and efficiently used to identify subjects at high-risk for DM who should be targeted for intensive prevention intervention.

The 2 h PG depends on insulin secretary capacity of pancreatic beta cells, peripheral insulin sensitivity, and hepatic glucose output and uptake whereas FPG largely depends on hepatic glucose production. While HbA1c reflects glucose metabolism over the past 1–2 months [16], can be converted into the estimated average glucose levels [20], has smaller variability than FPG and 2 h PG [21], and is closely correlated with post-load glucose in its low range and correlated with FPG in its high range [22]. Thus, HbA1c could cover a wider range of pathophysiological processes of DM than FPG. In our study, HbA1c showed almost the same overall predictability for DM in the future as FPG. In some previous studies, HbA1c seemed to be inferior to FPG with respect to the risk prediction and detection [11,12]. This might partly be due to the application of ADA criteria for the diagnosis of DM [11,12]. In our data, 70% of new cases of DM was identified by isolated 2 h PG (data not shown) and these subjects would not be identified as DM by the ADA criteria. In our country, HbA1c ≥6.5% has been used as a supportive test for the diagnosis of DM for past 10 years [23]. The International Expert Committee appointed by the ADA, the European Diabetes Association for the Study of Diabetes, and the International Diabetes Federation has recommended diagnosing DM by using HbA1c, since June 2009 [24]. Moreover, HbA1c has been provided a treatment target for patients with DM in many organizations including JDS [23]. Thus, HbA1c could be used in different stages of the diseases: screening, diagnosis and treatment. Meanwhile, HbA1c measurement by enzymatic method (Arkray, Kyoto) has become possible at a reasonable cost [25]. This satisfactorily correlates with HbA1c measurement by the HPLC method, does not need standardization, and is more economical than it measurement by HPLC method. This might be a rationale for recommending HbA1c in evaluating future DM risk.

Recently, we have shown that FPG ≥5.56 mmol/l is the better predictor than metabolic syndrome or a constellation of cardiovascular risk factors except for FPG ≥5.56 mmol/l regardless of abdominal adiposity in the Funagata Study [26]. The same trend was obtained when HbA1c ≥5.3% replaced FPG ≥5.56 mmol/l (data not shown). This highlighted glucose itself as the screening test for DM in the future. In our data, HbA1c 5.3% corresponded to FPG 5.56 mmol/l for predicting DM (Fig. 1 and Table 2) and both cut-offs identified similar risk of DM (Table 1) and had equal detection rate of DM, especially from the group of subjects with baseline IGT (Tables 1 and 2). On the other hand, the proportion of people above the cut-off was significantly lower in HbA1c 5.3% than FPG 5.56 mmol/l. Thus, HbA1c 5.3% rather than FPG 5.56 mmol/l might be efficient to identify those targeted for intensive intervention. Since the decision of the screening cut-off is tentative, the cut-off for HbA1c applied in Japan of 5.2% [8] might be too low in our study subjects. Since HbA1c 5.2% could identify significantly more incident cases from those with IGT than FPG 5.56 mmol/l or HbA1c 5.3%, the use of HbA1c 5.2% would make markedly high proportion of subjects (= one third of the entire screened population) who would be followed by intensive intervention.

There are limitations in our study. First, despite concerted efforts to maximize follow-up, the participation rate at 5-year of follow-up was 60%, which, although comparable to other studies of this nature, could potentially bias our results. When comparing baseline characteristics between those who did and did not participate in follow-up, the participants were younger and were healthier than non-participants (data not shown). This is in line with the frequent observation of "healthy participants' effect", which has also been reported in other studies [27]. This would lead to an underestimation of the true cumulative incidence in the general population, and thus our results are conservative. Second, the study population is approximately 10-years older than the representative sample of the Japanese general population [7], and this may have influenced our results. The relevance of Japanese cut-off of 5.2% for HbA1c to screen subjects requiring health guidance in the screening program [8] should be further examined in other Japanese studies. Third, FPG and 2 h PG in this population were assessed only once at both baseline and follow-up. The inter- and intra-coefficients of variations in glucose values may have caused some random misclassification in glucose categories [21], and thereby influenced our results. Fourth, the total number of incident cases is too small to obtain conclusive cut-off discriminating risks and performance as the screening between different strata. Fifth, we did not run sex-stratified analysis due to limited number of incident cases but did adjustment by sex. Since the crude proportion of incident case in men was double-folds higher than women, the overall predictabilities of DM based on ROC curve analysis did not differ between sexes for each glucose indicators or not differ across three glucose indicators in both

Table 2 – Performance (%) [95% confidence interval] of cut-offs on three glucose indicators for predicting DM at 5-year follow-up.

Variables	Cut-offs	Number (%)	% Sensitivity	% Specificity	100-Positive predictive value (%)	100-Negative predictive value (%)
FPG	5.56 mmol/l	233 (19.6)	61.4 [48.8–74.0]	82.5 [80.3–84.7]	85.0 [80.4–89.6]	2.3 [1.4–3.3]
2 h PG	7.80 mmol/l	136 (11.4)	61.4 [48.8–74.0]	91.1 [89.4–92.7]	74.3 [66.9–81.6]	2.1 [1.2–3.0]
HbA1c	5.1%	490 (41.2)	86.0 [76.9–95.0]	61.0 [58.2–63.9]	90.0 [87.3–92.7]	1.1 [0.4–1.9]
	5.2%	360 (30.3)	73.7 [62.3–85.1]	71.9 [69.3–74.5]	88.3 [85.0–91.6]	1.8 [0.9–2.7]
	5.3%	170 (14.3)	56.1 [43.3–69.0]	87.8 [85.9–89.7]	81.2 [75.3–87.1]	2.5 [1.5–3.4]
	5.4%	113 (9.5)	45.6 [32.7–58.5]	92.3 [69.3–74.5]	77.0 [69.2–84.8]	2.9 [1.9–3.9]

FPG: fasting plasma glucose, 2 h PG: 2 h plasma glucose.

sexes (data not shown). Sixth, the application of micro- and macro-vascular complication as the hard end point was not unable in the current study. However, notwithstanding the limitations, our study has notable strengths, being population-based, consisting of both men and women, having FPG and 2 h PG to enable rigorous biochemical diagnosis of DM based on either FPG or 2 h PG criteria and a well-phenotyped sample at baseline and follow-up.

In conclusion, HbA1c can be practically used to screen high-risk of future DM in a general Japanese population. It could also effectively be used in association with IGT who could be targeted for intensive prevention intervention.

Conflicts of interest

The authors declare that they have no conflict of interest.

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REFERENCES

[1] International Diabetes Federation, Diabetes Atlas, 2nd ed., The Federation, Brussels, 2003.
[2] W.C. Knowler, E. Barrett-Connor, S.E. Fowler, R.F. Hamman, J.M. Lachin, E.A. Walker, et al., Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, N Engl J. Med. 346 (2002) 393–403.
[3] J. Tuomilehto, J. Lindström, J.G. Eriksson, T.T. Valle, H. Hämäläinen, P. Ilanne-Parikka, et al., Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance, N Engl J. Med. 344 (2001) 1343–1350.
[4] R. Kawamori, N. Tajima, Y. Iwamoto, A. Kashiwagi, K. Shimamoto, K. Kaku, On behalf of Voglibose Ph-3 Study Group, Voglibose for prevention of type2 diabetes mellitus: a randomized, double-blind trial in Japanese individuals with impaired glucose tolerance, Lancet 373 (2009) 1607–1614.
[5] R.R. Holman, S.K. Paul, M.A. Bethel, D.R. Matthews, H.A. Neil, 10-year follow-up of intensive glucose control in type 2 diabetes, N Eng J Med 359 (2008) 1577–1589.
[6] H.C. Gerstein, M.E. Miller, R.P. Byington, D.C. Goff Jr, J.T. Bigger, J.B. Buse, et al., Effects of intensive glucose lowering in type 2 diabetes, N Engl. J. Med. 358 (2008) 2545–2559.
[7] http://www.mhlw.go.jp/houdou/2008/04/h0430-2.html. (In Japanese).
[8] T. Kohro, Y. Furui, N. Mitsutake, R. Fujii, H. Morita, S. Oku, et al., The Japanese national health screening and intervention aimed at preventing worsening of the metabolic syndrome, Int. Heart J. 49 (2008) 193–203.
[9] G. Nijpels, C. Popp-Snijders, P.J. Kostense, L.M. Bouter, R.J. Heine, Fasting proinsulin and 2 h post-load glucose levels predict the conversion to NIDDM in subjects with impaired glucose tolerance; the Hoorn study, Diabetologia 39 (1996) 113–118.
[10] Q. Qiao, J. Lindstrom, T.T. Valle, J. Tuomilehto, Progression to clinically diagnosed and treated diabetes from impaired glucose tolerance and impaired fasting glycaemia, Diabet. Med. 20 (2003) 1027–1033.
[11] C. Droumaguet, B. Balkau, D. Simon, E. Caces, J. Tichet, M.A. Charles, et al., Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR), Diabetes Care 29 (2006) 1619–1625.
[12] K. Inoue, M. Matsumoto, Y. Kobayashi, The combination of fasting plasma glucose and glycosylated hemoglobin predicts type 2 diabetes in Japanese workers, Diabetes Res. Clin. Pract. 77 (2007) 451–458.
[13] American Diabetes Association. Standards of medical care in diabetes 2006. Diabetes Care 20 (2006) s4–s42.
[14] World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation, Part1: Diagnosis and Classification of Diabetes Mellitus. WHO, Geneva, 1999.
[15] M. Daimon, T. Oizumi, T. Saitoh, W. Kameda, A. Hirata, H. Yamaguchi, et al., Funagata Study. Decreased serum levels of adiponectin are a risk factor for the progression to type 2 diabetes in the Japanese Population: the Funagata study, Diabetes Care 27 (2003) 15–20.
[16] K. Shima, J. Endo, M. Oimomi, I. Oshima, Y. Omori, Y. Katayama, Interlaboratory difference in GHb measurement in Japan - the fourth report of the GHb Standardization Committee, the Japan Diabetes Society, J. Jpn. Diabetes Soc. 40 (1997) 321–326 (In Japanese).
[17] M. Tominaga, H. Makino, G. Yoshino, K. Kuwa, I. Takei, Y. Aono, et al., Japanese standard reference material JDS Lot 2 for haemoglobin A1c. II: present state of standardization of haemoglobin A1c in Japan using the new reference material in routine clinical assays, Ann. Clin. Biochem. 42 (2005) 47–50.
[18] M. Tominaga, H. Makino, G. Yoshino, K. Kuwa, I. Takei, Y. Aono, et al., Japanese standard reference material for JDS Lot 2 haemoglobin A1c. I: comparison of Japan diabetes Society-assigned values to those obtained by the Japanese and USA domestic standardization programmes and by the International Federation of Clinical Chemistry reference laboratories, Ann. Clin. Biochem. 42 (2005) 41–46.
[19] M.H. Zweig, G. Campbell, Receiver operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine, Clin. Chem. 39 (1993) 561–577.
[20] D.M. Nathan, J. Kuenen, R. Borg, H. Zheng, D. Schoenfeld, R.J. Heine, For the A1c-Derived Average Glucose (ADAG) Study Group, Translating the A1C assay into estimated average glucose values, Diabetes Care 31 (2008) 1473–1478.
[21] E. Selvin, C.M. Crainiceanu, F.L. Brancati, J. Coresh, Short-term variability in measures of glycemia and implications for the classification of diabetes, Arch. Intern. Med. 167 (2007) 1545–1551.
[22] L. Monnier, H. Lapinski, C. Colette, Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA (1c), Diabetes Care 26 (2003) 881–885.
[23] Treatment Guide for Diabetes 2007. Japan Diabetes Society, Bunkodo, 2007.
[24] The International Expert Committee. International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care 32 (2009) 1–8.
[25] http://www.arkray.co.jp/nm/press/20070404.html.(In Japanese).

[26] T. Nakagami, N. Tajima, T. Oizumi, S. Karasawa, K. Wada, W. Kameda, et al., Raised fasting plasma glucose a better predictor of diabetes than the IDF definition of the metabolic syndrome, Diabetes Res. Clin. Pract. 85 (2009) 19–21.

[27] N.G. Forouhi, J. Luan, S. Hennings, N.J. Wareham, Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990–2000, Diabet Med. 24 (2007) 200–207.