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Comparison of Predicted Energy Expenditure in Japanese Patients with Non-Alcoholic Fatty Liver Disease to Establish a Suitable Nutrition Intervention

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Summary The incidence of non-alcoholic fatty liver disease (NAFLD) is increasing in Western and Asian countries, including Japan. NAFLD includes the condition of non-alcoholic steatohepatitis, which can progress to end-stage liver disease. Weight reduction based on basal energy expenditure (BEE) is considered to be the only established treatment for patients with NAFLD. However, a formula that is suitable for predicting BEE in Japanese patients with NAFLD remains to be determined. We enrolled 77 Japanese patients who were diagnosed with NAFLD according to histological findings. Their BEE was measured (mBEE) by indirect calorimetry. Physical findings, laboratory data and their predicted BEE (pBEE) values were compared with the mBEE values. All pBEE values were evaluated as a root mean squared error (RMSE) and an accurate estimation. The mBEE values correlated with the patient's weight, skeletal muscle mass, and age. Most of predictive formulae overestimated BEE in NAFLD patients in the present study. In contrast, the Kyoto equation provided an accurate prediction. Most prediction formulae included body weight as a reference of the skeletal muscle mass and were established using data from a healthy study population. However, differences in muscle mass exist among different races, and body composition differs between healthy individuals and those with high BMIs. The improved accuracy of the Kyoto equation is likely due to the similar backgrounds of the patients in the present study. The Kyoto equation is the most suitable formula for estimating BEE in Japanese patients with NAFLD.

Key Words indirect calorimetry, Kyoto equation, NAFLD, non-alcoholic fatty liver disease, basal energy expenditure

Non-alcoholic fatty liver disease (NAFLD) is one of the principal features of metabolic syndrome, which has become an emergent public health problem in many countries in recentyears (*1–3*). The incidence of NAFLD is increasing along with the escalation in the incidence of metabolic syndrome (*4, 5*). In the majority of cases, NAFLD is associated with a good prognosis; however, approximately 10–30% of NAFLD patients are affected with nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and end-stage liver disease (*6–8*). To prevent the progression to liver cirrhosis from NASH, effective treatment must be established for NAFLD. Several pharmaceutical interventions have been investigated; however, thus far none has been approved for general use (*9, 10*).

Obesity is considered to be one of the most important risk factors for NAFLD (*11*). Liver injuries associated with NAFLD have been reported to be improved by weight reduction (*12–14*). Weight reduction is therefore generally recommended as an initial step in the management of NAFLD. A nutritional intervention protocol for weight reduction was prepared according to basal energy expenditure (BEE).

Several formulae have been proposed as easy-to-use calculations of BEE. The Harris-Benedict (*15*), Owen (*16, 17*), Mifflin (*18*), Schofield (*19*), and Food and Agriculture Organization of the United Nations/World Health Organization/United Nations University (FAO/WHO/UNU) equations (*20*) have been used internationally. In Japan, the Dietary Reference Intakes for Japanese (Japan-DRI) provides the standard BEE values according to sex and age (*21*). Two such formulae have been recently proposed. One is the Kyoto equation by Ikeda et al., which was developed after an analysis of Japanese patients with diabetes mellitus (*22*). The other is the National Institute Health and Nutrition (NIHN) equation that has been proposed by Tabata et al., which will be developed based on an analysis of healthy Japanese individuals (*23, 24*). Although the importance of nutritional intervention in NAFLD patients is recognized, a predictive BEE (pBEE) formula that is appropriate for the prediction of BEE in Japanese individuals with NAFLD remains to be elucidated.

To optimize nutritional interventions in NAFLD patients, a formula that allows for the accurate prediction of BEE is needed. For this purpose, we compared the pBEE values, using several pBEE formulae, to the

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Table 1. The formulae for predicting basal energy expenditure.
pEE formula (kcal/d)

Harris-Benedict	655.0955+9.5634×BW [kg]+1.8496×Height [cm]−4.6756×age [y]	
Owen	Male:	879+10.2×BW [kg]
	Female:	795+7.18×BW [kg]
Mifflin	9.99×BW [kg]+6.25×Height [cm]−4.92×age [y]+5 (Male) or −161 (Female)	
Schofield	Male:	(18–29 y);15.057×BW [kg]+692.2
		(30–59 y); 11.472×BW [kg]+873.1
		(> 60 y); 11.711×BW [kg]+587.7
	Female:	(18–29 y); 14.818×BW [kg]+486.6
		(30–59 y); 8.126×BW [kg]+845.6
		(> 60 y); 9.082×BW [kg]+658.5
FAO/FAO/WHO/ UNU WHO1	Male:	(18–29 y); 15.3×BW [kg]+679,
		(30–59 y); 11.6×BW [kg]+879
		(> 60 y); 13.5×BW [kg]+487
	Female:	(18–29 y); 14.7×BW [kg]+496
		(30–59 y); 8.7×BW [kg]+829
		(> 60 y); 10.5×BW [kg]+596
FAO/FAO/WHO/ UNU WHO2	Male:	(18–29 y); 15.4×BW [kg]−27×Height [m]+717,
		(30–59 y); 11.3×BW [kg]+16×Height [m]+901,
		(> 60 y); 8.8×BW [kg]+1128×Height [m]−1071
	Female:	(18–29 y); 13.3×BW [kg]+334×Height [m]+35,
		(30–59 y); 8.7×BW [kg] − 25×Height [m]+865,
		(> 60 y); 9.2×BW [kg]+637×Height [m]−302
Japan-DRI	Male:	(18–29 y); 24.0×BW [kg]
		(30-49 y); 22.3×BW [kg]
		(> 50 y); 21.5×BW [kg]
	Female:	(18–29 y); 22.1×BW [kg]
		(30-49 y); 21.7×BW [kg]
		(> 50 y); 20.7×BW [kg]
Adjusted-DRI	Male:	(18–29 y); {24.0+(10.8–0.173×BW [kg])}×BW [kg]
		(30-49 y); {22.3+(10.8–0.173×BW [kg])}×BW [kg]
		(> 50 y); {21.5+(10.8–0.173×BW [kg])}×BW [kg]
	Female:	(18–29 y); {22.1+(8.9–0.172×BW [kg])}×BW [kg]
		(30-49 y); {21.7+(8.9–0.172×BW [kg])}×BW [kg]
		(>50 y); {20.7+(8.9–0.172×BW [kg])}×BW [kg]
Kyoto	10×BW [kg]−3×age [y]+125 {(if male)+750}	
NIHN	{0.0481×BW [kg]+0.0234×Height [cm]−0.0138×age [y]−0.4235 (Male) or 0.9708 (Female)} ×1000/4.186	

measured BEE (mBEE) values, calculated by indirect calorimetry, of 77 NAFLD patients in whom NAFLD was histologically confirmed. We calculated the difference between pBEE and mBEE and analyzed the root mean squared error (RMSE) and accurate estimation.

MATERIAL AND METHODS

Subjects. Between April 2010 and September 2014, 122 patients were diagnosed with fatty liver in our hospital. The criteria for eligibility in this study were as follows: the elevation of liver enzymes and the diagnosis of fatty liver by ultrasonography with the absence of any other causes of liver injury, such as viral infections, drug exposure, autoimmune disease, congenital metabolic disorders or excessive drinking (as defined by an average consumption of alcohol of <20 g/d). Among the patients, 77 patients consented to undergo a liver biopsy and indirect calorimetry. NAFLD was confirmed in all 77 patients according to the histological findings. The study complied with the provisions of the Declaration of Helsinki and was approved by the Ethics Committee of Iwate Medical University (HG H22-6).

Measurements and calculations. BMI was calculated using the following formula: BMI=weight (kg)/(height ×height) (m^2). The Kyoto, NIHN, Japan-DRI, Mifflin, Owen, Harris-Benedict, Schofield, WHO1 and WHO2 equations were used as pBEE formulae. For the Japan-DRI equation, the Ministry of Health, Labour and Welfare proposed adjusting for body weight (*21*). Therefore, the equations with weight adjustment (adjusted-DRI) were also examined. The pBEE formulae that were used in the present study are summarized in Table 1.

Indirect calorimetry. Indirect calorimetry was performed in the morning, after a 10-h overnight fast during hospitalization for a liver biopsy. mBEE was measured by computed open-circuit indirect calorimetry (AE-310S; Minato Medical Science Co., Osaka, Japan). Period flow and gas calibration were performed prior to each mea-

Table 2. Characteristics of the patients with NAFLD in the present study.

		All (n=77)	NAFL (n=41)	NASH (n=36)
Age	y	51.5±14.2	51.8±12.2	51.2±16.4
Male: Female		27:50	18:23	9:27
BMI	kg/m^2	28.3±4.2	27.6±3.5	29.3±4.8
Height	cm	159±9.4	160.9±8.2	157.2±10.4
BW	kg	72.4±15.2	71.7±12.3	73.2±18.2
FFM	Kg	44.5±10.4	46.1±9.3	42.5±11.7
SMM	kg	25.3±7.0	26.0±6.5	25.6±7.8
BFM	kg	27.2±9.1	25.6±8.5	29.4±9.7
BFP	%	36.5±8.0	34.8±8.4	38.8±7.4
WHR		0.96±0.05	0.96±0.05	0.98±0.05
AST	IU/L	40.4±31.3	32.8±30.9	49.1±29.9
ALT	IU/L	51.2±41.3	41.0±29.2	62.9±49.7
γ-GTP	IU/L	83.9±87.0	87.9±80.6	79.4±94.8
TG	mg/dL	134.4±81.8	145.1±74.0	122.3±89.0
HDL-C	mg/dL	54.7±13.5	57.2±12.6	51.9±14.2
LDL-C	mg/dL	119.5±33.7	130.2±32.3	107.1±32.3
HbA1c	%	5.90±0.87	5.82±0.63	6.01±1.1
HOMA-IR		3.66±4.29	2.82±1.56	3.68±2.31
mBEE	kcal	1,387±239	1,384±181	1,392±296

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BFM, Body fat mass; BFP, Body fat percentage; BMI, Body mass index; BW, body weight; FFM, free fat mass; γ-GTP, gamma-glutamyl transpeptidase; HDL-C, HDL-cholesterol; HbA1c, hemoglobin A1c; LDL-C, LDL-cholesterol; NAFLD, non-alcoholic fatty liver disease; TG, triglyceride; mBEE, measured basal energy expenditure; SMM, smooth muscle mass; WHR, waist hip ratio.

surement. After resting for a minimum of 30 min, the patients were assessed in the supine position with a face-mask. A pump drew ambient air through the facemask at a constant rate. After equilibrium was reached for 10 min, respiratory exchange was performed continuously over 15 min. mBEE was obtained every minute.

mBEE was calculated from the oxygen consumption (VO_2) and carbon dioxide production (VCO_2) using Weir's equation [25]: mBEE=[3.94×VO_2 (mL/min)+1.11×VCO_2 (mL/min)]×1.44.

Bioimpedance assessments. Body composition was measured using an InBody720 device (Biospace, Tokyo, Japan). The device, which is a multi-frequency impedance plethysmography body composition analyzer, determines body composition according to an eight-point tactile electrode method that measures the resistance at five specific frequencies (1 kHz, 50 kHz, 250 kHz, 500 kHz, and 1 MHz) and the reactance at three specific frequencies (5 kHz, 50 kHz, and 250 kHz). The examination was performed on the day of the liver biopsy. The data regarding several variables, such as body weight (BW), body fat mass (BFM), body fat percentage (BFP) and skeletal muscle mass (SMM), were calculated using the Lookin'Body 3.0 software program. Free-fat mass (FFM) was calculated using the following formula: FFM=weight (kg)−body fat mass (kg).

Liver biopsies and histological assessments. Percutaneous needle biopsies were performed on liver segment 6 under ultrasonography using a 16 G needle. In order to definitively diagnose either NAFL or NASH, all liver biopsy specimens were examined for fibrosis, steatosis, hepatocyte ballooning and portal inflammation. The histological findings were determined according to the method proposed by Matteoni et al. (*7*). In order to limit information bias, two pathologists reported all of the histopathological findings.

Table 3. The correlation of mBEE to the laboratory data and physical findings.

vs. mBEE	r	95% confidence interval	p value
BW	0.779	0.6688-0.8559	p<0.05
FMM	0.754	0.6310–0.8403	p<0.05
SMM	0.753	0.6281-0.8398	p<0.05
Height	0.674	0.5256–0.7830	p<0.05
BMI	0.571	0.3924-0.7083	p<0.05
Age	−0.505	−0.6589−−0.311	p<0.05

Abbreviations: BMI, body mass index; BW, body weight; FFM, free fat mass; mBEE, measured basal energy expenditure; SMM, smooth muscle mass.

Laboratory data. All blood samples were collected on the day of the liver biopsy after overnight fasting. The levels of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (γ-GTP), total bilirubin (T-Bil), ferritin, hyaluronic acid (HA), type IV collagen (IV-collagen), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) were analyzed using an autoanalyzer (CA-BM2250, JEOL, Tokyo, Japan).

Table 4. Differences between the mBEE and the pBEEs of the indicated formulae.

Total	H-B	Owen	Mifflin	Japan-DRI	Adjusted-DRI	Schofield	WHO1	WHO2	Kyoto	NIHN
	1,467±289	1,432±243	1,361±301	1,557±371	1,313±183	1,503±293	1,524±292	1,523±302	1,363±217	1,365±288
Bias	−5.9±11.2	−3.8±10.5	2.0±12.2	−11.8±15.1	4.3±10.1	−8.7±12.6	−10.2±12.4	−10.1±13.0	1.1±9.4	1.6±11.4
RMSE	135±108	118±92	138±93	210±175	131±104	164±126	173±131	179±133	105±74	123±92
Accuracy	62.3%	63.6%	50.6%	41.6%	64.9%	51.9%	49.4%	46.8%	71.4%	54.5%
BMI										
Bias										
20–24.9	−2.0±8.9	−5.6±8.2	7.9±9.8	1.2±9.4	3.0±7.4	−5.2±10.4	−6.3±10.6	−6.1±11.0	2.8±7.6	7.5±9.0
25–29.9	−4.4±11.1	−3.2±10.7	2.6±12.5	−8.8±12.4	3.2±9.4	−7.7±12.2	−9.3±12.0	−9.1±12.8	2.2±9.4	2.6±11.4
30<	−10.2±11.6	−3.4±11.7	−2.3±11.8	−23.7±12.4	6.3±12.2	−12.1±13.8	−13.8±13.4	−13.8±13.8	−1.3±10.2	−3.2±10.8
RMSE										
20–24.9	88±69	98±67	131±80	92±76	69±78	108±87	116±88	115±98	70±77	118±83
25–29.9	112±102	117±79	136±94	151±119	117±58	147±112	154±118	163±121	102±67	118±95
30<	194±113	131±117	144±101	356±183	188±132	220±145	232±148	238±146	130±74	133±95
Accuracy										
20–24.9	64.7%	58.8%	41.2%	70.6%	82.4%	58.8%	64.7%	64.7%	82.4%	52.9%
25–29.9	72.7%	63.6%	57.6%	51.5%	75.6%	51.5%	51.5%	48.5%	75.6%	60.6%
30<	48.1%	66.7%	48.1%	11.1%	40.7%	48.1%	37.0%	33.3%	59.3%	48.1%
Histology										
Bias										
NAFL	−6.24±10.7	−5.08±10.6	0.67±11.9	−11.1±14.1	3.34±8.95	−9.29±12.6	−10.8±12.5	−11.1±13.1	0.96±8.66	0.62±10.9
NASH	−5.68±11.9	−2.46±10.5	3.61±12.6	−12.7±16.4	5.43±11.4	−8.11±12.7	−9.62±12.6	−8.99±13.0	1.27±10.4	2.86±12.0
RMSE										
NAFL	132±107	123±100	130±91	200±151	114±70	169±130	180±135	188±142	101±62	116±89
NASH	139±113	113±83	147±96	221±202	151±131	159±124	166±128	169±126	110±87	133±96
Accuracy										
NAFL	61.0%	61.0%	56.1%	36.0%	73.2%	46.3%	46.3%	43.9%	75.6%	56.1%
NASH	63.9%	66.7%	44.4%	44.4%	55.5%	58.3%	52.8%	50.0%	66.7%	50.0%

The bias was determined by subtracting the pBEE from the mBEE in each subject. The RMSE was computed as the expected absolute deviation of the pBEE from the mBEE.
Abbreviations: DRI, Dietary Reference Intakes; H-B, Harris-Benedict expenditure; mBEE, measured basal energy expenditure; NIHN, National Institute Health and Nutrition; pBEE, predictive basal energy expenditure, RMSE, root mean squared error.

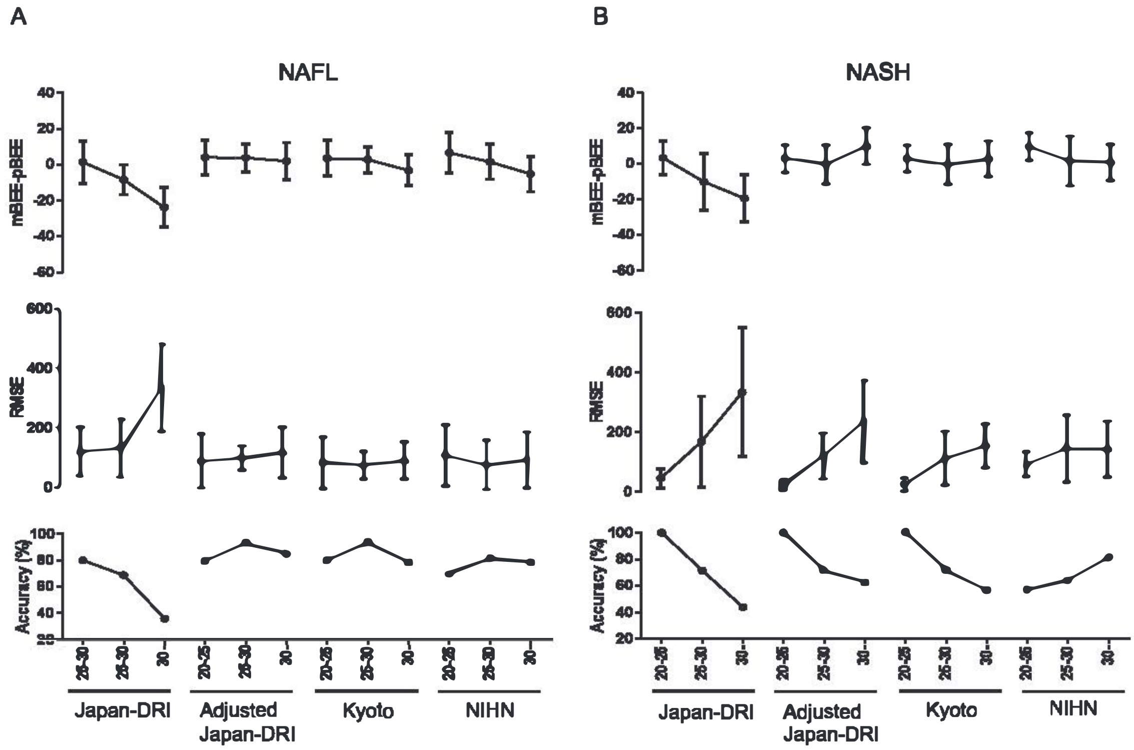

Fig. 1. Comparison of the Japan-DRI, adjusted-DRI, Kyoto and NIHN equations in each BMI group of NAFL and NASH patients. A) NAFL patients and B) NASH patients. The vertical axes show the value for predictive BEE (pBEE) subtracted from measured BEE (mBEE) (top graph), the root mean squared error (RMSE) (middle graph) and the accuracy (bottom graph). The horizontal axes reveal groups classified by BMI and the indicated predictive formulae.

Statistical analysis. The results of each measurement are expressed as the mean±standard deviation. The correlation between each pair of the parameters was analyzed by Spearman's correlation test. Comparisons between pBEE and mBEE were presented as Bland-Altman plots and evaluated by bias, RMSE and accurate estimation. Bias was determined by subtracting pBEE from mBEE in each subject. The RMSE was considered to account for each individual's error range, regardless of whether it was an over- or under-estimation. The RMSE was calculated as the expected absolute deviation of pBEE from mBEE. The proportion of pBEE within ±10% of mBEE was considered as another evaluation of the accuracy. Spearman's correlation was used to assess the statistical significance of the correlations. All statistical analyses were performed using the SPSS 17.0 software program (SPSS Inc., Chicago, IL).

RESULTS

The physical and biochemical characteristics of the patients (Table 2): Since none of the 77 patients consumed excessive amounts of alcohol, they were diagnosed with NAFLD, which was further classified as NAFL (n=41) and NASH (n=36) using Matteoni's classification. The subjects were characterized by a high BMI, a high west-hip (WH) ratio and high BFM. The mean AST, ALT and γ-GTP levels exceeded the normal range (40.4±31.3 IU/L, 51.2±41.3 IU/L, and 83.9±87.0 IU/L, respectively).

SMM, FFM and BW were well-correlated with mBEE in patients with NAFLD: To investigate the factors that were associated with mBEE, several parameters, including the physical and biochemical data of the patients were compared withmBEE. BW, FFM, SMM, height, and BMI were positively correlated with mBEE (r=0.779, p<0.05; r=0.754, p<0.05; r=0.753, p<0.05; r=0.674, p<0.05; and r=0.571, p<0.05, respectively) (Table 3). In contrast, patient age was negatively correlated with mBEE (r=−0.505, p<0.05). These data indicated that the mBEE was closely related to physical parameters in NAFLD patients as well, although they had been recognized in general subjects.

Predictive formulae of BEE compared in NAFLD patients: All pBEEs were calculated using the indicated formulae (Table 1). The results of bias, RMSE and accurate estimation evaluations for each formula are shown in Table 4. The Mifflin, adjusted-DRI, Kyoto, and NIHN equations underestimated BEE. In contrast, the Harris-Benedict, Owen, Japan-DRI, Schofield, WHO1 and WHO2 equations overestimated BEE (Table 4). All of the equations tended to overestimate BEE in patients with high BMI, except for adjusted- DRI.

Predictive formulae based on Japanese populations compared in Japanese patients with NAFLD: Because the predictive equations derived from Caucasians tend to overestimate BEE of non-Caucasians (*26–29*), we focused on the difference among the Kyoto, Japan-DRI, adjusted-DRI, and NIHN equations. According to classi-

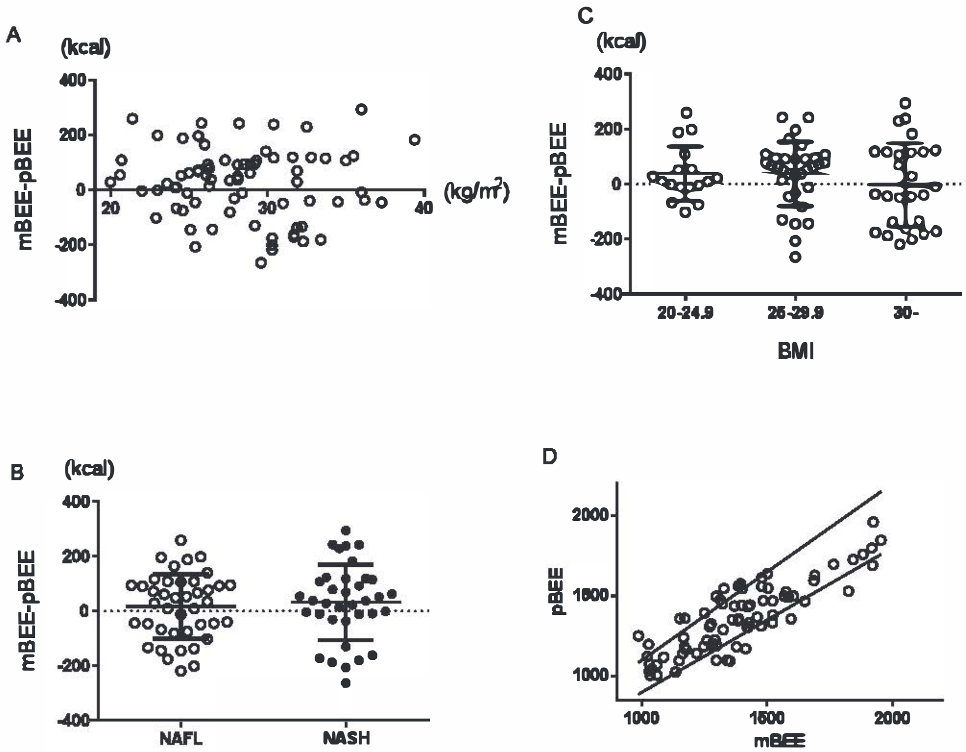

Fig. 2. The Kyoto equation predicted measured BEE (mBEE) with high accuracy in patients with NAFLD. A, B and C) The vertical axes reveal the value for predictive BEE (pBEE) subtracted from measured BEE (mBEE), which was defined as "bias." The horizontal axes reveal BMI in A), histological classification in B), and classification according to the BMI in C). D) The open circles indicate each subject. The upper line indicates 110% of mBEE, while the lower line indicates 90% of mBEE.

fication by BMI, Japan-DRI computed less-accurate pBEE values in patients with high BMI. In contrast, NIHN overestimated the pBEE values in patients with low BMI. The adjusted-DRI and Kyoto equations predicted accurate BEE in lower BMI groups. We next confirmed the predictive capability of each formula among the NAFL and NASH groups. The adjusted-DRI, Kyoto and NIHN equations computed lower accurate BEE values in the NASH group compared with the NAFL group (Table 4). To evaluate the accuracy in NAFL and NASH patients, the two groups were divided by BMI. Japan-DRI overestimated BEE in the higher BMI groups of both groups (Fig. 1A and 1B). Interestingly, the Kyoto and adjusted-DRI equations demonstrated lower accuracy in the high BMI group of NASH patients. In contrast, the NIHN equation showed relatively high accuracy in the high BMI group of NASH patients (Fig. 1B).

The Kyoto equation was a good predictor of mBEE in patients with NAFLD: The Kyoto equation was found to have the highest accuracy (pBEE was closest to mBEE) and lowest deviation compared with the other predictive equations (Table 4). The variability of pBEE in the Kyoto equation is presented in Bland-Altman plots in Fig. 2A–C. The pBEE values of most patients were within 200 kcal of mBEE (Fig. 2A). This tendency was not associated with the histological diagnosis (Fig. 2B). However, pBEE was found to be inaccurate in patients with higher BMI values (Fig. 2C). The accuracy of the Kyoto equation is demonstrated in Fig. 2D. pBEE, as calculated by the Kyoto equation, tended to be overestimated in patients with lower BMI values and underestimated in patients with higher BMI values (Fig. 2D).

DISCUSSION

Excessive calorie intake leads to the accumulation of fat in subcutaneous areas and various organs of the body. The liver is the central organ of energy storage. NAFLD is a typical example of fat accumulation due to hypernutrition. Importantly, in some patients NAFLD progresses to liver cirrhosis due to NASH. NAFLD should therefore be treated. Although the primary choice of treatment for NAFLD should be the correction of the calorie balance by nutritional intervention, energy expenditure in Japanese NAFLD patients has not been elucidated yet. Thus, the aim of this study was to investigate a suitable predictive formula for BEE in Japanese NAFLD patients.

We measured BEE of patients with NAFLD by indirect calorimetry, and the results were compared using several prediction equations. The Kyoto equation demonstrated both the smallest RMSE value and the highest accuracy of the equations, even among predictive formulae established using data from Japanese populations (Table 4). Thus, we considered the Kyoto equation to be the most accurate formula for the prediction of BEE in Japanese patients with NAFLD. The Kyoto equation showed the highest accuracy for two reasons: the equation was derived from (1) Japanese patients, and (2) patients with diabetes and higher BMIs.

Most of the equations used in the present study were derived from healthy and non-obese populations. However, the subjects in the present study had higher BMI values. Moreover, Mongolians show lower BEE than Caucasians with similar BW (*30*, *31*) due to a lower FFM in comparison to Caucasians with similar BW (*32*, *33*). According to these data, the Kyoto equation was developed in a background similar to that of the present study. Therefore, equations other than the Kyoto equation tended to predict higher energy expenditure than mBEE, thus leading to the overestimation of BEE.

In the present study, mBEE was more strongly correlated with BW than with the FFM or SMM. Previous studies have shown that the FFM was more strongly correlated with mBEE than BW (*23*, *32*). We hypothesize that fatty degeneration of the skeletal muscle, which has been reported in NAFLD patients, may be involved in this tendency (*34*). We suspect that the SMM of the subjects in the present study might lower their energy expenditure due to fatty degeneration; as a consequence, the correlation of mBEE to both the SMM and the FFM would be weaker than the correlation with BW. Interestingly, the adjusted-DRI and Kyoto equations predicted a lower accuracy of BEE in the high BMI group (BMI >30) among NASH patients than in NAFL patients, although there was no significant difference in the SMM among these groups (data not shown). Further studies to investigate the relationship between fatty degeneration of the muscle and BEE will extend our knowledge regarding the pathophysiology of NAFLD.

Our findings indicated that the Kyoto equation is the most suitable formula for estimating BEE in Japanese patients with NAFLD. Therefore, a prospective study of nutritional intervention therapy for Japanese NAFLD patients should be planned according to BEE estimation using the Kyoto equation.

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