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Original Article

Evaluation of skeletal muscle mass indices, assessed by bioelectrical impedance, as indicators of insulin resistance in patients with type 2 diabetes

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Abstract. [Purpose] This study aimed to investigate the association between two skeletal muscle mass indices and insulin resistance, and to determine the skeletal muscle mass index that is beneficial in evaluating insulin resistance in patients with type 2 diabetes mellitus. [Participants and Methods] This study evaluated 136 male and 100 female patients with type 2 diabetes mellitus. The skeletal muscle mass was evaluated by bioelectrical impedance analysis. Two skeletal muscle mass indices were investigated as the appendicular skeletal muscle mass index (appendicular skeletal muscle mass divided by the square of height) and relative total skeletal muscle mass (total skeletal muscle mass as a percent of body weight). The homeostasis model assessment of insulin resistance was used as a marker of insulin resistance. Associations were investigated by grouping the participants according to gender and age (<60 or ≥60 years). [Results] The appendicular skeletal muscle mass index was positively associated with the homeostasis model assessment of insulin resistance, except in male patients aged ≥60 years, whereas the relative total skeletal muscle mass was significantly inversely associated with the homeostasis model assessment of insulin resistance, in all patient groups. The cutoff values of the relative total skeletal muscle mass for the presence of insulin resistance were 37.9% and 32.5% in male and female patients, respectively. [Conclusion] This finding suggests that relative total skeletal muscle mass may be a better indicator of insulin resistance than appendicular skeletal muscle mass index is, in patients with type 2 diabetes mellitus.

Key words: Type 2 diabetes, Insulin resistance, Skeletal muscle mass

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by decreased insulin secretion and increased insulin resistance (IR). The skeletal muscle is one of the major target organs of insulin and accounts for approximately 75% of whole-body insulin-stimulated glucose uptake[1)]. Therefore, a decrease in the skeletal muscle mass causes a decrease in whole-body glucose uptake, resulting in the development of IR and the onset and progression of T2DM[2–6)]. Moreover, the evaluation of skeletal muscle mass is very important in the treatment and care of patients with T2DM.

Since the skeletal muscle mass fundamentally correlates with body size and the absolute value is not appropriate when

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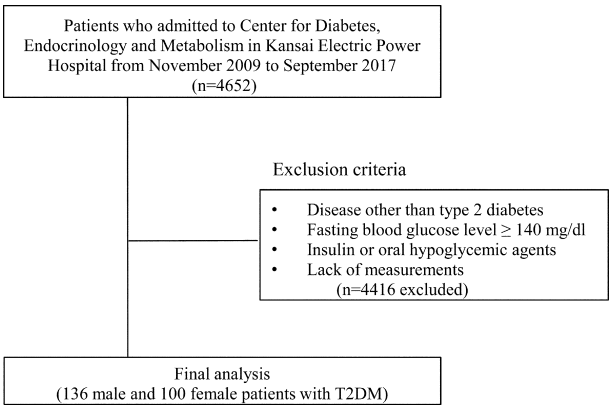

Fig. 1. Flow chart of the study.

evaluating the adequacy of skeletal muscle mass, several indices for quantifying skeletal muscle mass have been proposed. The two major skeletal muscle mass indices are appendicular skeletal muscle mass index [ASMI, the appendicular skeletal muscle mass (ASM) divided by the square of the height (ASM/height^2)][7] and relative total skeletal muscle mass [RTSM, total skeletal muscle mass (TSM) as a percentage of body weight][8]. Recently, the Asian Working Group for Sarcopenia (AWGS) established a consensus for diagnosing sarcopenia[9]. AWGS recommended ASMI as a method of evaluating sarcopenia. However, little attention has been paid to the role of ASMI in IR[3]. In previous reports, RTSM has been widely used to investigate the relationship with IR[2–6]; however, it has never been examined which skeletal muscle mass index is better for evaluating IR in patients with T2DM. The purpose of this study was to investigate the association between two skeletal muscle mass indices and IR and to determine which skeletal muscle mass index is beneficial in evaluating IR in patients with T2DM.

PARTICIPANTS AND METHODS

Out of the 4,652 cases who admitted to Center for Diabetes, Endocrinology and Metabolism in Kansai Electric Power Hospital from November 2009 to September 2017, this study included 136 male and 100 female patients with T2DM, that were with a fasting blood glucose level of <140 mg/dl and were not treated with insulin or oral hypoglycemic agents (Fig. 1). The Kansai Electric Power Hospital Ethics Committee approved this study (No. 29-141). Patients had the right to refuse to participate in the study by opt-out at any time.

The clinical data for each patient were retrospectively collected from electronic medical records in the hospital, which include baseline age, height, body weight, hemoglobin A1c level, duration of diabetes, diabetic complications, fasting glucose level, fasting insulin level, body fat mass percentage, and skeletal muscle mass. Skeletal muscle mass and body fat percentage was evaluated with bioelectrical impedance analysis (InBody S20, InBody Japan Inc., Japan). Skeletal muscle mass indices were ASMI (ASM/height^2) and RTSM (TSM/weight). Body mass index (BMI) was calculated by dividing the body weight by the square of the height. The homeostasis model assessment of IR (HOMA-IR) was used as a marker of IR. HOMA-IR was calculated by dividing the product of the fasting glucose level (mg/dl) and the fasting insulin level (μU/ml) by 405[10]. HOMA-IR value of ≥2.5 was considered to indicate the presence of IR[11].

Since aging and gender affect skeletal muscle mass, the participants were divided into four groups according to gender and age. Age was categorized as a <60 years and ≥60 years.

All the data are presented as mean ± standard deviation. Pearson product-moment correlation coefficients were used to determine the correlations between variables. A receiver operating characteristic curve was used to calculate a cutoff value for determining IR (HOMA-IR ≥2.5). Statistical significance was defined as $p<0.05$. Ekuseru-Toukei 2012 for Windows (Social Survey Research Information Co., Ltd., Japan) was used for the statistical analysis.

RESULTS

Table 1 shows the characteristics of the study participants. ASMI was significantly positively associated with HOMA-IR in all the groups, except male ≥60 years group (Table 2). By contrast, RTSM showed significant inverse association with HOMA-IR in all the groups. A receiver operating characteristic curve analysis revealed that the cutoff values of RTSM to identify the presence of IR were 37.9% in all the male and 32.5% in the female participants (Table 3). Both ASMI and RTSM showed significant correlations with BMI and body fat percentage; however, while ASMI positively correlated with BMI and body fat percentage, RTSM showed significant negative correlations with BMI and body fat percentage (Table 4).

Table 1. Characteristics of participants according to gender and age

	Male		Female	
	<60 years	≥60 years	<60 years	≥60 years
Total participants	79	57	46	54
Age (years)	47.4 (8.3)	67.4 (5.8)	50.4 (6.9)	69.3 (6.1)
Height (m)	1.70 (0.06)	1.66 (0.06)	1.57 (0.05)	1.53 (0.07)
Body weight (kg)	79.2 (16.0)	66.3 (9.6)	71.0 (16.4)	60.2 (10.6)
BMI (kg/m^2)	27.4 (5.0)	24.2 (3.1)	28.8 (6.4)	25.8 (4.6)
Body fat percentage (%)	28.4 (7.9)	26.3 (6.8)	39.1 (8.9)	38.7 (8.7)
HbA1c (%)	7.5 (1.4)	7.1 (0.7)	7.7 (1.5)	7.0 (0.8)
Duration of diabetes (years)	3.3 (3.7)	4.4 (6.0)	2.2 (3.3)	3.3 (7.3)
Diabetic neuropathy	15 (19.0)	16 (28.1)	7 (15.2)	10 (18.5)
Diabetic retinopathy	5 (6.3)	4 (3.5)	6 (13.0)	6 (11.1)
Diabetic nephropathy	12 (15.2)	10 (17.5)	7 (15.2)	5 (9.3)
Fasting glucose level (mg/dl)	111 (18)	113 (16)	115 (15)	109 (14)
Fasting insulin level (μU/ml)	7.6 (8.7)	5.1 (2.9)	10.0 (5.7)	6.8 (4.4)
HOMA-IR	1.85 (0.98)	1.43 (0.89)	2.86 (1.68)	1.84 (1.23)
ASM (kg)	24.4 (3.2)	21.0 (3.1)	17.8 (2.9)	15.0 (2.5)
ASMI (kg/m^2)	8.43 (0.80)	7.64 (0.80)	7.25 (1.01)	6.42 (0.82)
TSM (kg)	31.1 (4.0)	26.7 (3.9)	22.9 (3.7)	19.2 (2.8)
RTSM (%)	40.0 (4.5)	40.3 (4.0)	33.1 (4.7)	32.9 (5.0)

All values are expressed as mean (standard deviation) or number (%).
ASM: appendicular skeletal muscle mass; ASMI: appendicular skeletal muscle mass index; BMI: body mass index; HbA1c: hemoglobin A1c; HOMA-IR: homeostasis model assessment of insulin resistance; RTSM: relative total skeletal muscle mass; TSM: total skeletal muscle mass.

Table 2. Simple linear regression analysis for HOMA-IR in patients with T2DM

	Male		Female	
	r	p	r	p
Total participants				
ASMI	0.36	**	0.55	**
RTSM	−0.60	**	−0.40	**
<60 years				
ASMI	0.43	**	0.56	**
RTSM	−0.66	**	−0.53	**
≥60 years				
ASMI	0.11		0.37	**
RTSM	−0.51	**	−0.35	**

ASMI: appendicular skeletal muscle mass index; HOMA-IR: homeostasis model assessment of insulin resistance; T2DM: type 2 diabetes mellitus; RTSM: relative total skeletal muscle mass.
**p<0.01.

Table 3. Receiver operating characteristic curve of RTSM showing IR

	Cut off	Sensitivity	Specificity	AUC
Male	37.9	87.0	77.0	0.848
Female	32.5	73.3	57.1	0.695

AUC: area under the curve; IR: insulin resistance; RTSM: relative skeletal muscle mass.

Table 4. Simple linear regression analysis for ASMI and RTSM in patients with T2DM

	ASMI		RTSM	
	r	p	r	p
Male				
Age	−0.55	**	−0.01	
HbA1c	0.15		−0.07	
Duration of diabetes	−0.12		0.19	*
BMI	0.80	**	−0.69	**
Body fat percentage	0.31	**	−0.90	**
Female				
Age	−0.50	**	−0.10	
HbA1c	0.17		−0.12	
Duration of diabetes	−0.15		0.07	
BMI	0.79	**	−0.74	**
Body fat percentage	0.45	**	−0.86	**

ASMI: appendicular skeletal muscle mass index; BMI: body mass index; HbA1c: hemoglobin A1c; RTSM: relative total skeletal muscle mass; T2DM: type 2 diabetes mellitus.
*p<0.05, **p<0.01.

DISCUSSION

In this study, two skeletal muscle mass indices in patients with T2DM indicated different associations with IR. ASMI showed positive association with HOMA-IR with the exception of the group of older male participants. In contrast, RTSM showed inverse association with HOMA-IR in all the groups. These findings suggest that RTSM may be a better indicator of IR than ASMI in patients with T2DM.

Insulin is known to enhance muscle protein synthesis and inhibit muscle protein breakdown[12]. Both IR and insulin deficiency lead to the reduction of insulin signaling in the skeletal muscle. The abnormality of muscle protein metabolisms[13, 14] and reduction in skeletal muscle mass[15, 16] in patients with T2DM have been observed, and T2DM is considered an independent risk factor for sarcopenia[17]. The assessment of ASMI is recommended by AWGS when evaluating sarcopenia. In this study, ASMI showed positive association with IR, indicating that those who had larger ASM exhibited higher HOMA-IR. With the exception of older male participants, these results are also observed in all the groups. This reason remains unclear; however, one possibility is that ASMI is calculated by dividing ASM by the square of the height and does not consider the influence of body fat mass. The cause of IR is not only reduction in skeletal muscle but also increased body fat mass. Overweight and obesity are induced by decreased physical activity and overeating which result in hypersecretion of insulin[18]. Increased insulin secretion increases not only skeletal muscle mass but also fat mass[19]. Therefore, the increase in ASMI may indirectly reflect the increase in fat mass. The simple linear regression analysis showed that ASMI positively correlated with BMI and body fat percentage while RTSM negatively correlated with those items, supporting the hypothesis. Only elderly male participants did not show the association, which may be interpreted that the above supposed hypothesis does not apply to this population, maybe because elderly men have lower fat mass than women and absolute muscle mass plays higher role in inducing IR.

Conversely, RTSM was negatively associated with IR. In previous studies, skeletal muscle mass divided by body weight was reported to be inversely associated with IR[2–6]. IR is associated closely with overweight and obesity[20]. Adipose tissue expansion initiates a cascade of inflammatory events that contribute directly to defective insulin signaling and glucose uptake, resulting in systemic IR[21]. Because RTSM includes not only skeletal muscle mass but also fat mass, decrease in skeletal muscle mass and body weight reflect the increase in fat mass and was thought to be a better marker associated with IR.

The cutoff value of RTSM to predict IR has not been reported so far. Because the assessment of IR requires invasive procedures such as hyperinsulinemic-euglycemic clamp and blood test, evaluation of IR is not simple. However, recently, the home-use scale which can easily measure body composition including skeletal muscle mass using a bioelectrical impedance method has become commercially available. Therefore, IR can be possibly assessed by measuring skeletal muscle mass non-invasively at home, which would be useful for health management and observation of the effect of nutrition and exercise interventions.

Nevertheless, this study has several limitations. First, IR assessment was only performed by HOMA-IR, which is one of the convenient clinical markers. HOMA-IR is proven to show strong correlation with IR assessed by hyperinsulinemic-euglycemic clamp which is a gold standard for IR assessment[22]. Therefore, we believe that our results have certain reliability. Second, ASM and TSM were evaluated by bioelectrical impedance analysis. We did not determine the hydration status of the participants before body composition assessment. The validity of this method may be affected by abnormal body water balance in obese state. Third, the study participants were patients who were hospitalized for diabetes education and care. Therefore, patients who had acutely deteriorated glucose metabolism might be included in this study.

In conclusion, the two major indices of skeletal muscle mass showed different associations with IR. Although ASMI was positively associated with IR, RTSM was negatively associated with IR independent of gender and age, suggesting that RTSM is a better indicator of IR than ASMI in patients with type 2 diabetes. In addition, our results showed that the cutoff values of RTSM (37.9% for men and 32.5% for women) would be useful for IR assessment in patients with T2DM.

Conflict of interest

Honoraria for lectures (Yutaka Seino): ARKRAY, Inc., Becton, Dickinson Co., Boehringer Ingelheim Co., Ltd., Kao Corporation, MSD K.K., Ono Pharmaceutical Co., Ltd., Novo Nordisk Pharma Ltd., Taisho Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd.,

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