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SPECIAL REPORT

New glycemic targets for patients with diabetes from the Japan Diabetes Society

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ABSTRACT

In the 'Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013', a new concept of the glycemic control in patients with diabetes in Japan has been declared from the Japan Diabetes Society. The main objective value of HbA1c was set to <7% from the perspective of preventing microvascular complications. On the other hand, the objective in cases where objectives can be attained by appropriate dietary or exercise therapy, or during pharmacotherapy without the occurrence of side effects such as hypoglycemia was set to <6%, and the objective in cases where intensification of treatment was considered difficult due to side effects such as hypoglycemia or for other reasons was set to <8%. Treatment objectives should be established individually, in consideration of age, duration of disease, organ damage, risk of hypoglycemia, support structure, and etc.

INTRODUCTION

Diabetes is a metabolic disease with the main symptom of chronic hyperglycemia caused by insufficient insulin action. Most symptoms cannot be noticed when the degree of the metabolic disorders caused by insufficient insulin action is mild. Therefore, diabetes may not be discovered for a long time. However, thirst, polydipsia, polyuria, and weight loss are observed in the metabolic state where the blood-sugar level is significantly higher. Moreover, this more advanced condition leads to acute complications such as disturbance of consciousness and coma, and may also lead to death if effective therapy is not provided. The risk of developing characteristic long-term complications (retinopathy, nephropathy, and neuropathy) is high even when mild metabolic disorders continue for a long time. Moreover, arteriosclerosis of the whole body is accelerated with diabetes, and this can cause myocardial infarction, cerebral infarction, and arteriosclerosis obliterans of the lower extremities. In addition, diabetes causes a decrease in resistance to bacterial infection.

The goal of diabetes therapy is to prevent the onset and exacerbation of short-term and long-term complications, to maintain quality of life (QOL), and to achieve a life span that is comparable to that of a healthy person.

NEW OBJECTIVES OF GLYCEMIC CONTROL IN SUBJECTS WITH DIABETES

It is evident from some epidemiological analyses that the risks of onset and progression of microangiopathy and macroangiopathy are reduced with better glycemic control. There is no clear standard indicating the degree to which glycemic control has to be improved to prevent the onset of complications. Evidence has been reported in Japan that the onset and progression of microangiopathy could be prevented with HbA1c (JDS) levels of <6.5% [HbA1c (NGSP) 6.9%] [1]. However, the risk of the onset and progression of macroangiopathy is high beginning at the early stage of impaired glucose intolerance, where only the postprandial blood glucose level is high[2]. Therefore, the ideal goal of glycemic control is to correct fasting and postprandial hyperglycemia, and not just hyperglycemia and hypoglycemia over the course of 1 day, and as a result to normalize HbA1c values (a reflection of the average blood glucose level over the past 1–2 months). Therapy has to be provided without delay, because the absence of early glycemic control after the diagnosis of

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diabetes is associated with the onset of long-term complications or death (legacy effect)[3,4]. Specifically, not providing or interrupting the therapy for diabetes will have a detrimental effect on the long-term prognosis of the patient. Also, there are reports of microangiopathy and an increase in mortality rate due to sudden or excessive correction of glycemic control[5].

The goals of glycemic control should be determined individually in light of the patient's age, duration of diabetes, status of complications, risk for hypoglycemia as well as the support system available to address such complications or hypoglycemia.

However, the glycemic goal of HbA1c <7.0% is recommended to ensure prevention of diabetic complications. In this regard, supportive evidence was available from the Kumamoto Study[1], in which patients with HbA1c <6.9% were found to be less likely to develop microangiopathy.

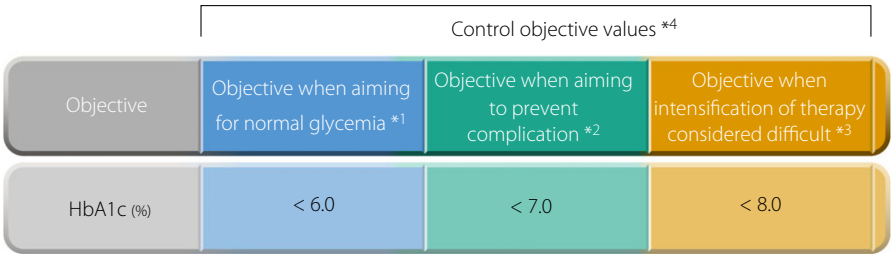
HbA1c target level was set to <7.0%, as the Kumamoto Study examined only limited cases and consideration was taken of the target levels of other countries[6]. A fasting blood glucose level <130 mg/dL and a 2-h postprandial blood glucose level <180 mg/dL were used as an approximate guideline for the corresponding blood glucose levels. The values were determined from the relationship between HbA1c values and fasting blood glucose levels based on reports from Ito *et al.*[7] and Honda *et al.*[8] in addition to the results of the Kumamoto Study.

In addition to HbA1c 7%, HbA1c 6% and 8% should also be kept in mind as measures of glycemic control in daily clinical practice. HbA1c 6% represents the best target in ensuring normalization of glucose levels, ideally, with appropriate diet/exercise therapy alone or with drug therapy without causing adverse events, such as hypoglycemia. This target is set for young individuals with a short duration of diabetes without a past history of cardiovascular disease. For example, The United Kingdom Prospective Diabetes Study (UKPDS) enrolled patients with a short history of diabetes and reported that the risk of microangiopathy and macroangiopathy decreased with HbA1c (NGSP) values at around 6.0%[9].

In contrast, HbA1c 8% serves as a measure of glycemic control that needs at least to be achieved in patients in whom intensive therapy is not feasible due to hypoglycemia or other factors as well as the threshold above which treatment needs to be modified or changed to improve glycemic control. Continuity was observed in the relationship between HbA1c and the occurrence of microangiopathy, although there was no threshold; for example, the trend for increased risk of retinopathy increased with HbA1c (NGSP) values >8.0%[10]. The onset of microvascular complications was significantly high in the conventional therapy group of UKDPS for HbA1c (NGSP) with a median value of 7.9%[11], and hence, an HbA1c value of 8.0% was set as one of the delimiters (Figure 1).

Moreover, the earlier evaluation was mainly from the perspective of the risk of microangiopathy. The DECODE study[12] revealed that higher blood glucose levels after the 75 g oral glucose tolerance test (OGTT; 2-h test) is a risk factor that is independent of blood pressure and lipids in cardiovascular diseases.

The necessity of strict glycemic control during pregnancy (during the period before pregnancy up to the delivery) also has to be kept in mind.



Treatment objectives are established individually, in consideration of age, duration of disease, organ damage, risk of hypoglycemia, support structures, etc.

*1 Objective in cases where objectives can be attained by appropriate dietary or exercise therapy, or during pharmacotherapy without the occurrence of side effects such as hypoglycemia.
*2 From the perspective of preventing complication, HbA1c target value is set below 7%. A fasting blood glucose level <130 mg/dL and a 2-hour postprandial blood glucose level <180 mg/dL were used as an approximate guideline for the corresponding blood glucose levels.
*3 Objective in cases where intensification of treatment is considered difficult due to side effects such as hypoglycemia or for other reasons.
*4 All objective values are for adults, not including pregnant women.

Figure 1 | Glycemic control objectives. The main objective value of HbA1c was set to <7% from the perspective of preventing complications. The objective when aiming to normal glycemia was set to <6%, and the objective when intensification of therapy considered difficult was set to <8%.

CONCLUSIONS

In the 'Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013', a new concept of the glycemic control in patients with diabetes in Japan has been declared. The main objective value of HbA1c was set to <7% from the perspective of preventing microvascular complications. On the other hand, the objective when aiming to normal glycemia was set to <6%, and the objective when intensification of therapy considered difficult was set to <8%. Treatment objectives should be established in each subject, considering the age, duration of disease, organ damage, risk of hypoglycemia, support structure, and etc.

ACKNOWLEDGMENT

This new concept was initially described in 'Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013' in Japanese, and was widely announced at the 56th annual meeting of the Japan Diabetes Society (JDS) held in Kumamoto, Japan in 2013, and therefore called 'Kumamoto Declaration 2013'. The English-language edition of 'Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013', which was simplified for publication, was appeared on JDS website in May 2014. We would like to thank committee members of 'Evidence-based Practice Guideline for the Treatment for Diabetes in Japan 2013' and the Directors of JDS for their contribution to establish this concept.

DISCLOSURE

Eiichi Araki has received honoraria for lectures from Drug Company Astellas Pharma Inc., and honoraria for manuscripts from Medical Review Co., Ltd., and Total clinical research grants from Astellas Pharma Inc., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation, Daiichi Sankyo Company, Limited, Taisho Pharmaceutical Holdings Co., Ltd., Masakazu Haneda has received honoraria for lectures from Drug Companies Mitsubishi Tanabe Pharma Corporation, Boehringer Ingelheim GmbH, Taisho Toyama Pharmaceutical Co., Ltd., Astellas Pharma Inc., and Total clinical research grants from Astellas Pharma Inc., Ono Pharmaceutical Co., LTD., Daiichi Sankyo Company, Limited, Takeda Pharmaceutical Company Limited., and MSD, Kohjiro Ueki has received honoraria for lectures from Drug Company MSD, and courses endowed by companies, etc. from Drug Companies MSD, Novo Nordisk Pharma Ltd., and Boehringer Ingelheim GmbH, Masato Kasuga, Takeshi Nishikawa, Tatsuya Kondo, and Takashi Kadowaki have no conflict of interest.

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