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EDITORIAL

Type 2 diabetes mellitus prevention strategy: Target and goal in Japanese men

The estimated number of people with type 2 diabetes worldwide was approximately 415 million people in 2015, and that number should reach more than 642 million in 2040 (IDF Diabetes Atlas, 7th edition), thus prevention of type 2 diabetes is a major challenge for public health professionals throughout the world. In Japan, approximately 7.8 million Japanese were estimated to have type 2 diabetes in 1990, and the number gradually increased to reach more than 22.1 million in 2007. Subsequently, however, the number decreased though by a small margin, and was estimated to be approximately 20.5 million in 2012 according to the Ministry of Health, Labor and Welfare. The apparent break in the rise of the prevalence of diabetes in Japan is probably related to the *tokutei kenshin*, formally called *tokutei kenko shinsa*; that is, annual medical checkup, which was legislated in 2008[1–3]. The *tokutei kenshin* is an annual medical examination in Japan that was established with a special focus on metabolic syndrome, namely visceral fat syndrome. Under this system, when the results of clinical examination and laboratory tests show that the examinee has or is at high risk of metabolic syndrome, s/he receives assistance in reviewing her/his lifestyle for improvement (specific health guidance), which is called *tokutei hoken shido*. The purpose of this educational program is lifestyle intervention that can lead to prevention of potential lifestyle-related diseases, such as diabetes, hypertension, dyslipidemia and cardiovascular diseases.

Type 2 diabetes results from both genetic predisposition and environmental risk factors, such as obesity, visceral fat accumulation and physical inactivity. Therefore, lifestyle interventions, especially those designed to reduce bodyweight, are thought to be effective in preventing or delaying the onset of the disease. In fact, several large-scale intervention trials in the USA and Europe have concluded that lifestyle interventions designed to reduce bodyweight prevent or delay the onset of type 2 diabetes in subjects with impaired glucose tolerance (IGT). However, most of the participants in the aforementioned studies were obese, and especially in the Diabetes Prevention Program[4], the mean body mass index (BMI) of the participants was more than 30 kg/m^2 at baseline, which makes them very different from the Japanese population. One Japanese study[5] that analyzed the correlation between weight reduction and change in glycemic control in men suggested that bodyweight reduction is an effective strategy for prevention of type 2 diabetes in men with visceral fat accumulation. The study showed that in Japanese men with glycated hemoglobin (HbA1c) levels of 5.6–6.4%, who are considered prediabetics, reduction in bodyweight within 1 year correlated positively with the change in HbA1c in men with visceral fat accumulation, but not in those without visceral fat accumulation, irrespective of BMI (whether BMI was ≥25 kg/m^2 or not). This suggests that weight reduction could be effective in preventing diabetes, especially in individuals with visceral fat accumulation, and that assessment of visceral fat, rather than BMI, seems more important in identifying those individuals that would benefit most from lifestyle intervention. In this context, the *tokutei hoken shido*, which focuses on metabolic syndrome (visceral fat syndrome), is reasonable and should be effective in preventing diabetes. Then, to what extent should bodyweight be reduced to prevent the development of type 2 diabetes?

In the Diabetes Prevention Program in USA, a randomized clinical trial designed to prevent the development of diabetes in patients with IGT[4], the incidence of type 2 diabetes was reduced by 58% after 2.8 years with an average weight reduction of 5.6 kg (loss of approximately 6% of bodyweight) in the intensive lifestyle intervention group compared with the placebo group, with an average weight loss of 0.1 kg. In the same study, loss of more than 5–7% of bodyweight reduced the risk of type 2 diabetes by more than 90%. Similarly, a Japanese observational study[6] showed that in Japanese men with visceral fat accumulation and HbA1c level of 5.6–6.4%, a weight loss of ≥4.3% significantly reduced the risk of diabetes by approximately 80% compared with the bodyweight gain group (mean weight gain, 2.8%) during the 3-year study period, whereas weight loss of <4.3% did not have a significant impact on the risk of diabetes. The aforementioned study shows that to produce a clinically meaningful reduction in the risk of diabetes, at least 4–5% bodyweight reduction should be achieved by those Japanese men with visceral fat accumulation and HbA1c of 5.6–6.4%. In that study[6], approximately 14% of the participants did achieve more than 4.3% bodyweight reduction. In addition, the population-attributable risk by ≥4.3% weight reduction was estimated to be 7.8%. Thus, the tentative goal of at least 4–5% bodyweight reduction is not only theoretical, but rather, clinically practical, and can be achieved by individuals in the real world. Using the same approach, the study also reported that the risk of diabetes can be minimized by reducing waist circumference by ≥5.5%. Quantitative data on these two parameters could potentially serve as important indices to improve the *tokutei hoken shido*.

As individuals with IGT are already at high risk of atherosclerogenesis, it is also important to identify those with

Table 1 | Proposed strategy for prevention of type 2 diabetes in Japanese men

	Individuals	
	With excess visceral fat	Without excess visceral fat
Normal glucose tolerance at high-risk	Lifestyle intervention aimed at reducing bodyweight (or waist circumference)	?
Impaired glucose tolerance	Lifestyle intervention aimed at reducing bodyweight (or waist circumference) by >4–5%	Lifestyle modification and use of alfa glucosidase inhibitor?

normal glucose tolerance (NGT) who could progress to glucose intolerance and design interventions to delay such deterioration. In this context, the report by Akita *et al.*[7] proposes a strategy that can prevent deterioration of glucose tolerance in NGT with abdominal obesity. The study showed that plasma glucose levels at 0 and 60 min of the oral glucose tolerance test were significant predictors of deterioration of glucose tolerance, with optimal cut-off values of 95 and 158 mg/dL, respectively. In addition, the study reported that the rate of deterioration of glucose tolerance did not decrease with reductions in visceral fat when data of the entire group of participants with NGT were analyzed. Rather, the rate tended to decrease with reductions in visceral fat in high-risk NGT participants, which was determined by values of the aforementioned predictors, that exceeded the cut-off levels. These results suggest that reduction of visceral fat is probably not beneficial in all individuals with NGT, but only in high-risk NGT with abdominal obesity. Thus, they believe that individuals with high-risk NGT and abdominal obesity, determined by those predictors, should receive lifestyle intervention designed to reduce visceral fat to prevent any further deterioration of glucose tolerance to IGT.

We have discussed here those individuals with visceral fat accumulation. Then, what should we do about those without abdominal obesity? Pharmacological approaches have also been investigated, and glucose-lowering agents, such as metformin, pioglitazone, acarbose, as well as insulin, effectively delay or prevent the progression of IGT to type 2 diabetes. However, most of the participants in those studies were also obese. Under these situations, Kawamori *et al.*[8] reported that voglibose can reduce the development of type 2 diabetes in high-risk Japanese individuals with IGT, including non-obese subjects. In the study, risk of progression to type 2 diabetes was lower in patients treated with voglibose, in addition to lifestyle modification on a standard diet and regular exercise, than in those on placebo (hazard ratio 0.595, 95% CI 0.433–0.818). Furthermore, the risk of development of type 2 diabetes was lower in the voglibose group compared with the placebo group without obesity (hazard ratio 0.449, 95% CI 0.248–0.813) as well as with obesity (hazard ratio 0.622, 95% CI 0.412–0.940). Their report seems very unique in that the patients were only Japanese and included many non-obese individuals. The results suggest that the use of alfa-glucosidase inhibitor is a potentially effective strategy to prevent diabetes in non-obese (or no visceral fat accumulation) IGT patients.

In summary (Table 1), lifestyle intervention aimed at reducing bodyweight (or visceral fat) should be provided to Japanese men with visceral fat accumulation and IGT, as well as to those with high-risk NGT to prevent type 2 diabetes. In addition, any weight reduction program set for Japanese men with visceral fat should be designed to reduce bodyweight (or waist circumference) by more than 4–5% for optimal diabetes risk minimization. Although it is not clear at this stage whether such intervention is also effective in individuals without abdominal obesity, the use of alfa-glucosidase inhibitor in addition to lifestyle modification could be a feasible strategy that can potentially prevent type 2 diabetes in non-obese individuals. Further studies in Japanese women and also in older adults are required to formulate a strategy for prevention of diabetes in these individuals.

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