frequency at 75 and 95 m/min.

Discussion

This is the first study to investigate whether changes in step frequency have independent effects on the validity of step-count functions and predicted energy cost assessed by accelerometers. The LC underestimated the step counts at normal or high step frequency at low walking speed. The AM also underestimated them at all step frequencies at low walking speed, whereas the ASP did not across any of the trials. The degree of the percentage error of the step counts in all accelerometers was affected by speed, but not by step frequency. The LC underestimated METs at the low or normal step frequency at all walking speeds, whereas overall underestimation was less across trials in the AM and ASP.

The present study clearly demonstrated that LC, AM, and ASP have very accurate step-count functions at normal walking speed with normal step frequency at which each subject feels comfortable walking. Schneider et al. (2003) demonstrated that LC had more accurate step-count functions compared with 7 other pedometers during a 400-m track walk at self-selected speeds for adults, and its error in detecting actual steps taken was within±3%. Actually, Cao et al. (2010) reported no significant differences between LC and AM in daily walking step counts for adults. The error of −2.4% (LC), −1.2% (AM), and 0.0% (ASP) at normal walking speed with normal step frequency in the present study meet the Japanese Industrial Standard set by the Ministry of Industry and Trading criteria indicating that error should be within 3% (3 steps of 100) (Hatano, 1993). Therefore, it is considered that LC, AM, and ASP are among the pedometers which are very accurate and sufficiently reliable to administer to large groups.

At low walking speed, the LC underestimated the step counts at the normal and high frequency while the AM underestimated them at all step frequencies. In contrast, the ASP had accurate step-count functions across all trials. The present results correspond with those of other studies using electronic pedometers that underestimated step counts at walking speeds slower than about 55 m/min (Crouter et al., 2003; Le Masurier and Tudor-Locke, 2003; Le Masurier et al., 2004). Thus, the impact on the accelerometers (sensitivity) during slow walking for the LC and AM might be too weak to detect a "threshold" of capturing a step, whereas ASP had better reliability in detecting step counts even with slow walking. It was difficult to determine why the ASP had better accuracy than the AM in detecting step counts; however, the difference in the filtering system between the AM and the ASP might explain this. Even so, speed significantly contributed to the degree of the percentage error in all three accelerometers. Therefore, we suggest that accelerometers should be carefully used when assessing daily step counts, especially for persons who walk slowly.

The present study revealed that the LC underestimated METs at the low and normal step frequency at all walking speeds, and gross underestimation was found especially at low step frequency of high walking speeds. One possible explanation for the LC error is its own proprietary data-analyzing process, in which intensity levels are categorized using both the step counts and the maximum amplitude of vertical acceleration every four seconds. In this study, although higher energy cost was demanded at a low step frequency especially at a higher walking speed, the number of step counts by the LC would have conversely decreased due to the greater step length (lower step frequency). Therefore, a decrease in step counts at the low step frequency might cause the LC underestimation. The possibility that step frequency could strongly affect the validation of the LC was supported by the following results: Step frequency was the strongest predictor (β=0.87) and speed was the second strongest (β=−0.51) of the error between the measured and predicted METs in the multiple regression analysis. Therefore, changes in step frequency would individually and markedly affect the accuracy of the LC.

Another possible reason for the LC underestimation may be that in the data-analyzing process, it uses only four thresholds from maximum amplitudes of vertical acceleration when determining the intensity levels (i.e., noncontinuous variables). For example, if the maximum amplitudes of vertical acceleration during walking altered by both low and normal step frequency at a fixed walking speed are between 0.15–0.76 G, the difference in intensity levels between the low and normal step frequency will be determined by the difference in the step counts. However, as mentioned above, the number of step counts by the LC would have been decreased due to the low step frequency, despite the higher energy cost. This might be one explanation for the LC error.

Compared with the results of the LC, the AM and ASP showed less error in measuring METs across trials. Multiple regression analysis indicated that step frequency did not affect AM accuracy. Although ASP accuracy was affected by step frequency, it only explains 10% of the error. Better validity of the AM and ASP compared with the LC might be partly due to the higher capability of the triaxial accelerometers in assessing multiple-directional accelerations as continuous variables. In the earlier studies, anteroposterior or vertical acceleration contributed to a highly accurate estimation of physical activity under normal walking conditions in which step frequency was concurrently changed with an increment in speed (Bouten et al., 1994; Kumahara et al., 2004). However, in our experimental protocol (i.e., various step frequencies altered at a fixed walking speed), the difference in vertical acceleration between the low and normal step frequency was much less than the difference between the low and normal step frequencies in the METs measured by the Douglas bag method. Moreover, the major acceleration component at a low step frequency was in the anteroposterior direction, but in the vertical direction at a high step frequency. Based on our results, we suggest that the AM and ASP assure more accuracy than the LC for estimating intensity or energy costs under various walking conditions.

In the present study, the degree of the percentage error of METs was affected by step frequency both in the AM and ASP. Significant underestimation was found in AM at all low step frequencies of all walking speeds, but in ASP only at low step frequency of high walking speed. As shown in the raw data of the three accelerations, the total values using the output of the three accelerations at the high walking speed was around 16% higher at the low step frequency than at the normal step frequency. However, the difference in the measured METs from the Douglas bag at the high walking speed was around 25% higher at the low step frequency than at the normal step frequency. The discrepancy of 16% and 25% might therefore result in higher error at the low step frequency of high walking speed in the AM and ASP. Furthermore, the present study showed that METs estimated by the AM tended to be entirely underestimated across trials compared with METs estimated by the ASP (Fig. 2). Because the minimum amplitude of the acceleration sensor was similar between the AM (4 mG) and the ASP (3 mG), the sensitivity of the minimum amplitude of the acceleration sensor did not affect the error of the AM. Therefore, we consider that AM accuracy may be improved by using more suitable equations to precisely measure energy costs altered by the various walking patterns.

The present study has the following limitations. First, our results using young healthy subjects might not be readily generalized to children or older adults due to different characteristics such as the length and mass of legs and body movement. In addition, the elderly have been known to walk and step so slowly that their walking movements are greater in mediolateral directions (Dean et al., 2007). Therefore, further research is needed to evaluate the accuracy of an accelerometer for other aged subjects under the same conditions and to calibrate for more accurate estimations. Second, we cannot exclude differences between walking on a treadmill indoors and freely walking outdoors. However, in general, the energy costs of treadmill and over-ground walking on a firm surface are similar (Hall et al., 2004). Hence, we thought that using the treadmill in our experimental protocol was adequate to obtain more precise and reliable data as a basic study.

In conclusion, these results suggest that accelerometers can cause errors in step-count functions at a low walking speed. Furthermore, in the measurement of energy costs, LC may cause great errors especially for the group with various step frequency and speed, whereas AM and ASP, which are tri-axial accelerometers, cause fewer errors but the degree of the percentage error is affected by step frequency.

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Validity of Predictive Equations for Basal Metabolic Rate in Japanese Adults

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Validity of Predictive Equations for Basal Metabolic Rate in Japanese Adults

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Summary Many predictive equations for basal metabolic rate (BMR) based on anthropometric measurements, age, and sex have been developed, mainly for healthy Caucasians. However, it has been reported that many of these equations, used widely, overestimate BMR not only for Asians, but also for Caucasians. The present study examined the accuracy of several predictive equations for BMR in Japanese subjects. In 365 healthy Japanese male and female subjects, aged 18 to 79 y, BMR was measured in the post-absorptive state using a mask and Douglas bag. Six predictive equations were examined. Total error was used as an index of the accuracy of each equation's prediction. Predicted BMR values by Dietary Reference Intakes for Japanese (Japan-DRI), Adjusted Dietary Reference Intakes for Japanese (Adjusted-DRI), and Ganpule equations were not significantly different from the measured BMR in either sex. On the other hand, Harris-Benedict, Schofield, and Food and Agriculture Organization of the United Nations/World Health Organization/United Nations University equations were significantly higher than the measured BMR in both sexes. The prediction error by Japan-DRI, Adjusted-DRI, and Harris-Benedict equations was significantly correlated with body weight in both sexes. Total error using the Ganpule equation was low in both males and females (125 and 99 kcal/d, respectively). In addition, total error using the Adjusted-DRI equation was low in females (95 kcal/d). Thus, the Ganpule equation was the most accurate in predicting BMR in our healthy Japanese subjects, because the difference between the predicted and measured BMR was relatively small, and body weight had no effect on the prediction error.

Key Words basal metabolic rate, predictive equation, Japanese, validity

To maintain body weight, energy from food intake must equal energy expenditure. The estimated energy requirement (EER) is defined as the average dietary energy intake that is predicted to maintain energy balance in healthy adults of a given age, gender, weight, height, and level of physical activity consistent with good health (*1*).

Total energy expenditure (TEE) can be divided into basal metabolic rate (BMR), diet-induced thermogenesis, and physical activity (*2*). Calculated from the normal physical activity level (PAL=TEE divided by BMR) of about 1.75 for Japanese (*3*) and Caucasians (*4*), BMR accounts for about 60% of TEE in an adult with normal physical activity in daily life. Therefore, in healthy individuals, EER is usually BMR multiplied by physical activity level, and in unhealthy individuals (patients in clinical settings), EER is BMR multiplied by an activity factor and stress factor (*5*). Thus, it is important to accurately evaluate BMR. However, because of the relatively high cost, limited availability of equipment, the time needed for the measurements, the need for the subject to be in a fasting state, and the need for adequately trained personnel, equations that predict BMR are frequently applied in clinical and field settings instead of indirect calorimetry (*6*).

The international guidelines for nutrition treatment of the American Society for Parenteral and Enteral Nutrition recommend using the Harris-Benedict equation or indirect calorimetric measurement to evaluate BMR (*7*). However, 60% of 515 hospitals in Japan reported the calculation of EERs from body weight (*8*). In addition, only 1.9% of the hospitals carried out indirect calorimetric measurement of BMR. In the clinical setting, the patients' energy expenditure must be estimated accurately because overfeeding or underfeeding

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Table 1. Physical characteristics of subjects.

	All (n=365)	Males (n=163)		Females (n=202)		p values
	Mean±SD	Mean±SD	Range	Mean±SD	Range	
Age (y)	41±17	43±15	20–79	39±18	18–76	0.041
Height (cm)	163.3±9.0	170.3±6.9	146.4–187.7	157.6±5.9	140.8–172.1	<0.001
Weight (kg)	59.5±11.9	67.1±11.2	45.5–110.2	53.3±8.2	36.1–99.1	<0.001
Body mass index (kg/m^2)	22.2±3.1	23.1±3.0	16.8–36.4	21.5±3.0	16.5–36.4	<0.001

Differences between males and females were evaluated by unpaired t-test. p values: males vs. females.

may have adverse effects, such as electrolyte imbalance and gastrointestinal problems (*9*).

BMR is usually calculated from predictive equations using data such as age, sex, height, and weight (*10*). The Harris-Benedict equation (*11*), Schofield equation (*12*), and the Food and Agriculture Organization of the United Nations/World Health Organization/United Nations University (FAO/WHO/UNU) equation (*13*) are internationally used. Harris-Benedict equations were developed from energy expenditure measurements in young Caucasian males and females in 1919 (*11*). Schofield and FAO/WHO/UNU equations were developed using a database of 7,173 subjects (aged from under 3 y to over 60 y) including approximately 45% Italian subjects (*12–15*) and about 50 young Japanese subjects (*16*). Previous studies show that the predictive equations derived mainly from measurements made on Caucasian subjects tend to overestimate BMR in Asians (*9, 10*) as well as in Caucasian subjects (*10, 17–21*). However detailed information on the validity for each sex and age group in Japanese is not available.

In Japan, Dietary Reference Intakes for Japanese (Japan-DRI) provides BMR standards (standard BMR per unit weight) according to sex and age category, and the data for these standards were from a Japanese BMR database (*22, 23*). BMR can be calculated as BMR standards multiplied by body weight. However, the validity of the predictive equations including the predictive equations for BMR standards from the Japan-DRI and the equations for BMR standards to adjust BMR standards for individuals with relatively large or small body weight (*24*) have not been examined in healthy Japanese subjects. In addition, we recently developed new predictive equations for sleeping metabolic rate and BMR in Japanese (*25*).

In the present study, we examined the validity of applying three BMR equations used for Japanese, and three internationally used equations developed mainly from energy expenditure measurements in Caucasian subjects, to healthy Japanese adults.

MATERIALS AND METHODS

Subjects. The data used for the current analysis were collected from different experimental studies that followed a similar methodology. A total of 365 apparently healthy Japanese subjects (163 males and 202 females subjects) were enrolled through personal contact, internet communication, or poster advertisements. The subjects included students, housewives, office workers, and medical colleagues. None had diseases that might affect metabolic rate. The study protocol was explained in advance to the subjects, who were instructed to eat a normal diet and do normal, but not vigorous, physical activity beginning 1 d before measurements. All studies were carried out in the National Institute of Health and Nutrition (Tokyo) and Oita Prefecture. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethical Committee of the National Institute of Health and Nutrition in Tokyo, Japan. All of the subjects signed an informed consent form.

Anthropometric and body composition. Physical characteristics of the subjects are summarized in Table 1. Anthropometric measurements were performed according to the method of Lohman et al. (*26*). Body weight was measured to the nearest 0.1 kg using an electronic scale (YK-150D, YAGAMI, Nagoya, Japan), and body height to the nearest 0.1 cm using a stadiometer (YL-65, YAGAMI). Measurements were performed in light clothing and underwear. The light clothing was weighed and subtracted from the total to obtain body weight with minimal clothing (underwear). Body mass index (BMI: kg/m^2) was calculated as body weight (kg) divided by square of body height (m^2).

Measurements of BMR. Subjects came to the laboratory on the previous night and stayed overnight, or came in the early morning. In the latter case, they were asked to minimize walking prior to their laboratory visit and BMR measurement. Travel time was considered to be within 15 to 90 min in most cases. In most of the previous studies, especially for the Japan-DRI, Schofield, and FAO/WHO/UNU equations, BMR was measured under the latter condition (*23*). BMR was measured in the post-absorptive state (12 h or more after the last meal). Measurements were performed in a room at constant temperature (approximately 25°C). After entering the laboratory, subjects rested in the supine position for at least 30 min, and wore a face mask. In the case of overnight stay, the subjects were quietly awakened at 0700 and had a face mask attached while remaining in bed for 30 min. Two samples of expired air were collected in Douglas bags over each of two 10-min periods, and the mean of the two values was used for analysis.

Mass spectrometer (ARCO-1000 and ARCO-2000, Arco System, Kashiwa, Japan) were used to analyze the

Table 2. Predictive equations for basal metabolic rate used in the present study.

Predictive equations (kcal/d)	Age range	Males	Females
Japan-DRI (2010)	18–29	24.0×W	22.1×W
	30–49	22.3×W	21.7×W
	50–69	21.5×W	20.7×W
	70 over	21.5×W	20.7×W
Japan-DRI with adjustment for body weight (Adjusted-DRI)	18–29	[24.0+(10.8−0.173×W)]×W	[22.1+(8.9−0.172×W)]×W
	30–49	[22.3+(10.8−0.173×W)]×W	[21.7+(8.9−0.172×W)]×W
	50–69	[21.5+(10.8−0.173×W)]×W	[20.7+(8.9−0.172×W)]×W
	70 over	[21.5+(10.8−0.173×W)]×W	[20.7+(8.9−0.172×W)]×W
Harris-Benedict		66.4730+13.7516×W+5.0033×H −6.7550×A	655.0955+9.5634×W+1.8496×H −4.6756×A
Schofield	18–29	(0.063×W+2.896)×1,000/4.186	(0.062×W+2.036)×1,000/4.186
	30–59	(0.048×W+3.653)×1,000/4.186	(0.034×W+3.538)×1,000/4.186
	60 over	(0.049×W+2.459)×1,000/4.186	(0.038×W+2.755)×1,000/4.186
FAO/WHO/UNU	18–29	(64.4×W−113.0×H/100+3,000)/4.186	(55.6×W+1,397.4×H/100+146)/4.186
	30–59	(47.2×W+66.9×H/100+3,769)/4.186	(36.4×W−104.6×H/100+3,619)/4.186
	60 over	(36.8×W+4,719.5×H/100−4,481)/4.186	(38.5×W+2,665.2×H/100−1,264)/4.186
Ganpule		(0.0481×W+0.0234×H−0.0138×A −0.4235)×1,000/4.186	(0.0481×W+0.0234×H−0.0138×A −0.9708)×1,000/4.186

W: weight (kg), H: height (cm), A: age (y).

oxygen and carbon dioxide concentrations. The volume of expired air was determined using a dry gas volume meter (DC-5, Shinagawa, Tokyo, Japan) and converted to the volume under conditions of standard temperature, pressure, and dry gas (STPD). Gas exchange results were converted to BMR (kcal/d) using Weir's equation (*27*). To examine whether overnight stay before the BMR measurement caused a significant difference in the observed BMR, analysis of covariance with BMR as the dependent variable and gender, age, height, and body weight as covariates was employed. No significant effect of the measurement conditions was observed (stayed overnight: 1,275±15 kcal/d (mean±SE), came in the early morning on the day: 1,268±6 kcal/d (mean±SE), $F=0.163$, $p=0.687$).

Predictive equations of BMR. Predictive BMR was calculated using the Japan-DRI (*22*), Harris-Benedict (*11*), Schofield (*12*), FAO/WHO/UNU (*13*), and Ganpule (*25*) equations (Table 2). For the Japan-DRI equations, the Ministry of Health and Welfare proposed adjusting for the effect of body weight (*24*). Therefore, the equations with this adjustment (Adjusted-DRI) were also examined.

Statistical analysis. Results are presented as the mean±standard deviation (SD). Statistical significance was set at $p<0.05$ for all predictors. Differences between males and females were evaluated by an unpaired *t*-test. In addition to the mean±SD of the difference, total error (TE) was used to determine how accurately predicted BMR matched measured BMR. This statistic includes two sources of variation, one attributable to the lack of association between the two sets of measurement (standard error of estimate) and one attributable to the difference between the means (*28*). Statistical significance of differences between measured and predicted values was analyzed by one-way analysis of variance (ANOVA) and Dunnett's post hoc test. The relationship between difference of BMR (predicted minus measured BMR) and weight was examined using Pearson's correlation. Statistical analyses were performed using SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA).

Table 3. Measured basal metabolic rate (kcal/d and kcal/kg weight/d) in each sex and age group.

Age range	BMR (kcal/d) Mean±SD	BMR (kcal/kg weight/d) Mean±SD
Males ($n=163$)		
All	1,452±219	21.8±2.4
18–29	1,492±151	23.5±2.2
30–39	1,532±250	22.0±2.2
40–49	1,489±222	21.0±2.0
50–59	1,395±184	21.7±2.8
60–69	1,321±142	20.6±2.0
70–79	1,220±170	20.2±1.5
Females ($n=202$)		
All	1,122±136	21.2±2.4
18–29	1,132±122	22.2±2.6
30–39	1,168±122	21.6±2.4
40–49	1,196±161	21.3±1.9
50–59	1,090±114	19.6±1.8
60–69	1,085±110	20.1±1.7
70–79	968±107	20.1±1.9

RESULTS

The average weight and height of subjects in each age and gender group were comparable to national standard heights and weights (*29*) (Table 1). Average

Table 4. Predicted basal metabolic rate and mean differences from measured basal metabolic rate in males and females.

	Predicted BMR Mean±SD (kcal/d)	Mean differences±SD (kcal/d)	ANOVA *p* values	Post hoc test *p* values
Males (n=163)			<0.001	
Japan-DRI (2010)	1,504±258	53±155		0.080
Adjusted-DRI	1,428±109	−23±160		0.781
Harris-Benedict	1,550±223	99±132		<0.001
Schofield	1,607±186	155±142		<0.001
FAO/WHO/UNU	1,634±194	183±147		<0.001
Ganpule	1,480±174	28±122		0.628
Females (n=202)			<0.001	
Japan-DRI (2010)	1,148±178	26±122		0.161
Adjusted-DRI	1,122±88	0±96		1.000
Harris-Benedict	1,272±119	150±103		<0.001
Schofield	1,246±109	124±100		<0.001
FAO/WHO/UNU	1,254±111	132±98		<0.001
Ganpule	1,132±131	10±99		0.934

Mean differences: mean of difference between predicted and measured basal metabolic rate. Significance was determined by one-way ANOVA and Dunnett's post hoc test. Post hoc test *p* values: predicted vs. measured.

Table 5. Difference between the predicted and measured basal metabolic rate in each sex and age group.

Age range	n	Japan-DRI (2010) (kcal/d)	Adjusted-DRI (kcal/d)	Harris-Benedict (kcal/d)	Schofield (kcal/d)	FAO/WHO/UNU (kcal/d)	Ganpule (kcal/d)	ANOVA *p* values
Males (n=163)								
18–29	35	51±159	12±97	153±91*	168±98*	168±100*	25±87	<0.001
30–39	43	32±158	−90±188	131±134*	145±151*	187±151*	27±139	<0.001
40–49	34	101±157	−33±178	116±127*	201±138*	243±138*	41±126	<0.001
50–59	23	−2±131	−40±160	40±152	220±155*	263±155*	8±152	<0.001
60–69	16	68±173	34±110	29±110	23±108	57±112	38±108	0.774
70–79	12	80±89	90±105	−18±92	75±100	59±115	29±99	0.260
Females (n=202)								
18–29	80	9±136	0±105	211±95*	119±104*	120±105*	49±103*	<0.001
30–39	32	18±133	−21±91	143±89*	121±90*	132±89*	8±99	<0.001
40–49	26	31±101	−29±100	86±93	108±104*	121±102*	−41±83	<0.001
50–59	24	71±110	16±66	138±63*	211±65*	223±64*	23±65	<0.001
60–69	23	41±97	8±78	79±80*	67±77	97±83*	−37±84	<0.001
70–79	17	32±93	57±86	86±83*	129±86*	126±72*	−48±73	<0.001

Significance was determined by one-way ANOVA and Dunnett's post hoc test. *p<0.05 predicted vs. measured.

values of age, height, weight, and BMI were lower for females than for males. Table 3 shows measured BMR (kcal/d and kcal/kg weight/d) in males and females.

Tables 4 and 5 show predicted BMR. The mean values of BMR predicted by the Harris-Benedict equation, Schofield equation, and FAO/WHO/UNU equation were significantly higher than the measured BMR. Mean errors for equations developed for Japanese (Japan-DRI equation, Adjusted-DRI equation, and Ganpule equation) were smaller than those of internationally used equations (Harris-Benedict equation, Schofield equation, and FAO/WHO/UNU equation) in most age groups of both sexes. The mean errors of the predicted BMR by internationally used equations were significantly higher than the measured BMR in most age groups. However in the 60–69- and 70–79-y-old groups of males, the predicted BMR values were not significantly higher than the measured BMR.

TE values are shown in Table 6. TE of the Ganpule equation was low in both sexes (125 and 99 kcal/d, respectively). In addition, TE using the Adjusted-DRI equation was low in females (95 kcal/d). On the other hand, TE of the Japan-DRI equation was 163 kcal/d in males and 124 kcal/d in females, TE of the Adjusted-DRI equation was 162 kcal/d in males. TE values were higher for other equations than for equations developed for Japanese. In particular, TE of the FAO/WHO/UNU equation was largest in males and that of the Harris-Benedict equation was largest in females. In males, TE of the Ganpule equation was the lowest in all age categories except those over 60 y old. In males, the TE of the FAO/WHO/UNU equation was 278 kcal/d in the 40–49-y-old group, and those of the Schofield and FAO/WHO/UNU equations were higher in the 50–59-y-old

Table 6. Total errors of the prediction equations for basal metabolic rate in each sex and age group.

Age range	*n*	Japan-DRI (2010)	Adjusted-DRI	Harris-Benedict	Schofield	FAO/WHO/UNU	Ganpule
Males							
All	163	163	162	165	210	234	125
18–29	35	164	97	177	194	194	90
30–39	43	160	206	186	208	239	140
40–49	34	185	179	171	243	278	131
50–59	23	170	161	154	267	303	149
60–69	16	144	112	110	107	123	111
70–79	12	117	135	90	122	125	99
Females							
All	202	124	95	182	159	165	99
18–29	80	136	105	231	158	159	114
30–39	32	132	92	168	150	158	98
40–49	26	104	102	125	149	157	91
50–59	24	129	67	151	220	232	68
60–69	23	104	77	111	101	127	90
70–79	17	96	101	118	154	144	86

$$\text{Total error (kcal/d)} = \frac{\Sigma(\text{predicted BMR} - \text{measured BMR})^2}{n}.$$

group than the other predictive equations (267 and 303 kcal/d, respectively), as these equations grossly overestimated BMR in these subjects. In females, the TE values of the Adjusted-DRI and Ganpule equations were low. The TE of the Harris-Benedict equation was highest in 18–29-y-old females. In 50–59-y-old females, the TE values of the Schofield and FAO/WHO/UNU equations were higher than those of the other predictive equations (220 and 232 kcal/d, respectively).

Relationship between the difference of BMR (predicted minus measured BMR) and weight is shown in Fig. 1. The difference was significantly correlated with body weight positively for Japan DRI equations in both sexes and Harris-Benedict equation in males and negatively for Adjusted DRI equations in both sexes and Harris-Benedict equation in females. For the Schofield, FAO/WHO/UNU, and Ganpule equations, there was no significant correlation between the prediction error and body weight.

DISCUSSION

The Japan-DRI equation, Adjusted-DRI equation, and Ganpule equation for both sexes predicted BMR relatively accurately, while the internationally adopted equations of Harris-Benedict equation, Schofield equation, and FAO/WHO/UNU equation overestimated BMR. The prediction error by Japan-DRI, Adjusted-DRI, and Harris-Benedict equation was significantly correlated with body weight in both sexes. The present study suggests that the Ganpule equation is likely to be the most accurate in predicting the BMR of healthy Japanese, because the TE and mean difference between predicted and measured BMR were relatively small in many sex and age groups, and weight had no effect on the predicted error.

The most important innovation of the present study is that the validity of various predictive equations for BMR, including the Japan-DRI and Ganpule equations was examined in sex and age groups of larger size. Values of BMR in young healthy Japanese females and in a few other age groups of Japanese have been reported (*30, 31*), but there has been no recent report evaluating the validity of predictive equations for BMR in healthy Japanese subjects.

Japan-DRI equations were developed based on the data for Japanese subjects with standard body size 50 y ago. Although body composition may have changed in the interim (*30*), these earlier values are still being used. Schofield equations and FAO/WHO/UNU equations were developed based on data from a population of many races (*12–14*). However, the data used to develop the Schofield equation were mostly from young European military and police recruits, including 2,279 males and 247 females, with 45% being of Italian descent. Although the age range of the study sample was 19 to 82 y, the elderly were minimally represented (*32*). Average BMR values were reported to be higher in these Italians than in other Caucasian study participants (*33, 34*). The data of only 53 young Japanese adults reported in 1926 were included in the database (*16*). Asians are reported to have lower BMR than Europeans by 10–12% (*35*), even after adjustment for body composition. Harris-Benedict equations were developed using data obtained in healthy normal weight Caucasian males (n=136) aged 16–63 y and females (n=103) aged 15–74 y, including only three males and six females over 60 y old. Although in each age group and in the female group, the subjects used to evaluate the Harris-Benedict equation and those used in the present study were of comparable average weight and height, the average difference in BMR between these studies (Harris-Benedict and the present study) was about 200 kcal/d, and the mean error of the Harris-Benedict estimate was 211 kcal/d in the present study.

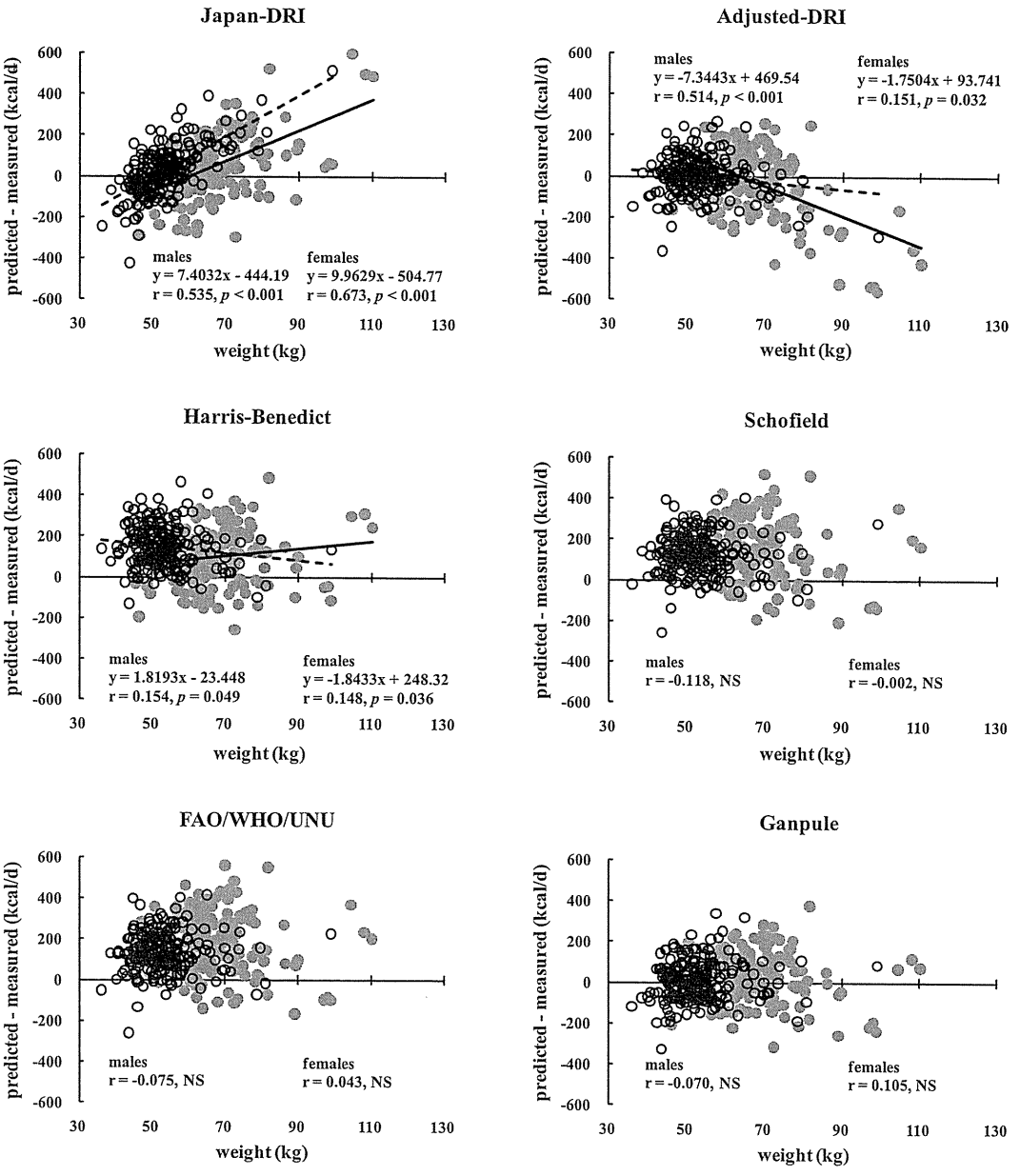

Fig. 1. Relationship between difference of basal metabolic rate (predicted minus measured basal metabolic rate) and weight in males and females. Males, black circle (●) and straight line (——); females, white circle (○) and dashed line (- - -).

Harris-Benedict equations have been criticized for including a few obese subjects (mean BMI 21.4±2.9 kg/m^2 in males, 21.5±4.1 kg/m^2 in females), for having inadequate representation at the young and old extremes of age, and for having a systematic error of 5 to 15% (*36*). The Ganpule equation was recently developed using data from 137 healthy Japanese adults and the standard error of estimate of the regression analysis was low (prediction error=7.3%).

The Japan-DRI equation overestimated BMR by 100 kcal/d or less in most age groups (Tables 4 and 5). The recently reported difference between values predicted by the Japan-DRI equation and measured values for young healthy Japanese females was 70 kcal/d (*30*). The mean difference from measured values was lower for the Adjusted-DRI and Ganpule equations than for the Japan-DRI equation in most age groups of females. Mean difference and TE values were smaller using the Japan-DRI equations, Adjusted-DRI equations, and Ganpule equation than the internationally used equations (Harris-Benedict, Schofield, FAO/WHO/UNU) in both sexes (Tables 4–6). In particular, the TE was lower for the Ganpule equation than the other equations in most age groups in males except in the 60–69- and 70–79-y-old groups. On the other hand, TE values for the Adjusted-DRI equation and Ganpule equation were small in females. The values of Adjusted-DRI equation and Ganpule equation in females were comparable in the 18–69-y-old female groups. TE in 18–29-y-old females was higher for the Harris-Benedict equation than for the other equations, mainly due to the large mean error between predicted and measured values, and not due to the SD. The TE for the Schofield equation and FAO/WHO/UNU equation were high, especially in 40–59-y-old males. Thus, these internationally used equations are inadequate for healthy Japanese subjects.

The equations currently recommended for international use have been reported to overestimate BMR in some previous studies. For Caucasians, the Harris-Benedict equation overestimated the BMR of healthy females by 14–24% (*17*, *18*). On the other hand, the Harris-Benedict equation overestimated BMR by 8–19% in healthy Chinese adults (*37*). Case et al. (*9*) reported that the Harris-Benedict equation and FAO/WHO/UNU equation overestimated BMR by about 100 kcal/d in 36 Asian females including Japanese females. Ganpule et al. (*25*) and Yamamura and Kashiwazaki (*31*) showed that FAO/WHO/UNU equations overestimated BMR in Japanese subjects to a similar degree. Thus, these internationally used equations have been reported to overestimate BMR for Asians including Japanese. The results in the present study were comparable to those of previous studies in general, while the mean error of the Harris-Benedict estimates was smaller in the present study. TE values for the Harris-Benedict equation and Ganpule equation were comparable in the 70–79-y-old male group. Melzer et al. (*6*) reported that the Harris-Benedict equation showed the lowest mean error (−41 kcal/d) in elderly healthy Caucasian adults. Therefore, the Harris-Benedict equation may be used for elderly Japanese females because its TE was smaller in the over-60-y-old groups than in other age groups. However, the TE was larger in young females for the Harris-Benedict equation than for the other equations. Thus, the use of the Harris-Benedict equation is inappropriate for all patients in clinical settings. The reason that prediction by Harris-Benedict equation is relatively accurate only for elderly females is unclear. It should be noted that there are gender differences between the coefficients for body weight, height, and age in these equations. The intercept is much larger for females than for males (655.1 vs. 66.47) and the other coefficients are smaller for females than for males.

The mean differences in BMR between the Japan-DRI in both sexes and Adjusted-DRI equations in males were highly influenced by weight. For individuals with larger body weight, the difference between predicted BMR by Japan-DRI equations and measured BMR was larger in both sexes, while the difference by Adjusted-DRI equations was smaller and negative in males with larger body weight. For Harris-Benedict equations in both sexes and the Adjusted-DRI equation in females, the effect of body weight on the prediction error was small but significant, as also reported by Tanaka et al. (*38*) for obese subjects. Yamamura and Kashiwazaki (*31*) reported that, for lean subjects (BMI≤18.4 kg/m^2) over 18 y old, the difference between the observed and predicted values (calculated by the Japan-DRI equation) was higher than the predicted values (calculated by the other equations). In contrast, the difference was less for normal-weight subjects (18.5 kg/m^2≤BMI≤24.9 kg/m^2). Japan-DRI equations are just multiple of body weight, and do not have an intercept term. It is inappropriate to express metabolic rate data per body weight or per kg of fat-free mass, as the relationship between metabolic rate and body weight or fat-free mass has an intercept significantly different from zero (*39*). Therefore, systematic error can be expected (*39*) and some adjustments for body size are needed when using Japan-DRI equations. However, the adjustment for body weight in the Adjusted-DRI equation was adequate for females but not for males (Fig. 1). Adequate adjustment of the coefficients may decrease the prediction errors. For the Ganpule, Schofield, and FAO/WHO/UNU equations, weight had no effect in either sex. The Ganpule equation can be used for all age groups of Japanese, because the TE and mean difference between predicted and measured BMR are small, and weight has no effect on the prediction error.

The present study examined the validity of predictive equations for BMR. The conditions of BMR measurement must be considered. Historically, BMR was defined as the energy expenditure of an individual 12 h after the last meal while that individual lay quietly at rest at normal ambient and body temperatures and in the absence of either physical or psychological stress (*11*, *23*). However, in most reports about Harris and Benedict (*11*), Schofield (*12*), FAO/WHO/UNU (*13*), and Japan-DRI equations, subjects were permitted to walk or ride to a laboratory early on the morning of testing, and expired air was collected after quiet rest for about 30 min. Berke et al. (*40*) found that for elderly people, the resting metabolic rate was higher in outpatient condition than in inpatient condition. On the other hand, Turley et al. (*41*) found no difference in BMR measured in the morning after an overnight clinic stay and BMR measured in the morning after 30 min of rest after traveling by car from home. In Japan, most of the BMR values measured at Nagasaki University, Tokushima University, or Showa Medical University in the 1950s–1960s were not obtained after an overnight stay (*23*), and the Japan-DRI equation was created using these data. The Schofield and FAO/WHO/UNU equations were developed using BMR measurements from many reports, and much of the BMR data was not obtained after an overnight stay (*12*). Likewise, the BMR data used to develop the Harris-Benedict equation were not obtained after an overnight stay (*11*).

The most important limitation of the present study is that body composition was not measured. Weight and height, which can be easily obtained in clinical as well as epidemiological settings, were used. In general, body weight affects BMR. However, the relatively large prediction errors by the Harris-Benedict, Schofield, and FAO/WHO/UNU equations may be due to difference in the body composition between subjects in the present study and subjects in the original studies (*42*). Cunningham (*43*) reported that lean body mass was the only predictor of BMR. Although body weight, height, age, and sex can account for variance in BMR as well as body composition (*25*, *37*), body composition data might have helped interpret the results of the present study.

Our findings indicate that the Ganpule estimates of BMR are the most accurate in healthy Japanese subjects. BMR per body weight can only be used for predic-

tion of BMR in individuals of normal weight.

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Obese Japanese Adults with Type 2 Diabetes Have Higher Basal Metabolic Rates than Non-Diabetic Adults

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Obese Japanese Adults with Type 2 Diabetes Have Higher Basal Metabolic Rates than Non-Diabetic Adults

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Summary Several cross-sectional studies in Pima Indians and Caucasians have indicated that obese individuals with type 2 diabetes have a higher basal metabolic rate (BMR) than healthy, obese individuals. However, no study has investigated this comparison in Japanese subjects, who are known to be susceptible to type 2 diabetes due to genetic characteristics. Thirty obese Japanese adults with pre-type 2 diabetes ($n=7$) or type 2 diabetes ($n=13$) or without diabetes ($n=10$) participated in this study. BMR was measured using indirect calorimetry. The relationships between residual BMR (calculated as measured BMR minus BMR adjusted for fat-free mass, fat mass, age, and sex) and biomarkers including fasting glucose, glycosylated hemoglobin (HbA_{1c}), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-R), triglycerides, and free fatty acids were examined using Pearson's correlation. BMR in diabetic subjects adjusted for fat-free mass, fat mass, age, and sex was 7.1% higher than in non-diabetic subjects. BMR in diabetic subjects was also significantly ($p<0.05$) higher than in non-diabetic subjects. There was a significant correlation between residual BMR and fasting glucose ($r=0.391$, $p=0.032$). These results indicate that in the Japanese population, obese subjects with type 2 diabetes have higher BMR compared with obese non-diabetic subjects. The fasting glucose level may contribute to these differences.

Key Words basal metabolic rate, Japanese, obesity, diabetes, predictive equation

As type 2 diabetes and obesity are closely related, the number of patients with type 2 diabetes in Japan has increased as a result of the rise in prevalence of obesity (*1*). In general, the fundamental treatment for type 2 diabetes is improvement in lifestyle such as diet and physical activity, associated with pharmacotherapy (*2*). Control of daily energy balance remains one of the most important treatment principles. Management of daily energy balance is usually conducted by diet control and maintenance of higher levels of physical activity. Accurate assessments of energy intake and energy expenditure are therefore required during treatment of diabetes.

Several cross-sectional studies have examined whether or not individuals with type 2 diabetes have a higher basal metabolic rate (BMR). Previous studies in Pima Indians (*3*) and Caucasians (*4*) using calorimetry showed obese subjects with type 2 diabetes had 5.2% and 6.9% higher BMR, adjusted for body composition, compared with their respective non-diabetic counterparts. Although the physiological mechanisms responsible for the increased BMR in individuals with type 2 diabetes are poorly understood, several mechanisms have been proposed to explain this change in BMR. These include increases in protein turnover (*5*), futile substrate cycling (*6*), gluconeogenesis (*7*), plasma glucagon (*8*), and sympathetic nervous system activity (*3*). As Japanese people are susceptible to type 2 diabetes (*9*), mainly due to a lower ability to secrete insulin than Caucasians (*10*), this genetic characteristic may provide different results in BMR than similar studies in Pima Indians or Caucasians (*3*, *4*). However, no study has examined whether BMR is higher in Japanese subjects with type 2 diabetes compared to subjects without diabetes.

As BMR may be different between individuals with non-diabetes, pre-diabetes or diabetes, some adjustments may be necessary when BMR is calculated in these groups. As the majority of clinical facilities are unable to carry out indirect calorimetry, BMR is usually estimated from predictive equations using data including age, sex, height, and weight (*11*). Previous studies indicate that predictive equations derived mainly from measurements in Caucasian subjects tend to overestimate BMR in both Asians (*11*, *12*) and Caucasians (*11*, *13–17*). We recently developed new predictive equations for BMR in the Japanese population (*18*). One of these equations was shown to be the best predictor of BMR amongst several predictive equations in healthy Japanese subjects (*19*). However, no study has investigated the validity of several of these published equations in Japanese subjects with type 2 diabetes.

The purpose of the present study was therefore to compare BMR between subjects with non-diabetes, pre-diabetes or diabetes in the obese Japanese population.

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Table 1. Physical characteristics and metabolic parameters in subjects with non-diabetes, pre-diabetes, or diabetes.

	Non-diabetes (n=10)		Pre-diabetes (n=7)		Diabetes (n=13)		ANOVA p value
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range	
Male/female	5/5		3/4		8/5		
Age (y)	54±3	51–59	53±3	50–57	53±3	50–59	0.760
Height (cm)	165.3±10.0	151.5–179.2	162.9±7.7	155.0–174.0	165.3±8.7	152.0–176.6	0.826
Weight (kg)	81.1±7.2	69.3–93.5	82.0±10.7	67.0–97.7	87.4±12.4	70.2–116.5	0.317
Body mass index (kg/m^2)	29.7±1.7	27.7–33.2	30.9±3.3	27.9–38.0	32.0±3.5	28.1–39.2	0.211
Body fat (%)	33.7±7.4	24.0–45.4	36.3±8.9	23.4–45.6	36.5±6.6	24.0–46.0	0.627
FM (kg)	26.9±4.5	21.2–34.5	29.5±8.0	20.9–44.6	31.7±6.2	23.1–45.7	0.206
FFM (kg)	54.1±10.2	41.6–71.1	52.4±11.4	40.8–68.5	55.8±11.2	41.6–73.0	0.808
Fasting glucose (mg/dL)	99±5	92–109	111±10	90–121	130±17[a,b]	100–168	<0.001
Log$_e$ HbA_{1c}	1.8±0.0	1.7–1.8	1.8±0.1	1.7–1.9	1.9±0.2[a]	1.6–2.5	0.016
[HbA_{1c} (%)]	5.9	5.7–6.0	5.9	5.4–6.4	7.1	5.0–12.6	
Log$_e$ fasting insulin	1.8±0.4	1.0–2.3	2.5±0.7[a]	1.5–3.3	2.3±0.6	1.5–3.5	0.019
[Fasting insulin (μU/mL)]	6.5	2.8–10.1	14.9	4.4–27.4	12.1	4.3–33.8	
HOMA-R	1.6±0.6	0.7–2.5	4.1±2.4	1.3–8.2	3.8±2.7	1.5–11.8	0.030
Triglycerides (mg/dL)	149±66	76–268	221±119	87–410	153±89	51–384	0.221
Free fatty acid (mEq/L)	0.4±0.2	0.1–0.7	0.5±0.1	0.4–0.7	0.5±0.2	0.3–1.0	0.339

FM: fat mass. FFM: fat-free mass. HbA_{1c}: glycosylated hemoglobin. HbA_{1c} and fasting insulin were log transformed. HOMA-R=fasting insulin×fasting glucose/405. Differences between the non-diabetes, pre-diabetes and diabetes groups were evaluated by one-way ANOVA and Bonferroni post hoc test. [a]$p<0.05$ vs. non-diabetes, [b]$p<0.05$ vs. pre-diabetes.

The second aim of the study was to examine the validity of several predictive equations for BMR in these subjects.

MATERIALS AND METHODS

Subjects. The subjects in the study were 50- to 59-y-old obese subjects who resided in Saku City (Nagano Prefecture in Japan). The subjects were selected randomly from participants in the Saku Control Obesity Program (SCOP). The details of SCOP are described elsewhere (*20*). Thirty obese Japanese adults without diabetes (n=10), or with pre-type 2 diabetes (n=7) or type 2 diabetes (n=13) participated in this study. Two diabetic patients were treated by diet and exercise prescription, and one diabetic patient by metformin or glibenclamide therapy. Another diabetic patient who had experienced a diabetes patient education program in the past was included also, whereas those on insulin therapy were excluded. The subjects were instructed to eat a usual diet and carry out normal, but not vigorous physical activity beginning 1 d before the measurements. All the investigations were carried out in the Saku Central Hospital. This study was conducted according to the guidelines of the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethical Committee of the National Institute of Health and Nutrition in Tokyo, Japan and the Ethical Committee of the Saku Central Hospital. The study protocol was explained to the subjects prior to enrollment, and all the subjects signed an informed consent form.

Anthropometric and body composition. The physical characteristics of the subjects are summarized in Table 1. Body weight was measured to the nearest 0.1 kg and body height to the nearest 0.1 cm using an automatic scale (Tanita, BF-220, Tokyo, Japan). The measurements were performed in light clothing and underwear. The light clothing was then weighed and subtracted from the total to obtain body weight with minimal clothing (underwear). Body mass index (BMI: kg/m^2) was calculated as body weight (kg) divided by square of body height (m^2). Percentage body fat was measured using a bioelectrical impedance technique (Tanita, BF-220). Fat-free mass (FFM) and fat mass (FM) were calculated from percentage body fat and body weight.

Measurements of BMR. The subjects came to the hospital in the early morning and were asked to minimize walking prior to the laboratory visit and BMR measurement. In the majority of previous studies, especially in those using the dietary reference intakes for Japanese (Japan-DRI), Schofield, or the Food and Agriculture Organization of the United Nations/World Health Organization/United Nations University, the subjects also came to the laboratory in the early morning (*21*). BMR was measured in the post-absorptive state at least 12 h after the last meal. Measurements were performed in a room at a constant temperature of approximately 25°C. After entering the hospital, the subjects rested in the supine position wearing a face mask for at least 30 min. Two samples of expired air were collected in Douglas bags over two 10-min periods, and the mean of the two values used in the analyses.

The expired air was sampled and the O_2 and CO_2 concentrations measured using a gas analyzer (Arco System, AR-1, Kashiwa, Japan) with a galvanic O_2 sensor and an infrared CO_2 sensor. Prior to each of the consecutive measurements, the gas analyzer was calibrated using atmospheric air. The volume of expired air was

Table 2. Predictive equations for basal metabolic rate used in the present study.

Predictive equations (kcal/d)		
	Males	Females
Ganpule	(0.0481×W+0.0234×H−0.0138×A−0.4235)×1,000/4.186	(0.0481×W+0.0234×H−0.0138×A−0.9708)×1,000/4.186
Japan-DRI (2010)	21.5 ×W	20.7 ×W
Harris-Benedict	66.4730+13.7516×W+5.0033×H−6.7550×A	655.0955+9.5634×W+1.8496×H−4.6756×A
Schofield	(0.048×W+3.653)×1,000/4.186	(0.034×W+3.538)×1,000/4.186
Owen	879+(10.20×W)	795+(7.18×W)
Mifflin	5+(9.99×W)+(6.25×H)−(4.92×A)	−161+(9.99×W)+(6.25×H)−(4.92×A)

W: weight (kg), H: height (cm), A: age (y). Predictive equations for 50- to 59-y old obesity subjects were used.

determined using a dry gas volume meter (Shinagawa, DC-5, Tokyo, Japan) and then converted to the volume under conditions of standard temperature, pressure, and dry gas (STPD). The gas exchange results were converted to BMR (kcal/d) using Weir's equation (*22*).

Predictive equations of BMR. Predictive BMR was calculated using the Ganpule (*18*), Japan-DRI (*23*), Harris-Benedict (*24, 25*), Schofield (*26*), Owen (*14, 15*), and Mifflin (*16*) equations (Table 2). The Japan-DRI provided the BMR standards (standard BMR per unit weight) according to age and sex category, with the data for these standards being obtained from a Japanese BMR database (*21, 23*). The Owen and Mifflin equations were developed using data obtained from adults including obese subjects.

Blood samples. Venous blood samples were collected after a fast of at least 12 h for measurement of fasting glucose, glycosylated hemoglobin (HbA_{1c}), insulin, triglycerides, and free fatty acid. The value of the internationally used HbA_{1c} (%) (HbA_{1c} [NGSP]) defined by the NGSP (National Glycohemoglobin Standardization Program), was calculated by adding 0.4% to the obtained HbA_{1c} (JDS) (%) defined by the Japan Diabetes Society (JDS) (*27*). Insulin and free fatty acids were examined using the laboratory testing services provided by SRL Inc. (Tokyo, Japan). Insulin (μIU/mL) was measured using CLEIA (Lumipulse Presto Insulin, Fujirebio Inc.), which has a minimal detection limit of 0.3 μIU/mL. Free fatty acid (mEq/L) was determined using an enzymatic assay (NEFA-SS 'Eiken,' Eiken Chemical Co. Ltd., Tokyo, Japan) with a sensitivity of 0.005 mEq/L. Other blood parameters were analyzed in the clinical laboratory of Saku Central Hospital. HOMA-R was calculated as fasting insulin (μIU/mL)×fasting glucose (mg/dL)/405.

All subjects underwent a 75-g oral glucose tolerance test. The subjects were divided into three groups according to the Diagnosis Criteria Exploratory Committee of the Japan Diabetes Society (2010) (*27*): non-diabetes (n=10), pre-diabetes (n=7), and diabetes (n=13).

Statistical analysis. The results are expressed as the mean±standard deviation (SD). Statistical significance was set at $p<0.05$. The Kolmogorov-Smirnov test was used for statistical testing of normality. HbA_{1c} and fasting insulin were log transformed as the data were not normally distributed. Differences in body composition, blood parameters, and BMR (kcal/d, kcal/kg weight/d and kcal/kg FFM/d) among the three groups were evaluated using one-way analysis of variance (ANOVA) and the Bonferroni post hoc test. Analysis of covariance (ANCOVA) with BMR as the dependent variable and FFM, FM, age, and sex as covariates was carried out. In order to examine the mechanism for differences in BMR, the blood sample measurements such as fasting glucose were added to FFM, FM, age, and sex in ANCOVA. The interaction terms with sex and body composition variables were examined in these analyses. Multiple linear regression models were also constructed using BMR as the dependent variable and FFM, FM, age, and sex as the independent variables. Gender was treated as a binomial variable (0 for male subjects, 1 for female subjects). Body height was not adjusted for, as it did not contribute significantly to BMR in the models ($p>0.05$). The relationships between the residual (measured BMR minus BMR after adjustment for FFM, FM, age, and sex) and fasting glucose, $\log_e HbA_{1c}$, $\log_e$ fasting insulin, HOMA-R, triglycerides, and free fatty acid were examined using Pearson's correlation coefficients. The statistical significance of differences between measured BMR and predicted equation BMR was analyzed by one-way ANOVA with repeated measurements and Dunnett's post hoc test, while differences between predicted and measured BMR values among non-diabetes, pre-diabetes, and diabetes were evaluated by one-way ANOVA and Bonferroni's post hoc test. The statistical analyses were performed using SPSS for Windows (version 18.0; SPSS Inc., Chicago, IL, USA).

RESULTS

No significant difference was observed in body composition among the three groups (Table 1). The subjects with diabetes had significantly higher fasting glucose and $\log_e HbA_{1c}$ levels than subjects with non-diabetes. There was no interaction between sex and diabetes diagnosis in the relationship to BMR (F=2.166, p=0.137). Moreover the interaction terms with sex and body composition variables in ANCOVA with BMR as the dependent variable were not significant. Therefore, both sexes were combined in all analyses. After adjustment for FFM, FM, age, and sex the BMR in subjects with diabetes was 7.1% higher than in non diabetic subjects (Table 3). The ANCOVA showed fasting glucose

Table 3. Basal metabolic rate in subjects with non-diabetes, pre-diabetes, or diabetes.

	Non-diabetes (n=10) Mean±SD	Pre-diabetes (n=7) Mean±SD	Diabetes (n=13) Mean±SD	ANOVA p value	ANCOVA p value
Measured BMR (kcal/d)	1,486±182	1,484±183	1,711±221[a]	0.018	—
(kcal/kg weight/d)	18.3±1.5	18.2±1.4	19.6±1.5	0.054	—
(kcal/kg FFM/d)	27.9±3.3	29.0±4.4	31.2±3.6	0.106	—
Adjusted BMR (FM, FFM, age, sex) (kcal/d)	1,531±98	1,537±95	1,648±98[b]	—	0.021
Adjusted BMR (FM, FFM, age, sex, fasting glucose) (kcal/d)	1,535±128	1,538±99	1,644±132	—	0.171

Measured BMR: measured basal metabolic rate. FFM: fat free mass. Adjusted BMR: analysis of covariance with BMR as the dependent variable and FFM, FM, age, sex, and fasting glucose as covariates was carried out. Differences among the non-diabetes, pre-diabetes, and diabetes groups were evaluated by one-way ANOVA and the Bonferroni post hoc test, [a]$p<0.05$ vs. non-diabetes, and also by ANCOVA and the Bonferroni post hoc test, [b]$p<0.05$ vs. non-diabetes.

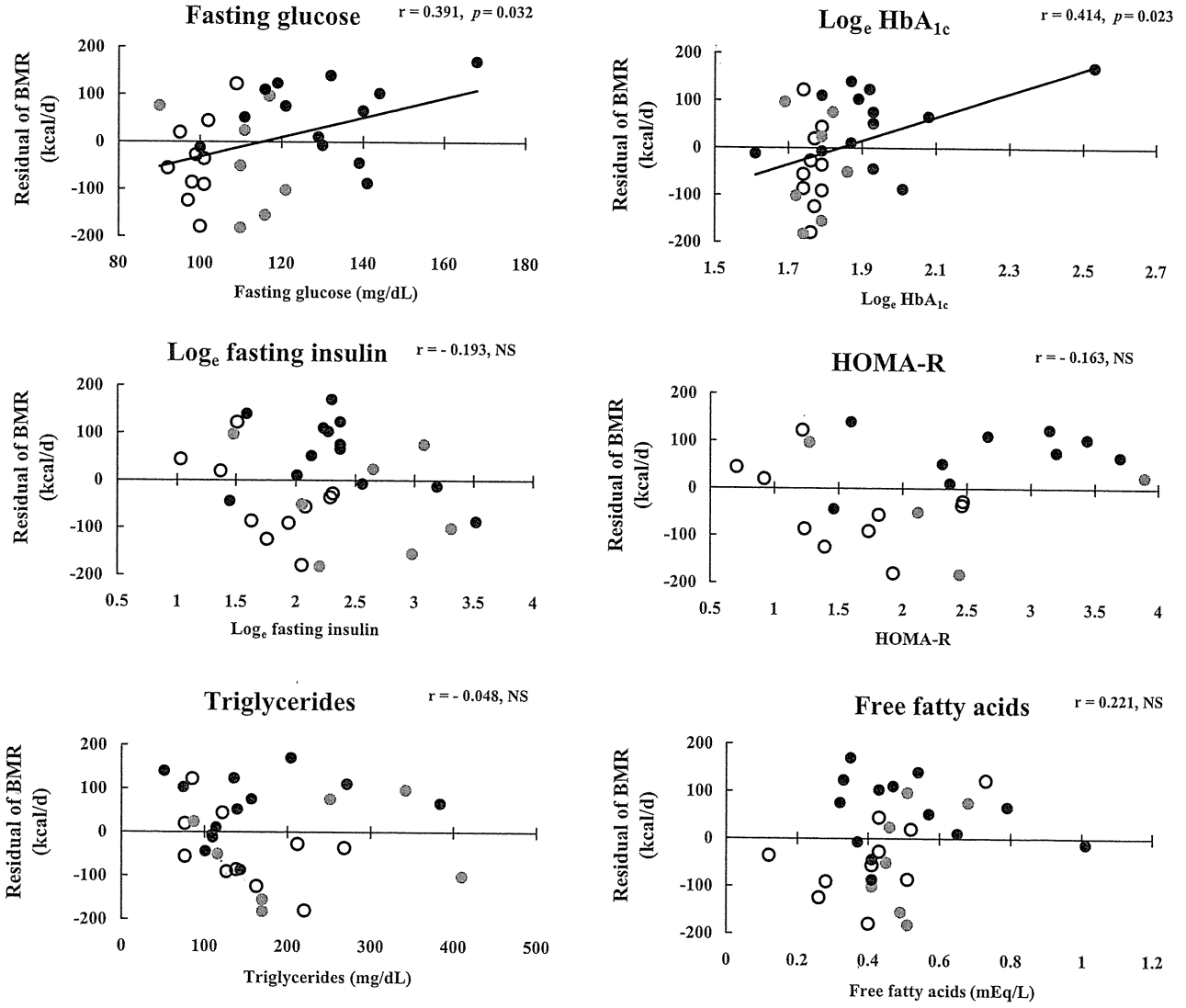

Fig. 1. Relationship between residual (measured BMR minus BMR adjusted for FM, FFM, age, and sex) and fasting glucose, log$_e$ HbA$_{1c}$, log$_e$ fasting insulin, HOMA-R, triglycerides and free fatty acids in subjects without diabetes, pre-diabetes or diabetes. HbA$_{1c}$ and fasting insulin were log transformed. Non-diabetes, white circles (○); pre-diabetes, gray circles (◍); diabetes, black circles (●). The regression lines are for all the subjects.

was an independent determinant of BMR, in addition to FFM, FM, age, and sex. After adjusting for fasting glucose in addition to FFM, FM, age and sex, there were no significant differences in BMR among the three groups. Furthermore, multiple regression analysis demonstrated 81% of the variability (R^2) in BMR was explained by FFM, FM, age, and sex, while fasting glucose as an additional independent variable explained

Table 4. Predicted basal metabolic rate in subjects with non-diabetes, pre-diabetes, or diabetes.

	Mean±SD (kcal/d)	Mean difference±SD (kcal/d)	ANOVA[a] *p* value	Post hoc test[b] *p* value	ANOVA[c] *p* value
Non-diabetes (n=10)			<0.001		
Ganpule	1,511±194	25±119		0.844	0.019[d]
Japan-DRI	1,712±175	227±117		<0.001	0.222
Harris-Benedict	1,584±196	99±127		0.002	0.061
Schofield	1,660±209	175±117		<0.001	0.068
Owen	1,548±219	62±123		0.094	0.075
Mifflin	1,499±209	13±126		0.990	0.026[d]
Pre-diabetes (n=7)			0.001		
Ganpule	1,502±214	17±148		0.977	
Japan-DRI	1,727±241	242±132		<0.001	
Harris-Benedict	1,583±210	98±159		0.111	
Schofield	1,648±222	163±185		0.002	
Owen	1,532±229	48±198		0.734	
Mifflin	1,486±226	2±167		1.000	
Diabetes (n=13)			<0.001		
Ganpule	1,601±237	−110±99		<0.001	
Japan-DRI	1,856±290	146±147		<0.001	
Harris-Benedict	1,692±253	−19±110		0.898	
Schofield	1,766±263	55±98		0.065	
Owen	1,649±264	−62±99		0.032	
Mifflin	1,585±242	−126±100		<0.001	

Mean difference: Mean of difference between predicted and measured BMR. ANOVA[a]: Significance of differences between predicted and measured BMR analyzed by one-way ANOVA with repeated measurements and Dunnett's post hoc test. Post hoc test[b]: Predicted vs. Measured. ANOVA[c]: Differences in predicted equation between non-diabetes, pre-diabetes and diabetes evaluated by one-way ANOVA and Bonferroni post hoc test. [d]$p<0.05$, Bonferroni post hoc test, non-diabetes vs. diabetes.

another 3% of the variability in BMR.

The relationships among residual BMR (measured BMR minus BMR after adjustment for FFM, FM, age, and sex) and fasting glucose, $\log_e$ HbA_{1c}, $\log_e$ fasting insulin, HOMA-R, triglycerides, and free fatty acids are shown in Fig. 1. Residual BMR correlated significantly with fasting glucose (r=0.391, p=0.032) and $\log_e$ HbA_{1c} (r=0.414, p=0.023), although there was no significant correlation between residual BMR and $\log_e$ fasting insulin, HOMA-R, triglycerides, or free fatty acid.

Table 4 shows differences between BMR predicted from six equations and measured BMR in subjects with non-diabetes, pre-diabetes, or diabetes. Predicted BMR values by Ganpule, Owen and Mifflin equations were not significantly different from the measured BMR in non- or pre diabetes. On the other hand, for diabetes there was no significant difference between measured and predicted BMR calculated by Harris-Benedict and Schofield equations. The differences between BMR predicted by Ganpule and Mifflin equations and measured BMR was significant lower in subjects with diabetes than in subjects without diabetes. The prediction error by Ganpule and Mifflin equations were similar to that calculated when BMR was adjusted for FM, FFM, age, and sex (Table 3). For the other equations, no significant differences were found between predicted and measured BMR.

DISCUSSION

This study compared BMRs among subjects with non-diabetes, pre-type 2 diabetes and type 2 diabetes in the obese Japanese population. The results showed that obese Japanese subjects with type 2 diabetes had significantly higher BMR than obese Japanese without diabetes. A similar trend has been demonstrated in previous studies. Furthermore, given the significant relationship we observed between residual BMR and fasting glucose, it is possible that fasting glucose level may be a factor in the higher BMR found in obese subjects with type 2 diabetes.

Several previous studies have examined whether or not BMR in patients with type 2 diabetes is higher than in non-diabetic subjects. Huang et al. (*28*) reported that BMR in these patients was 8.4% higher in females and 4.6% higher in males than in the corresponding non-diabetic subjects. Maiolo et al. (*29*) also reported that BMR was 35% higher in diabetic patients. It is important to note that BMR was not adjusted for body composition in these studies which may explain a large portion of the increase in BMR. On the other hand, two previous studies performed similar comparisons after adjustment for BMR. Fontvieille et al. (*3*) showed in Pima Indians that the BMR in patients with type 2 diabetes (weight: 107±33 kg, body fat: 32±9%) was 5.2% higher than in non-diabetic subjects (weight: 99±24 kg, body fat: 39±7%). Bitz et al. (*4*) also compared BMRs between subjects with or without type 2 diabetes in Caucasians and showed that BMR in the diabetic subjects (BMI: 35.5±3.7 kg/m^2) was 6.9% higher than in non-diabetic subjects (BMI: 34.1±4.7 kg/m^2). In the

present study, BMR adjusted for FFM, FM, age, and sex, was significantly higher in diabetic compared with non-diabetic subjects (7.1%) (Table 3). Surprisingly, the adjusted BMR in patients with diabetes was higher than in non-diabetic subjects. These three studies using adjusted BMR obtained similar results in different ethnicities.

Although the physiological mechanisms responsible for the increased BMR in individuals with type 2 diabetes are poorly understood, several mechanisms have been proposed to explain this increase. These include increased energy costs during hyperglycaemia, for example gluconeogenesis, protein turnover, and sympathetic nervous system activity (*3*). Bitz et al. (*4*) reported that free fatty acids may be a potential mediator in several mechanisms associated with increased BMR. Gougeon et al. (*30*) reported that BMR adjusted for weight, FFM, age, and sex was significantly higher in subjects with type 2 diabetes with a fasting plasma glucose >180 mg/dL than those with a level <180 mg/dL (*30*). They used a fasting plasma glucose level of 180 mg/dL as it represents the concentration considered to be the glycosuria threshold which reflects poor control. Gougeon et al. (*30*) also reported that fasting plasma glucose was a significant independent variable and increased the prediction of BMR by more than 3%. In the present study, we showed a significant relationship between residual BMR and fasting glucose (Fig. 1). After adjusting for fasting glucose in addition to FFM, FM, age and sex, there were no significant differences in BMR among the three groups (Table 3). Fasting glucose as an additional independent variable explained another 3% of the variability in BMR by multiple regression analysis. Therefore, the degree to which fasting glucose contributes to BMR was similar in different ethnicities. Weyer et al. (*31*) reported that a higher endogenous glucose output (EGO) was a relatively late finding in the development of type 2 diabetes and typically was not evident until the transition from impaired glucose tolerance (IGT) to diabetes. The extent to which the energy cost of EGO contributes to increased BMR is, therefore, probably less in individuals with IGT than in those with diabetes. In the present study, BMR in pre-diabetic subjects was not significantly higher than that measured in non-diabetic subjects. Fasting glucose values were also similar in non-diabetic and pre-diabetic subjects, which may have contributed to the similar BMR values we observed between the two groups. This result supports the results of Weyer et al. (*31*). In summary, higher BMR in obese subjects with type 2 diabetes may be related to fasting glucose level.

One of the limitations of the present study is the relatively small sample size. In the present study, both sexes were combined. Moreover, one diabetic patient who received metformin or glibenclamide therapy and another diabetic patient who had experienced diabetes patient education program in the past were included. However, more detailed analyses with larger samples size are needed for the better understanding of the effects of sex and medication. In panticular, there is some possibility that medication affects the relationship between blood glucose and BMR through the suppression of blood fasting glucose.

As the majority of clinical facilities do not have indirect calorimetry, BMR is usually estimated from predictive equations using data such as age, sex, height, and weight (*11*). A predictive equation of BMR in obese subjects is important to provide the basis for an individualized treatment plan for weight loss (*28*). In the present study, we examined the validity of six predictive equations for BMR in Japanese subjects with non-diabetes, pre-diabetes or diabetes. The Ganpule (*18*) and Japan-DRI (*21*, *23*) equations were developed based on data from Japanese subjects. The Harris-Benedict (*24*, *25*), Schofield (*26*), Owen (*14*, *15*), and Mifflin (*16*) equations are used internationally. The Harris-Benedict equation is the most common method for calculating BMR (*26*), while the Owen (*14*, *15*) and Mifflin (*16*) equations were developed in adults including obese subjects.

Huang et al. (*28*) demonstrated that the Harris-Benedict equation overestimated BMR in diabetic males and underestimated the value in diabetic females, while Gougeon et al. (*30*) reported that BMR predicted by the Owen equations did not differ significantly from measured BMR in obese diabetic males. In the present study, the differences between BMR predicted by Ganpule and Mifflin equations and measured BMR was significant lower and negative for most predictive equations in subjects with diabetes than in subjects without diabetes. In the present study, ANCOVA showed that the differences in average prediction error of the Ganpule and Mifflin equation among the three groups were comparable to the differences obtained after adjustment for FM, FFM, age, and sex. BMR was underestimated by 110 and 126 kcal/d in diabetes, while predicted BMR was comparable to measured BMR in the non-diabetes and pre-diabetes groups. Therefore, adjustment should be made for diabetes when predicting BMR.

In conclusion, obese Japanese with type 2 diabetes have higher BMR than obese Japanese without diabetes. This phenomenon appears to be similar in different ethnicities such as Pima Indians, Caucasians, and Asians. Although the physiological mechanisms responsible for the increased BMR in subjects with type 2 diabetes remain unclear, the fasting glucose level could be a major factor contributing to this increase. Furthermore, the difference between the prediction errors of the Ganpule and Mifflin equation in subjects with and without diabetes tended to be significant and was comparable to those when BMR was adjusted for FM, FFM, age, and sex. It is therefore important to pay attention to the prediction error for BMR in diabetic patients in the clinical setting.

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