

# Shifting the Disease Management Paradigm From Glucose

## What are the cons?

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**V**ascular comorbidities and complications are the major causes of excessive mortality and costs in patients with diabetes (1,2). For more than half a century, overwhelming evidence has been accumulating that demonstrates significant harmful effects of hyperglycemia. As shown in the Multiple Risk Factor Intervention Trial (MRFIT) study, at any given level of major cardiovascular risk factors, diabetes is associated with an odds ratio of 2–4 for cardiovascular mortality, in comparison with subjects without diabetes (3).

In a recently published 18-year follow-up study on the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects from Finland, the adjusted hazard ratio for patients with type 1 diabetes versus no diabetes was 3.6 in men and 13.3 in women (4). The corresponding hazard ratios for type 2 diabetes were 3.3 and 10.1, respectively. This study confirms harmful effects of hyperglycemia shown in high-level controlled trials, such as the Diabetes Control and Complications Trial (DCCT) for type 1 diabetes (5) and the U.K. Prospective Diabetes Study (UKPDS) for type 2 diabetes (6). For 25 years, the Joslin Clinic conducted the Diabetes Natural History Study that followed up diabetic patients diagnosed between 1939 and 1959. The lifetime was 5 years less for men and 12 years less for women than for those in the general population (7). A unique 29-year complete follow-up study was conducted on 166 patients (mean age 63 years) with newly diagnosed type 2 diabetes. These

subjects were from a district outpatient department in East Germany. The study revealed a reduction in life expectancy by 5.3 and 6.4 years in men and women, respectively (8).

Thus, today, immense evidence exists on long-term follow-up, population-based studies in patients with types 1 and 2 diabetes. This evidence convincingly suggests that hyperglycemia or diabetes itself is a key risk factor not only for diabetes-related diseases, but also for cardiovascular and all-cause mortality. Based on their long-term population observational study, Juutilainen et al. (4) calculated an increment of cardiovascular mortality per increase of 1 unit (%) A1C of 52.5% in type 1 diabetes and of 7.5% in type 2 diabetes, respectively.

Recently, an interim analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study indicated that aggressive reduction of A1C to 6.4% in elderly patients with long-term type 2 diabetes and a baseline level of A1C of 8.1% was associated with a 22% higher mortality rate compared with the standard care group with a level of ~7.5% A1C (9). Therefore, the intensified polypharmacy treatment of hyperglycemia was stopped prematurely and a treatment target of A1C between 7.0 and 7.9% was recommended. This surprising outcome of intensified treatment of hyperglycemia could not be confirmed in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study, another large prospective trial for im-

proved diabetes control in patients with type 2 diabetes, which showed a 10% relative reduction in the combined outcome of micro- and macrovascular events in the group with more intensive A1C control (A1C 6.5%) compared with the standard control group (A1C 7.3%) (10). At the same time, the 13.3-year follow-up data of the Danish multifactorial intervention study in type 2 diabetes (STENO-2) were published on 160 patients randomly assigned to receive either intensive or conventional multimodal therapy with tight glucose control, use of renin-angiotensin system blockers, aspirin, and lipid-lowering agents (11). At the end of the intervention after 7.8 years, A1C was 7.9% for intensive therapy and 9% for conventional therapy. At the end of follow-up, A1C was 7.7 and 8.0%, respectively (difference not significant). Only a minority of patients reached the target A1C of 6.5% (after 7.8 years, 16 vs. 4%, and after 13.3 years, 18 vs. 11% for intensified versus standard treatment, respectively). By contrast, the majority of intensified treated patients reached targets of blood pressure and cholesterol levels. During the follow-up, 40 patients died in the standard treatment group versus 24 (30%) in the intervention arm ( $P = 0.02$ ). Diabetes-related microvascular diseases were also impressively reduced. By extrapolation of ACCORD interim results, and the convincing outcomes of better treatment of blood pressure and lipids with multiple drug combinations including aspirin, as was the case in the STENO-2 study, one could argue that it may be beneficial to shift diabetes management to control of major cardiovascular risk factors, e.g., hypertension, dyslipidemia, and increased procoagulatory activity. However, despite intensified treatment of blood pressure and dyslipidemia in STENO-2 in patients at the age of 54.9 years at entry, 30% died after 13.3 years when they averaged 66 years of age (11). This mortality rate of ~2% per year is comparable with the mortality rate of diabetic patients in the observational study of Juutilainen et al. (4) and is about fourfold higher than the rate of nondia-

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betic participants. Why then did the intensified-treated patients of the STENO-2 study die so early?

We agree with the conclusion of the authors that “early and meticulous implementation of current treatment guidelines remains a major challenge,” particularly with respect to hyperglycemia.

**IMPORTANCE OF THE GLUCOTRIAD AS A RISK FACTOR FOR DIABETES AND VASCULAR DISEASE**

As shown in numerous prospective studies, the deleterious effects of dysglycemia—fasting and postprandial hyperglycemia—develop before diabetes is diagnosed. In the Glucose Abnormalities in Patients with Myocardial Infarction (GAMI) study of patients with acute coronary syndrome, abnormal glucose tolerance was the strongest independent predictor of subsequent cardiovascular complications and death (12). In the Asian Pacific Study, fasting plasma glucose was shown to be an independent predictor of cardiovascular events up to a level of ~5.2 mmol/l (13). The authors calculated that a difference of 1 mmol/l in fasting plasma glucose may be related to reduction of cardiovascular disease by 23%. The importance of postprandial hyperglycemia is supported by rich evidence from prospective studies (14).

It was extrapolated from the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study that a reduction of 2-h postchallenge hyperglycemia by 2 mmol/l may be associated with a decrease in all-cause mortality by 28.8% (15). Based on the results of epidemiological reports, a near to normal control of fasting, as well as postprandial hyperglycemia, should be achieved, since risk of vascular disease starts before diabetes is diagnosed (13,16–18). A fresh look at old facts—importance of peaks and valleys, or in scientific terms, of quality of glucohomeostasis—was possible when reliable and precise continuous glucose measurement systems became available for clinical use. As shown by Monnier et al. (19), glucose fluctuations measured as mean average glycemic excursions were closely associated with oxidative stress generation, whereas average glycemic level was not. Today we have consistent data from pathophysiological investigations that glucose fluctuations may be a vascular risk factor in its own right (Fig. 1). Glucose fluctuations and hyperglycemia are triggers for inflammatory responses via increased mitochondrial

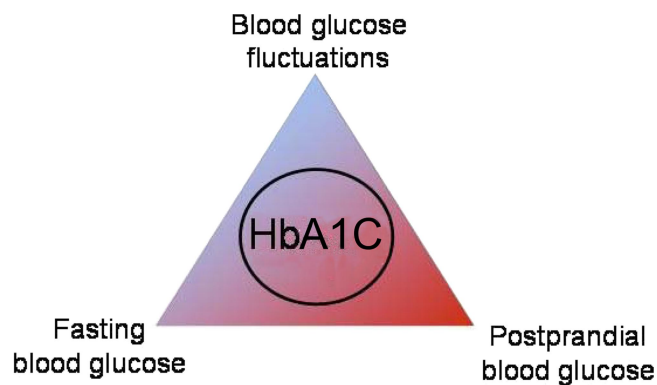


Figure 1—Glucotriad.

superoxide production (20) and endoplasmic reticulum stress (21). Inflammation leads to insulin resistance (22) and  $\beta$ -cell dysfunction, which further aggravates hyperglycemia. The molecular pathways that integrate hyperglycemia, oxidative stress, and diabetic vascular complications have been most clearly described in the pathogenesis of endothelial dysfunction (23). According to the response to injury hypothesis, endothelial dysfunction represents the first step of atherogenesis (24).

The results of these molecular investigations were confirmed by studies in patients. Acute hyperglycemia rapidly attenuated endothelium-dependent vasodilation (25,26) and reduced myocardial perfusion (27). Thus, direct effects of glucotoxicity, oxidative stress and low grade inflammation act in a vicious circle that impairs insulin sensitivity, accelerates and escalates loss of  $\beta$ -cells, impairs endothelial function and leads to microvas-

cular and macrovascular disease (Fig. 2). The best way to prevent chronic progression of type 2 diabetes is to keep the glucotriad in a normal range as shown in primary prevention trials with lifestyle (28,29) or drug intervention (28,30,31), respectively.

**Why is early and meticulous treatment of hyperglycemia so important?**

As previously discussed, endothelial dysfunction and the risk of vascular disease develops along a continuum starting at a level of fasting hyperglycemia below 5.6 mmol/l and of postmeal glucose below 7.8 mmol/l. For fluctuations, we have no data from prospective studies related to MAGE or standard deviation. There are, however, hints that indicate that valleys with glucose levels below 2.2 mmol/l are associated with an increased risk of cardiovascular mortality (32). Possible harmful effects of strict control of hyper-

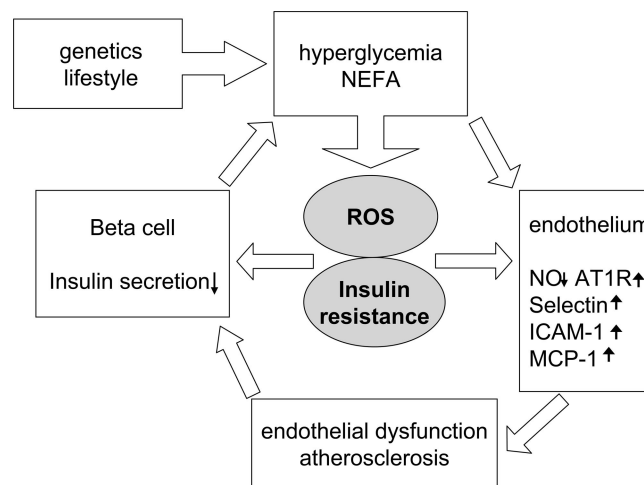


Figure 2—Harmful effects of hyperglycemia on  $\beta$ -cell and endothelial function. AT1R, angiotensin II type 1 receptor; ICAM-1, intercellular adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; NEFA, nonesterified fatty acids; ROS, reactive oxygen species.

glycemia obviously depend on the stage of diabetes and time of intervention. Thus, there may be a distinct improvement if hyperglycemia is controlled in the stage of pre-diabetes, or early diabetes when A1C is still below 8 or 7%, as shown in A Diabetes Outcome Progression Trial (ADOPT) and the UKPDS (31). In the ADOPT study, control of hyperglycemia was associated with improved  $\beta$ -cell function without an excessive risk of hypoglycemia (31). In the UKPDS, intensified glucose control was achieved with a significantly lower incidence of diabetes-related complications, as was the case in the Kumamoto (33) and DCCT studies (5). Even more important, intensive glucose control in those with newly diagnosed type 2 diabetes in the Diabetes Intervention Study (DIS) (34) and a post-trial legacy analysis of the UKPDS (35) was associated with significantly lower all-cause mortality. Conversely, aggressive treatment of long-term diabetes is associated with weight gain and high risk of hypoglycemia and may be associated with excessive mortality as indicated by the ACCORD study (9).

**CONCLUSIONS**—Recent evidence from pathophysiology, extensive clinical experience, and a number of well-controlled prospective studies clearly prove that hyperglycemia is a key risk factor for diabetes-related complications and a driving force for deterioration of  $\beta$ -cell function and cardiovascular disease resulting in a significant reduction of life expectancy. Therefore, early intervention to keep the glucotriad and A1C in a near-normal range should remain a high priority to protect our patients, together with integrated treatment of comorbidities, such as hypertension, dyslipidemia, and hypercoagulation. Shifting to a better form of individualized disease management does not imply that diabetologists should not maintain confidence in their well-established treatment strategies based on sound evidence and good clinical practice.

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