type 2 diabetic subjects [1]. However, the efficacy of SMBG for glycaemic control requires three or more daily blood testing for patients using multiple insulin injections [American Diabetes Association (ADA) level of evidence = A] [2]. In patients treated less frequently with insulin injection or oral hypoglycaemic agent (OHA) or diet alone, SMBG is recommended for achieving glycaemic goals by expert consensus and clinical experience (ADA level of evidence = E). Considering that the number of type 2 diabetes (T2D) patients is now growing rapidly all over the world, self-management will have to play an increasingly larger role in the treatment of diabetes [3].

Six randomized control trials (RCTs) of 36 full text articles indicated that the overall effect of SMBG was a statistically significant decrease of 0.39% in A_{1C}, compared with the control groups [4]. A meta-analysis of 1307 non-insulin-treated patients with T2D showed a decrease in A_{1C} level by 0.42% in SMBG-performed patients compared with SMBG-not-performed ones [5]. Three RCTs with 1000 patients indicated that improvement in glycaemic control with SMBG tended to be seen in studies with initial A_{1C} above 8% [6]. On the other hand, it was reported that the link from SMBG to improved glycaemia in non-insulin-requiring T2D is less definitive [7]. O'Kane *et al.* reported that SMBG had no effect on glycaemic control but was associated with higher scores on a depression subscale [8]. Tengblad *et al.* showed that the use of SMBG also was not associated with improved glycaemic control in any therapy category of patients with T2D in primary care [9]. Evidence from a meta-analysis of 2552 patients was not convincing for a clinically meaningful effect of clinical management of non-insulin-treated T2D [10].

However, ROSES trial showed that after 6 months, mean HbA_{1c} reduction was $1.2 \pm 0.1\%$ in the intervention group and $0.7 \pm 0.2\%$ in the control group, with an absolute mean difference between groups of -0.5% [11]. Most recently, Malanda *et al.* reviewed the efficacy of SMBG on glycaemic control in patients with T2D who are not using insulin and concluded that there was a statistically significant reduction of A_{1C} level with SMBG of -0.3% (95% CI -0.4 to -0.1, 2324 participant, nine trials) compared with that of the control group [12]. Thus, SMBG may be helpful for glycaemic control in non-insulin-treated T2D patients.

In Japan, SMBG is not broadly applied in non-insulin-treated T2D because it is not covered by health insurance. In addition, patients are often reluctant to perform SMBG because it looks painful at blood sampling. Partly for these reasons, the efficacy of SMBG on glycaemic control in Japanese patients with T2D is still undetermined. To approach this question, we conducted a clinical research study to determine both the effect of SMBG on glycaemic control and the value of a putatively less painful blood sampling technique on SMBG in OHA-treated T2D. In the current study, two puncture sites were compared, fingertip and palm, partly because many nurses answered that palm blood sampling was less painful than fingertip sampling in a preliminary questionnaire (40 of 48 nurses, less painful; eight of 48 nurses, equal) and partly because the blood glucose level by palm blood sampling has been reported to be almost equal to that by fingertip sampling [13]. We show here that SMBG is useful for glycaemic control in OHA-treated patients with T2D and that palm blood sampling, a less painful technique, is beneficial for SMBG.

Materials and methods

Participants

This SMBG-OHA study was a prospective, 24-week, randomized, single centre comparison study to evaluate the efficacy of SMBG on glycaemic control in OHA-treated T2D. Outpatients of Kyoto University hospital were recruited and randomized into three groups: fingertip group, palm group, and no SMBG group using balanced design (age, gender, A_{1C}, and diabetes duration). Seven physicians examined a similar number of patients. Inclusion criteria were as follows: T2D treated with only OHA; aged ≥ 20 years; A_{1C} level $\geq$ 6.2% or fasting blood sugar level ≥ 6.1 mmol/L; no improvement in $A_{1C} \geq 0.5\%$ within 3 months; and no experience of SMBG in 1 year. Exclusion criteria were as follows: type 1 diabetes; secondary diabetes; alcoholism; severe depression or severe psychological condition; malignancy; abnormal haemoglobinemia; participation in other clinical trials or studies; and patients unsuitable for this study judged by physicians. The study protocol was approved by the Institutional Review Board of Kyoto University Hospital (#C-275) and registered on University hospital Medical Information Network in Japan (UMIN000001525). Written informed consent was obtained from all subjects.

Intervention

The study's duration was 24 weeks. Subjects were screened for eligibility and gave informed consent and basic demographic information and medical history, and were provided with the One Touch Ultra Blood Glucose Monitoring System kit®, which allows both fingertip and palm blood sampling. Subjects who performed SMBG were trained once similarly by one of three of the physicians at enrollment; they were requested to perform three SMBG for at least 3 days each week except for seven SMBG on at least 2 days in the week before the next visit. All of the subjects visited the clinic every 6 weeks, and laboratory data including A_{1C}, the number of SMBG, physical findings, and all documented medications were collected. All subjects also received advice on diet and exercise at each visit of their primary physicians with the same education and treatment policies. Subjects and physicians filled in the original questionnaire on SMBG satisfaction at the final visit. In the patient's questionnaire, subjects were questioned on five different subjects: motivation to glycaemic control; willingness to treatment for diabetes; positive response to SMBG; usefulness of SMBG in glycaemic control; and willingness to continue SMBG. The physician's questionnaire raised three issues: patient's motivation to glycaemic control;

willingness of patients to treatment for diabetes; and usefulness of SMBG in glycaemic control.

Measurements

The primary endpoint was change in A_{1C}. Significant difference was determined when average reduction of A_{1C} level was larger than or equal to 0.4% among the SMBG group, fingertip group, and palm group. The value for A_{1C} (%) was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula A_{1C} (%) = A_{1C} (JDS) (%) + 0.4%, considering the relational expression of A_{1C} (JDS) (%) measured by the previous Japanese standard substance and measurement methods and A_{1C} (NGSP) [14]. The secondary endpoints were SMBG compliance (total number of SMBG tests), dropout rate, treatment changes, patient's satisfaction, and physician's satisfaction. When more than 80% of patients or physicians answered the questionnaire affirmatively, they were deemed satisfied with performance of SMBG. SMBG data sheets of the subjects were collected, and the number of SMBG tests was counted at every visit.

Statistical analysis

Sample size was estimated to be 49 in each group to detect a 0.4% change in A_{1C} in 24 weeks with a power 95%, alpha 0.05 two-tailed. To take dropout rate into account, the aim was to include 60 subjects in each group. A_{1C} outcomes and total number of SMBG tests were assessed blindly for statistical analysis. Analysis of variance and Dunnett's multiple comparison tests were used to examine the significance levels for reduction in A_{1C} between the no SMBG group, fingertip group, and palm group. Dependent samples Student's *t*-test was used to compare the means of A_{1C} level between baseline and 24 weeks in the no SMBG, fingertip and palm groups, respectively. Independent samples Student's *t*-test was used to compare the compliance of SMBG between the fingertip and palm groups. Difference in dropout rate between no SMBG, fingertip, and palm groups was analysed by Fisher's exact test. Patient's satisfaction and physician's satisfaction also were evaluated by Fisher's exact test. Person's product–moment correlation test was used to evaluate the relationship between SMBG compliance and change in A_{1C}. p values <0.05 were considered as statistically significant.

Results

Subjects

We screened 445 patients, and 307 patients were provisionally registered. Of these, 137 patients were eligible and were enrolled in the study (Figure 1). They were randomized to three groups: 46, no SMBG group; 46, fingertip group; and 45, palm group. There was no significant difference in the background of the subjects including OHAs (Table 1). No major differences were found in the socioeconomic status or level of education between the studied groups. Five subjects were dropped from the no SMBG group, 12 subjects were dropped from the fingertip group, and 11 subjects were dropped from the palm group (Figure 1). The dropout rate appeared to be higher in the fingertip group (26.1%) and the palm group (24.4%) than that in the no SMBG group (10.9%), but

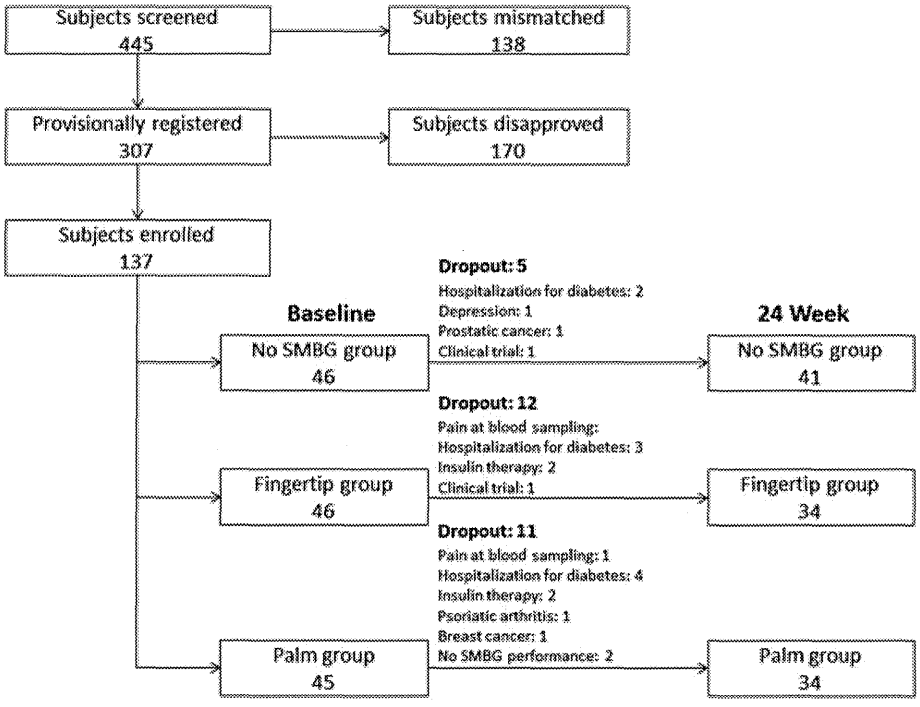

Figure 1. Flow chart of the study. SMBG, self-monitoring of blood glucose

Table 1. Demographic and clinical features of patients participating in the study

Subjects (137)	Age (years)	Female (%)	Diabetes duration (year)	A_{1C} (%)	Medication				
					SU (%)	Metformin (%)	TZD (%)	αGI (%)	Glinide (%)
No SMBG (46)	63.1 ± 11.9	41.3	8.4 ± 6.7	7.46 ± 0.76	71.7	37.0	8.7	20.0	15.2
Fingertip (46)	64.3 ± 10.0	43.5	8.5 ± 4.7	7.44 ± 0.91	69.6	34.8	10.9	19.6	15.2
Palm (45)	63.9 ± 9.4	42.2	8.2 ± 3.8	7.44 ± 0.85	71.1	33.3	8.8	22.2	13.3

SU, sulfonylurea; TZD, tiazolidine; αGI, alpha glucosidase inhibitor; SMBG, self-monitoring of blood glucose.

the difference was not significant ($p = 0.262$) (Table 2). The dropout rate due to pain at blood sampling appeared to be higher in the fingertip group (50.0%, six of 12 subjects) than that in the palm group (9.1%, one of 11 subjects), but the difference was not significant ($p = 0.116$) (Table 2). The final number of subjects who completed the study was 41 in the no SMBG group, 34 in the fingertip group, and 34 in the palm group (Table 2).

A_{1C} findings

A_{1C} level (mean ± SD) at 24 weeks was decreased from 7.25 ± 0.77% to 7.02 ± 0.59% in the fingertip group ($p < 0.05$) and from 7.35 ± 0.70% to 7.19 ± 0.67% in the palm group ($p < 0.05$) (Figure 2a). On the other hand, A_{1C} level (mean ± SD) was significantly increased from 7.44 ± 0.74% to 7.75 ± 0.85% in the no SMBG group ($p < 0.05$). Accordingly, A_{1C} level (mean ± SE) at 24 weeks was significantly decreased from baseline in the fingertip group (−0.23 ± 0.10%) and the palm group (−0.16 ± 0.06%) compared with that in the no SMBG group (+0.31 ± 0.07%) ($p < 0.05$) (Table 2). Thus, the difference in change in A_{1C} between the fingertip group or the palm group and the no SMBG group was −0.54% (95% CI −0.31 to −0.77, $p < 0.05$) and −0.48% (95% CI −0.29 to −0.67, $p < 0.05$), respectively (Table 2), but there was no statistically significant difference in A_{1C} reduction between the fingertip group and the palm group. There was no difference in hypoglycaemic events between the groups.

During the study, treatment with OHA was changed in four patients of the no SMBG group, in two patients of the fingertip group, and in seven patients of the palm group (Table 3). In treatment-unchanged subjects, A_{1C} level (mean ± SD) at 24 weeks was significantly decreased from 7.23 ± 0.77% to 6.98 ± 0.58% in the fingertip group

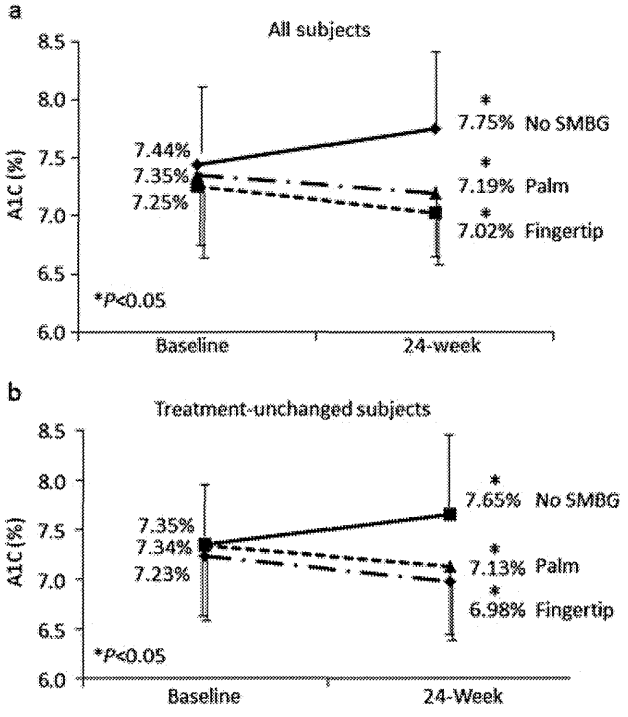

Figure 2. Change in A1C level. (a) A1C level at baseline and 24 weeks in the no SMBG, fingertip, and palm groups. (b) A1C level at baseline and 24 weeks in the no SMBG group, fingertip, and palm groups in treatment-unchanged subjects. SMBG, self-monitoring of blood glucose. *$p < 0.05$

($p < 0.05$) and from 7.34 ± 0.76% to 7.13 ± 0.72% in the palm group ($p < 0.05$), while it was significantly increased from 7.35% ± 0.68% to 7.65 ± 0.80% in the no SMBG group ($p < 0.05$) (Figure 2b). Change in A_{1C} (mean ± SE) at 24 weeks from baseline was +0.30 ± 0.08%, −0.25 ± 0.21%, and −0.21 ± 0.06% in the no SMBG, fingertip, and palm groups, respectively ($p < 0.05$) (Table 3). The difference in change in A_{1C} between the fingertip group or the palm group and the no SMBG group

Table 2. Change in A1C and SMBG compliance (total number of SMBG tests) in all subjects

Subjects number (137)	Final subjects number (129)	Dropout rate	Dropout rate due to pain	Change in A1C (mean ± SE)	ΔA1C from no SMBG (95% CI)	Total number of SMBG tests (mean ± SD)	SMBG frequency (times/day) (mean ± SD)
No SMBG (46)	41	10.9%	—	+0.31 ± 0.07%*	—	—	—
Fingertip (46)	34	26.1%	50.0%	−0.23 ± 0.10%*	−0.54%* (−0.31 to −0.77)	364 ± 160*	2.17 ± 0.92*
Palm (4)	34	24.2%	9.1%	−0.16 ± 0.06%*	−0.48%* (−0.29 to −0.67)	277 ± 154*	1.65 ± 0.92*

SMBG, self-monitoring of blood glucose.
*$p < 0.05$.

Table 3. Change in A1C and SMBG compliance (total number of SMBG tests) in treatment-unchanged subjects

Final subjects number (129)	Treatment changes	Change in A1C	Treatment-unchanged subjects	Change in A1C (mean ± SE)	ΔA1C from no SMBG (95%CI)	Total number of SMBG tests (mean ± SD)	SMBG frequency (times/day) (mean ± SD)
No SMBG (41)	4 Increased 4	+0.35%	37	+0.30 ± 0.08%*	—		
Fingertip (34)	Increased 2	+0.20%	32	−0.25 ± 0.21%*	−0.55%* (−0.29 to −0.81)	376 ± 160*	2.24 ± 0.95*
Palm (34)	7 Increased 5 Decreased 1 Drug change 1	−0.10%	27	−0.21 ± 0.06%*	−0.51%* (−0.30 to −0.72)	278 ± 148*	1.65 ± 0.88*

SMBG, self-monitoring of blood glucose.
*$p < 0.05$.

was −0.55% (95% CI −0.29 to −0.81, $p < 0.05$) and −0.51% (95% CI −3.0 to −7.5, $p < 0.05$), respectively (Table 3). There was no difference in hypoglycaemic events between the groups.

SMBG compliance

Total number of SMBG was defined as SMBG compliance. SMBG compliance (mean ± SD) by 24 weeks was 364 ± 160 (2.17 ± 0.95 times a day) in the fingertip group and 277 ± 154 (1.65 ± 0.92 times a day) in the palm group; SMBG compliance was significantly increased in the fingertip group compared with that in the palm group ($p < 0.05$) (Table 2). There was a weak, negative correlation between SMBG compliance and change in A_{1C} in the fingertip group (Person's product–moment correlation coefficient = −0.370, $p < 0.05$) (Figure 3a), the palm group (Person's product–moment correlation coefficient = −0.395, $p < 0.05$) (Figure 3b), and all SMBG (fingertip and palm) groups (Person's product–moment correlation coefficient = −0.376, $p < 0.01$) (Figure 3c). In treatment-unchanged

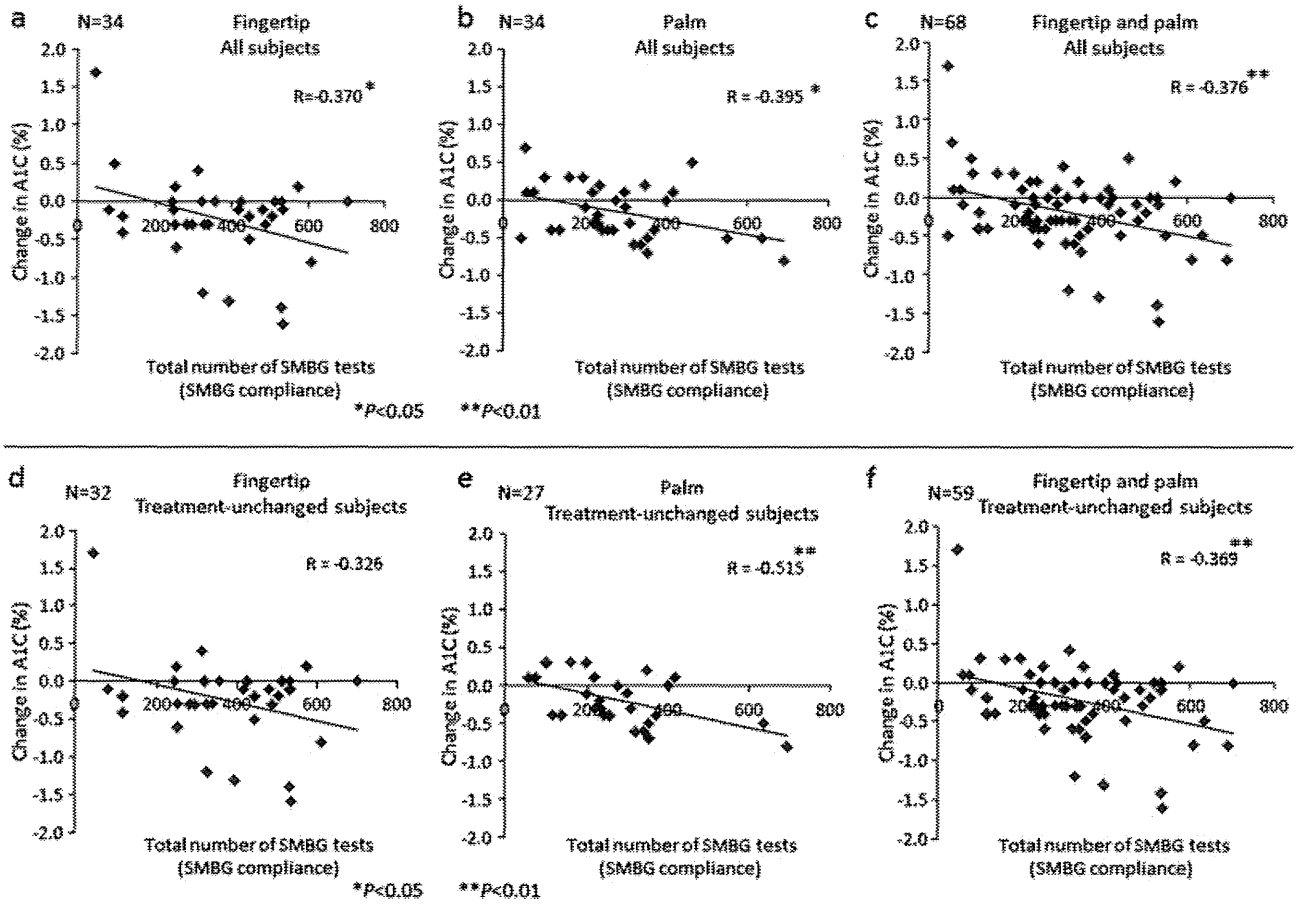

Figure 3. (a–c) Relationship between change in A1C and SMBG compliance (total number of SMBG tests) at 24 weeks in the fingertip group (a), the palm group (b), and all SMBG (fingertip and palm) groups (c) in all subjects. (d–f) Relationship between change in A1C and SMBG compliance (total number of SMBG tests) at 24 weeks in the fingertip group (d), the palm group (e), and all SMBG (fingertip and palm) groups (f) in treatment-unchanged subjects. SMBG, self-monitoring of blood glucose. *$p < 0.05$. **$p < 0.01$

subjects, SMBG compliance (mean ± SD) by 24 weeks was 376 ± 160 (2.24 ± 0.95 times a day) in the fingertip group and 278 ± 148 (1.65 ± 0.88 times a day) in the palm group (Table 3); SMBG compliance was significantly increased in the fingertip group compared with that in the palm group ($p < 0.05$). Correlation between SMBG compliance and change in A_{1C} was not found in the fingertip group (Person's product–moment correlation coefficient = −0.326), although a tendency seemed possible (Figure 3d). On the other hand, there was a negative correlation between SMBG compliance and change in A_{1C} in the palm group (Person's product–moment correlation coefficient = −0.515, $p < 0.01$) (Figure 3e) and all SMBG (fingertip and palm) groups (Person's product–moment correlation coefficient = −0.369, $p < 0.01$) (Figure 3f).

Patient's and physician's satisfaction with SMBG

Overall, 84.1% of the fingertip group and 90.2% of the palm group answered the questionnaire affirmatively. Thus, it appears that subjects were satisfied with SMBG. Although the proportion of patient's satisfaction seemed somewhat higher in the palm group, there was no statistically significant difference between the fingertip and palm groups ($p = 0.602$) (Table 4).

Physicians thought that patient's motivation to glycaemic control was significantly increased in the palm group by 94.1% compared with that in the fingertip group by 73.5% ($p = 0.045$) (Table 5). Overall, physicians answered the questionnaire affirmatively in 80.0% of the fingertip group and in 94.0% of the palm group. Thus, it appears that physicians also were satisfied with SMBG performed by both groups, but there was significantly greater approval in the palm group than that in the fingertip group ($p = 0.007$) (Table 5).

Discussion

In the present study, we show that SMBG is useful for glycaemic control in OHA-treated T2D. A_{1C} reduction was significantly greater in the fingertip and palm SMBG groups than that in the no SMBG group. SMBG compliance (total number of SMBG tests) was significantly higher in the fingertip group than that in the palm group, but SMBG compliance and change in A_{1C} were more correlated in the palm group than those in the fingertip group.

SMBG is recommended by ADA [2], International Diabetes Federation (IDF) [15], and other local guidelines [16,17], and is recognized as an integral part of self-management of patients using insulin therapy in T2D [18–20]. However, SMBG can improve glycaemic control only if it is carried out three or more times daily in patients using multiple insulin

Table 4. Patient's satisfaction

Questionnaire	Fingertip	Palm	*p* value
Motivation to glycaemic control	Increased 88.2%	Increased 97.1%	0.614
Willingness to treatment for diabetes	Increased 88.2%	Increased 76.5%	0.340
Encourage response to SMBG	Increased 70.6%	Increased 91.2%	0.174
Usefulness of SMBG in glycaemic control	Increased 88.2%	Increased 94.1%	0.673
Willingness to continue SMBG	Increased 85.3%	Increased 91.2%	0.709
Overall	Increased 84.1%	Increased 90.2%	0.602

SMBG, self-monitoring of blood glucose.

Table 5. Physician's satisfaction

Questionnaire	Fingertip	Palm	*p* value
Patient' motivation to glycaemic control	Increased 73.5%	Increased 94.1%	0.045*
Willingness of patients to treatment for diabetes	Increased 79.4%	Increased 93.9%	0.305
Usefulness of SMBG in glycaemic control	Increased 85.3%	Increased 94.1%	0.427
Overall	Increased 80.0%	Increased 94.0%	0.007*

SMBG, self-monitoring of blood glucose.
*$p < 0.05$.

injections (ADA level of evidence = A) [2]. SMBG is recommended by expert consensus or clinical experience for patients using less frequent insulin injections or OHA or medical nutrition therapy alone (ADA level of evidence = E) [2]. IDF has released a guideline on SMBG in non-insulin-treated T2D that maintains that SMBG is appropriate only when individuals with diabetes and their caregivers and healthcare providers have the knowledge, skills, and willingness to incorporate the necessary SMBG monitoring and therapy adjustments into their diabetes care plan [15].

Recently, Polonsky *et al.* reported that structured SMBG use significantly reduced the A_{1C} level in poorly controlled, non-insulin-treated T2D [21]. A_{1C} reduction from baseline to 12-months was 1.2% in structured testing groups with enhanced usual care, while it was 0.9% in an active control group with enhanced usual care. The difference in A_{1C} reduction between the two groups was 0.3%. They concluded that appropriate use of structured SMBG significantly improves glycaemic control and facilitates more timely/aggressive treatment changes in non-insulin-treated T2D. Bonomo *et al.* showed that relatively simple SMBG policy for T2D not on insulin could be potentially useful when performed with sufficient compliance [22]. Thus, Klonoff *et al.* summarized a consensus report about the current role of SMBG in non-insulin-treated T2D, which described that SMBG is an established practice for patients with non-insulin-treated T2D, and to be most effective, it should be performed in a structured format where information obtained from this measurement is used to guide treatment [23].

In the present study, subjects were encouraged to perform SMBG regularly and intensively, especially in the week before the next visit to the clinic, and to assess their SMBG data with the physician at every visit. Consequently, the average number of SMBG in all subjects was 2.17 times a day in the fingertip group and 1.65 times a day in the palm group, resulting in A_{1C} reductions by 0.54% and by 0.48% in 24 weeks, respectively, compared with that in the no SMBG group. In treatment-unchanged subjects, 2.24 SMBG a day in the fingertip group and 1.65 SMBG a day in the palm group resulted in A_{1C} reduction of 0.55% and 0.51%, respectively, compared with that in the no SMBG group. This evidence indicates that SMBG is useful for glycaemic control when patients perform SMBG regularly and healthcare providers assess SMBG data carefully with patients.

In all subjects, the relationship between SMBG compliance and change in A_{1C} was correlated in the fingertip, palm, and all SMBG (fingertip and palm) groups. In treatment-unchanged subjects, the correlation of SMBG compliance and change in A_{1C} was found in the palm and all SMBG (fingertip and palm) groups, and there was a tendency to correlate in the fingertip group. These findings may suggest that the greater the number of SMBG tests, the more the A_{1C} level might be improved. In addition, approximately once daily SMBG by fingertip or palm blood sampling was minimum for maintenance of A_{1C} level.

The total number of SMBG tests was higher in the fingertip group than that in the palm group. Pain at blood sampling was a cause of complaint regarding SMBG; six patients in fingertip group and one patient in palm group dropped out of the study because of pain. Thus, during the study, it is possible that less motivated patients were dropped and relatively highly motivated patients continued SMBG in the fingertip group. In fact, the number of subjects who performed SMBG less than 200 times in 24 weeks was smaller in the fingertip group compared with that in the palm group. Every patient was able to continue SMBG in the palm group, but sometimes continued to have puncture scars in their palms, in which case the total number of SMBG tests was lower than in the fingertip group. Overall, SMBG compliance in the fingertip group was higher than that in the palm group.

Some patients in the fingertip group who continued SMBG complained of pain at blood sampling; these patients did not perform SMBG frequently and answered the questionnaire that they were not willing to do SMBG in the future. Fear that SMBG is painful also is a barrier to the use of SMBG in patients. In fact, 55 of 170 (32.3%) patients refused to participate because of anticipated painfulness. It has been reported that an SMBG frequency of ≥ 1 per day is significantly related to higher levels of distress, worry, and depressive symptoms in non-insulin-treated patients [24]. The ZODIAC-17 study also showed that OHA-treated T2D patients experienced some worsening of their personal health perception [25]. On the other hand, structured SMBG can significantly improve glycaemic control without decreasing general well-being [21]. Thus, SMBG should be performed with reference to the patient's quality of life, and palm puncture, a less painful method of blood sampling, can be an alternative method for SMBG.

The present study shows that SMBG is helpful for glycaemic control in OHA-treated T2D and that a less painful technique for blood sampling such as palm puncture should be considered to encourage patients to continue SMBG. Although longer term observation is required, on the basis of our results, once daily SMBG can be useful to maintain a stable A_{1C} level in OHA-treated T2D.

Conflict of interest

This study was supported by Johnson & Johnson KK.

No other potential conflicts of interest relevant to this article were reported.

The study conception and protocol were by S.H., Y.S., and N.I. Subject training was by T.F., M.S., and Y.N. Patient examinations were by S.H., S.F., M.O., N.H., A.H., K.N., and N.I. The statistical analysis was by Y.N., D.T., and S.Y. The manuscript development was by S.H. and N.I.

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Original article

A new equation to estimate basal energy expenditure of patients with diabetes☆

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SUMMARY

Background & aims: Predictive equations for basal energy expenditure (BEE) derived from Caucasians tend to overestimate BEE in non-Caucasians. The aim of this study was to develop a more suitable method to estimate BEE in Japanese patients with diabetes using indices readily measured in clinical practice.

Methods: BEE was measured by indirect calorimetry under a strict basal condition in 68 Japanese patients with type 1 or type 2 diabetes. The best fitting equation was investigated by multiple regression analysis using of age, sex, and anthropometric indices. The resultant new equation was tested in a separate group of 60 Japanese patients with type 1 or type 2 diabetes, and the accuracy compared with existing equations.

Results: The best-fit equation was BEE [kcal/day] = 10 × (body weight)[kg] − 3 × (age)[y] + 125 (if male) + 750. Adjusted coefficient of determination was 81.0%. Root mean squared errors and accurate prediction in the validation set were 103 kcal/day and 78% for the new equation; 184 and 50 for Harris-Benedict; 209 and 38 for Oxford; 205 and 42 for Liu; and 140 and 63 for Ganpule.

Conclusions: This new equation is simpler and estimates BEE more accurately in Japanese patients with diabetes than the presently used equations do.

1. Introduction

Diet is the most fundamental and initial treatment for all patients with diabetes, and poor dietary management alone predicts poor subsequent glycemic control.[1] Estimation of daily energy expenditure for each patient is necessary for effective individualized diabetic meal planning. Resting energy expenditure (REE) or basal energy expenditure (BEE) is defined as the energy expended to maintain minimal metabolic activities, and is the main component of total daily energy expenditure. To estimate daily energy expenditure, REE or BEE is multiplied by a number specific to the various daily activities.

In healthy subjects, 65–90% of inter-individual variation in REE is explained by fat-free mass (FFM).[2] In patients with diabetes, FFM is also the main factor in REE and BEE,[3–5] and there is no difference in FFM-adjusted REE between mildly hyperglycemic patients and controls.[6] In clinical practice, BEE or FFM are not usually available. Equations factoring body weight, height, age and sex are widely used for clinical estimation of the daily energy requirement of patients with diabetes.[7] However, there has been little investigation of the comparative validity of these equations.

The existing predictive equations derived from Caucasians are unevenly applied to non-Caucasians, tending to overestimate energy expenditure.[8–11] This accords with the recent finding from the basal metabolic rate database that BEE is higher in Caucasians than in non-Caucasians.[12] However, REE is similar in Asians and Caucasians after adjustment for FFM, and BEE in Indians and

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Australians is similar after adjustment for FFM and fat mass.[13,14] To date, there are few equations to estimate energy expenditure specifically in Asian populations.[10,15]

Differences in the measurement technique of REE can cause biases.[12] In most studies evaluating energy expenditure, REE has been used rather than BEE. However, REE is defined less rigorously than BEE and is influenced by physical and psychological stress and ambient and body temperature.[16–18] Since BEE is measured early in the morning before the subject begins any physical activity and at least 10 h after ingestion of any food, drink, or nicotine, it remains remarkably constant on a daily basis.[16,18]

In the present study, by measuring BEE under strict conditions, we developed a new equation for estimation of BEE in Japanese patients with diabetes for use in a clinical setting.

2. Patients, materials and methods

2.1. Patients

Japanese patients with type 1 or type 2 diabetes admitted to the Department of Diabetes and Clinical Nutrition, Kyoto University Hospital, Kyoto, Japan for diabetes self-management education during the period of December 2007 through September 2009 were recruited for derivation study. Written, informed consent was obtained from all participants. During hospital stay, the participants had a prescribed diet with or without medications including oral hypoglycemic agents and insulin according to the treatment guide for diabetes of the Japan Diabetes Society.[19] Their physical activity was not restricted, but they did not engage in vigorous exercise. Participants were screened by medical history, physical examination, and laboratory testing to assure the absence of hepatic, pulmonary, thyroid, cardiac and renal dysfunction, macroalbuminuria, inflammatory diseases, and malignant tumors. Those who took steroids or beta blockers or had physical disabilities were excluded. The study protocol was approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee.

2.2. Indirect calorimetry

Basal energy expenditure (BEE) was measured in the morning under glycemic control with prescribed diet (29.1 ± 2.5 kcal/kg of standard body weight per day consisting of 52% carbohydrate, 20% protein, and 28% fat in energy component) and with medications when needed. Standard body weight (kg) was calculated by multiplying 22 (kg/m^2) by square of height (m). Whole-body oxygen consumption (VO_2) and carbon dioxide production (VCO_2) was measured for more than 10 min with indirect calorimetry (AE300S, Minato Medical Science, Osaka, Japan) by one investigator (KI) at the bedside of each patient under the strict condition described previously.[5,16,17] Briefly, an afebrile patient in a post-absorptive state after an overnight fast (14 h) with <180 mg/dL capillary plasma glucose remained in a supine position after waking on the bed in the ward without smoking or taking caffeine, and the measurements were performed at room temperature between 22 °C and 27 °C. After discarding the initial 5 min of recording, we took 5-min of data, in accord with the steady state definition,[17] during which the coefficient of variation for VO_2 per minute and VCO_2 per minute was achieved ≤10%, and applied them to the Weir formula with 24-h urinary urea nitrogen.[20]

2.3. Anthropometry and body composition

Height was measured on the day of admission. Body weight, skinfold thickness, and waist circumference were measured immediately after the measurement of BEE by one investigator (KI). Triceps-skinfold thickness (TSF) and mid-upper arm circumference (MAC) were measured in the non-dominant arm with the elbow bent at 90°. The physical markers were measured at least twice, and their respective mean values expressed according to Japanese standard method.[21] Arm muscle circumference (AMC) and arm muscle area (AMA) were calculated; AMC [cm] = MAC [cm] − π × TSF [mm]/10, AMA [cm^2] = (AMC [cm])^2 / 4π. Waist circumference was measured at the mid-point between the lowest rib and the iliac crest in a standing position at the end of gentle expiration keeping the measuring tape horizontal and just fitted to the skin. Hip circumference was measured at the widest part of the hip while standing. FFM and fat mass were measured by dual energy X-ray absorptiometry scanner (Discovery, Hologic, Bedford, MA, USA) within 3 days before and after measurement of BEE.

2.4. Other measurements

Glycated hemoglobin was measured by use of HPLC (ADAMS™ A1C HA8180, Arcray, Kyoto, Japan) and expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value [%] calculated by the formula HbA1c [%] = HbA1c [Japan Diabetes Society (JDS)] [%] + 0.4 [%], which considers the relational expression of HbA1c (JDS) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP).[22] Capillary glucose before each meal was measured by glucose meter (One Touch Ultra™, Johnson & Johnson, New Brunswick, NJ, USA) and expressed as capillary plasma glucose (PG). As a parameter of glycemic control, mean preprandial PG for three consecutive days before the measurement of BEE and fasting PG (FPG) just before the measurement of BEE are shown.

2.5. Testing the new equation

A separate data set of Japanese patients with type 1 or type 2 diabetes admitted to the same department for the same purpose during the period of June 2005 through December 2007 was drawn from the medical records for validation study. Inclusion/exclusion criteria and dietary condition during hospital stay were similar to that of the derivation sample.

Whole-body VO_2 and VCO_2 was measured after an overnight fast (14–16 h) for more than 15 min with the same calorimetry by one investigator (MI) on the same condition. Each patient was conveyed from their ward to the examination room by a healthcare staff member in a wheel chair and they rested in bed in a supine position for 30 min before the measurement of BEE. BEE was calculated from VO_2 and VCO_2 by use of Elwyn formula (BEE [kcal/day] = 3.581 × VO_2 [L/day] + 1.448 × VCO_2 [L/day] − 32.4).[16] Body weight was measured on the day of calorimetry.

The protocol of this validation study was also approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee.

2.6. Statistical analysis

Numerical data are summarized as means ± SDs. Categorical data were treated as dummy variables.

We first explored good estimators for FFM and fat mass in anthropometric indices, such as body weight, height, TSF, AMA, waist circumference and hip circumference, because FFM and fat mass are known as two major estimators of BEE. Correlations between these variables were evaluated by Pearson's correlation analysis. Multiple linear regression analysis was then performed to evaluate the contribution of anthropometric indices, age, and sex to FFM and fat mass. Next, a best-fit equation to estimate BEE from anthropometric indices, age, and sex was explored by multiple

linear regression analysis with consideration of estimators of FFM and fat mass.

For testing the validity of our new equation and comparing it with existing prediction equations, we calculated measures of accuracy. The mean percentage difference between BEE estimated and measured (bias) was considered systematic error. The root mean squared error (RMSE) was considered to reflect each individual's error range unrelated to whether it was over or under estimation. The proportion of patients with BEE estimated within ±10% of BEE measured was considered another measure of accuracy.[23]

Data were analyzed by use of Stata 11.0 (Stata Corporation, College Station, TX, USA). Statistical significance was set at $P < 0.05$ (2-tailed).

3. Results

Data were obtained and analyzed in 68 patients, of which 7 had type 1 diabetes and 61 had type 2 diabetes. Mean glycated hemoglobin (HbA1c) on admission was as high as 10.5%, but mean fasting plasma glucose just before the measurement of BEE (FPG) was as low as 113.7 mg/dL due to the treatments during hospital stay (Table 1). Additional characteristics of patients in the derivation set and the results of measurement are shown in Table 1.

Body weight had the highest correlation with FFM ($r = 0.90$), followed by arm muscle area (AMA), height and hip circumference ($r = 0.84$, 0.75 and 0.73, respectively) (Table 2). Waist circumference had the highest correlation with fat mass ($r = 0.91$), followed by hip circumference, triceps-skinfold thickness (TSF) and body weight ($r = 0.79$, 0.78 and 0.75, respectively).

Table 1
Characteristics of patients (derivation set).

	All	Male	Female
No. of patients	68	39	29
Type of diabetes (type1/type2) (n)	7/61	4/35	3/26
Age (years)	59.8 ± 11.2 (range 19–78)	58.3 ± 10.3	61.8 ± 12.2
Height (cm)	161.3 ± 9.5	167.6 ± 6.0	152.9 ± 6.3
Body weight (kg)	62.8 ± 14.7 (range 34.6–113.6)	67.3 ± 16.0	56.7 ± 10.2
BMI (kg/m^2)	24.0 ± 4.7	23.9 ± 5.3	24.2 ± 3.8
FFM (kg)	47.7 ± 10.6	53.4 ± 9.4	39.9 ± 6.5
Fat mass (kg)	16.0 ± 7.0	14.8 ± 8.0	17.8 ± 4.9
TSF (mm)	15.9 ± 7.8	13.1 ± 6.5	19.8 ± 7.8
AMA (cm^2)	44.6 ± 10.2	48.9 ± 9.7	38.8 ± 7.9
Waist (cm)	86.5 ± 12.4	86.2 ± 14.0	86.9 ± 10.3
Hip (cm)	91.3 ± 7.8	92.4 ± 8.5	89.8 ± 6.7
BEE (kcal/day)	1290 ± 217	1395 ± 210	1149 ± 130
FPG (mg/dL)	113.7 ± 25.8	113.3 ± 25.5	114.3 ± 26.6
PPPG (mg/dL)	143.5 ± 35.9	146.5 ± 39.7	139.3 ± 30.3
HbA1c (%)	10.5 ± 2.5	10.3 ± 2.4	10.8 ± 2.7
Duration of diabetes (years)	9.3 ± 7.8	10.9 ± 8.9	7.1 ± 5.5
Treatment			
Diet (kcal/SBW/day)	29.1 ± 2.5	28.9 ± 2.1	29.3 ± 3.0
Medications			
Ins only (n)	34	21	13
Ins + Met (n)	10	4	6
Ins + SU (n)	3	2	1
Ins + SU + Met (n)	1	0	1
SU (n)	8	5	3
SU + Met (n)	5	2	3
Met only (n)	4	3	1
None (n)	3	2	1

Data are means ± SD. BMI, body mass index; FFM, fat-free mass; TSF, triceps-skinfold thickness; AMA, arm muscle area; Waist, waist circumference; Hip, hip circumference; BEE, basal energy expenditure; FPG, fasting plasma glucose just before the measurement of BEE; PPPG, mean preprandial plasma glucose for three consecutive days before the measurement of BEE; HbA1c, glycated hemoglobin; SBW, standard body weight; Ins, insulin; SU, sulfonylurea; Met, metformin.

Table 2
Correlations between FFM, fat mass and anthropometric indices.

	FFM	FM	Ht	Wt	TSF	AMA	Waist	Hip
FFM	1.00	–	–	–	–	–	–	–
FM	0.38†	1.00		–	–	–	–	–
Ht	0.75‡	−0.12	1.00	–	–	–	–	–
Wt	0.90‡	0.75‡	0.49‡	1.00	–	–	–	–
TSF	0.13	0.78‡	−0.30*	0.46‡	1.00	–	–	–
AMA	0.84‡	0.48†	0.50‡	0.83‡	0.07	1.00	–	–
Waist	0.56‡	0.91‡	0.02	0.83‡	0.70‡	0.60‡	1.00	–
Hip	0.73‡	0.79‡	0.28*	0.90‡	0.50‡	0.73‡	0.83‡	1.00

Pearson's correlation coefficients ($n = 68$):*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$. FFM, fat-free mass; Ht, height; Wt, weight; TSF, triceps-skinfold thickness; AMA, arm muscle area; Waist, waist circumference; Hip, hip circumference.

In regression analysis for FFM, we selected body weight, AMA, height and hip circumference as potent estimators together with other plausible estimators, age and sex. As both AMA and hip circumference were strongly correlated with body weight and AMA was also strongly correlated with hip circumference, to analyze these three variables separately, we used three sets of independent variables, (body weight, height, age and sex), (AMA, height, age and sex), and (hip circumference, height, age and sex). The regressions revealed that all four variables were significant estimators for FFM in the first analysis (model 1 in Table 3), that AMA and height were significant in the second analysis (model 2) and that hip circumference, height and sex were significant in the third analysis (model 3). The first four variables accounted for 95% of variation in FFM, the second two variables 84%, and the third three variables 87%. For fat mass, we selected another three sets of independent variables, (waist circumference, age and sex), (hip circumference, TSF, age and sex) and (body weight, TSF, age and sex) because waist circumference had a strong correlation with hip circumference, TSF and body weight, and hip circumference also had a strong correlation with body weight. In the first analysis, only waist circumference and sex were significant estimators for fat mass, accounting for 86% of fat mass (model 4). In the second analysis, hip circumference, TSF and age were significant, accounting for 84% of fat mass (model 5). In the third analysis, body weight, TSF, age and sex were significant, accounting for 87% of fat mass (model 6).

We performed regression analysis to determine BEE with the most influential estimators (FFM and fat mass) and plausible additional estimators (age and sex), which together explained 81% of the variation (model 7 in Table 3). We then performed backward stepwise estimation, using three sets of variables, (significant variables in model 1 and 6; body weight, height, TSF, age and sex), (significant variables in model 2 and 4 plus age; AMA, height, waist, sex and age), and (significant variables in model 3 and 5; hip circumference, height, TSF, age and sex). The best fitting regression for BEE consisted of body weight, age and sex in the first analysis (model 8), height, waist, age and sex in the second analysis (model 9), and hip circumference, height, TSF and sex in the third analysis (model 10). The adjusted coefficient of determination in model 8 was 81%, which was larger than the 73% in model 9 and the 77% in model 10. The detailed results of model 8 are shown in Table 4.

We then simplified the resultant equation of model 8 to make it easy to use in clinical practice.

$$\mathrm{BEE} = 10 \times \text{body weight} - 3 \times \text{age} + 125(\text{if male}) + 750.$$

[BEE (kcal/day), body weight (kg), age (year)]

The bias of this equation in the derivation set was − 1.2 ± 6.4%; RMSE was 94 kcal/day; accurate estimation was 91%.

Table 3
Results of multiple regressions for FFM, FM and BEE.

	Adj. R^2		Model
FFM = −26.9 + 0.5 × Wt + 0.3 × Ht − 0.1 × Age + 3.9 × Sex[a]	0.95		1
FFM = −60.8 + 0.6 × AMA + 0.5 × Ht[b]	0.84		2
FFM = −102.8 + 0.8 × Hip + 0.5 × Ht + 4.5 × Sex[c]	0.87		3
FM = −26.3 + 0.5 × Waist − 2.6 × Sex[c]	0.86		4
FM = −45.4 + 0.5 × Hip + 0.4 × TSF + 0.1 × Age[d]	0.84		5
FM = −14.3 + 0.4 × Wt + 0.2 × TSF + 0.1 × Age − 5.1 × Sex	0.87		6
BEE = 691.6 + 11.6 × FFM + 8.9 × FM − 2.6 × Age + 106.7 × Sex	0.81		7
BEE = 748.4 + 10.4 × Wt − 3.0 × Age + 125.4 × Sex[e]	0.81	Model (1 + 6)	8
BEE = −332.3 + 6.1 × Ht + 9.5 × Waist − 4.6 × Age + 147.1 × Sex[f]	0.73	Model (2 + 4)	9
BEE = −1139.3 + 13.8 × Hip + 6.1 × Ht + 5.6 × TSF + 157.9 × Sex[c]	0.77	Model (3 + 5)	10

FFM, fat-free mass (kg); FM, fat mass (kg); BEE, basal energy expenditure (kcal/day); Wt, body weight (kg); Ht, height (cm); AMA, arm muscle area (cm^2); Hip, hip circumference (cm); Waist, waist circumference (cm); TSF, triceps-skinfold thickness (mm); Adj. R^2, adjusted coefficient of determination.
[a] Male = 1, female = 0.
[b] Age and sex were not significant determinants when added to this model.
[c] Age was not a significant determinant when added to this model.
[d] Sex was not a significant determinant when added to this model.
[e] Height and TSF were not significant determinants when added to this model.
[f] AMA was not a significant determinant when added to this model.

We then tested this new equation in a separate validation data set comparing it with existing equations (Table 5). Characteristics of patients in the validation set are shown in Table 6. The ratio of patients with type 1 and 2 diabetes was almost the same as in the derivation set. Mean age was similar to that in the derivation set, but there were more obese people in the validation set. FPG and PPPG, which represent the glycemic levels around the time of measurement of BEE, were higher, but HbA1c on admission was lower than that in the derivation set. Mean duration of diabetes was similar to that in the derivation set. Prescribed diet was almost the same as in the derivation set, but treatment with insulin was more common in the derivation set. The bias of the new equation was 4.8 ± 7.7%, RMSE was 103 kcal/day, and the percent of patients estimated within ±10% of measured value was 78%. The new equation had better validity than Harris and Benedict equation, Oxford equation, or the Liu equation and Ganpule equation (Table 7).

4. Discussion

We report a new equation to estimate BEE in Japanese patients with diabetes with higher accuracy compared to existing equations. As in other BEE estimation equations, the main estimator was FFM and additional estimators were fat mass, age and sex.[2–4,24] Stepwise estimation analysis of the estimators of FFM and fat mass in the present study revealed that no other indices improved fitting of the equation for BEE except body weight, age and sex. Although anthropometric indices are good estimators for body composition and they improve predictability of certain equations for BEE,[25,26] they were not as effective as body weight in the present study.

Table 4
Detailed result of model 8.

Dependent variable BEE[a]	Coef.[b]	95% CI[c]		Std. coef.[d]	$P > t$	Adj. R^{2e}
Independent variables						
Intercept	748.4	562.6	934.1		<0.001	0.810
Wt (kg)	10.4	8.6	12.1	0.70	<0.001	
Age (year)	−3.0	−5.2	−0.9	−0.16	0.007	
Sex (male = 1, female = 0)	125.4	75.6	175.1	0.29	<0.001	

[a] BEE, basal energy expenditure (kcal/day).
[b] Coef., partial regression coefficient.
[c] CI, confidence interval.
[d] Std. coef., standardized coefficient.
[e] Adj. R^2, adjusted coefficient of determination.

This accords with the finding that the standard error of the estimate of REE prediction by weight, height, sex and age was well within the range of the standard error of estimates from other FFM-derived prediction equation.[27] Since ethnic difference in BEE is derived from differences in body composition,[13] an ethnicity-specific constant term could more precisely estimates BEE,[4,12] but an ethnicity-specific coefficient of anthropometry is also valid.

We compared our new equation with existing equations such as Harris and Benedict, Oxford, Liu, and Ganpule because the Harris and Benedict equation is widely known in clinical practice in Japan, the Oxford equation was recently developed from a large number of subjects including many ethnicities, and the Liu equation and Ganpule equations were derived from Chinese and Japanese subjects, respectively.[7,10,12,15] The validation analysis revealed better validity of the new equation in Japanese patients with diabetes than any of the other equations.

BEE was measured under strictly controlled conditions in the present study. In addition, we confirmed the FPG of the patients to be < 180 mg/dL just before the measurement of BEE, since BEE is unaffected by the glucose level when its value is < 180 mg/dL.[5,6] As the mean FPG of patients in the derivation set was improved to 114 mg/dl just before the measurement of BEE due to the prescribed diet and medications during hospital stay, in contrast to the poor mean FPG level as high as 170 mg/dl just after admission, clinical application of this equation to patients with stable glycemic control is recommended.

Table 5
Equations to estimate BEE.[a]

	Formula	Reference
New equation	10 W − 3 A + 125 (if male) + 750[b,c]	
Harris and Benedict (1919)	Male: 13.75 W + 5.00 H − 6.76 A + 66.47[d] Female: 9.56W + 1.85 H − 4.68 A + 655.10	7
Oxford (2005)	Male: 18–30 years; 16.0 W + 545 30–60 years; 14.2 W + 593 60 + years; 13.5 W + 514 Female: 18–30 years; 13.1 W + 558 30–60 years; 9.74 W + 694 60 + years; 10.1 W + 569	12
Liu (1995)	13.88 W + 4.16 H−3.43 A − 112.40 (if female) + 54.34	10
Ganpule (2007)	(48.1 W + 23.4 H−13.8 A−547.3(if female) − 423.5)/4.186	15

[a] BEE, basal energy expenditure (kcal/day).
[b] W, weight (kg).
[c] A, age (year).
[d] H, height (cm).

Table 6
Characteristics of patients (validation set).

	All	Male	Female
No. of patients	60	36	24
Type of diabetes (type1/type2) (n)	6/54	3/33	3/21
Age (years)	58.9 ± 13.3 (range 21–82)	55.8 ± 13.5	63.6 ± 11.8
Body weight (kg)	66.9 ± 18.2 (range 41.1–138.0)	70.0 ± 19.2	62.2 ± 15.8
BMI (kg/m^2)	25.7 ± 6.7	24.6 ± 6.2	27.5 ± 7.2
BEE (kcal/day)	1260 ± 219	1342 ± 225	1137 ± 141
FPG (mg/dL)	132.1 ± 20.8	130.8 ± 20.5	133.9 ± 21.6
PPPG (mg/dL)	157.6 ± 32.3	156.7 ± 34.8	159.0 ± 28.9
HbA1c (%)	9.3 ± 1.5	9.5 ± 1.8	9.0 ± 1.1
Duration of diabetes (years)	10.0 ± 8.8	9.3 ± 8.4	11.0 ± 9.5
Treatment			
Diet (kcal/SBW/day)	29.4 ± 2.8	29.4 ± 3.0	29.4 ± 2.5
Medications			
Ins only (n)	28	15	13
Ins + Met (n)	2	1	1
Ins + SU (n)	2	2	0
SU (n)	13	9	4
SU + Met (n)	4	4	0
Met only (n)	3	1	2
None (n)	8	4	4

Data are means ± SD. BMI, body mass index; BEE, basal energy expenditure; FPG, fasting plasma glucose just before the measurement of BEE; PPPG, mean preprandial plasma glucose for three consecutive days before the measurement of BEE; HbA1c, glycated hemoglobin; SBW, standard body weight; Ins, insulin; SU, sulfonylurea; Met, metformin.

There are potential weaknesses of the present study. First, only a small number of patients with type 1 diabetes was included. However, no difference in the value of BEE between patients with type 1 and type 2 diabetes has been described to date. In type 1 diabetes, the elevated energy expenditure is observed only during insulin deprivation, and it returns to normal level by insulin treatment.[28] In type 2 diabetes, there is no difference in FFM-adjusted REE between mildly hyperglycemic patients and controls.[6] Thus, when they are under treatment, BEE in both type 1 and type 2 diabetes patients can be assumed comparable to that in healthy people. In addition, our validation data set has more background in common with the derivation set than the general population of Japanese patients with diabetes. We also did not measure BEE of healthy Japanese for comparison. It remains to be established whether or not the difference in BEE between Japanese patients with diabetes and healthy Japanese is insignificant when FPG of patients are <180 mg/dL.

Table 7
Evaluation of equations in validation set.

Equation	Estimated BEE per body[a]	Estimated BEE per kg Wt[b]	Bias[c]	RMSE[d]	Accurate estimation[e]
New equation	1317 ± 227	20.2 ± 2.3	4.8 ± 7.7	103	78
Harris and Benedict	1388 ± 309	21.1 ± 2.2	9.8 ± 9.4	184	50
Oxford	1420 ± 309	21.6 ± 2.3	12.3 ± 9.5	209	38
Liu	1407 ± 321	21.3 ± 2.1	11.1 ± 10.9	205	42
Ganpule	1323 ± 295	20.1 ± 2.4	4.5 ± 10.5	140	63

$n = 60$. Data are means ± SD.
[a] Estimated BEE per body, mean basal energy expenditure estimated per body (kcal/day).
[b] Estimated BEE per kg Wt, mean basal energy expenditure estimated per kg body weight (kcal/kg/day).
[c] Bias, mean percentage error between estimated and measured BEE ((BEE estimated − BEE measured)/BEE measured) (%).
[d] RMSE, root mean squared error (kcal/day).
[e] Accurate estimation, percent of the patients estimated by each equation within ±10% of measured value (%).

The values estimated from the proposed equation in the present study are well matched to the reference values for Japanese BEE (Dietary reference intakes) reported in healthy Japanese as values per body weight among different groups for age and sex.[29] In addition, when mean BEE values were calculated by the proposed equation from mean body weight and age reported in other studies including healthy Japanese and Chinese, estimated BEE values were in good agreement with measured values.[10,15,30]

We report a new equation using parameters readily available in clinical practice to estimate BEE of patients with diabetes in an Asian population. Further studies are required to in a wide range of populations to determine its usefulness in Asian clinical settings.

Statement of authorship

The authors' responsibilities were as follows: KI, SF, MG, and TK designed research; KI, CY, AH, MI, KN and KS conducted research; KI, MG, and SF analyzed data; KI and SF wrote the paper; and NI supervised research. All authors read and approved the final manuscript.

Conflict of interest

None of the authors had any conflict of interest.

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A hospital-based cross-sectional study to develop an estimation formula for 2-h post-challenge plasma glucose for screening impaired glucose tolerance☆

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ABSTRACT

Aims: To create and validate an estimation formula for 2-h post-challenge plasma glucose (2-hPG) as an alternative to oral glucose tolerance test (OGTT) for impaired glucose tolerance (IGT) screening.

Methods: 380 Japanese subjects (57.6% males, aged 58.5 (14.0); mean (SD) years) undergoing OGTT were included in this hospital-based cross-sectional study mainly at Kyoto University Hospital between 2000 and 2011. We determined the main predictive variables of 2-hPG from clinical variables and separated the subjects randomly into two groups: a derivation group to construct an estimation formula of 2-hPG on the basis of predictive variables and a validation group to evaluate the accuracy of the formula.

Results: Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) were highly correlated with 2-hPG measured by OGTT. Multiple linear regression analysis showed that estimated 2-hPG (e2-hPG) was calculated by the formula: e2-hPG = 1.66 × FPG (mmol/l) + 1.63 × HbA1c (%) − 10.11 (R^2, coefficient of determination = 60.2%). When the cut-off value was set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity, specificity, and negative predictive value (NPV) were 83.3%, 44.1%, and 74.3%, respectively. When the cut-off value was set lower (7.2 mmol/l), these values were 94.4%, 30.5%, and 85.7%, respectively. The area under the receiver operating characteristic (ROC) curve was 0.68.

Conclusions: This high-sensitive estimation formula may be a useful alternative to OGTT for IGT screening. For the levels ≤7.2 mmol/l, this formula may also be useful in cross-sectional study to identify people whose glucose tolerance is normal.

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1. Introduction

Impaired glucose tolerance (IGT) represents high risk not only for development of type 2 diabetes mellitus (DM) but also for cardiovascular disease [1–5]. A meta-analysis has shown that subjects with IGT have an annualized relative risk (95% confidence interval) for progression to DM of 6.35 (4.87–7.82) compared to those with normal glucose tolerance (NGT) [5]. Furthermore, it is known that lifestyle and pharmacological interventions for IGT are effective in preventing or delaying type 2 DM [6–9]. Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), Collaborative Analysis of Diagnostic Criteria in Asia (DECODA), and Funagata Diabetes study have shown a strong association between postprandial hyperglycemia such as that seen in IGT and cardiovascular risk [3,10,11]. Cardiovascular mortality in subjects with IGT is similar to that in type 2 DM and much greater than that in impaired fasting glucose (IFG) [12]. Thus, detection of IGT is critical for preventing type 2 DM and reducing diabetic complications.

The "gold standard" method for diagnosing IGT defined by 1998 World Health Organization (WHO) criteria uses the level of 2-h post-challenge plasma glucose (2-hPG) during oral glucose tolerance test (OGTT) [13]. However, it is difficult to implement this test in a large population due to time and expense requirements [14]. For this reason, alternative methods for identifying IGT without OGTT have been investigated. Neither fasting plasma glucose (FPG) nor hemoglobin A1c (HbA1c) can be used singly to predict IGT due to the low detection rate [15–18]; however, combined use of FPG and HbA1c has been shown to be more effective [19]. Age, gender and body mass index (BMI) also have effects on the accuracy of IGT screening with single use of FPG an HbA1c [17,20–23]. At this point in time, there is no validated estimation formula to screen IGT that takes the predictive variables into account.

We screened for predictive variables of 2-hPG in hospital-based Japanese subjects and were able to develop an estimation formula for 2-hPG based on these predictive variables. We also validated the derived estimation formula for IGT screening which would be available for clinical settings.

2. Subjects and methods

2.1. Subjects

Three hundred eighty Japanese subjects not taking oral hypoglycemic agents and undergoing 75 g OGTT were recruited in this cross-sectional study at the Department of Diabetes and Clinical Nutrition, Kyoto University Hospital and other hospitals during the period of December 2000 through October 2011. Inclusion criteria were: family history of type 2 DM, past history of gestational diabetes, more than 20 years old, BMI > 25 kg/m^2, positive result of urine glucose test or hyperglycemia at examination for regular medical checkup. Exclusion criteria were: history of type 1 DM, endocrine diseases, operations such as gastrectomy and pancreatectomy, treatment with medications known to affect glucose metabolism, and all conditions that might lead to misinterpretation of HbA1c, such as anemia. The study protocol was approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee and conducted according to the Declaration of Helsinki. Informed consent was obtained from all subjects.

2.2. Measurements

Physical variables (age, gender, height, body weight, BMI) and laboratory variables (plasma glucose, immunoreactive insulin (IRI), HbA1c) were taken. Each standard OGTT was administered according to the National Diabetes Data Group recommendations [24]. Blood samples for determination of blood glucose levels were collected at 0, 30, 60, 90, and 120 min after oral administration of 75 g glucose. As the index of insulin secretion, we used the insulinogenic index, the change in the ratio of insulin to glucose level during the first 30 min of OGTT: (IRI 30 min − fasting immunoreactive insulin (F-IRI))/(PG 30 min − FPG) [25,26].

2.3. Laboratory examination

PG was measured by glucose oxidase method using the Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). IRI was measured by two-site radioimmunoassay (Insulin Riabead II, Dainabot, Tokyo, Japan). HbA1c was measured using high performance liquid chromatography (HPLC) and is expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the formula: HbA1c (NGSP value) (%) = 1.02 × HbA1c (Japan Diabetes Society value) (%) + 0.25 [27]. The HbA1c measurements in International Federation of Clinical Chemistry (IFCC) units (mmol/mol) were also calculated.

2.4. Definitions

According to the 1998 WHO diagnostic criteria [13], the subjects were classified into the following four subgroups: NGT; FPG mmol/l < 6.1 mmol/l and 2-hPG < 7.8 mmol/l, IGT; FPG < 7.0 mmol/l and 7.8 mmol/l ≤ 2-hPG < 11.1 mmol/l, IFG; 6.1 mmol/l ≤ FPG < 7.0 mmol/l and 2-hPG < 7.8 mmol/l, DM: 7.0 mmol/l ≤ FPG or 11.1 mmol/l ≤ 2-hPG.

As shown in the supplemental table, sensitivity was defined as the proportion of subjects with IGT by OGTT who were predicted to have a positive result by the estimation formula: $\{a/(a+c)\} \times 100$ (%). Specificity was defined as the proportion of subjects without IGT who were predicted not to have IGT; $\{d/(b+d)\} \times 100$ (%). Positive predictive value (PPV) was defined as the proportion of subjects predicted to have IGT who were truly IGT by OGTT; $\{a/(a+b)\} \times 100$ (%). Negative predictive value (NPV) was defined as the proportion of subjects predicted not to have IGT who were truly not IGT by OGTT; $\{d/(c+d)\} \times 100$ (%). A receiver operating characteristic (ROC) curve was constructed by plotting sensitivity against the false-positive rate (100 − specificity) (%) over a range of cut-off values.

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2.5. *Statistical analyses*

Statistical analyses were performed according to the following steps.

(1) Background of the subjects: results were expressed as mean (standard deviation: SD or mean standard error: SE). Differences between the two groups were compared using the Student's *t*-test. *P* value < .05 (two-tailed) was considered as statistically significant.
(2) The relationship between two variables: the relationship between measured 2-h post-challenge plasma glucose (m2-hPG) and clinical variables was evaluated by scatter plot and Pearson's correlation coefficient (*r*).
(3) Derivation and validation: to avoid over-fitting of the estimation formula, two-step procedure was used. A total of 380 subjects were randomly divided into two groups at 1 to 1 ratio, a derivation group for constructing the estimation formula to screen IGT and a validation group without DM for evaluating the accuracy of the derived estimation formula.
(4) Construction of the estimation formula in the derivation group: higher values of correlation coefficient demonstrated in the previous step were regarded as predictive variables for m2-hPG, and the estimation formula of 2-hPG with these variables was then constructed by multiple linear regression analysis.
(5) Evaluation of the derived estimation formula in the validation group: the diagnostic characteristics such as sensitivity, specificity, PPV, and NPV of this derived estimation formula were calculated. The performance of the estimation formula was assessed by calculating the area under the ROC curve based on sensitivity and specificity [28]. In addition, we determined the adequate cut-off value by considering these values.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

3. Results

3.1. *Characteristics of the subjects*

Clinical characteristics of the subjects are shown in Table 1. Results of age and HbA1c are shown as mean (SD); the others are shown as mean (SE). Because the number of IFG (*n* = 9) was too small for analysis, we compared physical and metabolic

Table 1 – Characteristics of the subjects.

	NGT	IFG	IGT	DM	Total
Number (%)	126 (33.2)	9 (2.4)	106 (27.9)	139 (36.6)	380 (100)
Male (%)	60 (47.6)	6 (66.7)	50 (47.2)	103 (74.1)	219 (57.6)
Age (year)†	54.5 (15.5)	61.4 (15.5)	57.0 (13.3)	63.2 (11.6) **vs. NGT	58.5 (14.0)
BMI (kg/m^2)‡	23.5 (4.8)	26.1 (2.4)	25.9 (5.6) **vs. NGT *vs. DM	24.4 (3.5)	24.6 (4.7)
HbA1c (%)†	5.9 (0.6)	6.5 (0.6)	6.2 (0.5) ***vs. NGT	7.0 (0.6) ***vs. NGT ***vs. IGT	6.4 (0.7)
HbA1c (mmol/mol)	40.9 (6.1)	47.5 (6.3)	44.0 (5.2) ***vs. NGT	53.1 (6.5) ***vs. NGT ***vs. IGT	46.0 (8.0)
F-IRI (pmol/l)†	36.0 (24.8)	50.7 (32.6)	43.7 (28.1) *vs. NGT	41.7 (25.0) *vs. NGT	40.6 (26.2)
2-hIRI (pmol/l)†	222.3 (155.6)	354.7 (282.4)	351.9 (217.9) ***vs. NGT	274.2 (180.5) *vs. NGT **vs. IGT	282.7 (194.6)
FPG (mmol/l)†	5.1 (0.5)	6.5 (0.2)	5.5 (0.6) ***vs. NGT	7.0 (1.2) ***vs. NGT ***vs. IGT	6.0 (1.2)
2-hPG (mmol/l)†	6.2 (1.1)	6.8 (0.7)	9.4 (0.9) ***vs. NGT	14.6 (2.8) ***vs. NGT ***vs. IGT	10.2 (4.0)
Inslinogenic index‡	65.1 (38.4)	31.2 (24.2)	38.5 (24.6) ***vs. NGT	15.8 (6.5) ***vs. NGT ***vs. IGT	33.8 (17.9)

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; F-IRI, fasting immunoreactive insulin; 2-hIRI, 2-h immunoreactive insulin; FPG, fasting plasma glucose; 2-hPG, 2-h post-challenge plasma glucose; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, diabetes mellitus; SD, standard deviation; SE, standard error.

* $P < .05$.
** $P < .01$.
*** $P < .001$.
† Data are described means (SD).
‡ Data are described means (SE).

variables among the three other groups (NGT, IGT, and DM). The total of mean age (SD) is 58.5 (14.0) years and 57.6% are males. Age of DM subjects is the highest ($P < .01$ vs. NGT) and BMI of IGT subjects is the highest ($P < .01$ vs. NGT and $P < .05$ vs. DM, respectively) among the three groups. HbA1c is significantly higher, while insulinogenic index is significantly lower in subjects with DM than in those with NGT and IGT. Glucose and plasma insulin levels during OGTT are given in the supplemental figure. For plasma glucose, subjects with NGT are those with 5.1 (0.5) mmol/l of FPG and 6.2 (1.1) mmol/l of 2-hPG (Supplemental Figure A). For subjects with IFG, FPG is 6.5 (0.2) mmol/l and for those with IGT, 2-hPG is 9.4 (0.9) mmol/l. For subjects with DM, FPG is 7.0 (1.2) mmol/l and 2-hPG is 14.6 (2.8) mmol/l. Early-phase insulin secretion shown in Supplemental Figure B is already decreased in the IGT stage as shown in the previous Japanese study [29].

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2013.05.013.

3.2. *Relationship between two variables*

We evaluated the relationship among all pairs of continuous variables using scatter plot and calculated Pearson's correlation coefficient. Using this procedure, we found the predictive variables for m2-hPG in this target population.

Fig. 1 shows the scatter plot of m2-hPG and FPG (Fig. 1A) and that of m2-hPG and HbA1c (Fig. 1B) in OGTT of all subjects. The correlation coefficient (r) between two variables is 0.74 and 0.67, respectively. Except for these two variables, there is no higher correlation coefficient than 0.5 between m2-hPG and the physical, metabolic variables.

3.3. *Construction of the estimation formula in the derivation group*

First, all subjects were randomly divided 1:1 into the derivation group and the validation group to avoid over-fitting.

At a stage prior to this, FPG and HbA1c were substantiated as main predictive variables for m2-hPG, then the estimation formula with these variables was constructed by using the multiple linear regression analysis in the derivation group. The obtained linear regression equation (estimation formula) is e2-hPG = 1.66 × FPG (mmol/l) + 1.63 × HbA1c (NGSP: %) − 10.11, or e2-hPG = 1.66 × FPG (mmol/l) + 0.15 × HbA1c (mmol/mol) − 6.61. R^2 (coefficient of determination) is 60.2%. Moreover, we analyzed to determine whether inclusion of other variables known to affect 2-hPG improved the accuracy of this formula. Even though other variables such as BMI, age, gender, and IRI are included in the regression model, R^2 remains substantially unchanged (data not shown). FPG and HbA1c are thus the best predictors of 2-hPG based on the linear regression model and we concluded the estimation formula of 2-hPG shown in Fig. 2 in this derivation group.

3.4. *Evaluation of the derived estimation formula in the validation group*

The accuracy of this estimation formula: diagnostic characteristics such as sensitivity, specificity, PPV, NPV, and the area under the ROC curve were calculated in the validation group. Table 2 shows the results of sensitivity, specificity, PPV, and NPV for every 0.2 mmol/l of e2-hPG in this group. When the cut-off value is set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity, specificity and NPV of this formula are 83.3%, 44.1%, and 74.3%, respectively. When the cut-off value is ≤7.8 mmol/l of e2-hPG, sensitivity is retained more than 80%, and when lowered to 7.2 mmol/l of e2-hPG, sensitivity, specificity, and NPV are 94.4%, 30.5% and 85.7%, respectively. These results are plotted in Fig. 3. In the validation group, the ROC curves obtained by calculating sensitivity and specificity at possible cut-off points of estimated 2-hPG are also shown in Fig. 3. The performance of the estimation formula was assessed by calculating the area under the ROC curve, which is 0.68.

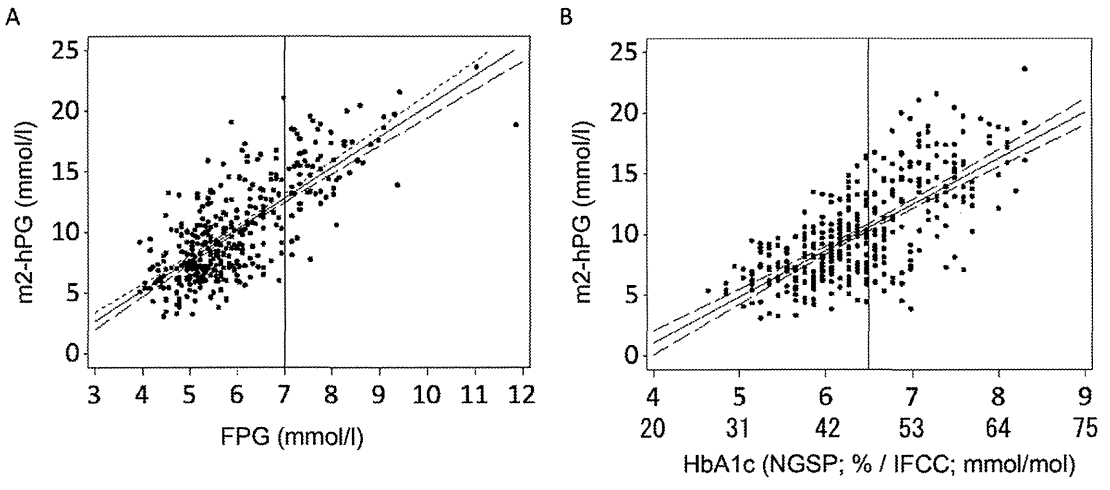

Fig. 1 – Scatter plot of measured 2-hPG (m2-hPG) and FPG in OGTT (A) and that of m2-hPG and HbA1c in OGTT (B); the correlation coefficient (r) = 0.74, 0.67, respectively.

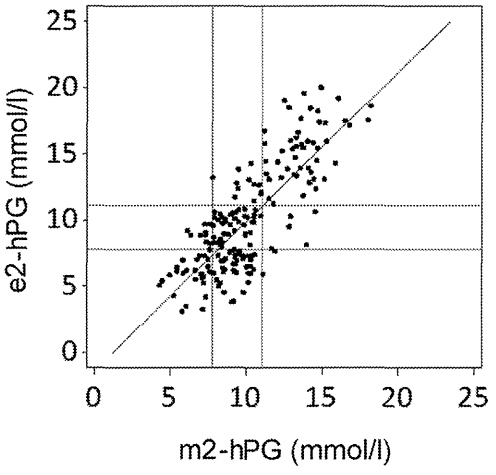

Fig. 2 – Scatter plot and the estimation formula of estimated 2h-PG (e2-hPG) in derivation group. e2-hPG = 1.66 × FPG (mmol/l) + 1.63 × HbA1c (%) − 10.11 (R^2 = 60.2%). e2-hPG = 1.66 × FPG (mmol/l) + 0.15 × HbA1c (mmol/mol) − 6.61 (R^2 = 60.2%).

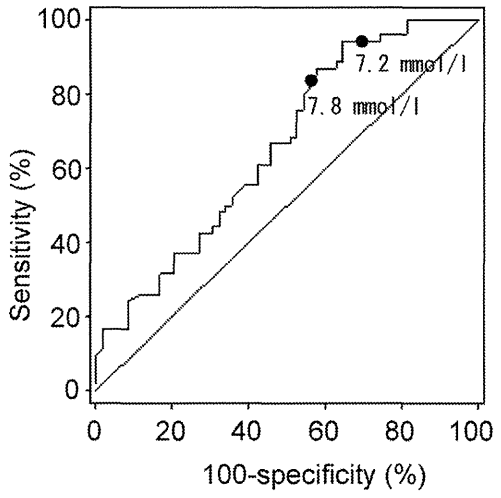

Fig. 3 – Receiver operating characteristic (ROC) curves obtained by calculating sensitivity and specificity at possible cut-off points of estimated 2-hPG in validation group. The horizontal axis shows the (100 − specificity) (%) and the vertical axis shows the sensitivity (%). When the cut-off value is set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity and specificity are 83.3% and 44.1%, respectively. When the cut-off value is set lowered to 7.2 mmol/l of e2-hPG, those are 94.4% and 30.5%, respectively. The area under the ROC curve is 0.68.

4. Discussion

In the present study, we found that the main predictive variables associated with m2-hPG are FPG and HbA1c from the data of 380 hospital-based Japanese subjects. We were able to develop a validated estimation formula for 2-hPG with these variables as an alternative to OGTT for IGT screening.

Studies have reported that lifestyle and pharmacological intervention for subjects with IGT can prevent or delay the onset of type 2 DM [6–9]. Detection and early intervention for these high-risk individuals is critical for preventing type 2 DM and reducing diabetic complications. Even though OGTT is the "gold standard" method for diagnosing IGT, in a large population that method is time-consuming and expensive [14].

Some studies have investigated alternative methods for evaluating IGT without performing OGTT [15–23]. The single use of FPG or HbA1c is not suitable for IGT screening because of the low detection rate [15–18]. It was reported in a systematic review that for detecting IGT by HbA1c or FPG separately, that sensitivity is around 50% [16]. Indeed, in our result, with single use of FPG or HbA1c, R^2 was 56.2% and 48.3%, respectively (Fig. 1), while using the estimation formula with both FPG and HbA1c, R^2 was 60.2% (Fig. 2) for IGT screening. This result is compatible with the previous study recommending the combined use of these two variables to be more effective than single use for detecting IGT [19]. But this study did not elucidate the influence of each of the variables on 2-hPG.

Table 2 – Summary of sensitivity, specificity, PPV, and NPV for every 0.2 mmol/l of estimated 2-hPG (e-2hPG) in the validation group.

Cut-off value of e2-hPG (mmol/l)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
6.8	96.3	23.7	53.6	87.5
7.0	96.3	25.4	54.2	88.2
7.2	94.4	30.5	55.4	85.7
7.4	87.0	37.3	56.0	75.9
7.6	87.0	40.7	57.3	77.4
7.8	83.3	44.1	57.7	74.3
8.0	70.4	47.5	55.1	63.6
8.2	66.7	52.5	56.3	63.3
8.4	61.1	57.6	56.9	61.8
8.6	53.7	62.7	56.9	59.7
8.8	50.0	66.1	57.4	59.1

PPV, positive predictive value; NPV, negative predictive value.

Caucasians generally have higher BMI and insulin resistance is important in progression from NGT to IGT [30], while Asians including Japanese are generally less obese and have higher insulin sensitivity than Caucasians. Several previous studies reported that BMI is a helpful factor for IGT screening [17,20–23]. High BMI (>27 or >30 kg/m^2) is associated with higher prevalence of IGT compared to that with BMI < 25 kg/m^2. Hiltunen et al. reported that higher BMI (>30 kg/m^2) was the best predictor of IGT in a Finland population-based study and Saydah SH et al. reported that BMI (>30 kg/m^2) and age in addition to FPG or HbA1c can be used to improve the sensitivity for detecting IGT without OGTT among U.S. populations [20,23]. Contrary to these reports, we did not find a high correlation between 2-hPG and BMI ($r = 0.03$). The proportion of obesity of these studies is high, the ratio of BMI > 27 kg/m^2 and >30 kg/m^2 are 53% and 24%, respectively [20,23], while in our study the mean (SD) of BMI was 24.6 (4.7) kg/m^2 and the ratio of obese subjects with BMI > 30 kg/m^2 are only 1%. It was reported previously that the difference with or without the obesity (BMI > 25 kg/m^2) did not contribute to IGT screening in Japanese [21]. The BMI used in the study was similar to that in our study (BMI: 23–25 kg/m^2). On the other hand, insulin secretion rather than insulin resistance is a more significant factor in progression from NGT to type 2 DM via IGT in Asian diabetes [29,31–35]. Indeed, in the present study insulin secretion is decreased gradually from NGT via IGT to type 2 DM (65.1, 38.5, 15.8, respectively) as in other previous reports in Asian diabetes [31,35] (Table 1). Taken together, the discrepancy of the correlation may be due to the ethnic differences such as BMI and insulin secretory capacity. The variables affecting 2-hPG during OGTT might differ among ethnic populations and require a different estimation formula and adequate cut-off value to identify IGT. It is also reported that age has an effect on the accuracy of IGT screening [22]. In our study, however, there was low correlation between 2-hPG and age ($r = 0.24$). The reason may be the different methods of analysis. We considered age from 20 to 89 years as a continuous variable rather than as a categorical one with relatively narrow age. In addition, gender was not an independent predictive variable for 2-hPG and even though included in the regression model, R^2 remains substantially unchanged in our study (data not shown).

Generally, the performance of a screening test depends on the cut-off value and it is rare to have both high sensitivity and specificity. The priority in this trade-off is determined by the characteristics of the condition to be diagnosed [36,37]. In the case of IGT, mis-identifying IGT subjects as normal (false negatives) is more critical than classifying healthy subjects as abnormal (false positives), since these subjects are at high risk for cardiovascular diseases as well as diabetes and its complications. Thus, a screening test for IGT should prioritize high sensitivity to decrease the false-negatives. As summarized in Table 2, when the cut-off value was set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity of this formula was 83.3%. However, even with this cut-off value, NPV still remained 74.3%. If the cut-off value was lowered to 7.2 mmol/l, NPV was up to 85.7% with 94.4% sensitivity. When a screening test has high sensitivity, subjects having a negative result can be judged as negative with high precision [36–39]. The rule of SnNout states that if a screening test has high sensitivity (Sn), a negative result (N) rules out (Out) the target disorder, which describes IGT in our study. In accord with this theory, using our high-sensitive estimation formula for IGT screening and with the cut-off value set to 7.2 mmol/l of e2-hPG with 94.4% sensitivity, the subjects with e2-hPG ≤ 7.2 mmol/l were ruled out of the diagnosis of IGT. Thus, further OGTT to diagnose whether or not they have IGT may not be necessary for these low risk subjects.

Our study has several limitations. One is the high prevalence of type 2 DM subjects in our hospital-based study. It is reported that the prevalence of type 2 DM varies across studies, in hospital-based studies ranging from 10 to 44% and in community-based studies ranging from 6.2 to 7.4% [16]. While the proportion of subgroups in OGTT would affect the efficacy of the estimation formula, there are at present no established data of general population-based or hospital-based studies. Thus, no comparisons are possible between our results with previous findings. Another limitation is screening bias because it is a cross-sectional study. There are no definite inclusion criteria—they depend on the individual judgment of each doctor. Our results regarding sensitivity, specificity, and cut-off value are internally validated, but it remains to be determined whether these findings apply to other populations: generation-based or higher BMI like Caucasian and so on. Therefore further studies are required to validate in the broader population.

In conclusion, our high-sensitivity estimation formula based on FPG and HbA1c may be useful in screening for IGT. More than 80% sensitivity of this formula was preserved at ≤7.8 mmol/l of e2-hPG in this hospital-based study. In addition, when the levels of e2-hPG are ≤7.2 mmol/l, this estimation formula can be used to identify subjects with normal glucose tolerance.

Conflict of interest

The authors declare that they have no conflict of interest.

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