Editorial

Glycemic control for prevention of vascular complications in diabetic patients

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Patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) show an increased risk of vascular complications such as cardiovascular disease and an increased mortality rate resulting in a decrease in life expectancy of between 5-15 years, depending on age at diagnosis.There are several methods to establish the diagnosis of type 2 diabetes (T2D). The American Diabetes Association (ADA) recommends the following: i. fasting plasma glucose (FPG ≥126 mg/dL after no caloric intake for at least 8 hours), ii. two hour postprandial glucose (PPG ≥200 mg/dL after a 75 g oral glucose load), iii. glycated hemoglobin (HbA1c) ≥6.5%, and iv. random plasma glucose ≥200 mg/dL in patients with classic symptoms of hyperglycemia. FPG and PPG reflect the random glucose concentration, whereas HbA1c reflects the mean blood glucose concentration of the previous 2 to 3 months. FPG and PPG contribute to HbA1c, but the interrelationship of the three types of measurements varies between patients and is complex, while the risk of diabetic complications is still unclear.(1)

There is strong epidemiological and pathophysiological evidence that hyperglycemia has a deleterious effect on cardiovascular profile. Patients with T2D who have high glucose and HbA1c levels are at high risk for cardiovascular complications. Glycemic fluctuation in the blood is reportedly associated with an increased risk of T2D complications. Glycemic fluctuation and chronic hyperglycemia may trigger an inflammatory response through increased endoplasmic reticulum stress and mitochondrial superoxide production. It has been known that the molecular pathways underlying hyperglycemia, low-grade inflammation and oxidative stress play a role in the pathogenesis of endothelial dysfunction, which constitutes the initial step of atherogenesis. Through this pathway, the initial atherogenesis induced by hyperglycemia may result in an increased probability for cardiovascular events in later life. The direct effects of glucose toxicity, oxidative stress and low-grade inflammation may be seenin decreased insulin sensitivity, reduction in the number of beta cells, and endothelial dysfunction, finally resulting in micro- and macrovascular complications.(2)

There are several methods for measuring and recording glycemic fluctuation. Self monitoring of blood glucose (SMBG) measures the daily glucose concentration atup to 8 time points. Another method, the continuous monitoring of glucose (CMG) system measures glycemic fluctuation in greater detail by means of more frequent measurement of glucose concentration. Measurement by SMBG frequently has the limitation of nocturnal hypoglycemia so that the experts are increasingly recommending the use of CMG for recording the daily glucose profile in clinical practice, with a target glucose concentration range of 70-180 mg/dL, although this is not an ideal range of glucose concentration. This target is commonly used in daily practice and has been considered safe and realistic.(3)

The target glucose concentrationrange is related to the risk of complications that may be experienced by the diabetic patient. A glucose concentration of above 180 to more than 400 mg/dL is categorized as high and hazardous, since it increases the risk of diabetic ketoacidosis, such as metabolic acidosis and ketonemia. On the other hand, low glucose concentrations below 70 mg/dL are also associated with various risks, such as convulsions, coma, and death.[4] The various risks associated with glycemic fluctuation consist of: 1. hypoglycemia, 2. macrovascular complications, and 3. oxidative stress as the mechanism of vascular damage. Glycemic fluctuation includeshyperglycemic episodes and even hypoglycemia. A study on 29 patients with well-controlled T2D, who had HbA1c levels of ≤7%, and were treated with metformin and sulfonylurea, with CGM monitoring for 5 days, showed that 18 patients (62%) had a history of asymptomatic hypoglycemic episodes.[5] The evidence shows a relationship between severe hypoglycemia and increased morbidity and mortality rates, such as increased occurrence of microvascular and macrovascular complications, deaths from cardiovascular events and other causes of death.[5]

Glycemic fluctuation has been reported to cause cardiovascular complications in T2D. The study designated as Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), whichwas conducted on more than 20,000 T2D patients, found that impaired glucose toleranceas determined by 2-hour post-prandial glucose (the main contributor to glycemic fluctuation), increased the risk of cardiovascular and all-cause mortality.[6] Diabetes is associated with a markedly increased risk of atherosclerotic vascular disorders, including coronary, cerebrovascular, and peripheral artery disease, which may account for the disabilities and high mortality rates in diabetics.[7] In addition, the Diabetes Intervention Study found a relationship between poor control of postprandial glucose and increased risk of myocardial infarction and death in 994 patients with T2D.[3] A study in Finland that had been conducted for 18 years showeda similar impact of T1D and T2D oncardiovascular mortality rate, with 5.2- and 4.9-fold increased risks for type 1 and type 2 diabetes, respectively.Glycemic fluctuation leads to excessive production of reactive oxygen species which has an impact on endothelial dysfunction.[4,8,9]

Rapid changesin both peak and diurnal glucose concentration is called glycemic fluctuation. Currently glycemic fluctuation is a potential therapeutic target in T2D. In normal individuals, food intake causes a momentary increase in glucose concentration to a higher than basal level. But this does not apply to T2D, where the basal glucose concentration is already relatively high, as a result of fasting hyperglycemia, so that control of post prandial blood glucose is required to see an increase in post-prandial glucose concentration. In such patients the glucose concentration can vary widely throughout the day, although the target HbA1c is well controlled. A study on T2D patients with well-controlled HbA1c (HbA1c <6.5%) who were using oral glucose lowering drugs, 24-hour monitoring of glucose concentration showed a unique pattern for each patient, with increased fluctuations in glucose concentration exceeding the target glucose range of 70-180 mg/dL.[3]

There was no unanimous support among the avaiable studies for the suggestion that a reduction in glucose concentration may decrease morbidity and mortality rates from vascular complications. Among the clinical trials investigating the relationship between glycemic control in T1D and T2D on the one hand and decreased risk of cardiovascular disease on the other hand, there were no convincing results in all of them. In the studies called Action in Diabetes and Vascular Disease: Preterax and Diamicron MR controlled evaluation (ADVANCE), the Veterans Affairs Diabetes Trial (VADT), and the Action to Control Cardiovascular Risk in Diabetes (ACCORD), there were no significant reductions in the risk of cardiovascular events in the treatment groups,

these results being caused by increased mortality rates.[10] The negative results of these studies were caused by the fact that the ACCORD study, which was specifically designedfor cardiovascular outcomes, was also discontinued before the sample size had been reached, because of an unexpected increase in mortality rate in the intervention group. There were also several studies with such a low power that they failed to give clear results. Such studies should be pooled in a meta-analytic studyso as to extract relevant information.[10,11]

The assumption that treatment of hyperglycemia can prevent all diabetic complications, including the macro- and microvascular is still subject to debate. The results of several clinical trials show that glucose lowering therapies can be hazardous in certain conditions. Some large scale clinical trials show that improvement in glycemic control is associated with decreased cardiovascular events, whereas hypoglycemia can increase death as a result of cardiovascular complications. Accurate glycemic control for avoiding hyperglycemic and hypoglycemic eventsis recommended to prevent diabetic cardiovascular complications, whilethere is an individual target approach for HbA1c level. The care of patients with diabetes requires comprehensive management to prevent cardiovascular complications, including other cardiovascular risk factors besides glycemia. [2]

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