Do we need new HbA1c target?

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Abstract

Introduction
HbA1c should be tested during the first and subsequent assessments in all diabetic patients since HbA1c reflects mean glycaemia over the past few months and has a strong predictive value for diabetic complications. Studies have shown that tight blood glucose control reduces complications in diabetic patients. The most important limiting factor for tight blood glucose control is hypoglycaemia. However, it is known that incretins (GLP-1 analogues and DPP-4 inhibitors), that have been increasingly used, do not cause severe hypoglycaemia.

The hypothesis
Drugs used in treating diabetes mellitus is one of the factors determining the glycaemic goals.

Evaluation of the hypothesis
DM is an important cause of morbidity and mortality that reduces quality of life and survival and that courses with microvascular (nephropathy, retinopathy, and neuropathy) and life threatening macrovascular complications such as atherosclerotic cardiovascular diseases due to chronic hyperglycaemia. Tight blood glucose control reduces complications in diabetic patients. The most important limiting factor for tight blood glucose control is hypoglycaemia. However, incretins (GLP-1 analogues and DPP-4 inhibitors), which have been increasingly used for treating diabetes, do not cause severe hypoglycaemia.

Conclusion
Therefore, glycaemic targets should be individualized according to the treatment.

Introduction
Glycated haemoglobin is the product of a ketoamine reaction between the free amino groups on the alpha and beta chains of the haemoglobin molecule and glucose as well as other sugars. When the N-terminal valine of the beta chain is glycated, a negative charge occurs, which leads to a separation between haemoglobin molecules. These separated molecules are called HbA1, of which HbA1c is the most common form (80%).

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Discussion
Testing of HbA1c levels should be included in all assessments of diabetic patients because HbA1c levels reflect mean glycaemia corresponding to the past few months and have a strong predictive value for diabetic complications.

HbA1c levels should be tested at least twice a year in patients in whom blood glucose levels are stable and therapeutic target is achieved, and once every three months in patients who switch to another therapy or in whom targeted glucose regulation cannot be achieved. For diabetic patients, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) recommend target HbA1c levels of <7%, ≤6.5% and ≤6.5%, respectively. However, current guidelines recommend individualisation of glycaemic targets in diabetic patients according to several factors such as duration of diabetes, life expectancy, risk of hypoglycaemia, pregnancy, presence of cardiovascular diseases and advanced micro or macrovascular complications.

According to the results of the United Kingdom Prospective Diabetes Study (UKPDS), each 1% decrement in HbA1c levels led to a proportional reduction in both microvascular complications (24% reduced risk) and mortality (17% reduced risk for diabetes-related death and 15% reduced risk for myocardial infarction)². In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, it was shown that the progression of early-stage microvascular complications was reduced in the intensive treatment arm. Similarly, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial, it was shown that progression to microalbuminuria was reduced with intensive therapy³. However, the ACCORD and the Veterans Affairs Diabetes Trial (VADT) showed that intensive glycaemic control (a target HbA1c of <6%) increased the risk of cardiovascular events and that this increment was associated with hypoglycaemia⁴. According to the ADA guidelines, HbA1c level in healthy individuals is ≤5.7%.

It was reported in the ACCORD study that all-cause mortality among patients below the age of 65 was lower and in
the ADVANCE study that combined major and macro and microvascular events among young patients in the tight glycaemic control group was lower. In the sub-group analysis of the VADT study, it was seen that the patients with a lower coronary calcium score had a tighter glycaemic control and fewer cardiovascular events.

While the UKPDS study examined newly-diagnosed Type 2 DM patients, the diabetes disease duration of patients in the VADT-ACCORD and ADVANCE studies was 8-11.5 years. As for the UKPDS long-term follow-up study, it also showed that the micro- and macro-vascular events were lower in the tight glycaemic control arm in a way similar to the results of the first group. In the VADT study, patients with CVD (cardiovascular disease) had diabetes for a duration of 2 years longer than those without the disease. These findings show that the early start of glycaemic control is more beneficial. This may especially be correct for patients who have family history of coronary artery disease at an early age.

Kumamoto study investigated the effect of multiple insulin therapy versus standard insulin therapy in Type 2 DM Japanese patients. A decrease in albuminuria and retinopathy progression with intensive treatment was identified.

Similarly, the ACCORD study also found decrease in the progression of retinopathy and neuropathy with tight glycaemic control. Therefore, a more aggressive glycaemic control may be considered for patients with early retinopathy or normal serum creatinine with microalbuminuria.

A glycaemic control that is close to normal also enhances the development of severe hypoglycaemia. In the studies, it was seen that severe hypoglycaemia developed 2-3 times more often with intense treatment. Among Type 2 diabetic patients of advanced age, severe hypoglycaemia attacks are related to dementia and such attacks may lead to MI and arrhythmia among patients with CVD. In the ACCORD and ADVANCE studies, the mortality rates among patients with at least one severe hypoglycaemia attack, the mortality rates were reported to be higher.

**Conclusion**

UKPDS and DCCT studies have shown that tight blood glucose control reduces complications in diabetic patients. The most important limiting factor for tight blood glucose control is hypoglycaemia.

However, incretins (GLP-1 analogues and DPP-4 inhibitors), which have been increasingly used for treating diabetes, do not cause severe hypoglycaemia. The duration of diabetes, patient’s age and life expectancy, accompanying diseases, known CVD and macro- and microvascular complications, unawareness about hypoglycaemia, the treatment regimen used are important factors in determining the metabolic control target diabetic patients. For that reason, the glycaemic control target may be individualized for every patient. Therefore, at least in patients undergoing incretin therapy, targeting an HbA1c level of <6 % can be considered.

**References**