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Blood glucose control: Where are we?

Hyperglycemia is a hallmark of diabetes mellitus; however, the significance of blood glucose control in patients with diabetes has only been investigated relatively recently in the long history of diabetes. Through the well-known Diabetes Control and Complications Trial, Kumamoto, and United Kingdom Prospective Diabetes Study studies, intensive blood glucose control indeed significantly prevented or delayed the development and/or progression of microangiopathies in both type 1 and type 2 diabetes; however, the effects on macroangiopathy were not certain in both populations. Several studies, such as Action to Control Cardiovascular Risk in Diabetes, Veterans Affairs Diabetes Trial, and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, showed that intensive blood glucose control did not lead to improvements in macroangiopathy in people with type 2 diabetes mellitus, and the Action to Control Cardiovascular Risk in Diabetes study showed a significantly increased risk of mortality in participants assigned to intensive blood glucose control. Follow-up studies of the Diabetes Control and Complications Trial (Epidemiology of Diabetes Interventions and Complications) and United Kingdom Prospective Diabetes Study consistently showed that the early intensive blood glucose control in newly detected type 1 or type 2 diabetes could lead to significant decreases in cardiovascular risks, as well as the risks of microangiopathies[1,2], however.

Thereafter, most guidelines set glycemic targets at <7.0%, but not close to normal, such as <6.5%, except in cases of young, relatively healthy and well educated participants, and recommend adopting early intensive control and individualization strategies, which should take into consideration diverse factors, such as comorbidities, age, complications and life expectancy. In fact, there is great concern surrounding the effects of these constellations of intervention studies on actual glycemic control, and a recent study from the USA reported that compared with the 2007–2010 period, the glycemic control and blood pressure control significantly declined in patients with diabetes in the 2015–2018 period[3]. We require more evidence on these two aspects of treatment strategies for the benefit of people with diabetes.

Diabetes, especially type 2 diabetes, is a heterogeneous disorder, and diverse pathophysiologies have been identified. On that account, it is noteworthy that several investigators have been trying to find both unidentified chances and barriers to successful blood glucose control. A study from Japan found that long working hours (≥60 h/week), and habitual skipping of breakfast and late evening meals, which is quite prevalent among the young generation worldwide, was associated with suboptimal blood glucose control in young male workers (aged 20–40 years)[4].

Another study examined the association between income levels and irregular physician visits, and reported that compared with those with <$2,000/month income, those with higher monthly income were less likely to have irregular physician visits, and those with irregular visits tended to have poor glycemic control[5]. One study reported that poor understanding of medications was associated with poor glycemic control (glycated hemoglobin [HbA1c] >8%). Another study investigated the association between depressive symptoms and glycemic control, and reported that higher depressive symptom scores could predict worse blood glucose control, especially in those with low family and friend support[6].

In contrast, even mild exercise (2–2.5 metabolic equivalents [every other week] or low-intensity resistance training with slow movement and tonic force generation [two times/week for 16 weeks]) could improve blood glucose control in aged type 2 diabetes patients[7]. A study reported that adaptive emotion-focused coping supports glycemic control in patients who do not use insulin[8]. These studies might look simple; however, they could have huge potential clinical implications in real practice, especially among the elderly population.

As the pathophysiology of diabetes seems different between Asian people and white people, we should investigate the clinical and genetic characteristics of Asian patients with diabetes. A study from Korea investigated the relationship between activity of natural killer cells, which are cytotoxic lymphocytes, and blood glucose control, and reported a significant association between HbA1c and decreased natural killer cell activity in patients with type 2 diabetes[9]. Another study from Japan compared antepartum clinical characteristics and postpartum glucose tolerance, and 45 genetic variants were also compared, and reported that antepartum postprandial glucose level, insulinogenic index, insulin secretion-sensitivity index 2 of the antepartum oral glucose tolerance test were independent predictors of postpartum abnormal glucose tolerance. Among 45 genetic variants tested, they found four genetic variants – rs266729 (*ADIPOQ*), rs601737 (*HNF4A*), rs5215 (*KCNJ11*) and rs7177055 (*HMG20A*) – three of which are related to insulin secretion, showed nominally significant associations with postpartum abnormal glucose tolerance[10]. Another study evaluated pancreatic α-cell function in patients with type 1 diabetes using arginine stimulation, artificial pancreas and euglycemic hyperinsulinemic

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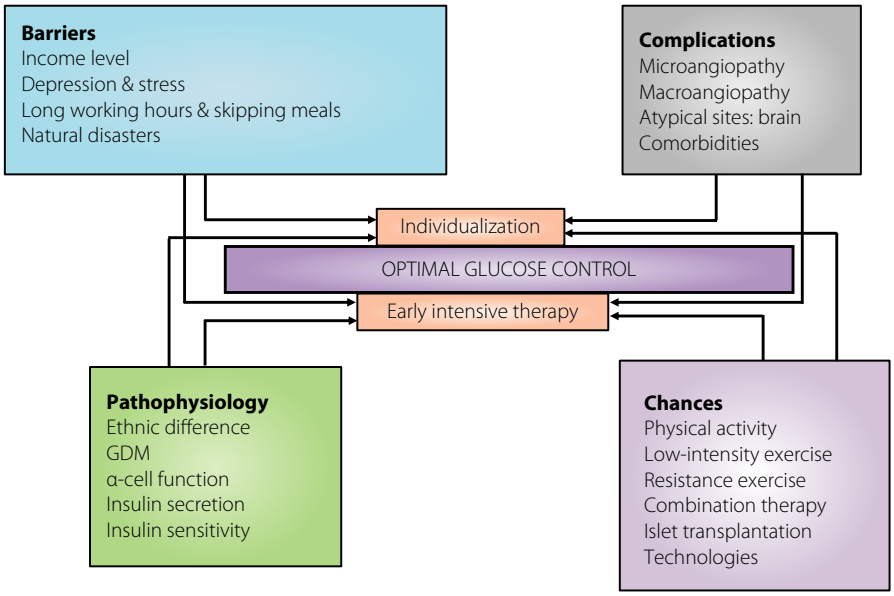

Figure 1 | The strategies of early intensive therapy and individualization are recommended for optimal blood glucose control in patients with diabetes mellitus from several long-term intervention studies. However, the target achievement rate is still very low worldwide, and there are many barriers to successful control and still unidentified pathophysiological mechanisms in patients with diabetes. Pathophysiological characteristics, such as ethnic difference and comorbidities, as well as several factors of either barrier or chance should be considered to attain the strategies of individualization and early intensive therapy. Approaches to overcome many barriers and to utilize the chances through studies on pathophysiology and management, and regional and global collaborations are urgently warranted. GDM, gestational diabetes mellitus.

glucose clamp, and continuous glucose monitoring (CGM) technologies, and reported that the area under the curve of glucagon measured by the sandwich enzyme-linked immunosorbent assay was associated only with insulin sensitivity; however, it was not associated with dawn index or glucose variability in these patients[11].

There have been serious natural disasters, such as earthquakes and tsunamis, worldwide, and, unfortunately, the Western Pacific and South-East Asia are two of the most severely affected areas. The effects of natural disasters on blood glucose control in people with diabetes are sometimes life-threatening, and a study from Japan investigated the time course and stress factors by comparing those parameters before and after the Kumamoto earthquake in both type 1 and type 2 diabetes patients. It was reported that in patients with type 1 diabetes, blood glucose control was maintained during the earthquake, most probably due to self-management of insulin doses. In areas of an absolute shortage of insulin, the earthquake could be devastating for people with type 1 diabetes. In patients with type 2 diabetes, however, blood glucose control seemed initially improved, followed by aggravation as a result of a shortage of medications and foods. These are very valuable findings to take into account in actual planning for disasters[12].

Studies adopting technologies, such as CGM and insulin pumps, have been very active in Asian countries. Several groups in Japan analyzed CGM data and glycemic parameters, such as glycated albumin, HbA1c, and 1,5-anhydroglucitol, and reported the values of each parameter corresponding to a time in range of 70%, and quite importantly, the possibility of discrepancy between CGM values and glycated albumin level in a certain subgroup of patients, such as those on hemodialysis. Although the CGM data are almost standardized, we require more studies to fill the gap between the technologies and actual blood glucose profile.

Blood glucose control can affect organs that are not well-known for diabetes complications, such as the brain. A study investigated the relationship between glycemic parameters, such as glycated albumin (GA), HbA1c and the GA/HbA1c ratio and brain atrophy, by analyzing >1,200 brain magnetic resonance imaging images from a large cohort. They found that elevated serum GA and GA/HbA1c ratio, not HbA1c, were significantly associated with global brain and hippocampal atrophy[13].

As to the pharmacological therapy, a study from Japan evaluated the effects of dulaglutide-combined basal plus insulin regimen on glycemic variabilities in hospitalized patients with diabetes, and reported that the dulaglutide-combined regimen significantly reduced the frequencies of hyperglycemia and hypoglycemia, and resulted in lower glycemic variability compared with the basal plus insulin regimen[14]. A Kyoto group compared the long-term effects of islet transplantation and multiple

daily injection/continuous subcutaneous insulin infusion, and reported that the islet transplantation group showed a significantly reduced risk of hypoglycemia, better glucose control and tolerable side-effects[15]. The present article focused on just some of the clinical studies on blood glucose control, and these are summarized in Figure 1.

DISCLOSURE

The author declares no conflict of interest.
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