.41, $P < 0.001$). Microvascular events, such as end-stage renal disease or retinal intervention, occurred at significantly lower rates in the intensively treated patients.

In summary, there is evidence that the achievement of glycemic goals is difficult and accompanied by serious side effects that partly mask the benefits. The ACCORD trial found that attempts to lower BG below an A1C of 6% were at the expenses of higher mortality. It also became obvious that treatment of hyperglycemia alone is not sufficient to reduce CV risk in diabetic patients and that treatment of dyslipidemia and arterial hypertension adds comparable protective effects. The STENO-2 study elegantly demonstrated this paradigm by showing that a multifactorial intervention reduced, in the long term, the risk of cardiovascular and microvascular events in this population.

Moreover, the postprandial phase is an important therapeutic target, and beyond hyperglycemia and hypertriglyceridemia, oxidative stress and dietary toxins have to be considered.

Therefore, physicians should focus their efforts on lowering risk factors (lipids, BP, and increased platelets adhesion) and endeavor, especially in patients at risk, to achieve an A1C between 7 and 7.5% with drugs that do not cause additional weight gain, have reduced side effects, and show a good cardiovascular safety profile.

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