Increased Resting Metabolic Rate in Patients With Type 2 Diabetes Mellitus Accompanied by Advanced Diabetic Nephropathy

Kiyoko Nawata, Motoi Sohmiya, Mikiko Kawaguchi, Masateru Nishiki, and Yuzuru Kato

Thirty-three patients with type 2 diabetes mellitus (16 men, 17 women) were divided into 3 groups based on urinary excretion of albumin (U-Alb)— group A: U-Alb < 30 mg/d; group B: 30 mg/d ≤ U-Alb ≤ 300 mg/d; and group C: 300 mg/d < U-Alb. Serum creatinine levels were lower than 2.0 mg/dL in all the subjects. There was no difference in age, sex, therapy, body weight, body mass index (BMI), lean body mass (LBM), or hemoglobin A_{1c} (HbA_{1c}) levels among the 3 groups. Resting metabolic rate (RMR) (kJ/h/m^2) and adjusted RMR for lean body mass (kJ/h/m^2) were significantly increased in group C compared with groups A and B. Hb concentrations, serum albumin levels, and creatinine clearance were much lower in group C than in groups A and B ($P < .001$). There were no difference in serum urea nitrogen, total cholesterol, cholinesterase and free thyroxine, or plasma insulin-like growth factor I (IGF-I) levels among the 3 groups. Linear regression analysis revealed an inverse correlation between RMR and serum albumin levels, correlation between RMR and U-Alb, and inverse correlation between RMR and Hb concentrations, respectively, in these patients. In conclusion, RMR in diabetic patients correlated directly with U-Alb and inversely with serum albumin and Hb concentration. These findings suggest that RMR is related with urinary albumin loss and anemia in patients with type 2 diabetes mellitus accompanied by diabetic nephropathy.

RESTING METABOLIC RATE (RMR) accounted for less than 60% to 75% of daily energy expenditure[1,3] and was changed by such metabolic and physical conditions as body temperature, thyroid function,[2] and aging.[3]

Diabetic patients are associated with metabolic abnormalities. Especially, diabetic patients with nephropathy are often malnourished and have a number of metabolic abnormalities, water retention, and diabetic complications.[4] It was reported that RMR was increased in patients with type 2 diabetes compared with weight-matched healthy subjects, and this difference was related to hepatic glucose production rate.[1,5] However, it remains to be elucidated how RMR changes in patients with diabetic nephropathy.

There have been conflicting reports on RMR in patients with renal failure.[6-11] In patients with nondialyzed chronic renal failure, RMR did not differ from that of normal subjects.[8,9] Diabetic nephropathy is completed to renal failure after passing through various metabolic stages with microalbuminuria and gross proteinuria. Therefore, RMR could be different in diabetic nephropathy than in other types of nephropathy.

In the present study, we investigated the effect of renal function on RMR in patients with type 2 diabetes mellitus accompanied by diabetic nephropathy.

MATERIALS AND METHODS

Subjects

Thirty-three patients with type 2 diabetes mellitus (16 men, 17 women) aged 41 to 77 years were studied. All the patients had type 2 diabetes mellitus for more than 5 years. They included 11 patients treated with diet only, 7 patients treated with oral antihyperglycemic agents (OHA), and 15 patients treated with insulin (Table 1). The patients were admitted to our hospital and maintained on the diet of 105 to 126 kJ per kg of ideal body weight from the time of admission. After 2 weeks, urine albumin excretion (U-Alb) for 24 hours of 2 consecutive days and serum creatinine levels were evaluated. The subjects were then divided into 3 groups based on U-Alb— group A: U-Alb < 30 mg/d; group B (microalbuminuria): 30 mg/d ≤ U-Alb ≤ 300 mg/d; and group C (gross albuminuria): 300 mg/d < U-Alb. Serum creatinine levels were less than 2.0 mg/dL in all the subjects. In group C, 4 patients (case no. 1, 42-year-old woman; case no. 2, 56-year-old man; case no. 3, 49-year-old woman; and case no. 4, 48-year-old man) had gross proteinuria (2.5 g/d). U-Alb values in these 4 patients were 4.13 g/d, 3.63 g/d, 2.70 g/d, and 2.68 g/d, respectively. In cases 1 and 3, edema and appetite loss were recognized. There were no objective and subjective signs in the other patients. Mean (±SD) body mass index (BMI), lean body mass (LBM), serum creatinine, serum albumin, and hemoglobin A_{1c} (HbA_{1c}) levels in the 4 patients were 21.7 ± 2.6 kg/m^2, 43.4 ± 7.2 kg, 1.25 ± 0.26 mg/dL, 2.9 ± 0.3 g/dL, and 6.63 ± 2.23%, respectively. There were no differences in BMI, LBM, serum creatinine, and HbA_{1c} levels between these 4 patients and the other patients in group C. Diabetic nephropathy was diagnosed by clinical course, laboratory data, and renal biopsy as previously described.[12] Protein intake was restricted to 0.8 g per kg of ideal body weight in group C from the admission. There were no differences in age, sex, therapy, body weight, BMI, LBM, and HbA_{1c} levels among the 3 groups. Written informed consent was obtained from all subjects.

Measurement of RMR and LBM

RMR was measured 2 to 3 weeks after admission. RMR was determined by indirect calorimetry using closed-circuit spirometry (Chestac 55V, Chest Co, Tokyo, Japan) in the early morning after the patients had rested in a supine position for more than 8 hours. All patients were instructed not to leave their bed after midnight and to lie quietly until RMR measurements were completed. The mean value of 3 consecutive measurements was used for statistical evaluation of RMR. The coefficiency of variation of this measurement was 4.1%. Body fat and LBM were determined using a bioelectrical impedance analyzer (Model HBF-300, Omron Co, Kyoto, Japan) as previously described.[13] The coefficiency of variation of this measurement was 0.5%.

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Table 1. Clinical Characteristics and Laboratory Data of Three Groups in Patients With Type 2 Diabetes Mellitus

Characteristic	Group A	Group B	Group C	*P* Value	Adjusted *P* Value (for LBM)
Age (years)	58.5 ± 2.8	59.4 ± 9.6	53.5 ± 9.0	.6319	.5594
Sex (M/F)	7/5	5/4	5/7		
Therapy (diet/OHA/insulin)	4/3/5	3/2/4	4/2/6		
Body weight (kg)	60.4 ± 10.4	63.6 ± 6.3	61.5 ± 9.8	.8819	.7565
Body mass index (kg/m^2)	24.0 ± 3.3	25.0 ± 2.1	24.0 ± 3.3	.6549	.6887
Body fat (kg)	17.9 ± 5.7	18.2 ± 3.8	16.0 ± 5.8	.7495	.7565
Lean body mass (kg)	43.1 ± 9.4	45.4 ± 8.5	45.2 ± 8.4	.9369	
Resting metabolic rate (RMR) (kJ/h/m^2)	136.0 ± 16.8	129.6 ± 16.3	167.0 ± 18.0	<.0001	.0008
HbA_{1C} (%)	6.9 ± 1.2	7.1 ± 1.2	7.1 ± 1.6	.7812	.8145
Hemoglobin (g/dL)	13.7 ± 1.3	13.7 ± 1.1	11.3 ± 1.3	.0005	<.0001
Serum albumin (g/dL)	4.28 ± 0.22	4.58 ± 0.27	3.47 ± 0.62	<.0001	<.0001
Urine albumin excretion (mg/d)	10 ± 8	57 ± 41	1,925 ± 1,270	<.0001	<.0001
Serum creatinine (mg/dL)	0.70 ± 0.13	0.70 ± 0.13	1.27 ± 0.37	<.0001	<.0001
Serum urea nitrogen (mg/dL)	15.7 ± 3.8	16.1 ± 4.0	19.6 ± 9.2	.1350	.0024
Creatinine clearance (mL/min)	87.4 ± 17.0	99.4 ± 22.7	43.8 ± 23.3	<.0001	<.0001
Serum total cholesterol (mg/dL)	190.8 ± 23.6	172.1 ± 30.4	196.8 ± 52.1	.5391	.5208
Serum cholinesterase (IU/L)	322.5 ± 96.5	320.6 ± 56.6	371.0 ± 127.6	.4980	.5188
Plasma IGF-I (ng/mL)	157.6 ± 52.8	117.4 ± 35.9	160.7 ± 82.3	.3191	.3119
Serum free thyroxine (ng/dL)	1.22 ± 0.21	1.24 ± 0.22	1.07 ± 0.19	.0974	.0949

NOTE. Data are expressed as means ± SD.

Assays

Blood samples were obtained after overnight fasting. Hb concentrations were measured using an automated hematology analyzer, XE-2100 (Sysmex Co, Kobe, Japan).[14] Serum creatinine, urea nitrogen, albumin, total cholesterol, and cholinesterase were measured using an automated analyzer, TBA-200FR (Toshiba Medical Systems Co, Tokyo, Japan).[15]. Free thyroxine levels were measured using a fully automated random access enzyme immunoassay system (AIA-1200, TOSOH Co, Tokyo, Japan).[16] Plasma insulin-like growth factor I (IGF-I) levels were determined by specific radioimmunoassay after acid-ethanol extraction as previously described.[17] Urinary albumin and creatinine levels were measured using an automated analyzer, LX-6000 (Eiken Chemical Co, Tokyo, Japan).

Statistical Analysis

Data were expressed as the mean ± SD. Data were analyzed by analysis of variance (ANOVA) in combination with Fisher's protected lest significant difference. Correlation between 2 parameters was evaluated by linear regression analysis. The adjustment for LBM (fat-free mass) was analyzed by analysis of covariance (ANCOVA). $P < .05$ was considered significant.

RESULTS

As shown in Table 1, RMR (kJ/h/m^2) and adjusted RMR for LBM (kJ/h/m^2) were much higher in group C than in groups A and B ($P < .001$). Hb concentrations, serum albumin levels, and creatinine clearance were much lower in group C than in groups A and B ($P < .001$). There was no difference in serum urea nitrogen, total cholesterol, cholinesterase and free thyroxine, and plasma IGF-I levels among the 3 groups.

As shown in Fig 1, the linear regression analysis revealed a correlation between RMR and LBM in groups A and B (group A, y = 1.198x + 88.83, $r = 0.757$, $P = .0044$; group B, y = 1.414x + 66.37, $r = 0.709$, $P = .0324$). However, it did not recognize correlation between RMR and LBM in group C (y = −0.777x + 201.74, $r = 0.349$, $P = .2656$).

As shown in Fig 2, the linear regression analysis revealed an inverse correlation between RMR (kJ/h/m^2) and serum albumin levels (Fig 2A, y = −16.90x + 214.19, $r = 0.439$, $P = .0107$), and Hb concentrations (Fig 2B, y = −4.84x + 206.59, $r = 0.348$, $P = .0475$), respectively, while it revealed a correlation

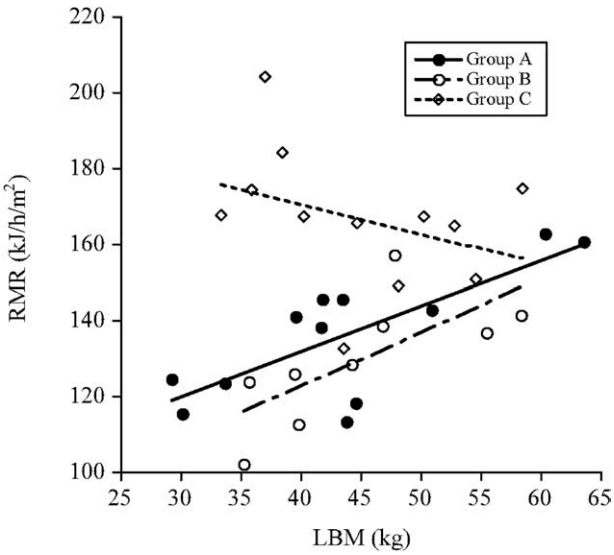

Fig 1. Relationship between RMR and LBM in 3 groups. The linear regression analysis revealed correlation between RMR (kJ/h/m^2) and LBM in groups A and B (group A, y = 1.198x + 88.83, $r = 0.757$, $P = .0044$; group B, y = 1.414x + 66.37, $r = 0.709$, $P = .0324$), but did not reveal correlation in group C (group C, y = −0.777x + 201.74, $r = 0.349$, $P = .2656$). Adjusted RMR for LBM (kJ/h/m^2) was significantly higher in group C than in groups A and B (group A, 136.5 ± 4.7 kJ/h/m^2; group B, 129.4 ± 5.4 kJ/h/m^2; group C, 166.6 ± 4.7 kJ/h/m^2; $P = .0008$).

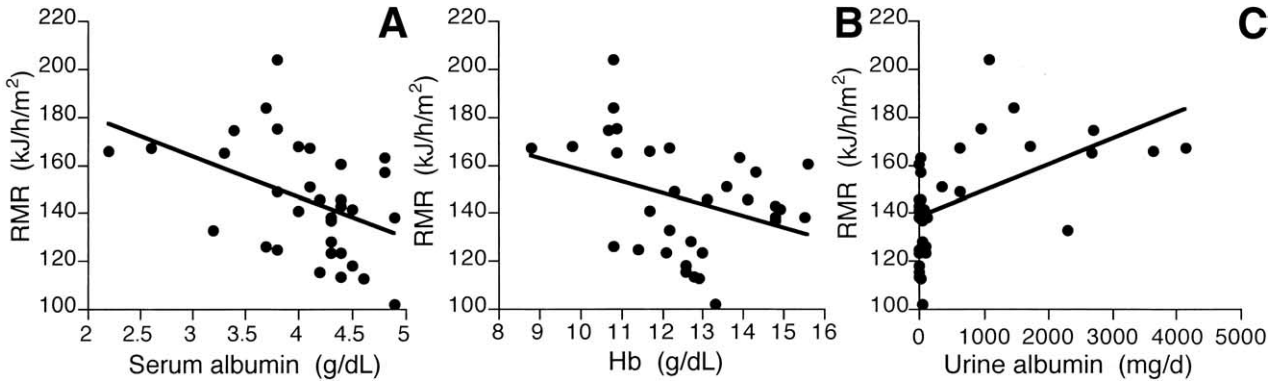

Fig 2. Relationship between RMR and serum albumin levels (A), between RMR and Hb concentrations (B), and between RMR and urinary excretion of albumin (C) in 33 patients with type 2 diabetes mellitus. The linear regression analysis revealed an inverse correlation between RMR (kJ/h/m^2) and serum albumin levels (A, y = −16.90x + 214.19, r = 0.439, P = .0107). The linear regression analysis revealed an inverse correlation between RMR and Hb concentrations (B, y = −4.84x + 206.59, r = 0.348, P = .0475). The linear regression analysis revealed a correlation between RMR and urine albumin excretion (C, y = 0.011x + 137.93, r = 0.531, P = .0015).

between RMR and urine albumin excretion (Fig 2C, y = 0.011x + 137.93, r = 0.531, P = .0015).

DISCUSSION

RMR is not affected by renal function in patients with chronic renal failure with conservative treatment or hemodialysis.[6,8] Although RMR is increased in patients with acute renal failure with sepsis, renal function could not influence energy expenditure as long as sepsis was absent, and wasting was a consequence of decreased food intake but not of hypermetabolism in chronic renal failure.[6] Recently, Neyra et al[18] reported that end-stage renal disease patients displayed increases in RMR over the predicted values derived using normal populations. They described that daily energy intake was less than required in all patient groups studied, suggesting that patients with renal failure could develop protein-calorie malnutrition because of increased RMR. In the present study, we found that RMR was increased in patients with type 2 diabetes accompanied by gross proteinuria, hypoalbuminemia, and anemia, suggesting that renal dysfunction may affect RMR in diabetic patients. The fact that the urine albumin was greatest and the serum albumin was lowest in the diabetic patients with the lowest glumerular filtration rate (GFR) raises the possibility that the independent controlling factor was GFR in these diabetic patients. Although we should evaluate using multivariate analysis, we could not do so because of the small number of patients. Therefore, further large-scale study is required.

RMR is higher in diabetic patients than in nondiabetic subjects.[19,20] The possible mechanism was explained by increased production of hepatic glucose. Hepatic glucose production and lipid oxidation were positively correlated with RMR and both were interrelated in patients with type 2 diabetes mellitus.[5] In the present study, there was no difference in HbA_{1c}, total cholesterol levels, or therapy for diabetes among the 3 groups.

Diet could affect RMR in patients with chronic renal failure. Protein restriction might reduce RMR. However, in clinically stable, nondialyzed uremic patients ingesting 0.55 to 0.60 g protein/kg/d, nitrogen balance is maintained with energy intakes below 126 kJ/kg/d without change of RMR.[9] Therefore, it is not likely that diet itself affected RMR in group C.

Nutrition status, such as BMI, is positively correlated with RMR.[21] Nutrition status is poor in diabetic nephropathy compared with other types of nephropathy such as chronic glomerulonephritis.[4] Diabetes itself contributes to malnutrition. However, indicators of nutrition status such as BMI, plasma IGF-I, and serum cholinesterase did not differ among the 3 groups. It has been reported that RMR was sensitive enough to minor changes in the availability of thyroxine.[22] However, there was no difference in serum free thyroxine levels in the present study.

In the present study, RMR was correlated with U-Alb, and inversely correlated with serum albumin levels and Hb concentrations. It is well known that anemia induces an increase of RMR.[23] However, there have been no reports of a linear relationship between RMR and serum albumin levels or Hb concentrations in patients with diabetic nephropathy. An increase of U-Alb results in a decrease of serum albumin levels, followed by increased albumin synthesis. Beard[24] reported that iron deficiency anemia is associated with alterations in many metabolic processes, including neurotransmitter synthesis and protein synthesis, and results in an increase of energy metabolism. Avesani et al[25] reported that nondialysis chronic renal failure (CRF) diabetic patients had higher resting energy expenditure (REE) than the CRF patients without diabetes mellitus. They described that mean protein intake was higher in the CRF diabetic group than in the CRF control group, and that mean protein equivalent of nitrogen appearance was also higher in the CRF diabetes patients, reflecting a higher protein intake and/or elevated protein breakdown. They concluded that metabolic disturbances of poorly controlled diabetes may account for the higher REE observed in the CRF diabetes. In the present study, however, plasma glucose levels were well controlled. Therefore, increased RMR in patients with diabetic nephropathy accompanied by gross proteinuria may contribute to increased protein synthesis for hypoalbuminemia due to urinary protein leakage and hypermetabolism due to anemia.

Nephrotic syndrome was associated with abnormal protein metabolism due to urinary loss of protein, abnormal endocrine system due to urinary loss of binding proteins, hypercoagulable state due to urinary losses of coagulation factors, and abnormal lipid metabolism.[26] Therefore, it is possible that multiple factors affect the

increase in RMR in patients with diabetic nephropathy. Furthermore, in patients with gross proteinuria and hypoalbuminemia, as primary impairment of salt and water excretion by the nephrotic kidney is major factor in pathogenesis of the edema, sodium and water metabolic abnormalities might be responsible for the change in RMR. In the present study, however, edema was seen in only two patients of group C.

Fat-free mass represents the best predictor of energy expenditure.[27] It was reported that RMR was not correlated with LBM.[28] In the present study, RMR was correlated with LBM in groups A and B, but not in group C. There was no difference in LBM among the 3 groups. Furthermore, there was no difference in LBM between nephrotic patients and non-nephrotic patients with proteinuria. Further studies should be required to elucidate the relationship among RMR, LBM, and U-Alb excretion.

Hospitalization reduces physical activity and RMR.[29] RMR increased during 3 days of stimulated microgravity using head-down tilt[30] and decreased after 42 days of bed rest.[31] In the present study, RMR was measured 2 to 3 weeks after admission in all patients.

RMR is elevated in many disorders. Daily energy expenditure is decreased in elderly individuals with chronic disease due to marked reduction in physical activity energy expenditure. These changes in daily energy expenditure often occur in the presence of increased REE.[32] As physical activity is restricted in patients with advanced nephropathy, the increased RMR may be compensated by reduced energy expenditure in physical exertion and thus free-living energy requirements may not be increased.

In conclusion, we found that RMR in diabetic patients correlated directly with U-Alb and inversely with serum albumin and Hb concentration. These findings suggest that RMR is related to urinary excretion of albumin and anemia in patients with type 2 diabetes mellitus accompanied by advanced diabetic nephropathy.

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