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ORIGINAL ARTICLE

The novel myokine irisin: clinical implications and potential role as a biomarker for sarcopenia in postmenopausal women

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Abstracts

Purpose To clarify the association of circulating irisin with muscle, liver and bone, and to evaluate irisin as a biomarker for sarcopenia in postmenopausal women.

Methods Quadriceps cross-sectional area (QcCSA), bone mineral density (BMD), liver attenuation (measured in Hounsfield units (HU)) were assessed using quantitative computed tomography in 153 postmenopausal women, mean age of 72.20 ± 5.96 years. Muscle strength and physical performance were evaluated by handgrip test and short physical performance battery, respectively. Serum irisin was measured by an enzyme-linked immunosorbent assay kit. In addition, 147 young women were recruited as a reference group to define cut-off values for sarcopenia.

Results Circulating irisin was positively correlated with QcCSA/body weight (BW) and liver HU even after adjusting for multiple covariates, and the serum level was significantly lower in the sarcopenia group (QcCSA/BW<−2SD of the mean values for young women) than in the presarcopenia (−2SD≤QcCSA/BW<−1SD) or control groups (1SD≤QcCSA/BW<2SD). Logistic regression models showed that the relationship between circulating irisin and prevalence of sarcopenia remained significant after adjusting for confounding factors (per 1.0 ng/mL decrease of irisin, odds-ratio = 1.95, 95% confidence interval 1.33–2.87, p-value = 0.001).

Conclusions In postmenopausal women, serum irisin may be used as a biomarker for sarcopenia, and we showed the potential for the development of irisin-based early screening and staging tool for sarcopenia.

Keywords Irisin · Sarcopenia · Aging · Screening

Introduction

Sarcopenia, characterized by loss of muscle mass and function, is a prevalent disorder in elderly individuals and it can lead to fragility and disability and eventually increase morbidity and mortality. With the increasing life expectancy and rapid growth of the aged population, sarcopenia became an emerging public health issue that gave rise to huge socioeconomic burden. However, the definitions of sarcopenia differ across countries or communities according to study working groups and no consensus has been made yet [1]. Several working groups developed their own definition of sarcopenia by using various imaging methods such as dual energy x-ray absorptiometry (DXA), and computed tomography (CT) with physical tests such as gait speed test and 6-min walk test [1]. However, defining sarcopenia using the above tests is not trivial in outpatient daily clinical setting. Therefore, a simple screening tool for the diagnosis of sarcopenia, which would help primary prevention, is needed. Biomarkers serve as indicators of biological

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processes that can be objectively measured and assessed [2]. Biomarker development for sarcopenia can facilitate diagnosis, support the tracking of changes over time, and help decision-making for clinical and therapeutic purposes. Currently, the most commonly suggested biomarkers for sarcopenia are inflammatory biomarkers such as C-reactive protein, interleukin-6, and tumor necrosis factor-α [3]. However, these biomarkers were not widely applied to diagnose sarcopenia, because they were not specific to sarcopenia and showed only weak association with clinical outcomes [4].

Irisin is a novel myokine and adipokine that is released into the circulation by cleavage of fibronectin type III domain containing protein 5 [5]. Because irisin is predominantly synthesized and secreted from the skeletal muscle, there have been several studies investigating the association of irisin with muscle [6–8]. However, the results were inconsistent. In our study, we primarily aimed to evaluate whether there is an association of irisin with sarcopenia, and investigate the possible role of irisin as a biomarker for sarcopenia in postmenopausal women. Furthermore, although there have been some studies regarding irisin and its association with fatty liver, osteoporosis, diabetes, and renal impairment [9–12], the results were unclear and inconsistent. Therefore, our secondary aim was to study the relationship between irisin and these clinical conditions.

Methods

Study participants

We enrolled a total of 153 postmenopausal women aged 60 years or older who visited the Severance hospital in Seoul, Korea, for their routine health check-up from April 2016 to September 2016. We excluded the participants who had been diagnosed with malignancy or severe hepatic impairments, and who had been treated with a glucocorticoid or menopausal hormone therapy during the 3 years prior to the study. Participants who had glycosylated hemoglobin (HbA1c) ≥ 6.5% at baseline and who had been treated with insulin or oral hypoglycemic agents were defined to have diabetes. Participant with an estimated glomerular filtration rate (eGFR) less than 60/ml/min/1.73 m^2 were regarded to have renal insufficiency. Height and body weight (BW) were measured. To define cut-off values for sarcopenia, we used data from 147 healthy young women who had completed quantitative computed tomography (QCT) from the Kangwha Study, a community-based prospective cohort study in Korea [13]. The Severance Hospital Institutional Review Board approved the study protocol (IRB No.4-2016-0126), and informed consent was obtained from all participants. In addition, all investigations were performed in accordance with the principles of the Declaration of Helsinki.

Biochemical measurements

Serum fasting glucose, fasting insulin, blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein, and 25-hydroxyvitamin D were measured. Homeostatic model assessment-insulin resistance (HOMA-IR), which is an index of insulin resistance, was calculated as previously described [14]. Serum aliquots were stored at a deep freezer (−70 °C). Serum irisin concentrations were measured using a commercially available ELISA kit (EK-067-29, Phoenix Pharmaceuticals; intra CV < 10%, inter-CV < 15%; detectable range = 0.1–1000 ng/mL)

Evaluation of the muscle, liver, and bone by QCT

The participants were scanned on a multidetector CT scanner (Light Speed QX-I scanner, GE Medical Systems, Waukesha, WI, USA) at 120 kVp, 120 mAs, with a 2.5-mm slice thickness, as previously described [15]. Volumetric bone mineral density (BMD) in mg/cm^3 was calculated at the spine and hip, and all scanned data were analyzed using QCT PRO software (Mindways Software, Austin, TX, USA). The cross-sectional area (CSA) of the quadriceps muscle/body weight (QcCSA/BW) was used as an index of muscle mass [16, 17]. Axial images were obtained using QCT, and CSA was measured using freehand-drawn regions of interest (ROIs). Quadriceps CSA were measured at the level of 7 cm from the lesser trochanter and the mean value of right and left areas was calculated and used for analysis. QCT images of 147 healthy women aged 27 to 40 years from a community-based cohort study were analyzed as a reference group for this study. Based on the reference group, sarcopenia was defined as QcCSA/BW < −2SD, presarcopenia as Qc CSA/BW<−1SD and ≥−2SD and control as <1SD and ≥−1SD of the reference group [16]. As an index of fatty infiltration within the muscle, we used the mean attenuation of coefficient, measured in Hounsfield units (HU). The mean HU was measured in the same ROIs as muscle CSA was measured.

Evaluation of muscle strength and physical performance

To estimate muscle strength and physical performance, the hand grip test and Short Physical Performance Battery (SPPB) were performed. Handgrip strength was evaluated by using a digital dynamometer (Grip Strength Dynamometer T.K.K.5401; Takei Co., Tokyo, Japan). Participants

Table 1 Correlation between the study variables–Irisin, muscle, bone, and liver

	Irisin	Age	BMI	Spine BMD	Hip BMD	Qc CSA /BW	Qc HU	Hand grip strength	SPPB score	Liver HU
Irisin	–									
Age	−0.268**	–								
BMI	−0.139	−0.096	–							
Spine BMD	0.183*	−0.339**	−0.050	–						
Hip BMD	0.084	−0.288**	0.111	0.377**	–					
Qc CSA/BW	0.318**	−0.143	−0.564**	0.281**	0.091	–				
Qc attenuation (HU)	0.220*	−0.057	−0.457**	−0.039	0.042	0.325**	–			
Hand grip strength	0.225**	−0.394**	0.126	0.258**	0.243**	0.099	0.016	–		
SPPB score	0.286*	−0.462**	−0.022	0.479**	0.465**	0.405**	0.097	0.463**	–	
Liver attenuation (HU)	0.218*	−0.081	−0.421**	0.132	0.025	0.453**	0.407**	0.079	0.214	–

Note: Pearson's correlation coefficients of the study variables

BMD bone mineral density, *Qc* quadriceps, *CSA* cross sectional area, *BW* body weight, *HU* Hounsfield unit, *SPPB* short physical performance battery

*$p < 0.05$; **$p < 0.01$

were asked to stand straight with their arms resting in neutral position, and grip strength was measured three times with each hand. The maximum score was recorded and used for the analysis. Moreover, the SPPB score was based on three tests, as follows: balance test, gait speed test, and chair stand test. Each test was scored between 0 and 4, and total score of 12 was the maximum score [18]. Among the 153 enrolled participants, 136 completed HGT and 67 performed the SPPB test.

Statistical analysis

Descriptive statistics were performed for the analysis of baseline characteristics. To evaluate association of irisin with the muscle, liver, bone, and laboratory findings, Pearson correlation analysis and linear regression test were performed. Analysis of variance was used to analyze significant difference of irisin concentrations among study groups. Logistic regression analysis and receiver operating characteristic (ROC) analysis were performed to evaluate irisin as a biomarker for sarcopenia. Values are expressed as means ± standard deviations. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences for Windows version 23.0 (SPSS, Inc., Chicago, Illinois, USA) and GraphPad Prism 5 (GraphPad Software Inc., San Diego, California, USA).

Results

The baseline characteristics of the participants are shown in Supplemental Table 1. The mean age of the participants was 72.20 ± 5.96 years, and their mean BMI was 23.38 ± 3.45 kg/m^2. Forty-six participants (30.1%) had diabetes, and 10 participants (6.5%) had renal insufficiency. The mean level of circulating irisin measured by ELISA was 8.61 ± 1.54 ng/mL. The intra-assay variability was 6.4%, and the inter-assay variability was 12.1%. Serum irisin was negatively correlated with age, and positively correlated with spine BMD, Qc CSA/BW, Qc HU, hand grip strength, SPPB score, liver HU and HDL (Table 1 and Supplemental Table 2). However, after adjusting for multiple confounding factors, only QcCSA/BW and liver HU were significantly associated with serum irisin (Table 2 and Supplemental Table 3). When participants were divided into lower, middle, and upper tertiles according to QcCSA/BW, serum concentration of irisin was the lowest in the lowest tertile group and the highest in the highest tertile group (Fig. 1a). Similar results were observed when participants were divided into three categories according to liver attenuation (HU). Serum irisin was the lowest in tertile 1 with the lowest liver HU, suggesting that participants with high fatty infiltration in the liver tend to have low circulating levels of irisin (Fig. 1b).

In the reference cohort, which was used to define cut-off values for sarcopenia, the mean age was 35.02 ± 1.84 years, the mean BMI was 22.63 ± 3.53 kg/m^2, and the mean QcCSA/BW was 71.78 ± 8.97 mm^2/kg. Sarcopenia was defined as QcCSA/BW less than 53.84 mm^2/kg, presarcopenia as QcCSA/BW more than 53.84 mm^2/kg and less than 62.81 mm^2/kg, and control as QcCSA/BW between 62.81 to 80.75 mm^2/kg. Among our study population, 42 participants were defined as having presarcopenia and 28 were defined as having sarcopenia. Participants with sarcopenia were more obese and insulin resistant than non-sarcopenic individuals. Furthermore, their BMD and muscle

strength were lower than those of non-sarcopenic participants (Table 3). Notably, circulating irisin level was significantly lower in the sarcopenia and presarcopenia groups than in non-sarcopenic participants (Fig. 1c). Furthermore, we merged patients with presarcopenia and sarcopenia as one sarcopenia group and performed logistic regression analysis. The lowest tertile of irisin group had significantly higher proportion of participants with sarcopenia compared with the highest tertile group. Moreover, the lowest tertile group had 4.67 times higher risk of having sarcopenia than the highest tertile group. Furthermore, the results showed that 1 ng/mL lower serum irisin concentration was associated with 95% higher risk of having sarcopenia. These associations remained significant even after adjusting for age, BMI, HOMA-IR and eGFR (Table 4). In addition, we determined the areas under the ROC curves (AUC) for predicting sarcopenia. The AUC of the irisin-only model was 0.69 for detecting sarcopenia, and the cut-off value of serum irisin level of 8.46 ng/mL showed maximal sensitivity (68%) and specificity (69%). Including age and BMI in the model increased the AUC up to 0.80, but additional incorporation of HOMA-IR and eGFR did not increase AUC (Fig. 2).

Table 2 Correlations of serum irisin with muscle cross sectional area and liver attenuation

	Qc CSA/BW		Liver HU	
	β	*p*-Value	β	*p*-Value
Irisin				
Model 0	0.318	<0.001	0.218	0.011
Model 1	0.199	0.013	0.197	0.021
Model 2	0.210	0.009	0.201	0.019
Model 3	0.193	0.019	0.167	0.042
Model 4	0.166	0.036	0.159	0.052

Note: Model 0 is unadjusted. Model 1 adjusted for age and BMI; model 2 adjusted for model 1 parameters + eGFR; model 3 adjusted for model 2 parameters + HOMA-IR; model 4 adjusted for model 3 parameters + spine BMD, hip BMD

Qc quadriceps, *CSA* cross sectional area, *BW* body weight, *HU* Hounsfield unit, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HOMA-IR* homeostatic model assessment-insulin resistance, *BMD* bone mineral density

Discussion

In our study, we showed that irisin was closely associated with sarcopenia and fatty infiltration of the liver in postmenopausal women. However, there was no association with BMD, renal function, and insulin resistance. In participants with sarcopenia, circulating irisin was significantly low and the relationship between irisin levels and the prevalence of sarcopenia remained significant after adjusting for confounding factors in the logistic regression models. Our findings suggested that irisin may serve as a biomarker for sarcopenia in postmenopausal women.

It has been suggested that elderly individuals who maintain high lean body mass (LBM) are less likely to have sarcopenia, whereas those who have low LBM tend to have sarcopenia [19]. DXA and CT scan are widely used to evaluate muscle mass; however, the equipment is not portable and contains a risk of radiation, which limits their use in primary care and mass screening settings. Although a simple questionnaire such as SARC-F (sluggishness, assistance in walking, rise from a chair, climb stairs, falls) is also used to assess sarcopenia, it may not be an appropriate screening tool due to low sensitivity (3.8% to 9.9%) [20]. Therefore, development of a biomarker for sarcopenia is required, and it would help easy screening of sarcopenia. In our study, we showed that 1 ng/mL lower serum irisin concentration was related to 95% higher risk of having sarcopenia. In addition, circulating irisin concentration of 8.46 ng/mL (68% of sensitivity and 69% of specificity) is recommended as a cut-off value for sarcopenia.

The definition of sarcopenia encompasses not only muscle mass but also muscle strength and physical performance [1]. Notably, in our study, although irisin was associated with muscle CSA, strength, and physical performance, only the relationship between irisin and muscle CSA remained statistically significant after adjusting for covariates, implying that circulating irisin levels may be

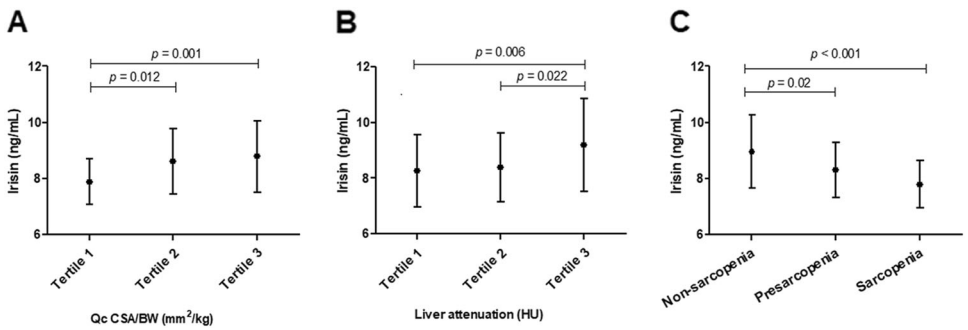


Fig. 1 Mean serum concentration of irisin according to **a** muscle area; **b** liver attenuation; and **c** the presence of sarcopenia. Symbols represent mean ± standard deviation

Table 3 Clinical characteristics of the particiapants according to the presence of presarcopenia or sarcopenia

Variables	Non-sarcopenia ($n = 38$)	Presarcopenia ($n = 42$)	Sarcopenia ($n = 28$)
Age (years)	71.47 ± 6.06	72.67 ± 5.87	73.89 ± 5.37
BMI (kg/m^2)	21.95 ± 2.87	23.23 ± 2.79**	26.21 ± 4.02**
Qc CSA/BW	70.31 ± 4.97	58.39 ± 2.57**	47.38 ± 4.61**‡
HOMA-IR	1.60 ± 0.69	2.37 ± 2.24	3.37 ± 2.81**
Spine BMD (mg/cm^3)	77.75 ± 22.67	63.42 ± 21.48	66.36 ± 17.53**
Hand grip strength	20.31 ± 3.98	19.22 ± 3.75	17.77 ± 4.25*
SPPB	10.43 ± 2.10	9.73 ± 2.63	8.67 ± 2.74

Note: Sarcopenia was defined as Qc CSA/BW<−2SD, presarcopenia as Qc CSA/BW<−1SD and ≥−2SD and control as <1SD and ≥−1SD of reference group

BMI body mass index, *Qc* quadriceps, *CSA* cross sectional area, *BW* body weight, *HOMA-IR* homeostatic model assessment-insulin resistance, *BMD* bone mineral density, *SPPB* short physical performance battery

*$p < 0.05$ compared with control group, **$p < 0.01$ compared with control group, ‡$p < 0.01$ compared with presarcopenia

determined by quantitative index rather than by functional parameters of the muscle. However, contradictory results were reported by Choi et al.; [6] they did not find any differences in irisin circulating levels relevant to muscle mass. The discordant finding may be due to the different baseline characteristics of the study population. They included both men and women, and the participants were relatively young (mean age of 40), whereas we included only postmenopausal women (mean age of 72.20). Age-dependent changes in irisin levels are more prominent in women compared with men [21]. Furthermore, sarcopenia is an age-related skeletal muscle loss, and a prevalent condition in the elderly population, but not in young individuals.

Although there have been several studies regarding the association of fatty liver with circulating irisin, the results were inconsistent [9, 22]. In our study, the lower liver HU, which suggests more fatty infiltration, was related to lower levels of irisin. Although the underlying mechanism is unclear yet, this result added some knowledge regarding the association of fatty liver with circulating irisin. In multiple adjusted models, sarcopenia had stronger associataion with irisin than fatty liver. However, considering that we did not perform accurate diagnostic tool for diagnosing fatty liver such as liver biopsy, we could not confirm which one weighs more on irisin level between fatty liver and sarcopenia.

In previous observational studies, irisin was associated with osteoporotic fractures. Palermo et al. previously reported that high levels of circulating irisin were correlated with low incidence of vertebral fracture; however, it was independent of BMD. We also observed that circulating irisin levels were not associated with spine BMD after adjusting for covariates. We speculated that the effects of irisin on the bone may have been limited after completion of modeling based accrual growth of the bone with thinning of periosteum in adults. Thereby, serum irisin may not be associated with BMD in our study, which was already implied by the limited effects of exercise on the bone in adults. Further studies are needed to clarify the association of irisin with bone fracture, and whether this is via enforcing muscle mass or bone mass.

The accuracy of irisin measurement using ELISA has been controversial, because the range of irisin levels was variable depending on various ELISA kits [11, 21, 23]. The reported level of circulating irisin was significantly different from 0.02–0.04 ng/mL to 1000–2000 ng/mL depending on the kits [11, 23–27]. The inconsistent results are thought to be due to the possibility of cross-reacting proteins contributin to the signal. These discrepancies called into question the reliability of ELISA kits and even the presence of circulating irisin. Finally, Jedrychowski et al. precisely quantified circulating irisin with targeted mass spectrometry and reported that irisin circulated at 3–5 ng/mL [28]. Based on this study, Perakakis et al. reviewed commercially available ELISA kits and determined that an ELISA kit by Phoenix Pharmaceuticals (EK-067-29), which measured irisin concentrations within the expected range according to tandem mass spectrometry, may be the best currently available kit [29]. In our. study, we used the best available ELISA kit (EK-067-29, Phoenix Pharmaceuticals) and the mean circulating irisin levels were 8.61 ng/mL, which was very close to the irisin concentration measured by tandem mass spectrometry. Furthermore, we also suggested a cut-off value for sarcopenia in Korean postmenopausal women. When using CT scan to diagnose sarcopenia, sarcopenia was defined as thigh muscle CSA/weight of 1SD below the sex-specific mean value for the young reference group [16]. While CT scan is currently used to evaluate sarcopenia, its use has been limited by the absence of cut-off values according to ethnicity and sex. In our study, we assessed QcCSA of 147 young community dwelling women and proposed a cut-off value of sarcopenia for Korean women.

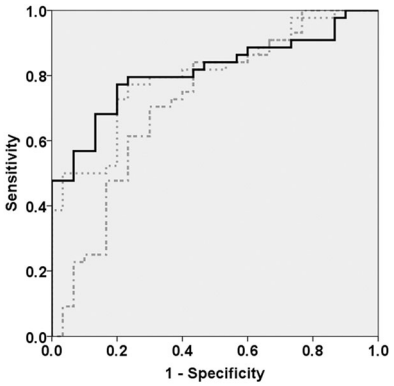
Table 4 Odds ratios of the relationship between irisin levels and prevalence of sarcopenia

Serum irisin	Number of participants	Number (%) of participants with sarcopenia	Unadjusted		Model 1		Model 2	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Tertile								
Lower (5.56–7.85 ng/mL)	51	30 (58.8)*	4.67 (1.72–12.65)	0.002	4.62 (1.40–15.30)	0.012	3.94 (1.03–14.97)	0.044
Middle (7.86–8.95 ng/mL)	51	25 (49.0)	1.94 (0.79–4.77)	0.147	1.94 (0.71–5.30)	0.194	1.70 (0.60–4.82)	0.319
Upper (8.96–14.85 ng/mL)	51	15 (29.4)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Continuous								
per 1.0 ng/mL lower			1.95 (1.33–2.87)	0.001	1.87 (1.21–2.91)	0.005	1.82 (1.15–2.89)	0.011

Note: Model 1: adjusted for age; model 2 adjusted for age, BMI, HOMA-IR and eGFR

OR odds ratio, *HOMA-IR* homeostatic model assessment-insulin resistance, *eGFR* estimated glomerular filtration rate, *BMD* bone mineral density

*$p < 0.01$ compared with upper tertile group



Independent variables	Discrimination of sarcopenia vs. normal	
	AUC (95%CI)	*p*-Value
Model 0 : Irisin	0.69 (0.60-0.80)	< 0.001
Model 1: Irisin, age and BMI	0.80 (0.72-0.88)	< 0.001
Model 2: Irisin, age, BMI, HOMA-IR and eGFR	0.80 (0.72-0.88)	< 0.001

Fig. 2 Receiver operating characteristic curve and areas under curve for predicting sarcopenia

Our study has several limitations. Our study only included postmenopausal women and it was a cross-sectional study, thereby causality could not be assessed. Fatty change of the liver was evaluated only with liver attenuation (HU) obtained by CT scan, without liver biopsy. However, it was reported that fatty liver could be reliably diagnosed by using criteria of liver attenuation <40 HU on CT scans [30]. In addition, most postmenopausal women were expected to have similar physical activity and we could not investigate each participants' daily physical activity level and its effect on serum irisin.

In conclusion, our study showed that low levels of circulating irisin were closely associated with sarcopenia in postmenopausal women. Our findings suggest that irisin is a potentially useful biomarker for early diagnosis and staging of sarcopenia. Further studies are needed to clarify the underlying mechanism supporting these associations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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