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Editorial

The Degree of Glycemic Control for the First Three Months Determines the Next Seven Years

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▸ See the article "Long-Term Changes in HbA1c According to Blood Glucose Control Status During the First 3 Months After Visiting a Tertiary University Hospital" in volume 37, number 38, e281.

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The increasing prevalence of type 2 diabetes mellitus (T2DM) is adding to the public health burden in Korea and around the world. In the Global Burden of Disease Study 2019,[1] diabetes was the third disease with a significant increase in the age-standardized disability-adjusted life-year (DALY) rate to 24.4% between 1990 and 2019. In addition, the diabetic macrovascular complications, ischemic heart disease and stroke, were also leading causes of DALYs in adults. However, despite the development of various antidiabetic agents, the target hemoglobin A1c (HbA1c) achievement rate is still low.[2] This is a major obstacle to preventing diabetic complications, which can be delayed by well-controlled diabetes.[3] Moreover, the early predictors of clinical outcome of T2DM were not yet fully understood from the real world evidence (RWE).[4,5]

In this issue of the *Journal of Korean Medical Science*, Kim et al.[6] reported that changes in early HbA1c levels after a university hospital visit could predict patient clinical outcomes. In this retrospective study, the authors grouped subjects into four by changes in HbA1c levels during the first 3 months after the initial visit: Best_group, ≥ 1.6% decrease; Better_group, 0.5–1.5% decrease; Neutral_group, ≤ 0.4% decrease or ≤ 0.4% increase; Worse_group, ≥ 0.5% increase. A total of 9,776 patients were followed of their HbA1c levels annually and monitored for stroke or acute coronary syndrome (ACS) for 7 years. HbA1c levels were significantly lower in the Best_group than in the other groups during the study period, and this phenomenon is maintained even in the subgroup analysis by the initial HbA1c hierarchy.

However, the Best_group did not significantly reduce the risk of macrovascular complications such as stroke and ACS compared to the other groups. The meta-analysis of four trials (ACCORD, ADVANCE, UKPDS, and VADT)[7] found that intensive glucose control prevented microvascular complications such as diabetic retinopathy and nephropathy at 5 years of follow-up. Furthermore, in the United Kingdom Prospective Diabetes Study (UKPDS) 10-year follow-up,[8] the early intensive treatment group decreased the risk of microvascular complications, but not macrovascular complications and all-cause mortality. Therefore, further studies to determine whether the Best_group can reduce the risk of microvascular complications compared with other groups may provide more information on the beneficial effects of early intensive glycemic control within 3 months.

This result can be explained by the glycemic legacy effect[3] and the premature decrease in pancreatic β-cell function.[5] The UKPDS demonstrated that the immediate intensive HbA1c lowering group (≥ 1% decrease) after diagnosis of T2DM had a 7-fold lower risk of myocardial infarction (MI) and all-cause mortality after 20 years compared to the delayed HbA1c lowering group.[3] Kim et al.[5] found that early target HbA1c achievement (HbA1c < 7.0% within 6 months) was associated with long-term stable HbA1c levels at target and reduced the risk of microvascular complications in newly diagnosed T2DM. The early target HbA1c achievement group had higher C-peptide levels than the late target HbA1c achievement group. That is, low C-peptide levels indicate pancreatic β-cell dysfunction, which leads to diabetic complications due to glucotoxicity and high glucose variability.[9]

The Vildagliptin Efficacy in combination with metfoRmIn For earlY treatment of type 2 diabetes (VERIFY) study[10] showed that initial dual therapy with synergistic combination in patients with newly diagnosed T2DM compared with initial metformin monotherapy maintained HbA1c levels significantly and consistently at target. However, most of the non-insulin-based drugs showed a glucose-lowering effect only when the pancreatic β-cell function remained at least 15-20%.[9] And in newly-onset T2DM patients, early initiation of insulin to achieve normal glucose reversed pancreatic β-cell dysfunction and cured it by up to 50%. Despite much clinical evidence and various approved anti-diabetic agents with low hypoglycemia risk, inconsistencies between guidelines and practice, clinical inertia, still remained.[11] In the early stages of T2DM, more intensive therapeutic strategies are needed to preserve pancreatic β-cell function and prevent diabetic complications. This study may provide a rationale for an optimal goal for HbA1c reduction and for rapid decisions to change treatment strategies early in the hospital visit.

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