폐기능과 요산 수치와의 관련성

김기태[1], 설재웅[2]

[1]을지대학교 대학원 시니어헬스케어학과, [2]을지대학교 보건과학대학 임상병리학과

The Relationship between Pulmonary Function and Serum Uric Acid Level in the Korean Population

Gi Tae Kim[1], Jae Woong Sull[2]

[1]Department of Senior Healthcare, General Graduate School, Eulji University, Seongnam, Korea
[2]Department of Biomedical Laboratory Science, College of Health Science, Eulji University, Seongnam, Korea

Background: Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and the ratio of FEV_1 to FVC (FEV_1/FVC) are considered as the major spirometry parameters. Serum uric acid is associated with increased risk of gout and cardiovascular disease. We analyzed the relationship between pulmonary function and serum uric acid level in the Korean men and women.

Methods: This study was based on the data collected during the 2016 Korea National Health and Nutrition Examination Survey (KNHANES VII-1). A total of 3,411 adults were retrieved from KNHANES VII-1. Among 3,411 adults, 1,500 were men and 1,911 were women.

Results: In this study, a significant negative correlation was observed between serum uric acid level and pulmonary function values only in females. Also, in the male non-smoker group, pulmonary function values were negatively associated with serum uric acid level (FVC %predicted, β=-0.014; FEV1 %predicted, β=-0.015).

Conclusions: In this study, hyperuricemia was associated with the low lung function in males and females. In order to obtain an accurate assessment of the association between hyperuricemia and pulmonary function values, further prospective cohort study in the future is necessary.

Korean J Health Promot 2019;19(4):196-201

Keywords: Uric acid, Lung diseases, Hyperuricemia, Vital capacity, Forced expiratory volume

INTRODUCTION

Forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the ratio of FEV_1 to FVC (FEV_1/FVC) are mainly used as spirometry measurement values.[1] Serum uric acid is the final metabolite of purine and has antioxidative potential. There exist various studies on the effects of pulmonary function on serum uric acid level.[2-4] In a study, higher serum uric acid values were proportional to higher values of pulmonary function.[3] In the Japanese general population, a significant association was observed between female lung function values and serum uric acid values along with a strong correlation between FVC %predicted and FEV1 %predicted.[5] Also, a few studies have demonstrated a close link between gout and hyperuricemia and the criteria for the abnormal values of serum

uric acid have been reported to differ depending on the gender.[6]

Chronic obstructive pulmonary disease (COPD) is affected by various environmental characteristics such as aging, infectious diseases, smoking, etc.[7] Hyperuricemia is the result of interactions of factors such as the genetic and environmental factors.[8] It has been reported that smoking exhibit a significant association with hyperuricemia in Koreans.[9] Smoking and FEV_1 values are identified as inflammatory markers.[10] Smoking leads to a decrease in lung function values.[11]

A recent study reported that uric acid levels were inversely associated with lung function.[5,12] In another Japanese study, the subjects with airflow limitation had higher uric acid levels compared to never-smoking subjects without airflow limitation.[13] However, relevant literature on the relationship between pulmonary function and serum uric acid considering smoking status is sparse in Korea. Thus, the aim of this study was to evaluate the association between pulmonary function and uric acid level with respect to smoking status.

METHODS

1. Study design and participants

This study was based on data collected from the 2016 Korea National Health and Nutrition Examination Survey (KNHANES VII-1). The KNHANES has been conducted since 1998, which is a collection of nationally representative, cross-sectional, population-based health and nutritional surveys. The original data was published on the KCDC website, and the research design and data collection method were approved by the KCDC's Ethics Committee. The participants were interviewed to gather information about sex, year of birth, past history, smoking and drinking, and physical activity. The staff measured the height, weight, waist circumference, and blood pressure of the individuals using standard protocols.[14] One cycle consists of 3 years of rolling samples, and in this study, the recently published survey cycle was analyzed. Pulmonary function tests (PFTs) were performed for the subject ≥40 years of age. Among 8,150 participants, participants <40 years and those who did not undergo spirometry were excluded. Also, participants who lacked data on smoking status were excluded. Thus, data from a total of 3,411 adults were retrieved from KNHANES VII-1. Among 3,411 adults, 1,500 were men and 1,911 were women. All participants voluntarily provided written informed consent.

2. Measurement of variables

The PFTs were performed for subjects aged ≥40 years according to guidelines of the American Thoracic Society/European Respiratory Society using a spirometry system (Vyntus Spiro [CareFusion, San Diego, CA, USA] or Dry rolling seal spirometers Model 2130 [SensorMedics, Yorba Linda, CA, USA]).[15] Spirometry was repeated at least three times to ensure reproducibility and validity and the results were calculated based on the predictive equation for the Korean population.[16] Pulmonary function was assessed based on FEV_1, FVC, and percentage predicted values for FEV_1 and FVC. The weight (kg), height (m), waist circumference (cm), and blood pressure (mmHg) of the participants were measured in the mobile examination center used for KNHANES. Body mass index (BMI) was calculated as kg/m^2. Blood pressure was measured thrice by the examiners and the average of the second and third measurement values was used for further analysis. Uric acid levels were measured via colorimetry determination with the uricase-catalase system (Hitachi automatic analyzer 7600-210; Hitachi Corporation, Tokyo, Japan). Hyperuricemia was defined as an serum uric acid concentration of more than 6 mg/dL in females and 7 mg/dL in males. The participants were classified into three smoking status based on the World Health Organization classification (non-smokers, ex-smokers, and current smokers).

3. Statistical analysis

Statistical analyses were performed using the Statistical software (IBM SPSS 25.0; IBM SPSS Statistics; IBM Corp., New York, NY, USA). The characteristics of the participants were described using means±standard deviation (SD) for continuous variables, and percentages and SD for categorical variables. To compare pulmonary function in the presence of hyperuricemia, the mean values of FVC, FVC %predicted, FEV_1, and FEV_1 %predicted were compared between the groups. Adjustment variables were age, BMI, smoking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), and fasting blood sugar (FBS). We performed simple and multiple linear regression analysis by first adjusting for age and BMI (model 1), then for age, BMI, smoking (model 2), and

lastly for age, BMI, smoking, FBS, SBP, and DBP (model 3). Associations between variables were examined using Pearson's correlation coefficient (r). The Pearson's correlation analysis between FVC, FVC %predicted, FEV$_1$, FEV$_1$ %predicted and uric acid in females was performed. The associations were estimated using odds ratios and 95% confidence intervals. All test P values were two-tailed and $P<0.05$ was considered significant.

Table 1. Characteristics of the study subjects

Variable	Males (n=1,500)	Females (n=1,911)
Age, y	58.3±11.5	58.1±11.1
Body mass index, kg/m^2	24.6±3.0	24.2±3.4
Fasting blood sugar, mg/dL	108.3±27.6	101.9±25.8
Systolic blood pressure, mmHg	123.3±15.6	121.0±17.0
Diastolic blood pressure, mmHg	78.1±10.7	74.9±9.1
Uric acid, mg/dL	5.7±1.3	4.4±1.0
FVC, L	4.1±0.7	2.9±0.6
FEV$_1$, L	3.0±0.7	2.3±0.5
FVC %predicted	88.8±12.3	91.8±12.5
FEV$_1$ %predicted	88.3±13.7	92.6±13.3
Smoking status		
Non-smoker	271 (18.1)	1,759 (92.0)
Ex-smoker	756 (50.4)	59 (3.1)
Current smoker	473 (31.5)	93 (4.9)

Values are presented as mean±standard deviation or number (%).
Abbreviations: FEV$_1$ %predicted, percent predicted forced expiratory volume in the first second; FEV$_1$, forced expiratory volume in the first second; FVC %predicted, percent predicted forced vital capacity; FVC, forced vital capacity.

RESULTS

A total of 1,500 males (44.0%) and 1,911 females (56.0%) were enrolled in our study. Table 1 shows the general characteristics of male and female participants. No big difference was observed in the mean age and BMI of males and females. FBS, SBP, and DBP were high in males. Male participants had higher FVC and FEV$_1$, but female participants had higher FVC %predicted and FEV$_1$ %predicted. Mean uric acid value was higher in males than in females (5.7 mg/dL in men and 4.4 mg/dL in women). Also, more male participants were smokers.

In univariable analysis, the uric acid level was strongly associated with a variety of parameters (Table 2). In females, FVC, FEV$_1$, FVC %predicted, and FEV$_1$ %predicted were significantly associated with serum uric acid levels. But, in males, FVC, FEV$_1$, FVC %predicted, and FEV$_1$ %predicted were not associated with serum uric acid levels (Table 2). In multiple linear regression analysis, FVC, FEV$_1$, FVC %predicted, and FEV$_1$ %predicted values were strongly associated with uric acid only in females (Table 3). Among male non-smoker groups in multivariable analysis, uric acid was associated with the pulmonary function and the results are shown in Table 4.

DISCUSSION

Our study revealed the existence of significant negative correlations between pulmonary function and uric acid levels only in females, which supports findings of previous

Table 2. Association between lung function and serum uric acids based on a simple linear regression model

Characteristic	Males (n=1,500)		Females (n=1,911)	
	β	P	β	P
Age, y	-0.008	0.008	0.014	<0.001
Body mass index, kg/m^2	0.072	<0.001	0.081	<0.001
Systolic blood pressure, mmHg	0.002	0.396	0.007	<0.001
Diastolic blood pressure, mmHg	0.008	0.021	0.008	0.003
Fasting blood sugar, mg/dL	-0.005	<0.001	0.003	0.004
FVC, L	0.063	0.190	-0.284	<0.001
FEV$_1$, L	0.075	0.152	-0.318	<0.001
FVC %predicted	-0.005	0.099	-0.013	<0.001
FEV$_1$ %predicted	-0.003	0.248	-0.005	0.007

Abbreviations: FEV$_1$ %predicted, percent predicted forced expiratory volume in the first second; FEV$_1$, forced expiratory volume in the first second; FVC %predicted, percent predicted forced vital capacity; FVC, forced vital capacity.

studies.[5,17] A study reported statistically significant uric acid levels in female COPD patients.[17] A Japanese study also reported a negative correlation between female lung function values and serum uric acid values.[5] However, a recent Korean study reported positive correlation between pulmo-

nary function and uric acid levels. The mean age of the study subjects was 40 years old.[18] In our study, mean age in the subjects was 58 years old.

The present study also showed the negative association between pulmonary function values and uric acid level in

Table 3. Association between lung function and serum uric acids based on a multiple linear regression model

Characteristic	Males (n=1,500)		Females (n=1,911)	
	β	P	β	P
Model 1				
FVC, L	0.004	0.943	-0.131	0.015
FEV$_1$, L	-0.042	0.552	-0.174	0.010
FVC %predicted	-0.004	0.199	-0.007	0.001
FEV$_1$ %predicted	-0.004	0.131	-0.006	0.001
Model 2				
FVC, L	0.003	0.959	-0.142	0.009
FEV$_1$, L	-0.041	0.572	-0.177	0.008
FVC %predicted	-0.004	0.192	-0.007	<0.001
FEV$_1$ %predicted	-0.004	0.139	-0.006	0.001
Model 3				
FVC, L	-0.012	0.842	-0.154	0.005
FEV$_1$, L	-0.051	0.481	-0.188	0.005
FVC %predicted	-0.005	0.107	-0.007	<0.001
FEV$_1$ %predicted	-0.004	0.098	-0.006	0.001

Model 1 was adjusted for age and BMI. Model 2 was adjusted for age, BMI, and smoking. Model 3 was adjusted like model 2 plus SBP, DBP, and FBS levels.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FEV$_1$ %predicted, percent predicted forced expiratory volume in the first second; FEV$_1$, forced expiratory volume in the first second; FVC %predicted, percent predicted forced vital capacity; FVC, forced vital capacity; SBP, systolic blood pressure.

Table 4. Association between lung function and serum uric acids by male smoking status based on a multiple linear regression model

Characteristic	Non-smoker (n=271)		Ex-smoker (n=756)		Current smoker (n=473)	
	β	P	β	P	β	P
Model 1						
FVC %predicted	-0.014	0.034	-0.006	0.107	0.003	0.546
FEV$_1$ %predicted	-0.013	0.031	-0.067	0.069	0.086	0.065
Model 2						
FVC %predicted	-0.011	0.103	-0.004	0.355	-0.001	0.798
FEV$_1$ %predicted	-0.013	0.038	-0.044	0.251	-0.020	0.691
Model 3						
FVC %predicted	-0.014	0.047	-0.005	0.258	-0.002	0.708
FEV$_1$ %predicted	-0.015	0.013	-0.006	0.069	0.003	0.552

Model 1 was a simple linear regression analysis. Model 2 was adjusted for age and BMI. Model 3 was adjusted like model 2 plus SBP, DBP, and FBS levels.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FBS, fasting blood sugar; FEV$_1$ %predicted, percent predicted forced expiratory volume in the first second; FEV$_1$, forced expiratory volume in the first second; FVC %predicted, percent predicted forced vital capacity; FVC, forced vital capacity; SBP, systolic blood pressure.

the male non-smoker group. The association between lung function and uric acid level was not observed in the male smoking group. In a Japanese study, serum uric acid levels in subjects with airflow limitation were higher than those in the never-smoking subjects with airflow limitation.[13] In our study, we did not analyze the association between lung function and uric acid by female smoking group because of small sample size for current female smokers.

Hyperuricemia can affect the status of diabetes, hypertension, kidney disease, and independently influence mortality. In addition, the prevalence of hyperuricemia is recognized as a public health problem worldwide.[19] Kidney function and serum uric acid level exhibit a significant correlation, hyperuricemia can occur due to an increase in serum uric acid levels under the condition of kidney disorder.[20] The higher uric acid levels have been linked with coronary heart disease (CHD) and there has been an increase in the risk of CHD associated with hyperuricemia.[21] According to the studies conducted in Korea, the prevalence rate of gout has been increasing annually.[22] The prevalence of hyperuricemia can be linked with gout and is considered as a threat to the health of young people.[9] Serum uric acid concentration has been reported to be positively correlated with insulin resistance marker (homeostatic model assessment for insulin resistance) and a higher concentration of serum uric acid is directly correlated with a higher incidence of hypertension. Also, it has been reported that serum uric acid concentration is positively correlated with high sensitivity C-reactive protein (hs-CRP), an inflammatory factor linked with hypertension.[23,24] Serum uric acid levels are sensitive to tissue injury and inflammation and exhibit an increase in a nonspecific way. The COPD patients were reported to have higher CRP values than the control group.[25]

In a study, patients with COPD had higher uric acid levels than the control group.[4] In a study, the uric acid level was higher for patients with severe COPD.[26] In some studies, hyperuricemia in COPD patients was identified as the biomarker of early death.[27] Compared to patients with low serum uric acid levels, patients with high serum uric acid levels had more severe airflow disorders and oxygen supply disorders; the uric acid level was higher in people with cardiovascular comorbidities than those without cardiovascular comorbidities.[28]

In the present study, we did not consider the differences between socio-economic status and lifestyle among the participants nor the data of patients diagnosed with the disease. In addition, participants who were taking uric acid-lowering agents were not identified. The frequency of food intake that could affect uric acid levels was not considered. Consequently, further analyses could not be performed. As this was a cross-sectional study, we were unable to verify the causality between pulmonary function values and differences in clinical outcomes of hyperuricemia. In future studies, it is necessary to investigate the association between the pulmonary function values and the inflammatory factor, and the linkage between uric acid and inflammatory factors.

In conclusion, FVC, FEV_1, FVC %predicted, and FEV_1 %predicted exhibited a significantly negative association with serum uric acid levels only in females. In this study, hyperuricemia was associated with the low lung function in males and females. FVC %predicted and FEV_1 %predicted were significantly negatively associated with serum uric acid levels in male non-smokers. This study suggest that uric acid levels can be a biomarker for the lung function. In order to obtain an accurate assessment of the association between hyperuricemia and pulmonary function values, further prospective cohort study in the future is necessary.

요   약

연구배경: 강제폐활량과 1초간 강제호기량 등은 폐기능의 지표로 측정된다. 또한 요산 수치는 통풍과 심혈관 질환의 위험요인이다. 본 연구에서는 한국인 남성과 여성에서 폐기능과 요산 수치와의 관련성을 분석하였다.

방법: 연구 대상자는 2016년 국민건강영양조사에 참여한 3,411명의 성인이다. 남성 1,500명, 여성 1,911명이 분석에 포함되었다.

결과: 여성에서 폐기능과 요산 수치와의 음의 상관성을 보였다. 남성의 경우에는 비흡연자에서 폐기능과 요산과의 통계학적으로 유의한 음의 상관성이 있었다. 남성에서의 1초간 강제호기량이 낮은 사람은 1초간 강제호기량이 높은 사람들에 비해서 고요산혈증과 유의한 관련성이 있었다. 여성에서도 강제폐활량이 낮은 사람은 강제폐활량이 높은 사람들에 비하여 고요산혈증과 유의한 관련성이 있었다.

결론: 본 연구에서 고요산혈증은 남성과 여성 모두에서 낮은 폐기능과 관련이 있었다. 인과관계를 더 정확히 알기 위해서는 추후 전향적인 코호트 연구가 필요하겠다.

중심 단어: 요산, 폐질환, 고요산혈증, 폐활량, 강제호기량

ORCID

Gi Tae Kim   https://orcid.org/0000-0001-7522-2888
Jae Woong Sull   https://orcid.org/0000-0002-5178-0065

REFERENCES

1. Barreiro TJ, Perillo I. An approach to interpreting spirometry. Am Fam Physician 2004;69(5):107-14.
2. Villegas R, Xiang YB, Cai Q, Fazio S, Linton M, Li H, et al. Prevalence and determinants of hyperuricemia in middle-aged, urban Chinese men. Metab Syndr Relat Disord 2010;8(3):263-70.
3. Nicks ME, O'Brien MM, Bowler RP. Plasma antioxidants are associated with impaired lung function and COPD exacerbations in smokers. COPD 2011;8(4):264-9.
4. Durmus Kocak N, Sasak G, Aka Akturk U, Akgun M, Boga S, Sengul A, et al. Serum uric acid levels and uric acid/creatinine ratios in stable chronic obstructive pulmonary disease (COPD) patients: are these parameters efficient predictors of patients at risk for exacerbation and/or severity of disease? Med Sci Monit 2016;22:4169-76.
5. Aida Y, Shibata Y, Osaka D, Abe S, Inoue S, Fukuzaki K, et al. The relationship between serum uric acid and spirometric values in participants in a health check: the Takahata study. Int J Med Sci 2011;8(6):470-8.
6. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol 2014;26(2):186-91.
7. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007;370(9589):765-73.
8. B L, T W, Hn Z, Ww Y, Hp Y, Cx L, et al. The prevalence of hyperuricemia in China: a meta-analysis. BMC Public Health 2011;11:832.
9. Kim Y, Kang J, Kim GT. Prevalence of hyperuricemia and its associated factors in the general Korean population: an analysis of a population-based nationally representative sample. Clin Rheumatol 2018;37(9):2529-38.
10. Gan WQ, Man SF, Sin DD. The interactions between cigarette smoking and reduced lung function on systemic inflammation. Chest 2005;127(2):558-64.
11. Burchfiel CM, Marcus EB, Curb JD, Maclean CJ, Vollmer WM, Johnson LR, et al. Effects of smoking and smoking cessation on longitudinal decline in pulmonary function. Am J Respir Crit Care Med 1995;151(6):1778-85.
12. Shibata Y, Inoue S, Watanabe M. Impact of reduced pulmonary function in the Japanese general population: lessons from the Yamagata-Takahata study. Respir Investig 2019;57(3):220-6.
13. Fukuhara A, Saito J, Sato S, Saito K, Fukuhara N, Tanino Y, et al. The association between risk of airflow limitation and serum uric acid measured at medical health check-ups. Int J Chron Obstruct Pulmon Dis 2017;12:1213-9.
14. Koran Centers for Disease Control and Prevention (KCDC). Korea National Health and Nutrition Examination Survey (KNHANES) [Internet]. Cheongju: KCDC; 2018. [Accessed Jul 27, 2018]. Available from: https://knhanes.cdc.go.kr/knhanes/main.do.
15. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995;152(3):1107-36.
16. Choi JK, Paek D, Lee JO. Normal predictive values of spirometry in Korean population. Tuberc Respir Dis 2005;58(3):230-42.
17. Sarangi R, Varadhan N, Bahinipati J, Dhinakaran A, Anandaraj, Ravichandran K. Serum uric acid in chronic obstructive pulmonary disease: a hospital based case control study. J Clin Diagn Res 2017;11(9):BC09-13.
18. Song JU, Hwang J, Ahn JK. Serum uric acid is positively associated with pulmonary function in Korean health screening examinees. Mod Rheumatol. 2017;27(6):1057-65.
19. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63(10):3136-41.
20. Marangella M. Uric acid elimination in the urine. Pathophysiological implications. Contrib Nephrol 2005;147: 132-48.
21. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2010; 62(2):170-80.
22. Kim JW, Kwak SG, Lee H, Kim SK, Choe JY, Park SH. Prevalence and incidence of gout in Korea: data from the national health claims database 2007-2015. Rheumatol Int 2017; 37(9):1499-506.
23. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 2005;69(8):928-33.
24. Sung KC, Suh JY, Kim BS, Kang JH, Kim H, Lee MH, et al. High sensitivity C-reactive protein as an independent risk factor for essential hypertension. Am J Hypertens 2003;16(6):429-33.
25. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 2004;59(7):574-80.
26. Garcia-Pachon E, Padilla-Navas I, Shum C. Serum uric acid to creatinine ratio in patients with chronic obstructive pulmonary disease. Lung 2007;185(1):21-4.
27. Zhang X, Liu L, Liang R, Jin S. Hyperuricemia is a biomarker of early mortality in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2015;10:2519-23.
28. Bartziokas K, Papaioannou AI, Loukides S, Papadopoulos A, Haniotou A, Papiris S, et al. Serum uric acid as a predictor of mortality and future exacerbations of COPD. Eur Respir J 2014;43(1):43-53.