Ther Adv Musculoskel Dis
2021, Vol. 13: 1–13
DOI: 10.1177/1759720X21993253

How much does fat mass change affect serum uric acid levels among apparently clinically healthy Korean men?

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Abstract

Objective: The aim of this study was to examine the impact of fat mass alteration on serum uric acid (SUA) levels in apparently clinically healthy men.

Methods: We evaluated 27,387 men who consecutively underwent health check ups between 2015 and 2017. We assessed the likelihood of achieving a SUA level of <0.41 mmol/L and compared the SUA levels according to fat mass changes.

Results: Compared with those without fat mass change (the reference group), the odds ratios (95% confidence interval) of achieving a SUA level of <0.41 mmol/L for fat mass decreases of ⩾2.5, 1.5–2.5, and 0.5–1.5 kg were 1.63 (1.45–1.82), 1.19 (1.06–1.34), and 1.07 (0.97–1.18), respectively, while those for a fat mass increase of ⩾2.5, 1.5–2.5, and 0.5–1.5 kg were 0.71 (0.64–0.78), 0.87 (0.79–0.97), and 0.95 (0.86–1.04), respectively. The corresponding beta-coefficients of SUA levels (mmol/L) were −0.26 [−0.29–(−0.23)], −0.12 [−0.16–(−0.09)], and −0.09 [−0.12–(−0.06)] for fat mass decreases of ⩾2.5, 1.5–2.5, and 0.5–1.5 kg, respectively. Every 1-kg fat mass reduction was associated with 9% increased odds of achieving the target SUA level. The multivariate SUA level difference per 1-kg fat mass gain was 2.97 μmol/L. Similar levels of association persisted among the prespecified subgroups.

Conclusion: We quantitatively demonstrated that fat mass reduction contributes to a clinically relevant decrease in SUA levels and a significant increase in the likelihood of achieving target SUA levels. Our findings may help to provide clear clinical guidance on fat mass alteration to reduce SUA levels in patients with hyperuricemia.

Keywords: fat mass, healthy, men, uric acid

Received: 26 August 2020; revised manuscript accepted: 3 January 2021.

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Introduction

Elevated serum uric acid (SUA) levels result in the build up of uric acid crystals in the joints, which leads to gout. Overweight and obesity are conditions with excessive fat accumulation that present a risk to health, and the incidence of obesity has continuously increased worldwide with its global prevalence estimated to increase to 18% in men and 21% in women by 2025.[1] Growing evidence has indicated that increases in adiposity or fat mass elevates SUA levels and can influence the onset of gout development.[2–12] The association between obesity and SUA levels can be attributed to reduced renal clearance of uric acid and the abundant activity of xanthine oxidase in adipose tissue.[6,7,13] Another possible explanation for the association appears to be increased leptin production and higher insulin resistance that play roles in the strong relationship between higher adiposity and hyperuricemia.[6–10]

As obesity shows a causal link with hyperuricemia, obesity management is important for lowering SUA levels. Recent,studies have confirmed that weight loss, achieved by dietary intervention or bariatric surgery, is effective in reducing SUA

levels.[2,3,14] Many rheumatology society guidelines recommend weight reduction in patients with hyperuricemia or gout despite a lack of sufficient data to support the possible decrease in SUA levels by weight reduction.

Evidence gathered on the association between fat mass and SUA level has seldom clarified the effect of the specific magnitude of fat mass change on SUA levels and, besides the population with high cardiovascular risk, the apparently healthy population has often been overlooked. Accurate measurement of fat mass should be prioritized to assess the impact of obesity on SUA levels. Currently, calculating the body mass index (BMI) is the customary approach to classifying overweight and obesity, and is determined solely by weight and height, reflecting not only body fat but also changes in muscle mass. Although BMI is used as a classic index for obesity and is known to correlate with body fat mass, it is not a precise indicator of body fat mass. Thus, obesity should be evaluated by a direct measure of fat mass. Bioelectrical impedance analysis (BIA) is a noninvasive method for the accurate estimation of body fat and a well-correlated measurement of body fat relative to lean mass.[15]

Therefore, this study aimed to examine the impact of changes in fat mass measured by BIA on SUA levels in apparently clinically healthy men through rigorous adjustments for potential confounders.

Methods

Subjects

We recruited subjects who consecutively participated in a health check-up program between 2015 and 2017, held at one of the Kangbuk Samsung Hospital Total Healthcare Centers in Seoul and Suwon. These regular examinations are predicated on the Industrial Safety and Health Laws in South Korea, which require annual or biennial free health check ups for all employees. Therefore, more than 80% of the subjects were employees of various companies and local governmental organizations or their spouses, while the others were participants who signed up at their own expense.

This study was performed on 78,653 Korean men who underwent comprehensive health screening examinations between January 2015 and December 2017. We excluded 21,924 men who had any of the following underlying conditions and medical histories at baseline: estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 ($n = 242$) or serum creatinine level ≥ 124 μmol/L ($n = 245$); history of heart disease ($n = 692$), hypertension ($n = 9959$), diabetes ($n = 3022$), stroke ($n = 362$), cancer ($n = 1415$), and liver cirrhosis on ultrasonography ($n = 40$); use of antipsychotic or antidepressant medication ($n = 452$); use of medication for hypertension ($n = 6061$), gout ($n = 519$), or hyperlipidemia ($n = 3735$). We further excluded those with missing data for any of the study variables, including the food frequency questionnaire (FFQ) for energy, calcium, vitamin C, total protein, total fat, or fiber ($n = 45{,}033$). A total of 27,387 men were included in the final analysis. The institutional review board of Kangbuk Samsung Hospital approved this study (#KBSMC 2019-09-001), and waived the requirement for informed consent owing to the use of nonidentifiable data.

Assessments of SUA level, fat mass, and other study variables

Comprehensive medical check ups, including laboratory tests and anthropometric measurements including height, weight, blood pressure (BP), and physical activity, were skilfully executed as previously described.[16,17] All the enrolled participants completed a 103-item, self-reported FFQ, which was a semi-quantitative form designated and validated in Korea.[18]

The collected data are presented as follows: age (years), weight (kg), height (m), smoking status (never, former, current), alcohol consumption (g/day), health-enhancing physical activity (HEPA) level, education level (high school or college graduate), medication and medical history, daily dietary intake of total energy (kcal), total protein (g), total fat (g), fiber (g), calcium (mg), and vitamin C (mg) based on the FFQ. BMI was calculated as body weight divided by the squared height (kg/m^2), and obesity was defined as BMI ≥ 25 kg/m^2, which represents the proposed cut-off for the Asian population.[19]

All participants were examined after an overnight fast. Serum levels of the following were measured as described elsewhere:[20] fasting glucose, total cholesterol, calcium, phosphate, low-density lipoprotein cholesterol (LDL-C), alkaline phosphatase (ALP), insulin, creatinine, and highly

sensitive C-reactive protein (hs-CRP). eGFR was calculated using the Modification of Diet in Renal Disease study equation.[21] SUA level was measured using the Fossati enzymatic reaction, which employs uricase with a Trinder-like end point (ADVIA 1650 Auto Analyzer, Bayer Diagnostics). Fasting insulin concentrations (μIU/ml) were measured enzymatically using a Hitachi 7600 Automatic Analyzer (Hitachi, Tokyo, Japan). The homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated as the fasting insulin concentration (mU/L) × fasting glucose level (mmol/L)/22.5.

Fat mass (kg) was measured using segmental BIA with eight tactile electrodes according to the manufacturer's instructions (InBody 3.0, Biospace, Seoul, Republic of Korea). The analyzer calculates the tissue and fluid compartments using an imperceptible electrical current passed through the pads placed on one hand and foot, while applying previously validated, empirically derived formulae.[22]

Statistical analysis

Continuous variables are presented as mean ± standard deviation and as medians and interquartile ranges, while categorical variables are presented as numbers and percentages. Fat mass change was defined as the difference in fat mass between the first and last examinations. Based on this change, the study population was categorized into seven groups as follows: increase in fat mass ⩾2.5, 1.5–2.5, and 0.5–1.5 kg; no change (–0.5–0.5 kg); decrease in fat mass ⩾2.5, 1.5–2.5, and 0.5–1.5 kg. According to the categories of fat mass variance, the variables of the study population were compared using the analysis of variance, Kruskal–Wallis H test, and the chi-square test.

Association between fat mass variance and SUA level variability was assessed using the multiple linear regression analysis, in which the change in SUA level (mmol/L) served as the dependent variable and the fat mass variance (seven groups) served as the independent variable, after extensive adjustments for potential confounders. The effect of fat mass variance on achieving the target SUA levels was also investigated using the binary logistic regression analysis, in which two target SUA levels were set and each was separately addressed as a dependent variable: <0.41 mmol/L, the universally acknowledged upper normal limit in men (normouricemia), and <0.35 mmol/L, the widely accepted therapeutic target in patients with gout (therapeutic target level). Of the multivariable regression analyses, model 1 was adjusted for age, education level, daily alcohol consumption, HEPA level, and systolic BP; model 2 for the intake of total energy, total protein, total fat, fiber, calcium, and vitamin C based on the FFQ, in addition to the variables listed in model 1; model 3 included the laboratory results of triglyceride level, hs-CRP level, eGFR, and HOMA-IR in addition to the listed variables of model 2.

Stratified analyses were carried out to compare the effect modification of fat mass variance on target SUA level achievement in the following prespecified subgroups: age (<38.8 years *versus* ⩾38.8 years), alcohol consumption (<20 g of alcohol per day *versus* ⩾20 g of alcohol per day), HEPA (no *versus* yes), BMI (<25 kg/m^2 *versus* ⩾25 kg/m^2), education level (⩽high school graduate *versus* ⩾college graduate), and HOMA-IR (<2.5 *versus* ⩾2.5). Each stratum was analyzed using the full model. Data from 13,585 subjects who repeated the health check up in 2015 and 2016 were also extracted. Interactions between fat mass change and subgroup characteristics were assessed using the likelihood ratio test to compare models with and without product terms. STATA version 16.1 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. A p value of < 0.05 was considered statistically significant.

Results

Characteristics of the study sample

Baseline characteristics of the study sample according to the seven categories of fat mass variance between 2015 and 2017 are shown in Table 1. The mean baseline age and SUA level were 38.8 ± 6.5 years and 0.36 ± 0.07 mmol/L, respectively. Prevalence of hyperuricemia was 25.8%. The mean fat mass and BMI were 18.0 ± 5.8 kg and 24.7 ± 2.9 kg/m^2, respectively. Fat mass change was observed in 79% of subjects (34% decrease, 45% increase). In the group with higher fat mass reduction, the baseline SUA, BMI, systolic BP, LDL-C, and HOMA-IR levels were significantly higher, while the baseline proportion of HEPA was significantly lower. Other than total fat intake, the difference in diet patterns seemed insignificant across the variance of fat mass.

Table 1. Baseline characteristics of the study population according to fat mass change* from 2015 to 2017.

	Overall	Fat mass change							p for trend
		Decrease			No change$	Increase			
		⩾2.5	1.5–2.5	0.5–1.5		0.5–1.5	1.5–2.5	⩾2.5	
Number‡	27,387	2884 (10.5)	2353 (8.6)	4083 (14.9)	5743 (21.0)	4974 (18.2)	3299 (12.0)	4051 (14.8)	
SUA (mmol/L)§	0.36 ± 0.07	0.38 ± 0.07	0.37 ± 0.07	6.0.37 ± 0.07	0.36 ± 0.07	0.36 ± 0.07	0.36 ± 0.07	0.36 ± 0.07	<0.001
Hyperuricemia‡	7075 (25.83)	892 (30.93)	640 (27.2)	1137 (27.85)	1382 (24.06)	1174 (23.6)	782 (23.7)	1068 (26.36)	<0.001
Age (years)§	38.8 ± 6.5	38.9 ± 6.3	39.6 ± 6.5	39.7 ± 6.6	39.4 ± 6.6	39.1 ± 6.5	38.2 ± 6.4	36.5 ± 6.2	<0.001
Fat mass (kg)§	18.0 ± 5.8	21.5 ± 6.2	18.8 ± 5.5	17.9 ± 5.4	17.2 ± 5.4	17.0 ± 5.5	17.2 ± 5.8	17.8 ± 6.0	<0.001
BMI (kg/m²)§	24.7 ± 2.9	26.2 ± 3.0	25 ± 2.7	24.6 ± 2.8	24.3 ± 2.7	24.3 ± 2.8	24.4 ± 3.0	24.8 ± 3.0	<0.001
Obesity‡	11,581 (42.29)	1818 (63.04)	1084 (46.07)	1668 (40.85)	2142 (37.30)	1815 (36.49)	1269 (38.47)	1785 (44.06)	<0.001
SBP (mmHg)§	113.8 ± 10.4	116.4 ± 10.7	114.5 ± 10.4	113.8 ± 10.4	113.4 ± 10.4	113.1 ± 10.2	113 ± 10.4	113.7 ± 10.3	<0.001
HEPA‡	4180 (15.26)	362 (12.55)	322 (13.68)	541 (13.25)	819 (14.26)	757 (15.22)	538 (16.31)	841 (20.76)	<0.001
Calcium (mmol/L)§	2.39 ± 0.07	2.39 ± 0.07	2.39 ± 0.07	2.39 ± 0.07	2.39 ± 0.07	2.39 ± 0.07	2.39 ± 0.07	2.39 ± 0.07	0.805
Phosphorus (mmol/L)§	1.12 ± 0.12	1.12 ± 0. 12	1.12 ± 0. 12	1.12 ± 0. 12	1.12 ± 0.12	1.12 ± 0. 12	1.12 ± 0. 12	1.12 ± 0. 12	<0.001
ALP (U/L)§	61.7 ± 14.3	62.4 ± 14.6	61.6 ± 14	61.6 ± 14	61.6 ± 14.1	61.6 ± 14.1	61.6 ± 14.7	61.4 ± 14.8	0.024
LDL-C (mmol/L)§	3.45 ± 0.8	3.59 ± 0.81	3.51 ± 0.76	3.51 ± 0.81	3.46 ± 0.79	3.42 ± 0.8	3.36 ± 0.8	3.32 ± 0.78	<0.001
eGFR (ml/min/1.73 m²)§∞	98.3 ± 14.8	98.7 ± 15.1	97.3 ± 14.5	97.9 ± 15.2	97.9 ± 14.7	97.8 ± 14.6	98.8 ± 14.6	99.5 ± 14.8	<0.001
hs-CRP (nmol/L)§	4.76 (2.85–9.52)	6.66 (3.80–12.38)	5.71 (2.85–9.52)	4.76 (2.85–9.52)	4.76 (2.85–8.57)	4.76 (2.85–9.52)	4.76 (2.85–9.52)	4.76 (2.85–8.57)	0.011
HOMA-IR (%)§	1.4 (0.9–2.1)	1.7 (1.2–2.5)	1.5 (1–2.2)	1.5 (1–2.2)	1.4 (0.9–2)	1.3 (0.9–2)	1.3 (0.9–2)	1.3 (0.9–1.9)	<0.001
Energy intake (kcal))¶,#	1433.4 (1099.6–1804.1)	1462.1 (1129.8–1854.7)	1447.3 (1118.5–1798.8)	1432.1 (1095.7–1773.9)	1431.1 (1112.3–1802.8)	1417.1 (1086.5–1769)	1440.7 (1105.8–1819.9)	1416.8 (1066.5–1848.4)	0.204
Calcium intake (mg)¶,#	240.5 (151.8–359.7)	246.9 (153–373.8)	240.9 (151.9–358)	236.9 (151.2–354.5)	240.7 (153.9–357.4)	233 (145.9–349.3)	244.5 (155.8–362.4)	246.8 (152–375)	0.154
Vitamin C intake (mg)¶,#	46.1 (25.2–75.8)	46.5 (25.1–75.6)	46.4 (25.6–75.8)	45.5 (25.7–75.9)	46.6 (25.8–76.1)	44.4 (24.3–74.4)	46.4 (25.9–76.2)	46.8 (24.3–76.8)	0.78
Total protein intake (g)¶,#	46.9 (34.3–63.3)	48.4 (35.2–65.4)	47.5 (34.7–64)	45.9 (34.2–61.6)	46.4 (34.3–62.2)	45.8 (33.2–61.5)	47.5 (34.8–64.1)	47.8 (34.2–66)	0.778
Total fat intake (g) ¶,#	27.2 (18–40.4)	28.7 (18.4–42.6)	26.9 (18–41.1)	26.4 (17.8–38.5)	26.7 (17.7–39.3)	26.3 (17.2–38.7)	27.7 (18.6–41.1)	28.9 (18.7–43.4)	0.008
Fiber intake (g)¶,#	2.8 (1.9–4.1)	2.8 (1.9–4.2)	2.9 (1.9–4.2)	2.8 (1.9–4.1)	2.8 (1.9–4.1)	2.8 (1.8–4)	2.8 (1.9–4.1)	2.8 (1.8–4.2)	0.475
Alcohol intake (g) ¶,#	10 (4–23)	10 (4–25)	10 (4–24)	10 (4–24)	10 (4–22)	10 (4–22)	10 (4–21)	10 (4–21)	0.002
Highest level education‡,**	24,303 (88.74)	2585 (89.63)	2124 (90.27)	3619 (88.64)	5069 (88.26)	4393 (88.32)	2905 (88.06)	3608 (89.06)	0.047
Current smoker‡	6904 (25.21)	722 (25.03)	590 (25.07)	1049 (25.69)	1441 (25.09)	1229 (24.71)	842 (25.52)	1031 (25.45)	0.856

*Fat mass change is the difference between fat mass of 2015 and that of 2017.
$No change is the fat mass change between −0.5 and +0.5.
Data are presented as number (percentage)‡. mean ± standard deviation§, or median (interquartile range)¶.
∞eGFR was calculated using the MDRD equation.
#Dietary data were extracted from the FFQs based on daily consumption.
**⩾College graduate.
ALP, alkaline phosphatase; BMI, body mass index; eGFR, estimated glomerular filtration rate; FFQ, food frequency questionnaire; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, highly sensitive C-reactive protein; LDL-C, low- density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; SBP, systolic blood pressure; SUA, serum uric acid.

Odds of achieving target SUA levels according to categories of fat mass changes

The multivariate odds ratios (ORs) of achieving normouricemia (<0.41 mmol/L) or the therapeutic target level (<0.35 mmol/L) per kg fat mass decrease was 1.09 [95% confidence interval (CI) 1.07–1.10] and 1.09 (1.08–1.10), respectively. Compared with those of the reference group (–0.5–0.5 kg), the ORs (95% CI) of achieving normouricemia for fat mass decreases of ⩾2.5, 1.5–2.5, and 0.5–1.5 kg were 1.63 (1.45–1.82), 1.19 (1.06–1.34), and 1.07 (0.97–1.18), respectively, whereas those for fat mass increase were 0.71 (0.64–0.78), 0.87 (0.79–0.97), and 0.95 (0.86–1.04), respectively (Table 2). The multivariate ORs of achieving the therapeutic target level for fat mass decreases of ⩾2.5, 1.5–2.5, and 0.5–1.5 kg were 1.54 (1.39–1.69), 1.13 (1.02–1.25), and 1.00 (0.92–1.09), respectively, while those for fat mass increase were 0.69 (0.63–0.75), 0.85 (0.77–0.93), and 0.90 (0.83–0.97), respectively (Table 2). Fat mass reduction of ⩾2.5 kg increased the odds of achieving the target SUA level by >2-fold in subjects with hyperuricemia at baseline [multivariate ORs, 2.08 (1.74–2.49) for <0.41 mmol/L and 2.31 (1.66–3.23) for <0.35 mmol/L)]. Overall, every 1-kg fat mass reduction was associated with 13% increased odds of achieving normouricemia in subjects with hyperuricemia at baseline (Supplemental Table S1).

Change in SUA levels according to fat mass change

The coefficient of the SUA level changed across the fat mass variance and exhibited a clear dose–response relationship (Figure 1). As shown in Table 3, the corresponding SUA level changes for fat mass decreases of 0.5–1.5, 1.5–2.5, and ⩾2.5 kg were –5.35 [–7.13–(–3.56)], –7.13 [–9.51–(–5.35)], and –15.46 [–17.25–(–13.68)] μmol/L, respectively. The corresponding SUA level changes for a fat mass increase of 0.5–1.5, 1.5–2.5, and ⩾2.5 kg were 3.56 (1.78–5.35), 5.94 (3.56–7.73), and 11.89 (10.11–13.68) μmol/L,respectively. The multivariate SUA level difference per 1-kg fat mass reduction was –3.56 [–4.16–(–2.97)] μmol/L.

Sensitivity analysis

To validate the consistency of our results, we performed a sensitivity analysis for the relationship between fat mass change and SUA levels according to clinically relevant subgroups such as age, alcohol intake, physical activity, obesity, education level, and insulin resistance (Table 4). The impact of fat mass variance to achieve both target SUA levels persisted across the prespecified subgroups. Changes in SUA levels with fat mass showed a similar pattern in both apparently clinically healthy men with high and low BMIs. In addition, we performed the analysis on 13,585 subjects who underwent the same health screening examinations in 2015 and 2016 (Supplemental Table S2). The ORs of achieving normouricemia for fat mass decreases of ⩾2.5, 1.5–2.5, and 0.5–1.5 kg were 1.49 (1.24–1.79), 1.28 (1.08–1.51), and 1.14 (1.00–1.30), respectively. The ORs of achieving the target SUA levels <0.41 and <0.35 mmol/L decreased by 21% and 18%, respectively, when fat mass increased >2.5 kg. The corresponding SUA level changes for a fat mass decrease of 0.5–1.5 kg, 1.5–2.5 kg, and ⩾2.5 kg were –5.94 [–8.32–(–3.56)], –7.13 [–10.11–(–4.16)], and –16.06 [–19.03–(–13.68)] μmol/L, respectively. The multivariate SUA difference per kg fat mass reduction was –2.97 [–3.56–(–2.97)] μmol/L (Supplemental Table S3). The coefficient of SUA level changes along the variance of fat mass showing a clear dose–response relationship (Supplemental Figure S1).

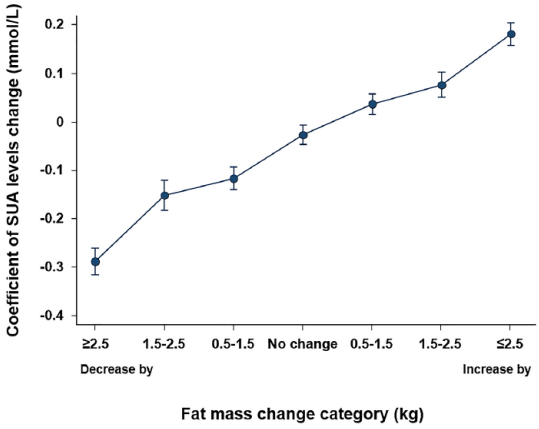

Figure 1. Relationship between fat mass change and SUA variability during the 2-year follow up. The closed dots indicate the beta-coefficients of SUA level change (± standard error), and the line connecting the individual dots highlights the direction and size of the SUA change according to the fat mass change. Each dot is an estimate from the linear regression model representing the adjusted dose–response associations between fat mass change and SUA level variability. SUA, serum uric acid.

Discussion

Our study reconfirmed a significant correlation between fat mass reduction and decreased SUA levels. Furthermore, the novelty of our study is

Table 2. The impact of fat mass* as a predictor for achieving target SUA levels.

Results for the target SUA level <0.41 mmol/L								
Fat mass change (kg)	**SUA level (mmol/L)**		**Model 1**		**Model 2**		**Model 3**	
	⩾0.41	**<0.41**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Fat mass 1 kg decreased			1.07 (1.06–1.08)	<0.001	1.07 (1.06–1.08)	<0.001	1.09 (1.07–1.10)	<0.001
Decrease								
⩾2.5	657 (22.78)	2227 (77.22)	1.57 (1.40–1.75)	<0.001	1.58 (1.41–1.76)	<0.001	1.63 (1.45–1.82)	<0.001
1.5–2.5	552 (23.46)	1801 (76.54)	1.15 (1.03–1.30)	0.016	1.16 (1.03–1.30)	0.014	1.19 (1.06–1.34)	0.004
0.5–1.5	984 (24.1)	3099 (75.9)	1.03 (0.93–1.13)	0.605	1.03 (0.93–1.13)	0.557	1.07 (0.97–1.18)	0.205
No change$ (–0.5–0.5)	1362 (23.72)	4381 (76.28)	1 (reference)		1 (reference)		1 (reference)	
Increase								
0.5–1.5	1217 (24.47)	3757 (75.53)	0.96 (0.88–1.05)	0.391	0.96 (0.88–1.06)	0.427	0.95 (0.86–1.04)	0.266
1.5–2.5	865 (26.22)	2434 (73.78)	0.92 (0.83–1.01)	0.089	0.92 (0.83–1.01)	0.093	0.87 (0.79–0.97)	0.011
⩾2.5	1283 (31.67)	2768 (68.33)	0.79 (0.72–0.87)	<0.001	0.79 (0.72–0.87)	<0.001	0.71 (0.64–0.78)	<0.001
Results for the target SUA level <0.35 mmol/L								
Fat mass change (kg)	**SUA level (mmol/L)**		**Model 1**		**Model 2**		**Model 3**	
	⩾0.35	**<0.35**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
Fat mass 1 kg decreased			1.07 (1.06–1.08)	<0.001	1.07 (1.06–1.08)	<0.001	1.09 (1.08–1.10)	<0.001
Decrease								
⩾2.5	1545 (53.57)	1339 (46.43)	1.51 (1.38–1.66)	<0.001	1.52 (1.38–1.67)	<0.001	1.54 (1.39–1.69)	<0.001
1.5–2.5	1308 (55.59)	1045 (44.41)	1.11 (1.01–1.23)	0.036	1.11 (1.01–1.23)	0.034	1.13 (1.02–1.25)	0.017
0.5–1.5	2322 (56.87)	1761 (43.13)	0.98 (0.90–1.07)	0.649	0.98 (0.90–1.07)	0.677	1.00 (0.92–1.09)	0.980
No change$ (–0.5– 0.5)	3182 (55.41)	2561 (44.59)	1 (reference)		1 (reference)		1 (reference)	
Increase								
0.5–1.5	2862 (57.54)	2112 (42.46)	0.92 (0.85–0.99)	0.028	0.92 (0.85–0.99)	0.030	0.90 (0.83–0.97)	0.009
1.5–2.5	1953 (59.2)	1346 (40.8)	0.89 (0.81–0.97)	0.009	0.89 (0.81–0.97)	0.009	0.85 (0.77–0.93)	<0.001
⩾2.5	2651 (65.44)	1400 (34.56)	0.75 (0.69–0.82)	<0.001	0.76 (0.69–0.82)	<0.001	0.69 (0.63–0.75)	<0.001

Model 1 was adjusted for age, level of education, daily alcohol intake, HEPA, and SBP; model 2 was adjusted for the intake of energy, calcium, vitamin C, total protein, total fat, and fiber based on FFQs in addition to the variables listed in model 1; model 3 was additionally adjusted for LDL-C, hs-CRP, eGFR, and HOMA-IR to the listed variables of model 2.
*The fat mass change is the difference between fat mass of 2015 and that of 2017.
$The category of no change is the fat mass change between –0.5 and +0.5.
CI, confidence interval; eGFR, estimated glomerular filtration; FFQ, food frequency questionnaire; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; SUA, serum uric acid.

that it quantified the amount of fat reduction using BIA specific to the actual fat content to achieve a clinical outcome in an apparently healthy population. This study demonstrated that the greater the reduction in fat mass, the greater the probability of achieving target SUA levels in apparently clinically healthy men. Furthermore, this study may help to predict the likelihood of

Table 3. Relationship between fat mass change* and SUA variability$ according to the categories of fat mass change during 2 years of follow up.

Fat mass change (kg)	Model 1		Model 2		Model 3	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
Fat mass 1 kg decreased	−0.06 (−0.07 to −0.05)	<0.001	−0.06 (−0.07 to −0.05)	<0.001	−0.06 (−0.07 to −0.05)	<0.001
Decrease						
⩾2.5	−0.26 (−0.29 to −0.22)	<0.001	−0.26 (−0.29 to −0.22)	<0.001	−0.26 (−0.29 to −0.23)	<0.001
1.5–2.5	−0.12 (−0.16 to −0.09)	<0.001	−0.12 (−0.16 to −0.09)	<0.001	−0.12 (−0.16 to −0.09)	<0.001
0.5–1.5	−0.09 (−0.12 to −0.06)	<0.001	−0.09 (−0.12 to −0.06)	<0.001	−0.09 (−0.12 to −0.06)	<0.001
No change‡ (−0.5– 0.5)	0 (reference)	–	0 (reference)	–	0 (reference)	0 (reference)
Increase						
0.5–1.5	0.06 (0.03–0.09)	<0.001	0.06 (0.03–0.09)	<0.001	0.06 (0.03–0.09)	<0.001
1.5–2.5	0.10 (0.07–0.13)	<0.001	0.10 (0.07–0.13)	<0.001	0.10 (0.06–0.13)	<0.001
⩾2.5	0.20 (0.17–0.23)	<0.001	0.20 (0.17–0.23)	<0.001	0.20 (0.17–0.23)	<0.001

Model 1 was adjusted for age, level of education, daily alcohol intake, HEPA, and SBP; model 2 was adjusted for the intake of energy, calcium, vitamin C, total protein, total fat, and fiber based on FFQs in addition to the variables listed in model 1; model 3 was additionally adjusted for LDL-C, hs-CRP, eGFR, and HOMA-IR to the listed variables of model 2.
*The fat mass change is the difference between fat mass of 2015 and that of 2017.
$SUA variability was calculated by the SUA level of 2017 subtracted from that of 2015.
‡The category of no change is the fat mass change between −0.5 and +0.5 kg.
CI, confidence interval; eGFR, estimated glomerular filtration rate; FFQ, food frequency questionnaire; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SUA, serum uric acid.

achieving target SUA levels in response to fat mass changes in apparently clinically healthy men. For example, an increase or decrease in fat mass of >2.5 kg was associated with 29% lower or 63% higher odds of achieving normouricemia than the reference. Furthermore, every 1-kg reduction in fat mass increases the chances of achieving normouricemia by 9%. The impact of fat mass change on SUA levels was modest, as every 1-kg reduction correlated to a 0.35 mmol/L decrease in SUA levels. This may be clinically useful in encouraging and counselling a patient with hyperuricemia attempting fat mass or weight reduction. To our knowledge, this is the first report to quantify the concrete impact of fat mass on SUA levels in apparently clinically healthy men.

Hyperuricemia and gout are highly correlated with BMI, and evidence supporting the effects of lowering SUA levels through weight control is available. In some studies, weight loss resulted in a higher chance of achieving a SUA level of <0.35 mmol/L.[2,3,23] Several others investigated the relationship between weight reduction and variance in SUA levels in subjects with high cardiovascular risk.[2,3,14] A small study of 12 patients with diabetes and morbid obesity undergoing bariatric surgery (mean 34.3 kg weight loss over 1 year) demonstrated a mean SUA reduction of 0.12 mmol/L.[14] In addition, the corresponding SUA level change was −0.03 mmol/L for a weight loss of >10 kg among men with a high cardiovascular risk.[3] As a corollary to these studies, the new 2020 gout management guideline has conditionally recommended weight reduction for overweight/obese patients with gout.[24] However, the level of evidence for weight reduction in reducing SUA levels was very low due to the lack of sufficient data.

Obesity or overweight, defined as excessive fat accumulation, is often accompanied by hyperuricemia because adipose tissue can produce uric

Table 4. Effect modification of fat mass change on achieving the target SUA levels by clinically relevant subgroups.

Results for the target SUA level <0.41 mmol/L								
	Fat mass change (kg)							***p* for interaction**
	Increase			**No change* (−0.5–0.5)**	**Decrease**			
	⩾2.5	**1.5–2.5**	**0.5–1.5**		**0.5–1.5**	**1.5–2.5**	**⩾2.5**	
Age, years								0.517
<38.8	0.67 (0.59–0.76)	0.89 (0.78–1.03)	0.95 (0.84–1.09)	1 (reference)	1.05 (0.91–1.21)	1.29 (1.08–1.52)	1.55 (1.32–1.81)	
⩾38.8	0.68 (0.58–0.79)	0.81 (0.7–0.94)	0.93 (0.81–1.06)	1 (reference)	1.08 (0.94–1.24)	1.12 (0.95–1.32)	1.69 (1.43–2.00)	
Alcohol, g/day								0.821
<20	0.68 (0.61–0.77)	0.85 (0.75–0.97)	0.92 (0.82–1.03)	1 (reference)	1.02 (0.91–1.15)	1.22 (1.06–1.42)	1.59 (1.38–1.83)	
⩾20	0.77 (0.65–0.92)	0.93 (0.77–1.12)	1.00 (0.85–1.19)	1 (reference)	1.16 (0.97–1.38)	1.13 (0.92–1.40)	1.72 (1.41–2.1)	
HEPA								0.018
No	0.74 (0.67–0.83)	0.85 (0.76–0.95)	0.93 (0.84–1.02)	1 (reference)	1.08 (0.97–1.20)	1.19 (1.05–1.35)	1.59 (1.41–1.8)	
Yes	0.59 (0.46–0.74)	1.03 (0.79–1.35)	1.10 (0.86–1.41)	1 (reference)	0.97 (0.75–1.27)	1.20 (0.87–1.66)	1.88 (1.36–2.61)	
BMI, kg/m^2								0.218
<25	0.68 (0.60–0.78)	0.85 (0.74–0.99)	0.89 (0.78–1.01)	1 (reference)	0.98 (0.86–1.13)	1.12 (0.94–1.34)	1.36 (1.12–1.65)	
⩾25	0.69 (0.60–0.79)	0.86 (0.74–1.00)	0.99 (0.86–1.13)	1 (reference)	1.12 (0.98–1.29)	1.21 (1.03–1.42)	1.60 (1.39–1.85)	
Education								0.958
⩽High school	0.73 (0.53–0.99)	0.84 (0.61–1.16)	0.95 (0.71–1.27)	1 (reference)	1.03 (0.76–1.41)	1.10 (0.74–1.64)	1.91 (1.31–2.80)	
⩾College graduate	0.71 (0.64–0.79)	0.88 (0.79–0.98)	0.95 (0.86–1.05)	1 (reference)	1.07 (0.96–1.19)	1.21 (1.07–1.37)	1.60 (1.42–1.81)	
HOMA-IR								0.761
<2.5	0.70 (0.63–0.78)	0.86 (0.77–0.97)	0.96 (0.87–1.07)	1 (reference)	1.05 (0.94–1.17)	1.18 (1.03–1.35)	1.65 (1.44–1.89)	
⩾2.5	0.73 (0.58–0.92)	0.91 (0.71–1.16)	0.89 (0.71–1.10)	1 (reference)	1.14 (0.96–1.36)	1.25 (0.97–1.61)	1.54 (1.24–1.93)	

(Continued)

Table 4. (Continued)

Results for the target SUA level <0.35 mmol/L								*p* for interaction
	Fat mass change (kg)							
	Increase			No change* (−0.5 to 0.5)	Decrease			
	⩾2.5	1.5–2.5	0.5–1.5		0.5–1.5	1.5–2.5	⩾2.5	
Age, years								0.696
<38.8	0.69 (0.61–0.77)	0.87 (0.76–0.99)	0.91 (0.81–1.02)	1 (reference)	0.99 (0.87–1.13)	1.18 (1.01–1.37)	1.64 (1.43–1.89)	
⩾38.8	0.62 (0.54–0.71)	0.79 (0.70–0.90)	0.88 (0.79–0.98)	1 (reference)	1.01 (0.9–1.13)	1.11 (0.97–1.27)	1.43 (1.25–1.63)	
Alcohol, g/day								0.919
<20	0.69 (0.62–0.76)	0.86 (0.77–0.96)	0.92 (0.83–1.01)	1 (reference)	1.01 (0.91–1.12)	1.19 (1.05–1.34)	1.59 (1.41–1.78)	
⩾20	0.68 (0.58–0.81)	0.82 (0.69–0.97)	0.85 (0.74–0.99)	1 (reference)	0.97 (0.83–1.14)	1.02 (0.84–1.22)	1.43 (1.21–1.70)	
HEPA								0.029
No	0.72 (0.65–0.79)	0.84 (0.76–0.93)	0.89 (0.82–0.97)	1 (reference)	1.02 (0.93–1.12)	1.16 (1.04–1.30)	1.58 (1.43–1.76)	
Yes	0.56 (0.45–0.69)	0.86 (0.68–1.08)	0.95 (0.77–1.17)	1 (reference)	0.89 (0.71–1.12)	0.97 (0.74–1.27)	1.26 (0.96–1.64)	
BMI, kg/m^2								0.520
<25	0.65 (0.58–0.73)	0.79 (0.71–0.89)	0.88 (0.8–0.97)	1 (reference)	0.96 (0.86–1.07)	1.03 (0.90–1.17)	1.39 (1.20–1.60)	
⩾25	0.70 (0.61–0.81)	0.92 (0.79–1.08)	0.91 (0.79–1.04)	1 (reference)	1.03 (0.90–1.19)	1.22 (1.04–1.43)	1.54 (1.34–1.76)	
Education								0.926
⩽High school	0.60 (0.46–0.79)	0.89 (0.68–1.17)	0.96 (0.75–1.21)	1 (reference)	0.97 (0.75–1.25)	1.03 (0.74–1.42)	1.52 (1.13–2.05)	
⩾College graduate	0.69 (0.63–0.76)	0.84 (0.76–0.92)	0.89 (0.82–0.97)	1 (reference)	1.00 (0.91–1.09)	1.14 (1.03–1.27)	1.53 (1.38–1.70)	
HOMA–IR								0.767
<2.5	0.68 (0.62–0.75)	0.84 (0.76–0.92)	0.91 (0.83–0.99)	1 (reference)	1.01 (0.93–1.11)	1.11 (1.00–1.24)	1.56 (1.4–1.74)	
⩾2.5	0.68 (0.52–0.89)	0.91 (0.70–1.18)	0.85 (0.68–1.07)	1 (reference)	0.9 (0.72–1.13)	1.23 (0.95–1.60)	1.41 (1.12–1.76)	

The multivariable model was adjusted for age, level of education, daily alcohol intake, HEPA, BMI, SBP, the intake of energy, calcium, vitamin C, total protein, total fat, and fiber based on FFQs, LDL-C, hs-CRP, eGFR, total cholesterol, triglyceride, and HOMA-IR.
*The category of no change is the fat mass change between −0.5 kg and +0.5 kg.
BMI, body mass index; eGFR, estimated glomerular filtration; FFQ, food frequency questionnaire; HEPA, health-enhancing physical activity; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, highly sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SUA, serum uric acid.

acid.[3,9–11,25] Several studies reported a strong relationship between high adiposity and hyperuricemia or incident gout;[2,10,12,26] Moreover, excessive android fat deposition has also been associated with increasing SUA levels.[27] Hyperuricemia is closely correlated with the degree of insulin resistance. Insulin resistance and hyperinsulinemia caused by visceral fat obesity have resulted in increased SUA levels through a decreased renal clearance rate of uric acid.[7,8] Furthermore, obese individuals have unusually high leptin levels, which play a role in hyperuricemia.[9,10] Xanthine oxidoreductase, which is responsible for uric acid production, is abundant in adipose tissue, therefore, its enzyme activity increases with fat mass, resulting in an increase in SUA levels.[11,28] Taken together, adiposity is a prominent determinant of hyperuricemia. However, reports with specific data regarding the impact of fat mass variance on SUA levels are limited.

Recently, BIA-based body composition analyzers are being used widely as a well-correlated measurement of body fat relative to lean mass in both Asian and Western populations.[29–31] Given its accuracy in measuring body fat mass, BIA was used for analyses.

In the present study, the impact of fat mass variance over 2–3 years on SUA levels was investigated. Compared with those for the reference, the ORs of fat mass gain and loss of >2.5 kg for achieving normouricemia were 0.71 (95% CI, 0.64–0.78) and 1.63 (1.45–1.82), respectively. A >2.5 kg decrease in fat mass was associated with 54% higher odds of achieving the therapeutic target SUA level than the reference. Considering that a fat mass reduction of ⩾1.5 kg significantly increased the possibility of achieving the target SUA levels, a fat mass reduction of at least 1.5 kg is required to achieve the target SUA level. Furthermore, the corresponding SUA level change for a fat mass decrease of ⩾2.5 kg within 2 years was −15.46 μmol/L. It was found that a 1-kg loss of fat mass over 2 years decreased SUA levels by 3.56 μmol/L. A positive statistical association between fat mass variance and SUA levels was also observed during the 1-year follow up. Participants with hyperuricemia at baseline also reduced their SUA to the target level by 2-fold through a fat mass reduction of ⩾2.5 kg. These findings suggest that the impact of fat mass changes on achieving the target level and changing SUA levels is more modest than expected. In this study, the chances of reaching the target SUA level according to a change of fat mass in the high and low BMI groups were almost the same. In 11 obese patients with gout, a mean weight loss of 5 kg resulted in a mean SUA level reduction of 0.06 mmol/L.[32] In 13 obese patients with gout, a mean weight loss of 7.7 kg resulted in a substantial SUA reduction of 0.1 mmol/L.[23] In the study of 12,379 men with high cardiovascular risk observed over a 7-year period, the effect of weight gain of ⩾10 kg on achieving normouricemia increased by approximately 4-fold.[3] The differences in patient population and the independent variables of body weight or fat mass may have accounted for the fluctuating results between the studies, rendering it impossible to compare directly their effects on SUA levels. However, the impact of fat mass or weight change on SUA levels in both apparently healthy Asian and Western men with high cardiovascular risk is suggested to be much smaller than expected. Nevertheless, the results of these studies have important clinical implications in providing a guide for nonpharmacologic treatments such as weight, BMI, or fat mass reduction, according to the high- or low-risk group of patients with asymptomatic hyperuricemia or gout. Providing this information to patients and physicians may have positive effects on handling SUA levels. Considering that lifestyle aspects such as energy-condensed food and convenient transportation result in morbid obesity, hyperuricemia, and gout, the importance of fat mass or weight reduction in subjects with hyperuricemia should not be overlooked despite the weaker urate-lowering effects.

Several strengths and potential limitations of this study deserve mention. The relationships among hyperuricemia, obesity, and obesity-associated comorbidities such as high BP, hypertriglyceridemia, or impaired fasting glucose, which together comprise metabolic syndrome, are well established.[25] Extensive adjustments for these confounding factors have been made. The specific degree of SUA level change according to fat mass change presented here would not only clinically guide lifestyle modifications for real-life subjects with hyperuricemia but also provide firm evidence for the association between fat mass and SUA level changes.

We acknowledge the limitations of an observational retrospective cohort study. Therefore, mitigations were attempted through extensive adjustments for various confounding factors. The optimal methods for fat mass reduction to maximize the decrease in

SUA level are also an important research topic to be investigated in the future. Second, excess weight gain has been shown to increase the risk of gout among patients with hyperuricemia, and weight loss has been documented to lower gout episodes and SUA levels. Hence, further studies to determine whether alterations in fat mass can actually reduce the incidence of gout and gout flare risks would be of great interest. Third, adiposity is usually determined by anthropometric measures such as BMI and/or waist circumference. BMI and/or waist circumference, which is a rough measure of body fat, does not provide a complete picture of the investigation of the association of SUA level with adiposity and cannot quantify the amount of adipose tissue. BIA may provide the crudest values for body composition compared with dual-energy X-ray absorptiometry and magnetic resonance imaging (MRI), which are recognized as the reference methods for body composition analysis. However, their radiation exposure levels or high costs are constraints on their use in clinical practice. The advent of BIA has easily solved these problems. Body-fat assessment using BIA is much more specific to actual fat content and thus provides a more accurate picture. Furthermore, BIA is inexpensive, portable, simple, safe, and quick to perform.[33,34] For these reasons, we thought that BIA was the most appropriate measure for the investigation of the association of SUA level with adiposity in subjects with asymptomatic hyperuricemia. Fourth, elevated SUA levels are closely associated with visceral fat accumulation. In recent years, the amount of visceral fat, rather than total body fat, has been found to mainly affect the development of metabolic complications caused by obesity. Among obese subjects, those with visceral fat obesity showed higher urate excretion than those with subcutaneous fat obesity.[35] Further studies on the effect of visceral fat mass, which is reliably quantified by MRI or computed tomography scan, on SUA levels will therefore be needed. Fifth, the subjects in this study were highly educated, middle-aged Korean men who regularly attended health screening examinations. Thus, generalization to non-Korean populations with different demographics may be limited. As only a few comparable studies that used such a large amount of data are available, additional research results are needed.

In conclusion, we quantitatively demonstrated that fat mass reduction contributes not only to a reduction in SUA levels, despite modest effects, but also to an increase in the likelihood of achieving normouricemia and target therapeutic SUA levels in apparently clinically healthy men. Our findings may help to provide clear clinical guidance on fat mass alterations to reduce SUA levels in real-life subjects with hyperuricemia.

Acknowledgements

The authors thank the health screening group at Kangbuk Samsung Hospital (Seoul, Republic of Korea) for their efforts during the study.

Author contributions

JKA, MYL, and JWH analyzed the data. JKA and JWH wrote the manuscript. JWH, MK, JHH, E-MK, and H-SC contributed to the discussion and reviewed and edited the manuscript. JKA and JWH conceptualized and designed the study, reviewed and edited the manuscript, and supervised the study. JKA was the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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