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대장선종 발생과 연관된 대사증후군의 위험 표지자로서의 혈청요산: 검진 대장내시경을 받은 한국인을 대상으로 한 연구

김효진[1,*], 김지은[2,*], 정지혜[1], 김은란[1], 홍성노[1], 장동경[1], 손희정[1,2], 이풍렬[1], 김재준[1], 김영호[1]
성균관대학교 의과대학 삼성서울병원 내과학교실[1], 건강의학센터[2]

Uric Acid Is a Risk Indicator for Metabolic Syndrome-related Colorectal Adenoma: Results in a Korean Population Receiving Screening Colonoscopy

Hyo Jin Kim[1,*], Jee Eun Kim[2,*], Ji Hye Jung[1], Eun Ran Kim[1], Sung Noh Hong[1], Dong Kyung Chang[1], Hee Jung Son[1,2], Poong-Lyul Rhee[1], Jae J. Kim[1], and Young-Ho Kim[1]

Department of Internal Medicine[1], Center for Health Promotion[2], Samsung Medical Center, Sungkyunkwan University College of Medicine, Seoul, Korea

Background/Aims: An association between serum uric acid and cancer risk has been noted over the past few decades. There is ongoing debate about whether hyperuricemia represents an independent risk factor for colorectal neoplasm. We investigated the association between serum uric acid and prevalence of colorectal adenoma considering numerous confounding factors.
Methods: A cross-sectional study was performed with individuals who underwent a routine health check-up examination, including a screening colonoscopy and blood chemistry. The association between serum uric acid and prevalence of colorectal adenoma was estimated from the results of a logistic regression analysis.
Results: Of the 1,066 participants, 402 had colorectal adenoma (37.7%). In univariate models, the prevalence of colorectal adenoma was higher in participants in the fourth quartile uric acid level, compared to those in the first quartile uric acid level (OR, 1.67; 95% CI, 1.17-2.42; p=0.004). However, no significant association was detected between serum uric acid and prevalence of colorectal adenoma in multiple logistic regression analysis. A number of metabolic syndrome components exhibited a strong association with the prevalence of colorectal adenoma in the multivariate model (OR, 3.46 for highest *vs.* lowest; 95% CI, 1.30-9.20; p=0.021). Moreover, serum uric acid was strongly associated with metabolic syndrome-associated variables, including waist circumference, fasting blood glucose, systolic blood pressure, diastolic blood pressure, triglyceride, and high-density lipoprotein.
Conclusions: Uric acid is not an independent risk factor for colorectal adenoma but is a risk indicator for metabolic syndrome-related colorectal adenoma. **(Korean J Gastroenterol 2015;66:202-208)**

Key Words: Colorectal neoplasms; Uric acid; Metabolic syndrome X

INTRODUCTION

An association between serum uric acid and cancer risk has been described over the past few decades.[1] It has been proposed that hyperuricemia is a radical scavenger and antioxidant involved in preventing carcinogenesis.[2,3] However, recent studies show that elevated serum uric acid is associated with cancer risk and mortality.[1,4,5] The explanation for

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교신저자: 김영호, 06351, 서울시 강남구 일원로 81, 성균관대학교 의과대학 삼성서울병원 내과학교실
Correspondence to: Young-Ho Kim, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University College of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea. Tel: +82-2-3410-3409, Fax: +82-2-3410-6983, E-mail: younghokim@skku.edu

*These authors contributed equally to this work as co-first authors of the paper.

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the more recent findings is that uric acid has complex pro-inflammatory properties.[1,6] In addition, malignant processes may be independently attributed to hyperuricemia through increased nucleic acid turnover during rapid cell proliferation and death.[7,8] Therefore, the relationship between serum uric acid and cancer risk remains unclear.

Elevated uric acid levels are common in subjects with insulin resistance, obesity, hypertension, diabetes, and hyperlipidemia, the components of metabolic syndrome.[9,10] Several studies describe uric acid as a reliable metabolic syndrome biomarker or a single common factor linking core components of metabolic syndrome.[11,12] Most of the metabolic syndrome components are associated with increased risk of cancer. Moreover, metabolic syndrome is associated with colorectal adenoma[13-15] and colorectal cancer.[16,17] Thus, this syndrome may be responsible for the observed associations between uric acid and cancer risk.

Whether hyperuricemia represents an independent risk factor for colorectal neoplasm is unclear, as the association is confounded by risk factors including metabolic syndrome, and has never been assessed while correcting for the confounding. Thus, we hypothesized that serum uric acid is strongly associated with colorectal adenoma. In this study, we evaluated the association between serum uric acid and the prevalence of colorectal adenoma in participants undergoing screening colonoscopy, while considering potentially confounding risk factors.

SUBJECTS AND METHODS

1. Subjects

The study population was comprised of 1,066 consecutive men and women who underwent a routine health check-up examination including a screening colonoscopy and blood chemistry at the Center for Health Promotion of the Samsung Medical Center (Seoul, Korea) from January 2011 to December 2011. Subjects were excluded for a prior history of flexible sigmoidoscopy or colonoscopy within the past 10 years,[18] and those with incomplete colonoscopy results. This study protocol was approved by the institutional review board at Samsung Medical Center (IRB file number: 2013-07-042).

2. Endpoint

The primary endpoint was the prevalence of colorectal adenoma. Participants with non-advanced or advanced adenoma were included in the adenoma group. Advanced adenoma was defined as adenoma with a diameter $\geq$10 mm, with a villous component, or with high-grade dysplasia.[19]

3. Screening colonoscopies and diagnosis of colorectal adenoma

All colonoscopies were performed by board-certified gastroenterologists who were blinded to the research design. A colonoscopy was considered complete if the cecum was visualized with adequate pre-procedural bowel preparation. All specimens were diagnosed from histological examinations by pathologists.

4. Clinical and laboratory assessments

A self-administrated health questionnaire and a detailed physical examination were routinely completed as part of the screening program. Personal history included questions on smoking, alcohol consumption, family history of colon cancer, history of medication use, and history of colonoscopy.

We measured height, weight, and blood pressure (BP). BMI was calculated by dividing measured weight (kg) by height squared (m^2). Waist circumference was measured at the midpoint between the inferior margin of the last rib and the superior iliac crest in a horizontal plane. Serum uric acid, fasting blood glucose (FBS), total cholesterol (TC), triglyceride (TG), LDL, and HDL were routinely assessed.

Metabolic syndrome was evaluated as defined by the National Cholesterol Education Program Adult Treatment Panel III[20] and was diagnosed when three or more of the following criteria were met: (1) Waist circumference in Asian men $\geq$90 cm and in Asian women $\geq$80 cm; (2) TG $\geq$150 mg/dL, or on drug treatment for elevated TG; (3) HDL $<$40 mg/dL in males and $<$50 mg/dL in females or on drug treatment for reduced HDL; (4) BP $\geq$130/85 mmHg or on drug treatment for hypertension; and (5) FBS $\geq$110 mg/dL or on drug treatment for elevated glucose.

5. Statistical analysis

The association between potential risk factors and colorectal adenoma was assessed using binary logistic regression analysis. OR and 95% CI were estimated to compare the three highest quartiles of risk factors to the first quartile. Four categories were used for systolic blood pressure (SBP) ($<$120,

120-130, 130-140, and ≥140 mmHg) and for diastolic blood pressure (DBP) (<70, 70-80, 80-90, and ≥90 mmHg). Height, BMI, waist circumference, uric acid, FBS, TC, TG, LDL, and HDL were grouped into quartiles. Metabolic syndrome was examined by creating four categories by clusters of five components (c1, 2, 3, and ≥4 of 5 components). Multivariate analysis was performed using logistic regression. The OR and 95% CI were calculated for each potential risk factor. The factors selected for evaluation in multivariate models included age, sex, smoking, drinking, height, SBP, DBP, BMI, waist circumference, uric acid, FBS, TC, TG, LDL, and HDL.

Two-sided null hypotheses of no difference were rejected if p-values were less than 0.05, or, equivalently, if the 95% CIs of risk point estimates excluded 1. Statistical analyses were performed using IBM SPSS Statistics for Windows release 20.0 software (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline characteristics of the study subjects

The baseline characteristics of the 1,066 participants are shown in Table 1. The mean (SD) age was 51.2 (1.4) years, and 67.7% were male. The proportions of current smokers and current drinkers were 26.9% and 72.5%, respectively. Among all patients, 402 had colorectal adenoma (37.7%), including 371 (34.8%) with non-advanced adenoma and 31 (2.9%) with advanced adenoma. The mean (SD) serum uric acid level was 5.4 (1.4) mg/dL.

2. Potential risk factors for colorectal adenoma

The prevalence of colorectal adenoma in crude models was significantly higher among older participants, males, current smokers, current drinkers, those with metabolic syndrome, taller subjects, and those with higher BMI, waist circumference, SBP, DBP, uric acid, FBS, TC, and TG levels (Table 2). A dose-response analysis revealed that the risk of colorectal adenoma increased by 18% for 1 mg/dL of serum uric acid level. The prevalence of colorectal adenoma was higher for patients in the fourth uric acid quartile, compared to those in the first uric acid quartile after adjusting for age. Male sex, current smoking, current drinking, DBP, height, BMI, waist circumference, TC, and TG were significantly associated with a higher prevalence of colorectal adenoma (Table 2). When patients were categorized by the number of metabolic syndrome components, a dose-response relationship was found with colorectal adenoma. In addition, serum uric acid was associated with metabolic syndrome-associated risk factors, such as BMI, waist circumference, SBP, DBP, FBS, TG, TC, and HDL. Serum uric acid level was most highly associated with BMI and waist circumference (Table 3).

Table 1. Baseline Characteristics of the Study Subjects

Characteristic	Overall (n=1,066)	Normal (n=664)	Adenoma (n=402)
Age (yr)	51.2±1.4	50.4±5.9	52.6±6.5
Male	722 (67.7)	411 (61.9)	311 (77.4)
Current smoker	287 (26.9)	161 (24.2)	126 (31.3)
Current drinker	773 (72.5)	465 (70.0)	308 (76.6)
Family history of colon cancer	13 (1.2)	9 (1.4)	4 (1.0)
Height (cm)	166.7±7.1	166.0±7.3	167.7±6.5
BMI (kg/m^2)	23.7±2.2	23.5±2.2	24.0±2.1
Waist circumference (cm)	84.7±7.4	83.9±7.4	52.6±6.5
SBP (mmHg)	121.6±16.9	120.4±16.2	123.7±17.6
DBP (mmHg)	78.2±11.4	77.2±11.3	79.7±11.5
Uric acid (mg/dL)	5.4±1.4	5.2±1.3	5.5±1.4
FBS (mg/dL)	95.4±16.4	94.0±14.4	97.8±19.0
Total cholesterol (mg/dL)	200.6±34.9	198.3±33.5	204.5±36.8
Triglyceride (mg/dL)	119.4±75.4	112.4±67.8	130.9±85.2
LDL (mg/dL)	128.4±32.5	126.2±31.0	131.9±34.6
HDL (mg/dL)	55.0±14.7	55.7±14.8	53.9±14.4
Prevalence of metabolic syndrome	119 (11.2)	55 (8.3)	64 (15.9)

Values are presented as mean±SD or n (%).
SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose.

Table 2. OR and 95% CI for Colorectal Adenoma by Potential Risk Factors

Risk factor	Categories				p-value
Sex	Female		Male		
Crude OR (95% CI)	1.00		2.10 (1.59-2.79)		<0.001
Age adjusted OR (95% CI)	1.00		2.16 (1.62-2.87)		<0.001
Smoking	Never or ex-smoker		Current smoker		
Crude OR (95% CI)	1.00		1.43 (1.08-1.88)		0.012
Age adjusted OR (95% CI)	1.00		1.64 (1.24-2.18)		0.001
Drinking	No-drinking		Current drinking		
Crude OR (95% CI)	1.00		1.40 (1.01-1.86)		0.02
Age adjusted OR (95% CI)	1.00		1.55 (1.16-2.08)		0.003
Metabolic syndrome components	≤1 of 5	2 of 5	3 of 5	≥4 of 5	
Crude OR (95% CI)	1.00	1.32 (1.26-2.96)	1.93 (1.26-2.96)	4.84 (1.85-12.62)	<0.001
Age adjusted OR (95% CI)	1.00	1.23 (0.90-1.67)	1.82 (1.18-2.80)	4.27 (1.62-11.27)	0.001
SBP (mmHg)	<120	120-130	130-140	>140	
Crude OR (95% CI)	1.00	1.00 (0.72-1.38)	1.55 (1.08-2.22)	1.67 (1.17-2.39)	0.006
Age adjusted OR (95% CI)	1.00	0.95 (0.68-1.33)	1.42 (0.98-2.04)	1.40 (0.97-2.03)	0.082
DBP (mmHg)	<70	70-80	80-90	>90	
Crude OR (95% CI)	1.00	1.23 (0.86-1.75)	1.33 (0.93-1.89)	2.06 (1.36-3.12)	0.006
Age adjusted OR (95% CI)	1.00	1.26 (0.88-1.80)	1.27 (0.89-1.82)	1.98 (1.31-3.01)	0.014
	Quartiles				
	Q1	Q2	Q3	Q4	
Height (cm)					
Mean	156.5	164.4	169.5	174.7	
Crude OR (95% CI)	1.00	1.36 (0.94-1.98)	2.11 (1.46-3.05)	1.81 (1.26-2.59)	<0.001
Age adjusted OR (95% CI)	1.00	1.40 (0.96-2.05)	2.36 (1.62-3.44)	2.20 (1.52-3.20)	<0.001
BMI (kg/m^2)					
Mean	18.2	21.5	23.9	26.3	
Crude OR (95% CI)	1.00	0.91 (0.16-5.03)	1.28 (0.23-7.07)	1.59 (0.29-8.80)	0.006
Age adjusted OR (95% CI)	1.00	0.67 (0.12-3.83)	0.91 (0.16-5.19)	1.16 (0.20-6.64)	0.009
Waist circumference (cm)					
Mean	74.6	82.1	86.5	92.8	
Crude OR (95% CI)	1.00	1.41 (0.97-2.05)	1.93 (1.31-2.83)	1.87 (1.31-2.68)	0.002
Age adjusted OR (95% CI)	1.00	1.35 (0.92-1.97)	1.81 (1.23-2.67)	1.69 (1.17-2.43)	0.010
Uric acid (mg/dL)					
Mean	3.6	4.8	5.8	7.2	
Crude OR (95% CI)	1.00	1.20 (0.83-1.74)	1.75 (1.23-2.47)	1.67 (1.17-2.42)	0.004
Age adjusted OR (95% CI)	1.00	1.23 (0.84-1.79)	1.77 (1.24-2.52)	1.81 (1.25-2.62)	0.002
FBS (mg/dL)					
Mean	80.5	88.5	95.1	113.6	
Crude OR (95% CI)	1.00	0.95 (0.66-1.38)	1.13 (0.78-1.63)	1.59 (1.12-2.26)	0.013
Age adjusted OR (95% CI)	1.00	0.92 (0.63-1.35)	1.05 (0.72-1.52)	1.36 (0.95-1.96)	0.134
Total cholesterol (mg/dL)					
Mean	157.5	188.0	209.9	245.5	
Crude OR (95% CI)	1.00	1.40 (0.98-2.01)	1.14 (0.79-1.63)	1.68 (1.18-2.40)	0.02
Age adjusted OR (95% CI)	1.00	1.38 (0.96-1.98)	1.12 (0.77-1.62)	1.67 (1.16-2.39)	0.026
Triglyceride (mg/dL)					
Mean	55.6	84.4	120.4	214.6	
Crude OR (95% CI)	1.00	1.09 (0.75-1.58)	1.75 (1.23-2.51)	2.05 (1.43-2.94)	<0.001
Age adjusted OR (95% CI)	1.00	1.04 (0.72-1.52)	1.62 (1.13-2.33)	2.01 (1.39-2.89)	<0.001
LDL (mg/dL)					
Mean	88.2	116.9	136.9	170.5	
Crude OR (95% CI)	1.00	0.96 (0.67-1.37)	1.01 (0.71-1.44)	1.40 (0.99-1.98)	0.118
Age adjusted OR (95% CI)	1.00	0.96 (0.67-1.38)	0.97 (0.68-1.40)	1.41 (0.99-2.00)	0.100
HDL (mg/dL)					
Mean	37.8	47.9	57.5	74.8	
Crude OR (95% CI)	1.00	0.85 (0.60-1.20)	0.73 (0.51-1.04)	0.63 (0.44-0.90)	0.065
Age adjusted OR (95% CI)	1.00	0.83 (0.58-1.19)	0.71 (0.50-1.02)	0.18 (0.45-0.93)	0.092

SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose.

Table 3. Correlation Coefficients for Baseline Metabolic Syndrome-related Risk Factors with Serum Uric Acid

	BMI (kg/m^2)	Waist circumference (cm)	SBP (mmHg)	DBP (mmHg)	FBS (mg/dL)	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)
Uric acid (mg/dL)	0.436***	0.425***	0.156***	0.294***	0.103**	0.063*	0.299***	−0.351***

SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood glucose; TC, total cholesterol; TG, triglyceride.
*p<0.05, **p<0.01, ***p<0.001.

Table 4. Multivariate Adjusted OR and 95% CI for Colorectal Adenoma

Risk factor	Categories				p-value
Model 1					
Triglyceride	Q1	Q2	Q3	Q4	
Adjusted OR (95% CI)	1.00	0.91 (0.62-1.34)	1.29 (0.88-1.89)	1.55 (1.06-2.28)	0.02
Model 2					
Total cholesterol	Q1	Q2	Q3	Q4	
Adjusted OR (95% CI)	1.00	1.34 (0.93-1.94)	1.11 (0.76-1.62)	1.65 (1.15-2.39)	0.036
Metabolic syndrome components	≥1 of 5	2 of 5	3 of 5	≤4 of 5	
Adjusted OR (95% CI)	1.00	1.09 (0.79-1.50)	1.58 (1.02-2.45)	3.46 (1.30-9.20)	0.021

Model 1 adjusted for age (continuous), sex, smoking, drinking, and quartiles of height, systolic blood pressure, diastolic blood pressure, BMI, waist circumference, uric acid, fasting blood glucose, total cholesterol (TC), triglyceride, LDL, and HDL.
Model 2 adjusted for age (continuous), sex, smoking, drinking, and quartiles of height, BMI, uric acid, TC, LDL, and the number of metabolic syndrome components.

3. Multivariate analysis of covariate factors for colorectal adenoma

Results from the multivariate models, adjusting for age, sex, smoking, drinking, and quartiles of height, SBP, DBP, BMI, waist circumference, uric acid, FBS, TC, TG, LDL, and HDL, are summarized in Table 4 (model 1). The relationship between TG and risk of colorectal adenoma was not confounded by other factors (OR, 1.55 for Q4 *vs.* Q1; 95% CI, 1.06-2.28; p=0.02). The multivariate model adjusted for age (continuous), sex, smoking, drinking, and quartiles of height, BMI, uric acid, TC, LDL, and the number of metabolic syndrome components are shown in Table 4 (model 2). The number of metabolic syndrome components exhibited a graded increase in OR for adenoma prevalence (OR, 3.46 for highest *vs.* lowest; 95% CI, 1.30-9.20; p=0.021), and participants with higher levels of TC were more likely to have colorectal adenoma (OR, 1.65 for Q4 *vs.* Q1; 95% CI, 1.15-2.39; p=0.036). Serum uric acid did not influence the prevalence of colorectal adenoma in the multiple logistic regression analysis.

DISCUSSION

Several studies have examined the relationship between serum uric acid and risk of colorectal cancer or colorectal cancer mortality.[4,5,21-24] These results were contrary to the hypothesized antioxidant and protective effects of serum uric acid against cancer, and supported serum uric acid level as a risk factor for cancer incidence and mortality.[2,25] Overall, consistent available evidence is insufficient to evaluate the risk of colorectal cancer among individuals with increased levels of serum uric acid.

In this study, higher levels of serum uric acid seemed to be associated with an increased prevalence of colorectal adenoma, with the risk nearly 1.7-fold higher in the highest quartile compared to the lowest quartile in univariate models. However, this association did not persist after adjusting for confounding variables, including age, sex, smoking, alcohol consumption, waist circumference, BMI, FBS, BP, and lipid parameters. Our results are consistent with previous findings that the number of metabolic syndrome components and elevated levels of TG and TC are independently associated with an increased prevalence of colorectal adenoma.[15,17]

Systemic inflammation, insulin resistance, and oxidative stress are suspected metabolic syndrome mechanisms for colorectal neoplasm. Among them, inflammation is an important pathophysiological factor that causes colorectal adenoma. It is postulated that circulating inflammatory cytokines, such as tumor necrosis factor-α and interleukin-6, induce metabolic derangement and are associated with colorectal adenoma.[13,15]

Furthermore, uric acid is involved in the metabolic pathway via the inflammatory response. High levels of serum uric acid may contribute in metabolic syndrome.[26-28] Uric acid is a reliable metabolic syndrome biomarker in young obese women, and has been identified as a single common factor linking core metabolic syndrome components.[11,12] In the present study, serum uric acid was significantly associated with metabolic syndrome-associated risk factors, such as BMI, waist circumference, SBP, DBP, FBS, TC, TG, and HDL. Similarly, a prospective study conducted by Colangelo et al.[23] reported strong associations between serum uric acid and plasma glucose, BMI, and BP. In another cross-sectional study, uric acid was associated with the majority of metabolic syndrome components.[29] Matsuura et al.[30] found that increased uric acid levels are closely related to obesity and body fat distribution. Similar results were reported in a study of male Japanese subjects.[31]

Although these reports described an association between serum uric acid and risk of colorectal cancer, the findings were not thoroughly adjusted for metabolic syndrome components or certain traditional risk factors. The risk of cancer mortality by uric acid level was assessed in a prospective cohort of Austrian women after adjusting solely for BMI among metabolic syndrome-related risks.[4] A large male cohort study reported an increased rate of cancer mortality with increasing uric acid level, but the study did not consider metabolic syndrome components, such as waist circumference, FBS, TG, or HDL.[5] However, we adjusted for confounding factors, including metabolic syndrome, to find a relationship among uric acid, metabolic syndrome, and colorectal adenoma. As a result, subjects with high uric acid levels are expected to have a higher frequency of colorectal adenoma than subjects with low uric acid levels. We also found a close relationship between uric acid and the number of metabolic syndrome components. Therefore, increased uric acid may not be an independent risk factor for colorectal cancer but is a proxy risk indicator for metabolic syndrome-related colorectal adenoma.

Our study was limited by its small sample size of 1,066 individuals, and only 402 participants had colorectal adenoma, rendering the conclusions tentative. This was a single center cross-sectional study; therefore, the results do not reflect repeated measures of uric acid and was restricted to a specific Korean population. Another limitation was that other factors influencing serum uric acid were not analyzed, such as kidney function, antihypertensive or other drugs, and a low salt/fat diet.

In summary, this study remedied the short comings of previous studies that did not consider metabolic syndrome-related risk factors and revealed that serum uric acid level is not an independent risk factor for colorectal adenoma. Additionally, a higher level of serum uric acid is observed to be a risk indicator for metabolic syndrome-related colorectal adenoma.

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