Estimated Resting Metabolic Rate and Body Composition Measures Are Strongly Associated With Diabetic Retinopathy in Indonesian Adults With Type 2 Diabetes

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OBJECTIVE

To investigate the associations of estimated resting metabolic rate (RMR), body fat (BF), subcutaneous fat (SCF), visceral fat (VF), fat-free mass (FFM) percentage, BMI, and waist circumference (WC) with diabetic retinopathy (DR) in Indonesian adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This was a community-based cross-sectional study of 1,184 subjects with type 2 diabetes. DR was assessed from fundus photography and categorized as mild, moderate nonproliferative DR (NPDR), and vision-threatening DR (VTDR). RMR and body composition parameters were measured using automated body composition scan. Logistic regression with semipartial correlation analysis was used.

RESULTS

DR and VTDR were present in 43.1 and 26.3% of participants, respectively. After adjustment for age, sex, diabetes duration, fasting glucose, systolic blood pressure, smoking, diabetic ulcer, and use of combined diabetes treatment, per SD increase in RMR (odds ratio [OR] 2.60 [95% CI 2.19–3.07]; $P < 0.001$) was associated with DR, while per SD increases in BF (0.66 [95% CI 0.56–0.78]; $P < 0.001$), FFM (0.69 [0.57–0.84]; $P < 0.001$), VF (0.77 [0.67–0.88]; $P < 0.001$), BMI (0.83 [0.73–0.94]; $P = 0.004$), and WC (0.81 [0.73–0.91]; $P < 0.001$) were inversely associated with presence of DR. Similar associations were found for VTDR. Among all variables, RMR had the largest contribution to the variance in the DR model (39%).

CONCLUSIONS

In this study, RMR and body composition measures were strongly associated with and contributed considerably to the presence and severity of DR. These findings, if confirmed, suggest that RMR and body composition may be strong markers that represent actual metabolic state in the pathophysiology of DR.

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Diabetic retinopathy (DR) is the most specific diabetic microvascular complication (1) and the most common cause of blindness among those of working age (1). Recent evidence suggested that ~30 million people worldwide had DR, and this number is growing owing to increasing number of people with diabetes (2). Hence, identifying potential modifiable risk factors is important in the management of DR. However, currently the understanding of DR pathophysiology remains incomplete, despite numerous studies investigating both systemic and local risk factors of DR (1,3).

To date, the three prominent systemic risk factors for DR—and other diabetic microvascular complications—as consistently demonstrated in previous studies are long diabetes duration, hyperglycemia, and hypercholesterolemia (4–8). It has been suggested that the severity of microvascular damage in diabetes depends on the duration of diabetes and is accelerated by high blood glucose and cholesterol (1,9,10). Therefore, these factors have been a therapeutic target for patients with diabetes with or without DR (1,8).

Apart from those risk factors, more recent evidence has demonstrated that a person's anthropometric measures such as BMI or waist circumference (WC) are potentially DR risk factors (11–13). BMI and WC might reflect a person's obesity, which could be related to subclinical inflammation owing to increased cellular oxidative stress and increased risk of DR (14,15). Nevertheless, evidence showing the associations of obesity and DR remains equivocal. For example, a study by Dirani et al. (11) showed that high BMI carried significantly higher risk of DR in the Australian population, while other studies showed the opposite (16). This discrepancy could be the result of differences in study population or race, or, importantly, this could be due to the fact that BMI or WC may not reflect the actual state of obesity.

In the last few years, there has been emerging interest in estimated resting metabolic rate (RMR) and body composition parameters, including percentage of body fat (BF), subcutaneous fat (SCF), visceral fat (VF), and fat-free mass (FFM), as markers of a person's metabolic state, which may better reflect the impact of obesity on human body (17,18). Those parameters can be quickly assessed by using bioimpedance analysis (BIA), which estimates the body composition based on different electricity flow in different media (e.g., electricity flows differently in water than in fat) (19–21). Previous studies have applied this method to estimate risk of cardiovascular diseases (22); however, none have applied BIA in persons with diabetes.

In this study, we aimed to investigate the associations of body composition measures with the presence and severity of DR in Indonesian adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Detailed study sampling and methodology have previously been described (23–25). Briefly, JOGED.COM (Jogjakarta Eye Diabetic Study in the Community) was a community-based cross-sectional study recruiting participants aged >30 years with type 2 diabetes confirmed by their family physician (using one of the following criteria: fasting plasma glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or A1C ≥6.5%). This study adhered to the principles of the Declaration of Helsinki. The ethics clearance, information sheet, and consent form were approved by the faculty institutional review board. We obtained written informed consent from all participants or verbal consent in the case of participants with blindness or inability to read or write, with approval from an accompanying family member when available.

We used multistage, clustered random sampling to select 24 community health centers (CHCs) included in this study of total 35 CHCs in the province with available diabetes care facilities. Included CHCs had a monthly session on health promotion activities, when blood glucose tests, nutritional education, and counseling services are provided for people with diabetes. Approximately 30–120 people with diabetes were randomly selected from the diabetes registry proportionate to the CHC coverage. These persons were then invited to attend the DR screening session by local health practitioners, without any involvement of any team members and without a priori knowledge of their respective eye health status. A potential participant was considered "noncontactable" if the person had moved from their residential address or did not respond to the invitation twice. A total of 1,435 persons with type 2 diabetes were invited to participate through family physicians or local health practitioners or nurses working in the selected CHC. There were 1,184 people (82.5%) with type 2 diabetes who participated in this study, of whom 1,138 (79.3%) had completed data with gradable retinal images (Supplementary Fig. 1).

Clinical Examination and Interview

All participants had blood pressure (BP) assessed by a trained nurse using a manual mercury sphygmomanometer. Two separate measurements were made for systolic and diastolic BP, and the average was recorded. In cases where there was a BP difference of 10 mmHg for systolic BP or 5 mmHg for diastolic BP during the first and second measurement, a third measurement was taken. The two closest BP measurements were then averaged. We defined a person to have hypertension if a person had systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg or if a person were on antihypertension medication, albeit their BP measurements were normal (26).

Blood biochemical parameters including fasting glucose level, total cholesterol and triglycerides, and serum urea creatinine were collected from each individual's medical records at the time of the screening. Our participants had routine blood examinations; thus, all individuals were confirmed to have diabetes and were treated by family physicians; therefore, the latest blood examination results (less than a month before the recruitment) were recorded.

The assessments of visual acuity and external eye condition were performed by senior ophthalmology registrars who were at least in the second year of the training program and included analysis of visual acuity, the presence of external eye diseases, and cataract. Presenting visual acuity was assessed at a distance of 6 m using the Snellen chart or an E chart. Participants using optical correction were asked to wear their spectacles during the visual acuity examination. If no characters were visible at a 6-m distance, visual acuity was assessed as finger counting, hand movement, perception of light, or no perception of light.

History of other systemic diseases including cardiovascular diseases, nephropathy, stroke, and peripheral artery

disease; physical activity; eating habits; and socioeconomic status was explored through detailed interview and medical records.

Measurement of Anthropometric and Body Composition Parameters

All participants had height, weight, WC, and hip circumference measured. Height was measured using a wall-mounted and adjustable tape. Measurement of WC and hip circumferences was performed using a 151-cm medical tape, and weight was measured using a calibrated digital weight scale (Omron Karada Scan Body Composition Scale HBF-375; Omron, Osaka, Japan). BMI was then calculated using the universally recognized formula (weight in kilograms divided by the square of height in meters) and categorized as underweight ($<$18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese ($\geq$30 kg/m^2). All measurements were performed by trained nurses or interns.

RMR was calculated using the World Health Organization–established formula that has been used in previous studies (27) after taking into account age, sex, weight, height, and obese or nonobese status. RMR provides an estimate of the minimum amount of energy that is required to sustain a body's daily function (28). RMR value was generated automatically from the full-body sensor body composition scan used in this study (Omron Karada Scan Body Composition Scale HBF-375). Body composition parameters, including estimated BMI, WC, BF, SCF, VF, and FFM percentage, were also obtained using BIA (21,29). Previous studies have applied BIA to estimate risk of cardiovascular diseases (22). BIA estimates the body composition based on different electricity flow in different media (e.g., electricity flows differently in water than in fat) (19). In detail, there were eight hand-to-foot sensors attached directly to the palm and foot skin. Each sensor on the palm transmits an electricity current that flows to another sensor on the foot and vice versa (21,29). The electricity current flows from palm to foot through different media. For example, the electricity flows easily in muscle and body water, where both the impedance and resistance is low (21,29). On the contrary, the electricity current does not flow through fat owing to high resistance and impedance (21,29).

This measurement was performed in a strict and standardized manner to ensure consistency in measurement. Participants were instructed to remove any heavy clothing, any jewelry, and any belongings from their pockets before these measurements were taken. They also took off all foot covers including shoes, slippers, and socks to ensure direct contact of feet with the foot sensors, and hand sensors were directly in contact with palms. We repeated these measurement in 30 subjects to show the intra- and interoperator reliability (intraclass correlation for intraoperator 0.94 and for interoperator 0.95).

Fundus Photography and Assessment of DR

Two-field retinal photographs were taken from each eye of all participants by a trained photographer, using Kowa Nonmyd-7 with Nikon D7000 (Nikon Corp., Tokyo, Japan). Assessment of DR was performed by a trained grader and adjudicated by a retinal specialist masked to the patient's clinical status. We categorized DR following the modified Airlie House classification as mild or moderate nonproliferative DR (NPDR) and vision-threatening DR (VTDR) (24). Macular edema was categorized as presence or absence of clinically significant macular edema (CSME), depending on the appearance of retinal hard exudates within the central fovea area. VTDR was defined to include severe NPDR, proliferative DR, and CSME (30,31). The intra- and interobserver agreement was assessed in over 300 eyes via comparing the grading results of the same images that were regraded by the same grader and by the retinal specialists (M.B.S. and F.S.W.), obtaining at least 0.85 intra- and intergrader agreement.

Statistical Analyses

We used Intercooled Stata (Stata/IC), version 12.1 (Stata Corp, College Station, TX), in the entire data analyses. Missing values were left unmanipulated owing to very little missing data (3.3%). All body composition parameters were analyzed as linear and categorical variables based on quartiles, and correlations between body composition variables were tested (Supplementary Table 1). DR was analyzed as binary (yes vs. no DR) or as categorical variables: mild NPDR, moderate NPDR, and VTDR. Baseline characteristics of participants were compared across four different DR severity classes. The χ^2 test was used to compare proportion variables, one-way ANOVA for means, and the Kruskal-Wallis test for medians. We used binary and multinomial logistic regression models to estimate the associations of body composition parameters with the presence and severity of DR. Multinomial logistic regression models were performed to assess associations between RMR and body composition measures and each category of DR severity (mild, moderate NPDR, and VTDR), and ordered logistic regression was used to assess the trend of these associations in increasing DR severity classes. For each DR severity group, we assigned a number in an increasing fashion to represent the increasing severity in the ordered logistic model: 0 for no DR, 1 for mild NPDR, 2 for moderate NPDR, and 3 for VTDR. Model 1 was adjusted only for age and sex, while model 2 was further adjusted for diabetes duration, fasting blood glucose, systolic BP, smoking, history of foot ulcer, and use of combined diabetes treatment. RMR and other body composition measures were included individually into the model to avoid overadjustment owing to high correlation between these variables. We performed Bonferroni correction for multiple comparisons testing and link test postestimation to test the fitness of every model. We selected variables that were significantly associated with DR and constructed a post hoc analysis to estimate the semipartial correlation of each variable in the model. Any possibility of nonlinear or curvilinear trends was tested previously using fractional polynomial regression.

RESULTS

Table 1 shows the comparison of participants' characteristics across different classes of DR severity. Participants with more severe DR were more likely to have been younger at diabetes diagnosis; to have longer duration of diabetes, higher fasting blood glucose, and higher systolic BP; and to more commonly have hypertension or history of peripheral neuropathy and foot ulcers, use diabetes treatment combination of insulin and oral medication, and live in a rural area compared with those with less severe DR. In addition, people who had more severe DR also had higher RMR but had lower BMI, WC, BF, SCF, and VF than those with less severe DR.

Table 1—Characteristics of study participants of JOGED.COM

	No DR	Mild NPDR	Moderate NPDR	VTDR	*P*
N	671	114	97	258	
Sex, % male	31.5	35.1	31.9	28.7	0.66
Smoking status, % current smoker	10.3	8.04	10.3	6.61	0.48
Hypertension, % yes	**34.1**	**37.2**	**41.7**	**48.4**	**0.001**
Hypercholesterolemia, % yes	37.3	33.8	31.7	30.6	0.15
Ischemic heart disease, % yes	19.8	18.6	20.3	15.9	0.18
Peripheral neuropathy, % yes	**52.2**	**59.6**	**60.4**	**62.0**	**0.021**
Foot ulcers, % yes	**10.2**	**9.73**	**10.4**	**25.6**	**<0.001**
Impotence, % yes	11.4	13.1	15.6	12.0	0.66
Diabetes treatment, % combine insulin + oral medication	**15.3**	**15.9**	**18.7**	**24.0**	**0.006**
Household income/month, % ≤100 USD	62.4	63.9	62.2	66.4	0.18
Residential area, % rural	**48.1**	**46.5**	**54.6**	**62.6**	**0.001**
Education level, % tertiary	13.5	12.5	12.6	11.6	0.36
Diabetes care, % never	13.2	12.4	7.37	8.95	0.074
Eye care, % never	95.2	94.	95.8	94.2	0.15
Age, years	58.1 (10.4)	58.0 (9.13)	59.8 (10.1)	58.1 (8.84)	0.37
Age at diagnosis, years	**53.1 (9.78)**	**51.9 (8.47)**	**54.0 (10.2)**	**50.8 (8.79)**	**0.012**
Duration of diabetes, years	**4 (0–40)**	**4.5 (0–22)**	**5 (0–40)**	**5.5 (0–33)**	**<0.001**
Fasting glucose, mg/dL	**156 (21.5)**	**157 (20.1)**	**167 (19.8)**	**179 (22.1)**	**0.03**
Systolic BP, mmHg	**130 (19.8)**	**130 (20.1)**	**133 (21.1)**	**136 (21.8)**	**<0.001**
Diastolic BP, mmHg	81.2 (11.5)	81.3 (10.3)	82.3 (9.4)	82.7 (9.3)	0.06
RMR, kcal	**1,281 (210)**	**1,292 (271)**	**1,322 (210)**	**1,590 (249)**	**<0.001**
Fat mass, %	**31.7 (7.14)**	**31.0 (7.06)**	**30.2 (7.02)**	**29.7 (7.18)**	**<0.001**
SCF, %	**25.9 (7.49)**	**25.1 (7.50)**	**25.0 (7.68)**	**24.7 (7.86)**	**0.016**
VF, AU**	**9.77 (5.41)**	**9.22 (5.19)**	**8.76 (4.75)**	**8.47 (5.01)**	**0.002**
FFM, %	24.4 (3.68)	24.5 (3.90)	24.2 (3.46)	24.6 (5.10)	0.55
BMI, kg/m^2	**24.9 (4.23)**	**24.5 (4.32)**	**24.4 (4.18)**	**24.2 (4.54)**	**0.04**
WC, cm	**90.9 (10.3)**	**89.6 (10.4)**	**88.9 (9.95)**	**88.8 (11.7)**	**0.002**

Data are mean (SD) or median (range) unless otherwise indicated. Values in boldface type indicate statistical significance. AU, arbitrary units. *P* value was estimated using χ^2 for proportions, ANOVA for means, and the Kruskal-Wallis test for medians. **VF distribution ranges from 0 to 30.

All participants' characteristics were similar among those with gradable compared with ungradable images, except that participants with ungradable images were older (24) (Supplementary Table 2).

Table 2 demonstrates that all body composition measures were associated with the presence of DR, except FFM. After adjustment for age, sex, duration of diabetes, fasting glucose level, systolic BP, smoking status, history of diabetic ulcer, and diabetes treatment, per SD increase in RMR (odds ratio [OR] 2.60 [95% CI 2.19–3.07]) was associated with increased odds of having any DR. In contrast, per SD increases in BMI (0.83 [0.73–0.94]), WC (0.81 [0.73–0.91]), BF (0.66 [0.56–0.78]), SCF (0.69 [0.57–0.84]), and VF (0.77 [0.67–0.88]) were significantly associated with decreased odds of having any level of DR.

In Table 3, we show that body composition parameters were also associated with the severity of DR, except for FFM. RMR was positively associated with increasing severity of DR (OR 1.02 [95% CI 0.75–1.40] for mild NPDR, 1.43 [1.04–1.96] for moderate NPDR, and 5.23 [4.08–6.70] for VTDR; *P* for trend <0.001), whereas increasing BMI, WC, BF, SCF, and VF were inversely associated with severity of DR. With regard to CSME, after adjustment for age and sex, per SD increase in RMR (2.60 [2.25–3.20], $P < 0.001$) was also significantly associated with presence of CSME, while FM (0.77 [0.66–0.92], $P = 0.003$) and VF (0.77 [0.64–0.93], $P = 0.008$) showed inverse associations with CSME appearance. Additional adjustment further for diabetes duration, fasting glucose level, systolic BP, smoking status, history of foot ulcer, and use of combined diabetes treatment did not change these associations (Supplementary Table 3).

Table 4 indicates the relative contribution of traditional DR risk factors and body composition parameters. Overall, RMR had the biggest contribution to the model (39%), while duration of diabetes, fasting blood glucose level, and systolic BP only contributed for 14, 11, and 8%, respectively. Other body composition measures only had little to no contribution to the model (7% to zero).

CONCLUSIONS

In this study, we have demonstrated that estimated RMR and body composition parameters including BF, SCF, VF, BMI, and WC were strongly associated with presence and severity of DR, independent of other systemic factors including diabetes duration, BP, diabetes medication, and other diabetes complications. Moreover, our noteworthy finding is that particularly RMR had significant contribution to DR in this study population—greater than other parameters, even diabetes duration, BP, and cholesterol level, which are long-established DR risk factors. Our findings therefore suggest that RMR and body composition measures may represent an individual's actual metabolic state better than anthropometric measures and signify their importance in the pathophysiology of DR.

To our best knowledge, this was the first study investigating RMR and various novel body composition measures in relation to DR. There was one study by Anan et al. (17) reporting that high VF value, measured by umbilical computed tomography scan, was correlated with higher risk of DR in a Japanese population with diabetes. This finding was in contrast to our study finding that VF was inversely associated with presence of DR. This difference could be due to a different study population, where they recruited patients from a clinic, or different severity stage of diabetes, as shown by the large proportion of our participants with other diabetes complications (17). Aside from body

Table 2—Associations of body composition parameters with presence of DR

Body composition parameters	*N*	Any DR				
		% DR	Model 1*	*P*	Model 2†	*P*
RMR, kcal						
First quartile, ≤1,167	289	5.6	Reference		Reference	
Second quartile, 1,168–1,303	296	8.1	1.60 (1.10–2.33)	**<0.001**	1.90 (1.27–2.82)	**<0.001**
Third quartile, 1,304–1,507	287	10.2	2.36 (1.64–3.41)		3.69 (2.43–5.60)	
Fourth quartile, ≥1,508	291	17.3	7.12 (4.90–10.4)		11.5 (7.41–17.9)	
Per 1-SD increase (252)			2.17 (1.89–2.49)	**<0.001**	2.60 (2.19–3.07)	**<0.001**
BF, %						
First quartile, ≤26.8	286	12.2	Reference		Reference	
Second quartile, 26.9–32.1	283	10.7	0.79 (0.57–1.11)	**<0.001**	0.62 (0.42–0.91)	**<0.001**
Third quartile, 32.2–36.5	284	9.6	0.65 (0.46–0.90)		0.42 (0.27–0.66)	
Fourth quartile, ≥36.6	283	8.8	0.58 (0.41–0.82)		0.34 (0.21–0.54)	
Per 1-SD increase (7.12)			0.81 (0.72–0.91)	**0.001**	0.66 (0.56–0.78)	**<0.001**
SCF, %						
First quartile, ≤19.3	288	12.2	Reference		Reference	
Second quartile, 19.5–26.6	283	9.7	0.74 (0.53–1.03)	**0.02**	0.48 (0.31–0.76)	**<0.001**
Third quartile, 26.7–31.1	284	9.7	0.72 (0.52–1.01)		0.38 (0.22–0.64)	
Fourth quartile, ≥31.2	281	9.3	0.66 (0.47–0.93)		0.34 (0.20–0.58)	
Per 1-SD increase (7.60)			0.86 (0.76–0.97)	**0.018**	0.69 (0.57–0.84)	**<0.001**
VF, AU**						
First quartile, ≤5.5	288	11.6	Reference		Reference	
Second quartile, 6.0–8.5	304	11.6	0.88 (0.63–1.23)	**0.007**	0.83 (0.59–1.17)	**0.001**
Third quartile, 8.8–12.0	279	10.4	0.84 (0.60–1.18)		0.76 (0.53–1.08)	
Fourth quartile, ≥12.5	264	7.9	0.61 (0.43–0.87)		0.51 (0.35–0.74)	
Per 1-SD increase (5.16)			0.82 (0.72–0.93)	**0.002**	0.77 (0.67–0.88)	**<0.001**
FFM, %						
First quartile, ≤21.8	291	9.2	Reference		Reference	
Second quartile, 21.9–23.8	298	9.3	1.00 (0.73–1.41)	0.09	1.05 (0.74–1.52)	0.059
Third quartile, 23.9–26.9	283	11.7	1.52 (1.00–2.13)		1.72 (1.19–2.48)	
Fourth quartile, ≥26.9	288	11.1	1.18 (0.85–1.66)		1.58 (0.98–2.54)	
Per 1-SD increase (3.83)			1.12 (0.99–1.27)	0.06	1.15 (1.01–1.30)	0.032
BMI, kg/m^2						
First quartile, ≤21.7	301	11.5	Reference		Reference	
Second quartile, 21.8–24.3	285	10.8	0.92 (0.66–1.28)	**0.016**	0.94 (0.67–1.33)	**0.003**
Third quartile, 24.4–27.1	292	10.2	0.81 (0.58–1.13)		0.77 (0.55–1.09)	
Fourth quartile, ≥27.2	281	8.9	0.67 (0.48–0.95)		0.59 (0.42–0.86)	
Per 1-SD increase (4.28)			0.87 (0.77–0.98)	**0.023**	0.83 (0.73–0.94)	**0.004**
WC, cm						
First quartile, ≤83	291	12.4	Reference		Reference	
Second quartile, 83.5–90	307	11.3	0.75 (0.54–1.04)	**0.004**	0.69 (0.49–0.96)	**<0.001**
Third quartile, 90.5–96.5	281	8.4	0.61 (0.43–0.85)		0.53 (0.37–0.76)	
Fourth quartile, ≥97	284	9.2	0.63 (0.45–0.89)		0.55 (0.39–0.78)	
Per 1-SD increase (10.4)			0.85 (0.77–0.95)	**0.004**	0.81 (0.73–0.91)	**<0.001**

Data are OR (95% CI) unless otherwise indicated. All *P* values are for linear trend. Values in boldface type indicate statistical significance. AU, arbitrary units. *Adjusted for age and sex. †Additionally adjusted for diabetes duration, fasting glucose level, systolic BP, smoking, foot ulcer, and use of combined diabetes treatment. **VF distribution ranges from 0 to 30.

composition measures, the associations between BMI, to represent obesity, and DR have been widely studied, albeit with equivocal findings. Studies conducted in Caucasian populations have generally demonstrated unfavorable associations between BMI and DR (11,32). For example, the Hoorn Study and Australian Diabetes Management Project all documented that higher BMI was significantly associated with higher risk of having DR (11,32). In contrast to this, data from Asian populations concurred with our findings that BMI was inversely associated with DR (16,33).

Findings from this study showing that RMR and other body composition measures were strongly associated with both presence and severity of DR are biologically plausible. In a recent study reporting similar findings, Man et al. (33) hypothesized that inadvertent weight loss may occur in individuals with longstanding inadequate diabetes control as consequences of multiple systemic insults or comorbidities. While this proposed mechanism is reasonable, more explanations are needed to better comprehend this complex mechanism. In support of this, our findings of positive associations between RMR and DR may offer more information. There have been a few studies documenting that elevated RMR was evident in individuals with progressive metabolic deterioration due to lack of diabetes control (34,35). Elevated RMR in individuals with diabetes has been associated with several mechanisms including excessive gluconeogenesis and catabolism, resulting in increased caloric uptake and higher rates of energy expenditure (34,35). Ongoing increased energy expenditure may have

Table 3—Associations of body composition parameters with severity of DR

Body composition parameters (per 1-SD increase)	Mild NPDR (*N* = 114)	Moderate NPDR (*N* = 97)	VTDR (*N* = 258)	*P* for trend
Model 1*				
RMR (252 kcal)	1.06 (0.83–1.36)	1.25 (0.99–1.58)	3.91 (3.21–4.78)	**<0.001**
BF (7.1%)	0.91 (0.74–1.10)	0.87 (0.71–1.07)	0.76 (0.66–0.87)	**<0.001**
SCF (7.6%)	0.89 (0.73–1.09)	0.88 (0.72–1.09)	0.85 (0.73–0.98)	**0.02**
VF (5.1)	0.90 (0.75–1.08)	0.86 (0.71–1.05)	0.76 (0.64–0.90)	**0.001**
FFM (5.4%)	1.11 (0.91–1.35)	1.11 (0.86–1.43)	1.12 (0.96–1.32)	0.08
BMI (4.28 kg/m^2)	0.89 (0.74–1.10)	0.88 (0.73–1.08)	0.84 (0.72–0.98)	**0.018**
WC (10.4 cm)	0.87 (0.73–1.05)	0.82 (0.68–0.99)	0.82 (0.69–0.96)	**0.004**
Model 2†				
RMR (252 kcal)	1.02 (0.75–1.40)	1.43 (1.04–1.96)	5.23 (4.08–6.70)	**<0.001**
BF (7.1%)	0.95 (0.73–1.24)	0.71 (0.55–0.93)	0.54 (0.44–0.67)	**<0.001**
SCF (7.6%)	0.92 (0.68–1.25)	0.73 (0.54–0.99)	0.59 (0.47–0.76)	**<0.001**
VF (5.1 AU)**	0.87 (0.71–1.08)	0.80 (0.64–0.99)	0.71 (0.58–0.85)	**<0.001**
FFM (5.4%)	1.08 (0.87–1.34)	1.38 (0.93–2.03)	1.36 (0.97–2.01)	0.05
BMI (4.28 kg/m^2)	0.89 (0.72–1.12)	0.87 (0.70–1.07)	0.77 (0.66–0.92)	**0.003**
WC (10.4 cm)	0.88 (0.72–1.07)	0.77 (0.63–0.94)	0.74 (0.63–0.89)	**0.001**

Data are OR (95% CI). All ORs and CIs were estimated using multivariable multinomial logistic regression referring to the group without DR. Values in boldface type indicate statistical significance. AU, arbitrary units. *Adjusted for age and sex. †Additionally adjusted for diabetes duration, fasting glucose level, systolic BP, smoking, foot ulcer, and use of combined diabetes treatment. **VF distribution ranges from 0 to 30.

a long-term impact on body weight or body composition regulation (34,35) that appears as sustained unintentional weight loss. With these findings taken together, it is plausible to further hypothesize that elevated RMR may well illustrate how diabetes perpetuates detrimental metabolic changes and thus impact on reduction of BMI, WC, BF, VF, and SCF, as apparent in our study population. Poor metabolic state would expose an individual to continuous risk of microvascular breakdown in the retina and elsewhere in the body, causing accelerated development and progression of DR (36). Eventually, individuals with lower BMI, WC, BF, VF, and SCF but elevated RMR had significantly greater chance of having DR and more severe forms of DR.

Table 4—Relative contribution of body composition parameters to DR

	Presence of DR			
	Unit increase	OR (95% CI)*	*P*	Semipartial correlation
Systemic factors				
Diabetes duration	1 year	1.32 (1.14–1.53)	<0.001	0.14
Fasting glucose	10 mg/dL	1.02 (1.00–1.04)	0.026	0.11
Systolic BP	10 mmHg	1.51 (1.13–2.03)	0.005	0.08
Use of combined diabetes treatment	Yes vs. no	1.37 (0.90–1.90)	0.06	
Foot ulcers	Yes vs. no	1.22 (0.79–1.86)	0.56	
Traditional anthropometric measures				
BMI	4.28 kg/m^2	0.98 (0.55–1.76)	0.96	
WC	10 cm	0.67 (0.52–0.88)	0.004	0.06
Novel body composition measures				
Metabolic rate	252 kcal	6.18 (4.32–8.83)	<0.001	0.39
BF	7.12%	0.55 (0.37–0.82)	0.003	0.07
SCF	7.59%	1.35 (0.76–2.43)	0.30	
VF**	5.16 AU	0.51 (0.31–0.83)	0.007	0.07
FFM	5.40%	0.69 (0.46–1.06)	0.09	

AU, arbitrary units. *Model simultaneously includes all variables, except for body composition variables, where each variable was included individually. **VF distribution ranges from 0 to 30.

This study has important clinical and research implications. First, we noted that RMR had the biggest contribution to DR relative to other factors. This particular finding provided indirect evidence that RMR may better reflect the summarized effects of long diabetes duration and insufficient systemic diabetes control such as high BP and suboptimal diabetes medication than other body composition parameters. Future longitudinal studies with multiple measurements of RMR or other body composition measures are needed. Second, in this context, we would have expected that RMR was inversely correlated with BMI, WC, or VF. Interestingly, our additional analyses showed counterintuitive findings that RMR and BMI, WC, or VF were positively correlated with each other (Supplementary Table 1) yet exhibiting opposite associations with DR (Table 2). These findings may nonetheless incite new speculation that RMR, BMI, WC, or other body composition measures might reflect different metabolic risks and therefore should be interpreted differently. Further studies are needed to provide more understanding of the processes underpinning these circumstances. Lastly, assessment of RMR seemed to provide more distinct information regarding an individual's actual metabolic state than other parameters and thus may potentially be used as a new intermediate or end point in clinical trials targeting improvement in the progression of DR. At the same time, our study also suggested that body composition measures may potentially be used as markers for assessing the impact of health promotion intervention aimed at optimal diabetes control in the population.

The strengths of this study are a good number of participants, with a high response rate; community-based recruitment; and diagnosis of DR using fundus photography by a trained grader. However, we acknowledge several limitations in our study. First, the use of a cross-sectional design limited the time inference of the predictor and outcomes. Hence, there is also an issue of potential reverse causality, in which more severe DR is a reflection of poor metabolic control in persons with diabetes with

consequential increased RMR and a pernicious pattern regarding body composition. Prospective studies are needed to assess the sequence of these associations. Second, the grading for DR was based on two-field fundus photographs, which is theoretically less sensitive than seven-field retinal photographs as used in large trials such as the Early Treatment Diabetic Retinopathy Study (ETDRS). However, we could have underestimated the presence of mild DR only if the retinal pathologies were present in the peripheral area of the retina; therefore, if we used seven-field retinal photography, we would have detected more instances of DR and thus the associations might have been stronger. Third, 17.5% of potential participants did not respond to the initial study invitation (response rate 82.5%). We could not obtain any information regarding their characteristics for comparison and did not have access to information regarding their DR status. Nonetheless, given that the number was relatively small, this would be unlikely to change the direction of the associations reported in this study. Fourth, the RMR values in this study were predicted from equations rather than measured directly using calorimetry. There have been several drawbacks of these equations identified in previous studies, such as greater measurement error in elderly and obese individuals (27,37,38). However, the majority of our participants were not obese and were aged between 40 and 60 years and so are not yet considered elderly. Aside from that, these equations were developed and validated in white populations; therefore, the degree of inaccuracy in Asian population is unknown. Nonetheless, errors due to these factors that would have occurred randomly would be more likely to deviate the associations toward the null—not in the opposite direction. At last, we relied on simplified BIA to measure body composition, which is not the gold standard. However, such methodology has been shown to have good reliability and accuracy when compared with standard methods (20,29,39,40), and the BIA scale used in this study was routinely calibrated throughout the study.

In summary, we report novel associations of body composition measures including BF, SCF, VF, and RMR with presence and severity of DR. Concurrently, we also documented that RMR had the most significant contribution to DR in this study population. Although studies are needed to further confirm these findings, our results suggest that RMR may represent an individual's actual metabolic state better than other anthropometric measures and established DR risk factors and thus could be a strong risk marker of DR and possibly other diabetes-related vascular complications.

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References

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet 2010;376:124–136
2. Yau JW, Rogers SL, Kawasaki R, et al.; Meta-Analysis for Eye Disease (META-EYE) Study Group. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556–564
3. Sasongko MB, Wong TY, Nguyen TT, Shaw JE, Jenkins AJ, Wang JJ. Novel versus traditional risk markers for diabetic retinopathy. Diabetologia 2012;55:666–670
4. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
5. Diabetes Control and Complications Trial Research Group. Progression of retinopathy with intensive versus conventional treatment in the Diabetes Control and Complications Trial. Ophthalmology 1995;102:647–661
6. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in Lancet 1998;352:1558]. Lancet 1998;352:854–865
7. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38 [published correction appears in BMJ 1999;318:29]. BMJ 1998;317:703–713
8. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA 2007;298:902–916
9. Klein BE, Moss SE, Klein R, Surawicz TS. Serum cholesterol in Wisconsin epidemiologic study of diabetic retinopathy. Diabetes Care 1992;15:282–287
10. Klein R, Klein BE, Moss SE. Is obesity related to microvascular and macrovascular complications in diabetes? The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Arch Intern Med 1997;157:650–656
11. Dirani M, Xie J, Fenwick E, et al. Are obesity and anthropometry risk factors for diabetic retinopathy? The Diabetes Management Project. Invest Ophthalmol Vis Sci 2011;52:4416–4421
12. Katusić D, Tomić M, Jukić T, et al. Obesity–a risk factor for diabetic retinopathy in type 2 diabetes? Coll Antropol 2005;29(Suppl. 1):47–50
13. Raman R, Rani PK, Gnanamoorthy P, Sudhir RR, Kumaramanikavel G, Sharma T. Association of obesity with diabetic retinopathy: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study (SN-DREAMS Report no. 8). Acta Diabetol 2010;47:209–215
14. Ong P, Sivanathan R, Borgulya G, et al. Obesity, inflammation and brachial artery flow-mediated dilatation: therapeutic targets in patients with microvascular angina (cardiac syndrome X). Cardiovasc Drugs Ther 2012;26:239–244
15. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res 2011;30:343–358
16. Lim LS, Tai ES, Mitchell P, et al. C-reactive protein, body mass index, and diabetic retinopathy. Invest Ophthalmol Vis Sci 2010;51:4458–4463
17. Anan F, Masaki T, Ito Y, et al. Diabetic retinopathy is associated with visceral fat accumulation in Japanese type 2 diabetes mellitus patients. Metabolism 2010;59:314–319
18. Carr DB, Utzschneider KM, Hull RL, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004;53:2087–2094
19. Dehghan M, Merchant AT. Is bioelectrical impedance accurate for use in large epidemiological studies? Nutr J 2008;7:26
20. Pietiläinen KH, Kaye S, Karmi A, Suojanen L, Rissanen A, Virtanen KA. Agreement of bioelectrical impedance with dual-energy X-ray absorptiometry and MRI to estimate changes in body fat, skeletal muscle and visceral fat during a 12-month weight loss intervention. Br J Nutr 2013;109:1910–1916
21. Pietrobelli A, Rubiano F, St-Onge MP, Heymsfield SB. New bioimpedance analysis system: improved phenotyping with whole-body analysis. Eur J Clin Nutr 2004;58:1479–1484
22. Lamb MJ, Byrne CD, Wilson JF, Wild SH. Evaluation of bioelectrical impedance analysis

for identifying overweight individuals at increased cardiometabolic risk: a cross-sectional study. PLoS One 2014;9:e106134
23. Sasongko MB, Agni AN, Wardhana FS, et al. Rationale and methodology for a community-based study of diabetic retinopathy in an Indonesian population with type 2 diabetes mellitus: the Jogjakarta Eye Diabetic Study in the Community. Ophthalmic Epidemiol 2017;24:48–56
24. Sasongko MB, Widyaputri F, Agni AN, et al. Prevalence of diabetic retinopathy and blindness in Indonesian adults with type 2 diabetes. Am J Ophthalmol 2017;181:79–87
25. Dharmastuti D, Agni A, Widyaputri F, et al. Associations of physical activity and sedentary behaviour with vision-threatening diabetic retinopathy in Indonesian population with type 2 diabetes mellitus: Jogjakarta Eye Diabetic Study in the Community (JOGED.COM). Ophthalmic Epidemiol 2017;25:1–7
26. Chobanian AV, Bakris GL, Black HR, et al.; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report [published correction appears in JAMA 2003;290:197]. JAMA 2003;289:2560–2572
27. Frankenfield D, Roth-Yousey L, Compher C. Comparison of predictive equations for resting metabolic rate in healthy nonobese and obese adults: a systematic review. J Am Diet Assoc 2005;105:775–789
28. Ravussin E, Burnand B, Schutz Y, Jéquier E. Twenty-four-hour energy expenditure and resting metabolic rate in obese, moderately obese, and control subjects. Am J Clin Nutr 1982;35:566–573
29. Jaffrin MY. Body composition determination by bioimpedance: an update. Curr Opin Clin Nutr Metab Care 2009;12:482–486
30. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie House classification. ETDRS report number 10. Ophthalmology 1991;98(Suppl.):786–806
31. Sasongko MB, Wong TY, Nguyen TT, et al. Serum apolipoprotein AI and B are stronger biomarkers of diabetic retinopathy than traditional lipids. Diabetes Care 2011;34:474–479
32. van Leiden HA, Dekker JM, Moll AC, et al. Blood pressure, lipids, and obesity are associated with retinopathy: the Hoorn Study. Diabetes Care 2002;25:1320–1325
33. Man REK, Sabanayagam C, Chiang PP-C, et al. Differential association of generalized and abdominal obesity with diabetic retinopathy in Asian patients with type 2 diabetes. JAMA Ophthalmol 2016;134:251–257
34. Weyer C, Bogardus C, Pratley RE. Metabolic factors contributing to increased resting metabolic rate and decreased insulin-induced thermogenesis during the development of type 2 diabetes. Diabetes 1999;48:1607–1614
35. Bogardus C, Taskinen M-R, Zawadzki J, Lillioja S, Mott D, Howard BV. Increased resting metabolic rates in obese subjects with non-insulin-dependent diabetes mellitus and the effect of sulfonylurea therapy. Diabetes 1986;35:1–5
36. Antonetti DA, Barber AJ, Bronson SK, et al.; JDRF Diabetic Retinopathy Center Group. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. Diabetes 2006;55:2401–2411
37. Frankenfield DC. Bias and accuracy of resting metabolic rate equations in non-obese and obese adults. Clin Nutr 2013;32:976–982
38. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39(Suppl. 1):5–41
39. Huang A-C, Chen Y-Y, Chuang C-L, et al. Cross-mode bioelectrical impedance analysis in a standing position for estimating fat-free mass validated against dual-energy x-ray absorptiometry. Nutr Res 2015;35:982–989
40. Xu L, Cheng X, Wang J, et al. Comparisons of body-composition prediction accuracy: a study of 2 bioelectric impedance consumer devices in healthy Chinese persons using DXA and MRI as criteria methods. J Clin Densitom 2011;14:458–464