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Original Article

Aging-Related Correlation between Serum Sirtuin 1 Activities and Basal Metabolic Rate in Women, but not in Men

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ABSTRACT

Sirtuin (SIRT) is a main regulator of metabolism and lifespan, and its importance has been implicated in the prevention against aging-related diseases. The purpose of this study was to identify the pattern of serum SIRT1 activity according to age and sex, and to investigate how serum SIRT1 activity is correlated with other metabolic parameters in Korean adults. The Biobank of Jeju National University Hospital, a member of the Korea Biobank Network, provided serum samples from 250 healthy adults. Aging- and metabolism-related factors were analyzed in serum, and the data were compared by the stratification of age and sex. Basal metabolic rate (BMR) decreased with age and was significantly lower in men in their fifties and older and in women in their forties and older compared with twenties in men and women, respectively. SIRT1 activities were altered by age and sex. Especially, women in their thirties showed the highest SIRT1 activities. Correlation analysis displayed that SIRT1 activity is positively correlated with serum triglyceride (TG) in men, and with waist circumference, systolic blood pressure, diastolic blood pressure, and serum TG in women. And, SIRT1 activity was negatively correlated with aspartate aminotransferase/alanine aminotransferase ratio in women ($r = -0.183$, $p = 0.039$). Positive correlation was observed between SIRT1 activity and BMR in women ($r = 0.222$, $p = 0.027$), but not in men. Taken together, these findings suggest the possibility that serum SIRT1 activities may be utilized as a biomarker of aging. In addition, positive correlation between SIRT1 activity and BMR in women suggests that serum SIRT1 activity may reflect energy expenditure well in human.

Keywords: Aging; Basal metabolic rate; Homeostasis; Sirtuin 1 activity

INTRODUCTION

Homeostasis is a state which body maintains physical functions and internal environments within a normal range, and the ability to keep homeostasis is generally decreased with aging [1]. This aging-accompanied change is a natural phenomenon, and reduced homeostatic control does not always contribute to the development of diseases. Normal range of aging homeostasis should be set in a different range from that of homeostasis in young adults. Altered conditions with healthy aging homeostasis are distinguishable from pathophysiological conditions because those are in part reversible and controlled [2].

Conflict of Interest
The authors declare that they have no competing interests.

Sirtuin (SIRT) is a well-known regulator of nutrients (glucose and lipid) metabolism and aging processes in nicotinamide adenine dinucleotide $(NAD)^+$-dependent (as protein deacetylase and/or mono adenosine diphosphate [ADP] ribosyltransferase) and -independent ways [3,4]. Among 7 SIRTs, SIRT1 was extensively investigated, and its regulatory roles and working mechanisms were identified relating to the effect of caloric restriction on life span [5-7].

SIRT1 exerts its effects by activating down-stream targets (e.g. forkhead box O1, peroxisome proliferator-activated receptor (PPAR) gamma, coactivator 1 alpha, and PPAR gamma), which differed by types of target tissues and stimulus [8-10]. Although the implication that SIRT1 can be a probable biomarker of aging is evident, little evidence was reported to support the hypothesis in human studies.

Enormous efforts were invested to identify metabolic biomarkers of aging utilizing the up-to-date technologies. Several models for estimating biological age (e.g. vessel/vascular age and hormonal age) were already introduced and applied in clinical setting [11-15]. A recent remarkable work developed the metabolic age score, the way to measure biological age via metabonomics [16]. Considering the significance of SIRT in aging, research should focus to apply SIRT to reflect aging and its related physiological/pathophysiological processes. However, evidence has not yet reported to validate serum SIRT activity as a biomarker of aging.

Therefore, we hypothesized that SIRT is a potential biomarker reflecting aging. To test this hypothesis, we identified the pattern of serum SIRT1 activity according to age and sex, and investigated how serum SIRT1 activity was correlated with other metabolic parameters in Korean adults. Because aging homeostasis is different from normal metabolic homeostasis, we need to identify the appropriate biomarkers for aging homeostasis, and try to provide evidence to address whether serum SIRT activity may be utilized as a biomarker of aging homeostasis.

MATERIALS AND METHODS

Study subjects

Fasting serum samples and a subset of data from 250 healthy adults (122 men and 128 women) were provided by the Biobank of Jeju National University Hospital, a member of the Korea Biobank Network. Serum samples were collected from subjects who visited the healthcare center of Jeju National University Hospital from 2009 to 2015. Fifty subjects for each age group (20's, 30's, 40's, 50's, and over 60's) were randomly selected and provided for analysis. The current research involving human participants has been reviewed by the Institutional Review Board (IRB) of Seoul Women's University (IRB-2015A-10).

Measurements

A subset of routine laboratory data was provided by the Biobank of Jeju National University Hospital. The aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR), atherogenic index (AI), and low-density lipoprotein-cholesterol (LDL-C) were calculated by the following equations [17]:

AAR = AST (IU/L)/ALT (IU/L)
AI=(Totalcholesterol[TC;mmol/L]–high-densitylipoprotein-cholesterol[HDL-C;mmol/L])/HDL-C(mmol/L)
LDL-C (mg/dL) = TC – HDL-C (mg/dL) – triglyceride (TG; mg/dL)/5.0

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And basal metabolic rate (BMR) was estimated by Harris and Benedict equation as follow [18]:

BMR (kcal/day) = 66 + (13.8 × body weight [kg]) + (5.0 × height [cm]) – (6.8 × age) for men
BMR (kcal/day) = 655 + (9.6 × body weight [kg]) + (1.8 × height [cm]) – (4.7 × age) for women

SIRT1 activity

SIRT1 activity was measured using a SIRT1 assay kit from Abcam (Cambridge, UK). Serum samples were mixed with specific substrates, NAD, and developed at room temperature. Then, SIRT1 activity was measured using a fluorometric microplate reader at 340/440 nm.

Statistical analysis

All statistical analyses were performed using SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA). Data were expressed as means ± standard deviation (SD). Student's t-test was performed to compare the differences in means between two groups, and 1-way analysis of variance (ANOVA) was performed to assess the differences in means across the age groups. Correlations between SIRT1 activity and other parameters were analyzed by Pearson's correlation analysis. Statistical significance was defined as $p < 0.05$.

RESULTS

Subject characteristics were given in **Table 1**. Men and women differed descriptively in a number of variables, including age, height, body weight, body mass index (BMI), waist circumference (WC), systolic blood pressure (SBP), diastolic blood pressure (DBP), AI, and

Table 1. Subject characteristics

	Total (n = 250)	Men (n = 122)	Women (n = 128)	p value
Age, yr	45.15 ± 14.26	47.14 ± 14.08	43.26 ± 14.23	0.031
Height, cm	163.70 ± 9.21	169.95 ± 7.19	157.27 ± 6.11	< 0.001
Weight, kg	62.87 ± 11.95	70.49 ± 10.30	55.02 ± 7.71	< 0.001
BMI, kg/m^2	23.31 ± 2.94	24.34 ± 2.70	22.24 ± 2.81	< 0.001
WC, cm	72.27 ± 9.03	73.62 ± 9.50	70.88 ± 8.33	0.031
HbA1c, %	5.52 ± 0.37	5.53 ± 0.36	5.51 ± 0.39	0.843
Insulin, μIU/mL	5.78 ± 3.39	5.99 ± 3.79	5.59 ± 3.02	0.521
SBP, mmHg	118 ± 11	121 ± 11	115 ± 11	0.001
DBP, mmHg	72 ± 9	74 ± 9	71 ± 8	0.031
BUN, mg/dL	13.18 ± 4.14	13.97 ± 4.25	12.43 ± 3.91	0.003
Creatinine, mg/dL	1.00 ± 0.18	1.13 ± 0.13	0.88 ± 0.12	< 0.001
AST, IU/L	23.10 ± 9.99	24.51 ± 10.42	21.76 ± 9.40	0.029
ALT, IU/L	22.87 ± 16.07	26.93 ± 18.36	19.00 ± 12.42	< 0.001
AAR	1.17 ± 0.37	1.05 ± 0.32	1.29 ± 0.39	< 0.001
γ-GTP, IU/L	28.49 ± 29.35	36.64 ± 36.99	20.66 ± 16.01	< 0.001
TG, mg/dL	89.24 ± 45.58	97.97 ± 43.73	81.00 ± 45.93	0.003
TC, mg/dL	191.04 ± 33.62	193.46 ± 33.63	188.73 ± 33.58	0.267
HDL-C, mg/dL	55.43 ± 13.10	51.98 ± 11.02	58.70 ± 14.09	< 0.001
LDL-C, mg/dL	118.05 ± 30.10	122.48 ± 31.61	113.82 ± 28.05	0.023
AI	0.71 ± 0.07	0.73 ± 0.07	0.68 ± 0.07	< 0.001
BMR, kcal/day	1,403 ± 234	1,555 ± 219	1,247 ± 116	< 0.001
SIRT1 activity (relative unit)	1.01 ± 0.22	1.03 ± 0.20	0.99 ± 0.24	0.154

Data are expressed as mean ± SD; p values for comparisons of means (2-sided t-tests) between men and women.

BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AAR, AST/ALT ratio; γ-GTP, gamma-glutamyl transferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; AI, atherogenic index; BMR, basal metabolic rate; SIRT, sirtuin; SD, standard deviation.

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BMR. Also, serum levels of blood urea nitrogen (BUN), creatinine, AST, ALT, AAR, gamma-glutamyl transferase, TG, HDL-C, and LDL-C were different between men and women.

Tables 2 and **3** showed age-related alterations of anthropometric and metabolic parameters in men and women. Height was significantly decreased with age in men and women, and WC was significantly altered with age in only women. Serum levels of BUN, AST activity, AAR, and LDL-C were significantly different among age groups in men. AST activities were significantly higher in men in their fifties than the other age groups. Men aged older than 60 years had high AAR. AI score was getting higher from twenties to fifties in men. BMR decreased with age and was significantly lower in their fifties and older compared with men in their twenties. Serum levels of hemoglobin A1c (HbA1c), SBP, DBP, BUN, AST activity, TG, TC, and LDL-C were significantly different among age groups in women. Women in their thirties had the highest levels of WC and DBP, even though body weight and BMI did not differ significantly by age groups in women. HbA1c showed age-dependent increases in women. TG, TC, BUN, and AI score were higher in women more than 60 years of age. BMR was significantly lower in women in their forties and older compared with women in their twenties. SIRT1 activities were altered by age and sex. Women in their thirties show the highest SIRT1 activities, even though SIRT1 activities were lower in their thirties than the other age groups in men.

Correlation analysis displayed that SIRT1 activity was positively correlated with serum TG concentrations in men, and with WC, SBP, DBP, and serum TG in women (**Table 4**). SIRT1 activity was negatively correlated with a hepatic function marker, AAR in women ($r = -0.183$, $p = 0.039$). Positive correlation was observed between SIRT1 activity and BMR in women ($r = 0.222$, $p = 0.027$), but not in men ($r = -0.012$, $p = 0.903$).

Table 2. Aging-related alterations of variables in men

	20's (n = 18)	30's (n = 26)	40's (n = 21)	50's (n = 32)	60's and over (n = 25)	p value
Height, cm	173.37 ± 7.80	173.43 ± 6.87	171.84 ± 7.09	168.55 ± 5.97	165.07 ± 5.45	< 0.001
Weight, kg	71.46 ± 14.30	73.61 ± 8.54	72.78 ± 11.52	70.55 ± 7.50	65.62 ± 9.48	0.082
BMI, kg/m^2	23.58 ± 3.11	24.52 ± 2.89	24.60 ± 3.25	24.80 ± 1.91	24.01 ± 2.65	0.644
WC, cm	71.00 ± 6.90	75.60 ± 7.65	75.41 ± 10.59	75.88 ± 10.81	69.88 ± 9.11	0.095
HbA1c, %	5.33 ± 0.36	5.47 ± 0.23	5.53 ± 0.35	5.66 ± 0.26	5.54 ± 0.48	0.257
Insulin, μIU/mL	7.10 ± 4.29	7.66 ± 5.00	5.65 ± 3.26	6.63 ± 3.70	3.95 ± 1.86	0.075
SBP, mmHg	121 ± 11	120 ± 10	121 ± 12	122 ± 10	120 ± 14	0.891
DBP, mmHg	71 ± 7	76 ± 8	75 ± 11	76 ± 11	70 ± 9	0.095
BUN, mg/dL	11.83 ± 2.49	12.32 ± 3.15	14.40 ± 3.12	14.12 ± 4.59	16.69 ± 5.15	< 0.001
Creatinine, mg/dL	1.09 ± 0.13	1.14 ± 0.12	1.18 ± 0.09	1.13 ± 0.14	1.12 ± 0.15	0.381
AST, IU/L	20.11 ± 5.88	22.54 ± 7.11	21.86 ± 5.92	30.09 ± 16.00	24.80 ± 6.61	0.004
ALT, IU/L	27.50 ± 19.29	27.81 ± 24.30	25.29 ± 14.21	30.22 ± 19.35	22.76 ± 11.53	0.640
AAR	0.88 ± 0.31	1.01 ± 0.30	1.01 ± 0.33	1.08 ± 0.29	1.20 ± 0.33	0.021
γ-GTP, IU/L	29.69 ± 18.61	39.19 ± 29.20	36.10 ± 22.29	34.48 ± 24.47	41.56 ± 66.25	0.875
TG, mg/dL	92.56 ± 53.35	106.04 ± 37.03	106.38 ± 41.93	91.71 ± 43.46	94.16 ± 45.50	0.605
TC, mg/dL	183.33 ± 33.01	185.00 ± 25.48	194.33 ± 24.22	204.63 ± 32.64	194.52 ± 45.45	0.143
HDL-C, mg/dL	53.22 ± 10.58	52.19 ± 10.70	49.24 ± 11.73	50.61 ± 9.75	54.84 ± 12.49	0.453
LDL-C, mg/dL	111.60 ± 26.47	111.60 ± 26.70	123.82 ± 22.05	137.83 ± 31.02	120.85 ± 40.19	0.010
AI	0.70 ± 0.07	0.72 ± 0.06	0.74 ± 0.06	0.76 ± 0.06	0.71 ± 0.07	0.011
BMR, kcal/day	1,734 ± 227	1,700 ± 133	1,613 ± 185	1,505 ± 126	1,337 ± 173	< 0.001
SIRT1 activity (relative unit)	1.00 ± 0.10	0.94 ± 0.20	1.10 ± 0.21	1.06 ± 0.20	1.04 ± 0.21	0.058

Data are expressed as mean ± SD; p values from 1-way ANOVA to assess the differences in means across the age groups.

BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AAR, AST/ALT ratio; γ-GTP, gamma-glutamyl transferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; AI, atherogenic index; BMR, basal metabolic rate; SIRT, sirtuin; SD, standard deviation; ANOVA, analysis of variance.

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Table 3. Aging-related alterations of variables in women

	20's (n = 32)	30's (n = 24)	40's (n = 29)	50's (n = 18)	60's and over (n = 25)	p value
Height, cm	160.40 ± 4.61	160.39 ± 7.01	155.57 ± 4.50	156.82 ± 4.85	151.95 ± 4.52	< 0.001
Weight, kg	54.79 ± 8.36	57.41 ± 8.61	53.41 ± 6.81	58.42 ± 6.69	52.30 ± 6.28	0.092
BMI, kg/m^2	21.28 ± 3.02	22.32 ± 3.09	22.04 ± 2.44	23.73 ± 2.23	22.66 ± 2.58	0.109
WC, cm	66.11 ± 8.86	75.05 ± 6.16	73.50 ± 9.44	73.69 ± 5.96	69.59 ± 6.79	0.001
HbA1c, %	5.27 ± 0.37	5.36 ± 0.31	5.49 ± 0.23	5.55 ± 0.38	5.76 ± 0.40	0.001
Insulin, μIU/mL	4.96 ± 3.96	7.31 ± 2.18	5.05 ± 2.47	4.08 ± 1.23	5.88 ± 3.40	0.143
SBP, mmHg	110 ± 10	115 ± 11	116 ± 10	121 ± 12	120 ± 10	0.004
DBP, mmHg	66 ± 9	75 ± 6	74 ± 9	74 ± 6	70 ± 7	0.001
BUN, mg/dL	10.94 ± 3.41	10.93 ± 3.47	12.02 ± 3.87	13.91 ± 3.64	15.17 ± 3.54	< 0.001
Creatinine, mg/dL	0.86 ± 0.15	0.91 ± 0.11	0.91 ± 0.10	0.83 ± 0.10	0.86 ± 0.11	0.058
AST, IU/L	17.44 ± 3.85	21.50 ± 7.82	20.14 ± 7.83	25.89 ± 9.78	26.44 ± 13.68	0.001
ALT, IU/L	15.63 ± 9.53	22.83 ± 16.01	16.66 ± 7.09	20.11 ± 8.57	21.56 ± 17.29	0.141
AAR	1.30 ± 0.41	1.11 ± 0.31	1.27 ± 0.30	1.33 ± 0.23	1.42 ± 0.53	0.074
γ-GTP, IU/L	15.00 ± 6.53	22.13 ± 15.09	24.24 ± 24.60	23.65 ± 10.42	19.92 ± 14.52	0.196
TG, mg/dL	73.19 ± 40.77	81.71 ± 33.09	68.14 ± 25.80	68.28 ± 28.54	114.40 ± 71.05	0.001
TC, mg/dL	170.66 ± 24.81	181.04 ± 27.74	190.55 ± 31.89	203.28 ± 34.08	206.64 ± 37.88	< 0.001
HDL-C, mg/dL	56.75 ± 14.02	58.67 ± 10.52	60.83 ± 16.95	64.11 ± 12.71	54.88 ± 13.88	0.217
LDL-C, mg/dL	99.27 ± 21.96	106.03 ± 25.38	116.00 ± 26.18	125.51 ± 29.31	128.88 ± 28.78	< 0.001
AI	0.66 ± 0.08	0.67 ± 0.06	0.68 ± 0.08	0.68 ± 0.05	0.73 ± 0.06	0.006
BMR, kcal/day	1,329 ± 83	1,312 ± 97	1,227 ± 77	1,232 ± 72	1,107 ± 66	< 0.001
SIRT1 activity (relative unit)	1.00 ± 0.22	1.13 ± 0.29	0.95 ± 0.19	0.91 ± 0.19	0.96 ± 0.23	0.017

Data are expressed as mean ± SD; p values from 1-way ANOVA to assess the differences in means across the age groups.

BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AAR, AST/ALT ratio; γ-GTP, gamma-glutamyl transferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; AI, atherogenic index; BMR, basal metabolic rate; SIRT, sirtuin; SD, standard deviation; ANOVA, analysis of variance.

Table 4. Correlation of each parameter with serum SIRT1 activity

	Men		Women	
	r	p value	r	p value
Height, cm	0.059	0.557	0.043	0.671
Weight, kg	0.020	0.841	0.180	0.075
BMI, kg/m^2	−0.018	0.855	0.163	0.106
WC, cm	−0.073	0.468	0.246	0.014
HbA1c, %	0.032	0.797	0.058	0.611
Insulin, μIU/mL	−0.082	0.546	0.182	0.145
SBP, mmHg	−0.033	0.739	0.217	0.031
DBP, mmHg	−0.073	0.468	0.246	0.014
BUN, mg/dL	0.025	0.787	−0.055	0.540
Creatinine, mg/dL	−0.126	0.167	−0.033	0.709
AST, IU/L	0.158	0.082	0.022	0.804
ALT, IU/L	0.104	0.253	0.131	0.141
AAR	0.019	0.835	−0.183	0.039
γ-GTP, IU/L	0.104	0.259	−0.044	0.627
TG, mg/dL	0.229	0.011	0.259	0.003
TC, mg/dL	0.027	0.767	0.152	0.086
HDL-C, mg/dL	−0.004	0.968	−0.031	0.727
LDL-C, mg/dL	−0.011	0.901	0.113	0.203
AI	0.074	0.419	0.140	0.116
BMR, kcal/day	−0.012	0.903	0.222	0.027

r = correlation coefficient.

SIRT, sirtuin; BMI, body mass index; WC, waist circumference; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AAR, AST/ALT ratio; γ-GTP, gamma-glutamyl transferase; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; AI, atherogenic index; BMR, basal metabolic rate.

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DISCUSSION

Chronological age is a representative counting of aging; however, it often does not correspond to the biological age of the individual. The biological age may be affected by genetic and environmental factors including diet, activity level, and metabolic/hormonal changes. SIRT is a key regulator of aging-related metabolic changes [5,19-21], and may be a potent biomarker of aging. However, practical application of SIRT as a biomarker of aging has not yet evidently reported or been available. The present results revealed that aging-related alterations of SIRT1 activity are distinct especially in women and that SIRT1 activity is significantly correlated with several anthropometric and metabolic parameters including BMR in women.

To test the hypothesis that serum SIRT1 activity may be used as a biomarker of aging, serum samples were provided via the Korea Biobank Network. Total 250 serum samples and a subset of data for 5 different age groups were provided. In general, several values of anthropometric and metabolic parameters were lower in women compared with those in men except HDL-C. Height loss with age displayed in men and women. Age-related differences in height have been observed in various studies including the Baltimore longitudinal study of aging [22]. Circulating levels of TG, TC, LDL-C, and AI were significantly increased at 60 years and over in women, but not in men. Alterations in lipid profiles are known features in postmenopausal women. Men aged more than 60 years showed the highest AAR. Previous study regarding the effect of aging on the liver in healthy male subjects demonstrated negative correlations between age and both liver volume and liver blood flow [23]. SIRT1 activity did not differ significantly between men and women.

Most human studies on SIRT1 investigated the effects of calorie restriction on SIRT1 rather than identifying the direct effects of SIRT1 on aging. Caloric restriction induces SIRT1 activation in human [24]. As in the above-mentioned study, human studies related to SIRT1 focused on the effects of caloric restriction on aging-related metabolic alterations. From these findings, the plausible explanation regarding SIRT1 and aging is that SIRT1 and its agonists contribute to the extension of lifespan by mimicking the effects of caloric restriction. Recent approaches to investigate the role of SIRT1 on aging have utilized single nucleotide polymorphisms (SNPs) to study the relationship between SIRT1 and longevity in human. The association between SIRT1 SNPs and longevity in healthy subjects was significant [25]. However, another study showed that common variants in SIRT1 were not associated with longevity in the Chinese population [26]. Collectively, there are limited evidences to explain the role of SIRT1 in human aging and aging process related to changes in BMR, WC, and other parameters, and further studies are needed.

In this study, a sex-dependent pattern was observed. Serum SIRT1 activity peaked at forties in men and at thirties in women. After the peaks, the SIRT1 activities were reduced with age, especially in women. Also, correlation between SIRT1 activity and BMR was significant only in women, and the direction of the correlation between the 2 parameters was opposite even though the correlation was significant only in women. Previous studies on SIRT activities suggested a sex-specific pattern of the SIRT activity [27]. Negative correlation was shown between SIRT1 deacetylase activity and age in men but not in women, and the SIRT1 activity was measured in skin tissues samples obtained from non-sun exposed areas of the pelvic region [27]. Besides this, it is hard to find the evidence regarding the sex-specific pattern of SIRT activity or serum SIRT activity in human. Therefore, current findings are meaningful in that they provide evidence that serum SIRT1 activity can be successfully measured and that the sex-dependent pattern of serum SIRT1 activity exists.

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Another interesting finding is that the correlation between serum SIRT1 activity and BMR is sex-dependent. Positive correlation between the 2 parameters was observed only in women. So far, evidence was not reported regarding the direct regulation of SIRT1 on BMR. However, various experiments using SIRT1 activators (e.g. resveratrol, S17834, and SRT1720) demonstrated that SIRT1 regulates energy expenditure by activating adenosine monophosphate (AMP)-activated protein kinase, which senses changes in AMP/adenosine triphosphate (ATP) ratio [28-30]. Also, resveratrol treatment in mice increased energy expenditure accompanying by increases in oxygen consumption and the expressions of thermogenesis-related markers in brown adipose tissue [31]. Considering that BMR is the main component of daily energy expenditure, these mechanisms may support the observed positive correlation between SIRT1 activity and BMR. We cannot explain why the correlation was not observed in men at this point. Age-stratified analysis may be useful to explain the sex-dependent differences in the correlation between SIRT1 activity and BMR. In addition, BMR values used in this study are from the estimation by Harris and Benedict equation [18] utilizing body weight, height, age, and sex. The indirect estimation of BMR may influence the correlation between BMR and other parameters, and cause misinterpretation.

Although an age-related pattern of serum SIRT1 activity and the positive correlation between serum SIRT1 activity and BMR have been observed in women, it is difficult to firmly conclude that serum SIRT1 activity is a reliable biomarker of aging and to generalize this finding to general population. It is possible that findings in this study reflect regional characteristics because serum samples were provided from Jeju National University Hospital. Nonetheless, we propose that SIRT1 activity can be successfully measured in human serum and that serum SIRT1 activities have an aging-related distinct pattern, which suggests the possibility that serum SIRT1 activities may be utilized as a biomarker of aging. In addition, positive correlation between SIRT1 activity and BMR in women suggests that serum SIRT1 activity may reflect energy expenditure well in human. Taken together, these findings will enable the application of serum SIRT1 activity to estimate biological age of an individual.

REFERENCES

1. Blagosklonny MV. Answering the ultimate question "what is the proximal cause of aging?". Aging (Albany, NY) 2012;4:861-77.
PUBMED | CROSSREF
2. Berghella AM, Contasta I, Marulli G, D'Innocenzo C, Garofalo F, Gizzi F, Bartolomucci M, Laglia G, Valeri M, Gizzi M, Friscioni M, Barone M, Del Beato T, Secinaro E, Pellegrini P. Ageing gender-specific "Biomarkers of Homeostasis", to protect ourselves against the diseases of the old age. Immun Ageing 2014;11:3.
PUBMED | CROSSREF
3. North BJ, Verdin E. Sirtuins: Sir2-related NAD-dependent protein deacetylases. Genome Biol 2004;5:224.
PUBMED | CROSSREF
4. Carafa V, Rotili D, Forgione M, Cuomo F, Serretiello E, Hailu GS, Jarho E, Lahtela-Kakkonen M, Mai A, Altucci L. Sirtuin functions and modulation: from chemistry to the clinic. Clin Epigenetics 2016;8:61.
PUBMED | CROSSREF
5. Wątroba M, Szukiewicz D. The role of sirtuins in aging and age-related diseases. Adv Med Sci 2016;61:52-62.
PUBMED | CROSSREF
6. Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B, Howitz KT, Gorospe M, de Cabo R, Sinclair DA. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 2004;305:390-2.
PUBMED | CROSSREF
7. Xu C, Cai Y, Fan P, Bai B, Chen J, Deng HB, Che CM, Xu A, Vanhoutte PM, Wang Y. Calorie restriction prevents metabolic aging caused by abnormal SIRT1 function in adipose tissues. Diabetes 2015;64:1576-90.
PUBMED | CROSSREF

https://doi.org/10.7762/cnr.2017.6.1.18

8. Chang HC, Guarente L. SIRT1 and other sirtuins in metabolism. Trends Endocrinol Metab 2014;25:138-45.
PUBMED | CROSSREF
9. Guarente L. Calorie restriction and sirtuins revisited. Genes Dev 2013;27:2072-85.
PUBMED | CROSSREF
10. Chen D, Bruno J, Easlon E, Lin SJ, Cheng HL, Alt FW, Guarente L. Tissue-specific regulation of SIRT1 by calorie restriction. Genes Dev 2008;22:1753-7.
PUBMED | CROSSREF
11. Zhang WG, Zhu SY, Bai XJ, Zhao DL, Jian SM, Li J, Li ZX, Fu B, Cai GY, Sun XF, Chen XM. Select aging biomarkers based on telomere length and chronological age to build a biological age equation. Age (Dordr) 2014;36:9639.
PUBMED | CROSSREF
12. Zhang WG, Bai XJ, Sun XF, Cai GY, Bai XY, Zhu SY, Zhang M, Chen XM. Construction of an integral formula of biological age for a healthy Chinese population using principle component analysis. J Nutr Health Aging 2014;18:137-42.
PUBMED | CROSSREF
13. Park J, Cho B, Kwon H, Lee C. Developing a biological age assessment equation using principal component analysis and clinical biomarkers of aging in Korean men. Arch Gerontol Geriatr 2009;49:7-12.
PUBMED | CROSSREF
14. Bae CY, Kang YG, Kim S, Cho C, Kang HC, Yu BY, Lee SW, Cho KH, Lee DC, Lee K, Kim JS, Shin KK. Development of models for predicting biological age (BA) with physical, biochemical, and hormonal parameters. Arch Gerontol Geriatr 2008;47:253-65.
PUBMED | CROSSREF
15. Bae CY, Kang YG, Piao MH, Cho B, Cho KH, Park YK, Yu BY, Lee SW, Kim MJ, Lee SH, Kim YJ, Kim DH, Kim JS, Oh JE. Models for estimating the biological age of five organs using clinical biomarkers that are commonly measured in clinical practice settings. Maturitas 2013;75:253-60.
PUBMED | CROSSREF
16. Hertel J, Friedrich N, Wittfeld K, Pietzner M, Budde K, Van der Auwera S, Lohmann T, Teumer A, Völzke H, Nauck M, Grabe HJ. Measuring biological age via metabonomics: the metabolic age score. J Proteome Res 2016;15:400-10.
PUBMED | CROSSREF
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
PUBMED
18. 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;105:775-89.
PUBMED | CROSSREF
19. Imai S, Armstrong CM, Kaeberlein M, Guarente L. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature 2000;403:795-800.
PUBMED | CROSSREF
20. Lin SJ, Defossez PA, Guarente L. Requirement of NAD and SIR2 for life-span extension by calorie restriction in Saccharomyces cerevisiae. Science 2000;289:2126-8.
PUBMED | CROSSREF
21. Yuan Y, Cruzat VF, Newsholme P, Cheng J, Chen Y, Lu Y. Regulation of SIRT1 in aging: roles in mitochondrial function and biogenesis. Mech Ageing Dev 2016;155:10-21.
PUBMED | CROSSREF
22. Sorkin JD, Muller DC, Andres R. Longitudinal change in height of men and women: implications for interpretation of the body mass index: the Baltimore Longitudinal Study of Aging. Am J Epidemiol 1999;150:969-77.
PUBMED | CROSSREF
23. Wynne HA, Cope LH, Mutch E, Rawlins MD, Woodhouse KW, James OF. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology 1989;9:297-301.
PUBMED | CROSSREF
24. Kitada M, Kume S, Takeda-Watanabe A, Tsuda S, Kanasaki K, Koya D. Calorie restriction in overweight males ameliorates obesity-related metabolic alterations and cellular adaptations through anti-aging effects, possibly including AMPK and SIRT1 activation. Biochim Biophys Acta 2013;1830:4820-7.
PUBMED | CROSSREF
25. Kim S, Bi X, Czarny-Ratajczak M, Dai J, Welsh DA, Myers L, Welsch MA, Cherry KE, Arnold J, Poon LW, Jazwinski SM. Telomere maintenance genes SIRT1 and XRCC6 impact age-related decline in telomere length but only SIRT1 is associated with human longevity. Biogerontology 2012;13:119-31.
PUBMED | CROSSREF

26. Lin R, Yan D, Zhang Y, Liao X, Gong G, Hu J, Fu Y, Cai W. Common variants in SIRT1 and human longevity in a Chinese population. BMC Med Genet 2016;17:31.
PUBMED | CROSSREF

27. Massudi H, Grant R, Braidy N, Guest J, Farnsworth B, Guillemin GJ. Age-associated changes in oxidative stress and NAD+ metabolism in human tissue. PLoS One 2012;7:e42357.
PUBMED | CROSSREF

28. Jiang S, Wang W, Miner J, Fromm M. Cross regulation of sirtuin 1, AMPK, and PPARγ in conjugated linoleic acid treated adipocytes. PLoS One 2012;7:e48874.
PUBMED | CROSSREF

29. Hou X, Xu S, Maitland-Toolan KA, Sato K, Jiang B, Ido Y, Lan F, Walsh K, Wierzbicki M, Verbeuren TJ, Cohen RA, Zang M. SIRT1 regulates hepatocyte lipid metabolism through activating AMP-activated protein kinase. J Biol Chem 2008;283:20015-26.
PUBMED | CROSSREF

30. Gu XS, Wang ZB, Ye Z, Lei JP, Li L, Su DF, Zheng X. Resveratrol, an activator of SIRT1, upregulates AMPK and improves cardiac function in heart failure. Genet Mol Res 2014;13:323-35.
PUBMED | CROSSREF

31. Andrade JM, Frade AC, Guimarães JB, Freitas KM, Lopes MT, Guimarães AL, de Paula AM, Coimbra CC, Santos SH. Resveratrol increases brown adipose tissue thermogenesis markers by increasing SIRT1 and energy expenditure and decreasing fat accumulation in adipose tissue of mice fed a standard diet. Eur J Nutr 2014;53:1503-10.
PUBMED | CROSSREF

https://doi.org/10.7762/cnr.2017.6.1.18