Elevated serum pentosidine and decreased serum IGF-I levels are associated with loss of muscle mass in postmenopausal women with type 2 diabetes mellitus

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Short running title: Pentosidine, IGF-I and muscle mass

Abstract:

Advanced glycation end-products (AGEs) play important roles in the progression of diabetic complications. Although sarcopenia is recently recognized as another complication associated with diabetes mellitus, its mechanism still remains unclear. In this study, we investigated the relationship between serum levels of pentosidine, which is one of AGEs, and insulin-like growth factor-I (IGF-I) versus skeletal muscle mass by whole body dual-energy x-ray absorptiometry in 133 postmenopausal women with type 2 diabetes. Relative skeletal muscle mass index (RSMI) was calculated by following formula; appendicular skeletal muscle mass divided by height in meters squared. Simple correlation analyses showed that serum pentosidine levels were significantly and negatively correlated with muscle mass of legs (r=-0.21, p=0.017) and RSMI (r=-0.18, p=0.022), and that IGF-I was significantly and positively correlated with muscle mass of arms and legs (r=0.23, p=0.008 and r=0.30, p=0.001, respectively) as well as RSMI (r=0.20, p=0.022). Moreover, after adjusting for age, duration of diabetes, serum creatinine, HbA1c, and IGF-I, pentosidine was significantly and negatively associated with RSMI (β=-0.27, p=0.018) and marginally with muscle mass of legs (β=-0.18, p=0.071). The associations between IGF-I and indices of muscle mass such as arms, legs and RSMI were still significant after additional adjustment for pentosidine (p=0.016, 0.019 and 0.021, respectively). These findings indicate that increased serum pentosidine and decreased IGF-I are independent risk factors for loss of muscle mass in postmenopausal women with type 2 diabetes.

Keywords: pentosidine, skeletal muscle mass, sarcopenia, diabetes mellitus, IGF-I

Introduction

Sarcopenia is a major disease with decreases in muscle mass and function, resulting in frailty and bedridden in elderly people. Because of the population aging, sarcopenia has become a worldwide social issue. Diabetes mellitus is known to be a major disease which causes a variety of vascular complications. Recently, sarcopenia has been recognized as one of diabetic complications. Previous studies have shown that patients with type 2 diabetes mellitus (T2DM) have significant excessive loss of appendicular lean mass, especially inferior limbs, compared with subjects without it [1-4]. However, the mechanism of diabetes-related sarcopenia still remains unclear.

Advanced glycation end-products (AGEs), which are produced by non-enzymatic reactions of carbohydrates with proteins, are known to be related to diabetic complications [5, 6] such as neuropathy [7, 8], retinopathy [9, 10], nephropathy [11], and osteoporosis [12-15]. Several studies suggested that AGEs accumulation in muscle caused loss of muscle mass [16, 17]. Moreover, Sun *et al.* demonstrated that women with elevated serum Carboxymethyllysin had a high risk of developing severe walking disability over 30 months of follow-up in 394 elderly women [18]. Most recently, we showed that AGEs directly inhibited myogenesis of C2C12 cells *in vitro* [19]. These findings suggest that AGEs are associated with the pathogenesis of sarcopenia in T2DM. However, to our knowledge, there are no studies on the relationship between AGEs and muscle mass in patients with T2DM.

As a decline in serum insulin-like growth factor-I (IGF-I) level occur with normal aging, it is thought that the hormonal level is associated with poor physical function or disability in elderly people. Circulating IGF-I, mainly produced in the liver via regulation by growth hormone and diet, acts in an endocrine manner, which exerts

anabolic effects on muscle growth [20-22]. It is previously reported that low serum IGF-I level was associated with decreased muscle strength and mobility in older women [23]. On the other hand, serum IGF-I levels decrease in poorly controlled diabetes [24, 25]. It is thus suggested that low serum IGF-I might be involved in the diabetes-related sarcopenia. However, little is known about the relationship between serum IGF-I levels and muscle mass in diabetic patients.

In the present study, we therefore examined the association of serum levels of pentosidine and IGF-I with indices of muscle mass in postmenopausal women with T2DM.

Materials and Methods

Subjects

The subjects in this study were 133 Japanese postmenopausal women with T2DM (age; 66.8 ± 9.5 years) who visited or admitted Shimane university hospital for treatments of diabetes. Subjects agreed to participate in this study and gave informed consent. This study was approved by the institutional review board of Shimane University Faculty of Medicine and complied with the Helsinki declaration. The reference number of the study approved by our ethical committee is No. 847. Nobody had hepatic dysfunction including cirrhosis, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, renal dysfunction, hypothyroidism or nutritional derangements that might cause changes in serum IGF-I levels.

Biochemical measurements

After overnight fasting, serum samples were collected. Biochemical markers were measured by standard methods as previously described [26, 27]. HbA1c was determined by high performance liquid chromatography. The value for HbA1c is estimated as an NGSP (National Glycohemoglobin Standaridization Program) equivalent value calculated by the formula: HbA1c (%) = HbA1c (JDS) (Japan Diabetes Society) (%) + 0.4% [28]. Serum pentosidine levels were detected using a competitive ELISA kit (FSK pentosidine ELISA kit; Fushimi Pharmaceutical, Kagawa, Japan) [27]. The inter- and intra-assay coefficients of variations of absorbance were 6.6 and 8.0%, respectively. Reference concentration of serum pentosidine in normal subjects is 26.1 ± 0.7 μg/ L. Serum IGF-I was measured by RIA with [^{125}I]-IGF-I as a competitive

radioligand and a polyclonal anti-human antibody [26]. Bound radioactivity was measured using a gamma counter and concentrations were determined relative to a standard curve prepared with recombinant human IGF-I. The CV of IGF-I measurement was 2.28%.

Measurement of lean body mass by whole body Dual-energy x-ray absorptiometry

Muscle mass of arms and legs as well as appendicular skeletal muscle mass (ASM) was measured by Dual-energy x-ray absorptiometry (QDR-4500, Hologic co., Bedford, MA). Relative skeletal muscle mass index (RSMI) was calculated by following formula; ASM/height^2, as previously described [29, 30].

Statistical analysis

Data are expressed as mean ± SD. Since HbA1c, pentosidine (PEN), IGF-I, and lean body mass showed skewed distribution, they were transformed to logarithms before simple or multiple regression analysis. All analyses were carried out using statistical computer programs, StatView (Abacus Concepts, Berkeley, CA). $P<0.05$ was considered to be significant.

Results

Simple correlations between indices of muscle mass and background data

Clinical characteristics of the subjects are shown in Table 1. The numbers of patients who had been taking insulin, sulfonylurea, metformin, pioglitazone, alpha-glucosidase inhibitors, statin, ACE inhibitor, and ARB, were 38, 31, 17, 7, 15, 58, 7 and 39, respectively. First, we investigated simple correlations of indices of muscle mass with background data including HbA1c, IGF-I, and PEN. As shown in Table 2, age was significantly and inversely correlated with muscle mass of legs (r=-0.30, p<0.001). Body mass index showed strong positive correlations with muscle mass of arms and legs as well as RSMI (r=0.71, p<0.001; r=0.75, p<0.001; r=0.80, p<0.001, respectively). Serum IGF-I levels were significantly and positively correlated with muscle mass of arms and legs as well as RSMI (r=0.23, p=0.008; r=0.30, p=0.001; r=0.20, p=0.022, respectively). Moreover, serum PEN levels were significantly and inversely correlated with muscle mass of legs and RSMI (r=-0.21, p=0.017; r=-0.18, p=0.039, respectively). In contrast, HbA1c levels were not correlated with any indices of muscle mass.

Multiple regression analysis between HbA1c, PEN, and IGF-I versus indices of muscle mass

Next, multiple regression analysis was then performed using indices of muscle mass as dependent variables and age, duration of T2DM, and serum creatinine, log (HbA1c), log (PEN), and log (IGF-I) as independent variables (Table 3). Serum IGF-I levels were significantly and positively associated with muscle mass of arms and legs as

well as RSMI (β=0.26, p=0.016; β=0.24, p=0.019; β=0.24, p=0.021, respectively). Moreover, serum PEN levels were significantly and inversely associated with RSMI (β=-0.27, p=0.008) and marginally with muscle mass of legs (β=-0.18, p=0.071). We examined additional multiple regression analyses without medications, which might affect the serum PEN levels, such as metformin, pioglitazone, statin, ACE inhibitor and ARB. Serum PEN levels were significantly and inversely associated with RSMI (β=-0.36, p<0.001, β=-0.24, p=0.030, β=-0.28, p=0.032, β=-0.27, p=0.009, β=-0.25, p=0.042, respectively).

Discussion

Sarcopenia is the progressive loss of muscle mass and strength with a risk of adverse outcomes such as disability, poor quality of life and mortality. Although sarcopenia is one of diabetic complication, it is unclear what factors are involved in the progression of sarcopenia in T2DM. In this study, multiple regression analyses showed that decreased serum IGF-I and elevated serum pentosidine were independently associated with reduction of muscle mass indices, suggesting that IGF-I and AGEs may cause sarcopenia in diabetic patients.

Previous studies have shown that AGEs are associated with muscle mass reduction [16, 18]. The expression of the receptor for AGEs in muscle is reported to increase with aging [16], suggesting that AGEs signal directly affects muscle. We recently demonstrated that AGEs directly inhibited the expression of myogenin and myoD in myoblastic C2C12 cells [19]. AGEs are produced by glycation and oxidative stress, and AGEs levels in the circulation are increased in diabetic patients [31]. Thus, we hypothesized that serum AGEs levels might be associated with diabetes-related sarcopenia. However, there are no studies on the relationship between AGEs and muscle mass in T2DM. In this study, we found that serum PEN levels were negatively associated with muscular indices estimated by whole body DXA. This association was independent of age, duration of diabetes, and serum IGF-I levels, suggesting that elevated serum AGEs might cause muscle mass reduction in diabetic patients.

In this study, serum PEN levels were associated with muscle mass of legs, but not arms. Previous studies showed that skeletal muscle function is more likely to be affected in the lower limbs than the upper limbs in T2DM [1-4]. The mechanism remains still unclear, but it is considered that diabetes-related sarcopenia is partially

associated with diabetic neuropathy, in which the lower limbs are predominantly involved. It has been shown that AGE signaling causes the development of diabetic neuropathy [32]. Thus, the present findings are rational to understand the association of AGEs with the muscle mass reduction especially in lower limbs in diabetic patients.

Serum IGF-I levels are known to decrease in poorly controlled type 2 diabetes [24, 25], and lower IGF-I levels are reported to be associated with diabetic complications [33]. IGF-I has anabolic action on bone metabolism, and we previously reported that lower serum IGF-I levels were associated with the presence of vertebral fractures in type 2 diabetes [26]. IGF-I has anabolic action also on myogenesis [20-22], and serum IGF-I levels were reported to be associated with muscle mass in non-diabetic subjects [34]. Therefore, we hypothesized that lower IGF-I levels might be associated with loss of muscle mass in patients with T2DM. In this study, IGF-I was significantly and positively associated with all muscular parameters even after the adjustment for age, duration of T2DM, serum creatinine, HbA1c and PEN. To our best knowledge, there are no clinical reports indicating the association between serum IGF-I and muscle mass in T2DM patients. Therefore, this is the first report showing the positive relationship between serum IGF-I and muscle mass in T2DM.

Our study has several limitations. First, the sample size was not large enough to make definite conclusions. Second, we analyzed only subjects who visited our hospital, a tertiary center, for treatment of diabetes mellitus. Therefore, the participants enrolled in this study might have relatively severe states of the disorders and might not be representative of Japanese patients. Third, although both decreased GH/IGF-I axis and increased serum PEN might enhance insulin resistance through loss of muscle mass, we did not evaluate insulin resistance. Finally, we found the significant association

between serum PEN and IGF-I levels versus muscle mass in a cross-sectional study. These findings suggest that elevated AGEs and decreased IGF-I levels in serum might be risk factors of sarcopenia. However, to reveal the causal relation between AGEs and IGF-I versus the progression of muscle mass reduction as well as the incidence of sarcopenia, it is necessary to conduct longitudinal studies.

In conclusion, the present study for the first time showed that serum PEN levels were inversely associated with indices of muscle mass in postmenopausal women with T2DM, while serum IGF-I levels were positively associated with them. These findings suggest that elevated serum PEN and decreased IGF-I levels are independent risk factors for sarcopenia in the population.

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Authors' roles: Conceived and designed the study: IK. Corrected and analyzed the data: KT and IK. Contributed equipment/materials: TS. Wrote the paper: KT and IK. Approving final version: All authors.

Conflict of intrest

The authors declare that they have no conflict of interest.

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Table 1.

Baseline characteristics of subjects

Number of patients	133
Age (years)	66.8 ± 9.5
Duration of diabetes (years)	11.3 ± 9.8
Body mass index (kg/m^2)	24.3 ± 4.8
Number of insulin	38
Number of sulfonylurea	31
Number of metformin	17
Number of pioglitazone	7
Number of αGI	15
Number of statin	58
Number of ACE inhibitor	7
Number of ARB	39
Serum creatinine (mg/dL)	0.64 ± 0.20
HbA1c (NGSP) (%)	8.2 ± 2.4
IGF-I (ng/mL)	132.2 ± 47.2
PEN (μg/mL)	0.038 ± 0.018
Left Arm (g)	1751.5 ± 298.7
Right Arm (g)	1845.2 ± 319.1
Arms (g)	3596.7 ± 605.2
Left Leg (g)	5411.6 ± 1015.7
Right Leg (g)	5379.1 ± 1061.8
Legs (g)	10790.7 ± 2062.2
RSMI (kg/m^2)	6.34 ± 1.01

HbA1c, hemoglobin A1c; IGF-I, insulin-like growth factor-I; PEN, pentosidine; RSMI, relative skeletal muscle mass index; αGI, alpha-glucosidase inhibitor;ACE, angiotensin converting enzyme; ARB, angiotensin 2 receptor blocker

Table 2.

Correlations of muscular parameters with HbA1c, IGF-1, and PEN

	log (arms)		log (legs)		log (RSMI)	
	r	*p*	*r*	*p*	*r*	*p*
Age	-0.14	0.113	-0.30	<0.001	-0.06	0.501
Duration of diabetes	-0.02	0.806	-0.04	0.681	0.02	0.839
Body mass index	0.71	<0.001	0.75	<0.001	0.80	<0.001
Serum creatinine	0.02	0.801	-0.04	0.688	0.07	0.417
log (HbA1c)	-0.10	0.264	-0.07	0.435	-0.05	0.551
log (IGF-I)	0.23	0.008	0.30	0.001	0.20	0.022
log (PEN)	-0.11	0.219	-0.21	0.017	-0.18	0.039

HbA1c, hemoglobin A1c; IGF-I, insulin-like growth factor-I; PEN, pentosidine; RSMI, relative skeletal muscle mass index

Table 3.

Associations between muscular parameters versus HbA1c, IGF-I, and PEN

	log (HbA1c)		log (IGF-I)		log (PEN)	
	β	*p*	β	*p*	β	*p*
log (arms)	-0.10	0.329	0.26	0.016	-0.11	0.288
log (legs)	-0.05	0.623	0.24	0.019	-0.18	0.071
log (RSMI)	-0.00	0.997	0.24	0.021	-0.27	0.008

Multiple regression analyses was performed using muscle indices as dependent variables and age, duration of diabetes, serum creatinine, log(HbA1c), log(IGF-I), and log(PEN) as independent variables.
HbA1c, hemoglobin A1c; IGF-I, insulin-like growth factor-I; PEN, pentosidine; RSMI, relative skeletal muscle mass index

Supplemental table 1.

Associations between muscular parameters versus HbA1c, IGF-I, and PEN in postmenopausal women with type 2 diabetes mellitus without metformin

	log (HbA1c)		log (IGF-I)		log (PEN)	
	β	*p*	*β*	*p*	*β*	*p*
log (arms)	-0.14	0.212	0.23	0.059	-1.37	0.174
log (legs)	-0.09	0.352	0.18	0.109	-0.25	0.015
log (RSMI)	-0.06	0.560	0.17	0.143	-0.36	<0.001

Multiple regression analyses were performed using muscle indices as dependent variables and age, duration of diabetes, serum creatinine, log(HbA1c), log(IGF-I), and log(PEN) as independent variables.

Supplemental table 2.

Associations between muscular parameters versus HbA1c, IGF-I, and PEN in postmenopausal women with type 2 diabetes mellitus without pioglitazone

	log (HbA1c)		log (IGF-I)		log (PEN)	
	β	*p*	*β*	*p*	*β*	*p*
log (arms)	-0.11	0.313	0.23	0.038	-1.37	0.307
log (legs)	-0.06	0.549	0.22	0.043	-0.25	0.168
log (RSMI)	-0.01	0.923	0.21	0.051	-0.36	0.030

Multiple regression analyses were performed using muscle indices as dependent variables and age, duration of diabetes, serum creatinine, log(HbA1c), log(IGF-I), and log(PEN) as independent variables.

Supplemental table 3.

Associations between muscular parameters versus HbA1c, IGF-I, and PEN in postmenopausal women with type 2 diabetes mellitus without statin

	log (HbA1c)		log (IGF-I)		log (PEN)	
	β	*p*	*β*	*p*	*β*	*p*
log (arms)	0.02	0.876	0.37	0.019	-0.19	0.140
log (legs)	0.12	0.369	0.42	0.005	-0.20	0.099
log (RSMI)	0.13	0.314	0.40	0.010	-0.28	0.032

Multiple regression analyses were performed using muscle indices as dependent variables and age, duration of diabetes, serum creatinine, log(HbA1c), log(IGF-I), and log(PEN) as independent variables.

Supplemental table 4.

Associations between muscular parameters versus HbA1c, IGF-I, and PEN in postmenopausal women with type 2 diabetes mellitus without ACE inhibitor

	log (HbA1c)		log (IGF-I)		log (PEN)	
	β	p	β	p	β	p
log (arms)	-0.09	0.394	0.23	0.037	-0.12	0.248
log (legs)	-0.02	0.863	0.23	0.032	-0.18	0.082
log (RSMI)	0.03	0.743	0.23	0.036	-0.27	0.009

Multiple regression analyses were performed using muscle indices as dependent variables and age, duration of diabetes, serum creatinine, log(HbA1c), log(IGF-I), and log(PEN) as independent variables.
ACE, angiotensin converting enzyme

Supplemental table 5.

Associations between muscular parameters versus HbA1c, IGF-I, and PEN in postmenopausal women with type 2 diabetes mellitus without ARB

	log (HbA1c)		log (IGF-I)		log (PEN)	
	β	p	β	p	β	p
log (arms)	-0.08	0.502	0.23	0.074	-0.09	0.450
log (legs)	-0.01	0.914	0.22	0.077	-0.15	0.189
log (RSMI)	0.02	0.885	0.23	0.084	-0.25	0.042

Multiple regression analyses were performed using muscle indices as dependent variables and age, duration of diabetes, serum creatinine, log(HbA1c), log(IGF-I), and log(PEN) as independent variables.
ARB, angiotensin 2 receptor blocker