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Increased prevalence of periodontitis with hypouricemic status: findings from the Korean National Health and Nutrition Examination Survey, 2016–2018

Ji-Young Joo [1,2,†], **Hae Ryoun Park** [2,3,†], **Youngseuk Cho** [4], **Yunhwan Noh** [4], **Chang Hun Lee** [5], **Seung-Geun Lee** [6,*]

[1]Department of Periodontology, Dental Research Institute, Pusan National University Dental Hospital, Yangsan, Korea
[2]Periodontal Disease Signaling Network Research Center, Dental and Life Science Institute, Pusan National University School of Dentistry, Yangsan, Korea
[3]Department of Oral Pathology, Pusan National University School of Dentistry, Yangsan, Korea
[4]Department of Statistics, Pusan National University College of Natural Sciences, Busan, Korea
[5]Department of Pathology, Pusan National University School of Medicine, Busan, Korea
[6]Department of Internal Medicine, Pusan National University School of Medicine and Pusan National University Hospital, Busan, Korea

ABSTRACT

Purpose: The aim of this study was to investigate the relationship between serum uric acid (SUA) levels and the risk of periodontitis in Korean adults using data from the Korean National Health and Nutrition Examination Survey (KNHANES).
Methods: This cross-sectional study used data from the KNHANES 2016–2018 and analysed 12,735 Korean adults aged ≥19 years who underwent oral examinations. Hypouricemia was defined as SUA <3 mg/dL in men and <2 mg/dL in women, and hyperuricemia was defined as SUA ≥7 mg/dL in men and ≥6 mg/dL in women.
Results: The weighted prevalence of hypouricemia and hyperuricemia was 0.6% and 12.9%, respectively. The overall weighted periodontitis rate was 30.5%. The frequency of periodontitis in subjects with hypouricemia, normouricemia, and hyperuricemia were 51.1%, 30.3%, and 30.6%, respectively. Study participants with hypouricemia were significantly older, had significantly fasting blood glucose levels, and had better kidney function than non-hypouricemic participants. In univariate logistic regression analyses, hypouricemia was associated with periodontitis, but hyperuricemia was not. The fully adjusted model revealed that the adjusted odds ratio of hypouricemia for periodontitis was 1.62 (95% confidence interval, 1.13–2.33), while the relationship between hyperuricemia and periodontitis in the multivariable logistic regression model was not significant.
Conclusions: The results of this study suggest that hypouricemia is associated with an increased risk of periodontitis.

Keywords: Health survey; Inflammation; Korea; Oxidative stress; Periodontitis; Uric acid

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***Correspondence:**
Seung-Geun Lee
Division of Rheumatology, Department of Internal Medicine, Pusan National University School of Medicine and Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, Korea.
Email: sglee@pusan.ac.kr
Tel: +82-51-240-7580
Fax: +82-51-241-7580

[†]Ji-Young Joo and Hae Ryoun Park contributed equally to this work.

ORCID iDs
Ji-Young Joo
https://orcid.org/0000-0002-4050-5797
Hae Ryoun Park
https://orcid.org/0000-0003-1908-0824
Youngseuk Cho
https://orcid.org/0000-0002-8403-4894
Yunhwan Noh
https://orcid.org/0000-0002-0504-0445
Chang Hun Lee
https://orcid.org/0000-0003-4216-2836
Seung-Geun Lee
https://orcid.org/0000-0002-5205-3978

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Ji-Young Joo, Hae Ryoun Park, Seung-Geun Lee; Data curation: Seung-Geun Lee, Yunhwan Noh; Formal analysis: Hae-Ryoun Park, Youngseuk Cho, Chang Hun Lee; Funding acquisition: Hae Ryoun Park; Investigation: Yunhwan Noh; Methodology: Ji-Young Joo, Youngseuk Cho, Seung-Geun Lee, Chang Hun Lee; Writing original draft: Ji-Young Joo, Yunhwan Noh, Seung-Geun Lee; Writing review & editing: Hae Ryoun Park, Youngseuk Cho, Chang Hun Lee, Seung-Geun Lee.

INTRODUCTION

Periodontitis is an inflammatory disease of the gums caused by the stimulation of the innate immune system and the production of inflammatory cytokines due to the presence of plaque bacteria. Although bacterial plaque is the causative factor, host susceptibility and immune response mainly determine the severity of periodontal destruction [1]. Host susceptibility to periodontitis appears to be determined by multiple factors, including age; genetic, epigenetic, and environmental factors (such as smoking, stress, and diet); and systemic diseases (such as diabetes mellitus [DM]) that may have protective or destructive effects on the host response [2]. The onset, progression, and disease severity of periodontitis have been reported to be higher in patients with systemic diseases, such as cardiovascular events and uncontrolled DM [3]. Controlling patients' systemic condition in addition to conventional periodontal therapy has been suggested as a way to improve responses to periodontal treatment [4,5].

In recent years, an increasing body of evidence has pointed to the role of oxidative stress in the environment, including lipid peroxidation and total antioxidant status, in the pathogenesis of periodontitis [6]. Increased oxidative stress could lead to pathological changes and, consequently, the destruction of host tissues; thus, the use of antioxidants that increase antioxidant activity in the host has been proposed as a potential novel therapeutic approach for managing periodontitis [7]. Therefore, to effectively manage periodontitis, it is important to identify patient risk factors or systemic diseases that can increase oxidative stress.

Uric acid (UA) is a heterocyclic organic compound and the end product of purine metabolism in humans. Serum uric acid (SUA) levels above or below the normal range are associated with various diseases. In a hyperuricemic state, UA can be crystallised and deposited as monosodium urate in the joints and adjacent tissues, which can cause inflammatory arthritis—that is, gout [8]. UA has potent antioxidant and scavenger activities against free radicals at a physiologic level, but it can also exhibit proinflammatory and pro-oxidant properties at a higher level [9]. Hence, epidemiological studies have reported that hyperuricemia is associated with diseases in which inflammation and oxidative stress play an important role in pathogenesis, such as metabolic syndrome, cardiovascular diseases, and chronic kidney disease [10,11]. However, relatively little is known about the clinical impact and biological relevance of hypouricemia, although it has been reportedly associated with an increased risk of cognitive dysfunction, osteoporosis, type 2 DM and malnutrition [12]. Considering the role of UA in the process of inflammation and oxidative stress, there may be an interplay between SUA levels and the development of periodontitis. *In vivo* experiments have investigated the relationship between periodontitis and UA levels outside the normal range, but there have been few clinical studies on patients and few large-scale studies [13-15]. This study investigated the association of hyperuricemia or hypouricemia with periodontitis in Korean adults using data from the Korean National Health and Nutrition Examination Survey (KNHANES).

MATERIALS AND METHODS

Study design and subjects

Data obtained from the seventh wave (2016–2018) of the KNHANES conducted by the Korea Disease Control and Prevention Agency (KDCA) were analysed in this study. The KNHANES is a triennial, nationwide, cross-sectional survey of the demographic, social, health, and

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nutritional status of non-institutionalised civilians in Korea, and it has been conducted since 1998 [16]. The KNHANES collects data regarding socioeconomic status, health-related behaviours, quality of life, anthropometric measures, biochemical profiles using fasting blood and urine, measures of dental health, and dietary intake through health interviews, health examinations, and nutrition surveys [16]. To establish a nationwide representative population, the KNHANES applied a 2-stage stratified cluster sampling method. Subjects aged ≥19 years were eligible for analysis (n=12,735).

Ethics approval statement

The KNHANES was performed according to the Declaration of Helsinki, and all participants provided informed consent. The study was approved by the Institutional Review Board (IRB) of Pusan National University Dental Hospital (IRB No. PNUDH-2020-030).

Data collection and study variables

The following demographic, anthropometric, and biochemical variables were obtained from the seventh wave of the KNHANES: age, residence, occupation, household income, education level, high-risk drinking, smoking status, physical activity, waist circumference, underlying diseases such as hypertension (HTN), DM and dyslipidaemia, body mass index (BMI), systolic blood pressure, diastolic blood pressure (DBP), fasting blood glucose level, haemoglobin A1c (HbA1c), total cholesterol, estimated glomerular filtration rate (eGFR), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), haemoglobin, high-sensitivity C-reactive protein (hs-CRP), SUA levels, and oral health status, including the frequency of dental visits, tooth brushing, dental floss use, interdental brush use, mouthwash and electric toothbrush use, the number of remaining teeth, permanent teeth with caries, and the presence of periodontitis. High-risk drinking was defined as consuming ≥7 drinks of alcohol per day for men and ≥5 drinks of alcohol per day for women more than twice a week [17]. Physical activity was defined as moderate exercise for ≥30 minutes or vigorous exercise for ≥20 minutes throughout the week according to the World Health Organisation (WHO) recommendations. The eGFR was calculated using the Modification of Diet in Renal Disease formula as follows: $eGFR=186\times(\text{serum creatinine})^{-1.154}\times(\text{age})^{-0.203}\times0.742$ (if female) [18]. Normouricemia was defined as SUA levels ≥3 mg/dL and <7 mg/dL for men and SUA levels ≥2 mg/dL and <6 mg/dL for women. Hypouricemia was defined as SUA levels <3 mg/dL for men and SUA levels <2 mg/dL for women, and hyperuricemia was defined as SUA levels ≥7 mg/dL for men and SUA levels ≥6 mg/dL for women [19,20]. Study participants were categorised as having hypouricemia, normouricemia, and hyperuricemia according to their SUA levels.

The WHO Community Periodontal Index (CPI) was used to assess periodontal status. The codes and criteria for CPI scoring were as follows: normal (CPI=0), gingival bleeding present (CPI=1), calculus felt during probing (CPI=2), a periodontal pocket of 4–5 mm (CPI=3), and a pocket of >6 mm (CPI=4). Periodontitis was defined as a CPI value of 3 or 4. The examined teeth were 11, 16, 17, 26, 27, 31, 36, 37, 46, 47, and periodontal pocket depths were measured at the mesiobuccal, midbuccal, distobuccal, distolingual, midlingual, and mesiolingual sites for each tooth using a WHO periodontal probe. Trained dentists examined the periodontal status of the participants. The inter-examiner mean kappa value was 0.89.

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Statistical analysis

All analyses were weighted to account for the complex sample design of the KNHANES and were performed according to the statistical guidelines for the analysis of raw data suggested by the KDCA. Continuous data were expressed as the weighted mean ± standard error (SE), and categorical data were presented as weighted frequencies with SE (%). For group comparisons, analysis of variance followed by the Bonferroni post-hoc test, the Student t-test, the chi-square test, and the Fisher exact test were used as appropriate. To determine the association of hypouricemia and hyperuricemia with the presence of periodontitis, sequential series of logistic regression models were developed, and the following variables were adjusted: model 1, unadjusted; model 2, sex- and age-adjusted; Model 3, adjusted for all variables in model 2 and BMI, high-risk drinking, smoking, and physical activity; model 4, adjusted for all variables in model 3 and HTN, DM, and dyslipidaemia; model 5: adjusted for all variables in model 4 and eGFR and ALT; model 6, adjusted for all variables in model 5 and haemoglobin and hs-CRP; and model 7, adjusted for all variables in model 6 and interdental brush use and mouthwash use. Data were analysed using SPSS version 23.0 (IBM, Armonk, NY, USA), and *P* values < 0.05 were considered statistically significant.

RESULTS

The baseline demographic and clinical characteristics of the study participants are described in **Table 1**. The weighted mean age was 51.1 years, and 56.2% of the participants were women. The weighted frequency of periodontitis was 30.5%. The weighted mean SUA level was 5.1 mg/dL (male: 5.9 mg/dL and female: 4.4 mg/dL). The weighted prevalence of hypouricemia, hyperuricemia, and normouricemia was 0.6%, 12.9%, and 86.5%, respectively (**Figure 1**). In addition, the weighted frequencies of hypouricemia, hyperuricemia, and normouricemia were 1%, 19.9%, and 79.1%, respectively, for male subjects and 0.2%, 6.9%, and 92.9%, respectively, for female subjects (**Figure 1**).

Table 2 shows the comparison of demographic and clinical characteristics according to SUA level. The frequency of periodontitis tended to be higher in subjects with hypouricemia than in those with normouricemia and hyperuricemia (hypouricemia, 51.1%; normouricemia, 30.3%; and hyperuricemia, 30.6%), but this difference was not statistically significant (*P*=0.112). For male subjects, a significant difference in the frequency of periodontitis according to the SUA levels was observed (hypouricemia, 58.7%; normouricemia, 38.8%; and hyperuricemia, 31%; *P*=0.023). However, the frequency of periodontitis in female subjects did not differ significantly according to SUA levels (hypouricemia, 29.5%; normouricemia, 24.9%; and hyperuricemia, 29.9%; *P*=0.224). Hypouricemic subjects were significantly older, had significantly higher fasting blood glucose levels, HbA1c, and eGFR, and had significantly fewer remaining teeth than normouricemic or hyperuricemic subjects. Participants with hyperuricemia had significantly higher waist circumference, BMI, DBP, total cholesterol, triglycerides, LDL cholesterol, AST, ALT, and haemoglobin, and had significantly lower HDL cholesterol levels than normouricemic or hypouricemic subjects. Significant differences were found in the frequency of females, high-risk drinking behaviour, and smoking status between hypouricemic, normouricemic, and hyperuricemic subjects.

The results of the logistic regression models to determine the association between hypouricemia and hyperuricemia with the presence of periodontitis are summarised in **Figure 2**. In the unadjusted model (model 1), hypouricemia (odds ratio [OR], 2.41; 95% confidence interval [CI], 1.64–3.53; *P*=0.022) but not hyperuricemia (OR, 1.02; 95% CI, 0.61–1.69; *P*=0.740) was

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Table 1. Baseline demographic and clinical characteristics of all study participants

Variables	Total (n=12,735)
SUA (mg/dL)	5.1±0.0
Demographic characteristics	
Age (yr)	51.1±0.2
Female sex	56.2 (0.0)
Urban residence	83.3 (1.8)
Occupation	
Managers and professionals	15.0 (0.2)
Clerical support workers	10.5 (0.2)
Service and sales workers	13.0 (0.1)
Skilled agricultural, forestry and fishery workers	3.6 (0.3)
Craft, plant, or machine operators and assemblers	10.0 (0.1)
Laborers	8.4 (0.1)
Unemployed	39.5 (0.2)
Household income	
≤24th percentile	25.0 (0.2)
25–49th percentile	25.1 (0.3)
50–74th percentile	25.2 (0.1)
≥75th percentile	24.7 (0.4)
Education level	
Elementary and/or junior high school graduated	29.7 (0.1)
Senior high school and/or college graduated	70.3 (0.1)
Lifestyle factors	
High-risk drinking	11.4 (0.2)
Smoking status	
Current	18.1 (0.0)
Former	21.2 (0.0)
Never	60.7 (0.0)
Physical activity	44.0 (0.6)
Waist circumferences, cm	82.2±0.1
BMI (kg/m^2)	23.9±0.0
Dental visit experience	42.7 (0.0)
Tooth brushing, times per day	
0	3.8 (0.0)
1	25.3 (0.2)
2	35.8 (0.1)
≥3	35.1 (0.4)
Dental floss use	23.7 (0.2)
Interdental brush use	18.5 (0.1)
Mouthwash use	23.4 (0.0)
Electric toothbrush use	4.7 (0.0)
Clinical factors	
Number of remaining teeth	26.6±0.0
Number of permanent teeth with caries	0.6±0.0
Periodontitis	30.5 (0.6)
Metabolic factors	
SBP (mmHg)	118.8±0.1
DBP (mmHg)	75.3±0.0
Fasting blood glucose (mg/dL)	101.1±0.1
HbA1c (%)	5.7±0.0
Total cholesterol (mg/dL)	191.9±0.1
eGFR	100.4±0.2
Triglyceride (mg/dL)	134.3±0.1
HDL cholesterol (mg/dL)	51.1±0.1
LDL cholesterol (mg/dL)	118±0.0
AST	23.1±0.0
ALT	22.3±0.1
Haemoglobin (g/dL)	14.0±0.0
hs-CRP (mg/L)	1.2±0.0
HTN	11.5 (0.1)
DM	14.3 (0.0)
Dyslipidaemia	13.2 (0.0)

Data are expressed as weighted mean ± standard error (SE) or weighted percentage (SE).
SUA: serum uric acid, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: haemoglobin A1c, eGFR: estimated glomerular filtration rate, HDL: high-density lipoprotein, LDL: low-density lipoprotein, AST: aspartate transaminase, ALT: alanine transaminase, hs-CRP: high-sensitivity C-reactive protein, HTN: hypertension, DM: diabetes mellitus.

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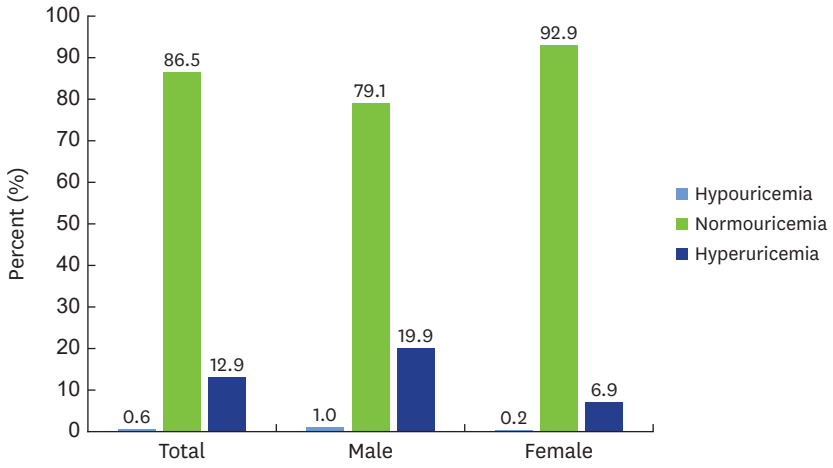

Figure 1. Frequency of hypouricemia, normouricemia, and hyperuricemia.

significantly associated with the presence of periodontitis. In the adjusted models (models 2, 3, 4, 5, 6, and 7), hypouricemia was significantly associated with an increased risk of periodontitis. In model 7, which adjusted for all potential demographic, metabolic, clinical, and lifestyle factors, the adjusted OR of hypouricemia for periodontitis was 1.62 (95% CI, 1.13–2.33; P=0.037). However, the relationship between hyperuricemia and periodontitis was not significant after adjusting for confounding factors (models 2, 3, 4, 5, 6, and 7).

DISCUSSION

In this study, the relationship between SUA levels and periodontitis in Korean adults was analysed using representative national survey data. This study identified that hypouricemia was associated with an increased risk of periodontitis after adjustment for potential confounding factors, suggesting a potential role of hypouricemia in the occurrence and development of periodontitis. The prevalence of hypouricemia was low (0.6%) in Korean adults, and hypouricemic subjects were older, had higher glycaemic status, and had better kidney function compared to non-hypouricemic subjects. However, no significant relationship was found between hyperuricemia and periodontitis.

To our knowledge, this is the first large-scale epidemiological study to provide evidence for a link between hypouricemia and the risk of periodontitis. A cross-sectional study by Byun et al. showed that subjects with hyperuricemia had a lower risk of periodontitis than those without hyperuricemia [21], but the researchers did not analyse the relationship between hypouricemia and the risk of periodontitis. The results for Byun et al. are in contrast with those of this study, where the risk of periodontitis in hyperuricemic subjects did not differ from those that are normouricemic. Some pilot studies reported that SUA levels in patients with periodontitis were higher than those in control groups [22,23]; however, there were also many contradictory results [15,24,25]. In addition, salivary UA and gingival crevicular fluid UA levels in patients with periodontitis were lower or comparable to those in controls in previous studies [25,26,27]. Chen et al. recently hypothesised that hyperuricemia may be a potential risk factor for periodontitis [28]. but there is not enough evidence to support this hypothesis, based on the results of this study as well as previous research. Conversely, it is reasonable to assume that lower UA levels are associated with a higher prevalence of periodontitis.

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Table 2. Comparisons of baseline demographic and clinical characteristics according to the serum uric acid levels

Variables	Hypouricemia (n=77)	Normouricemia (n=12,159)	Hyperuricemia (n=1,828)	*P* value
Demographic				
Age (yr)	58.2±0.1[a)b)]	51.1±0.1	48.9±0.4	0.026
Female	20.4 (0.6)	59.8 (0.1)	30.7 (0.0)	0.004
Urban residence	77.3 (0.7)	83.7 (1.8)	82.1 (2.3)	0.158
Occupation				0.086
Managers and professionals	10.2 (0.3)	14.9 (0.2)	17.4 (0.3)	
Clerical support workers	7.5 (0.2)	10.6 (0.2)	11.1 (0.4)	
Service and sales workers	13.9 (0.4)	13.3 (0.1)	12.1 (0.2)	
Skilled agricultural, forestry and fishery workers	0.6 (0.0)	3.6 (0.3)	3.2 (0.5)	
Craft, plant, or machine operators and assemblers	28.3 (0.9)	9.7 (0.1)	12 (0.6)	
Laborers	10.0 (0.3)	8.5 (0.2)	7.6 (0.1)	
Unemployed	29.5 (2.2)	39.4 (0.2)	36.4 (0.2)	
Household income				0.109
≤24th percentile	22.2 (0.9)	24.6 (0.2)	26.3 (0.0)	
25–49th percentile	27.3 (0.8)	25.3 (0.3)	23.5 (0.1)	
50–74th percentile	32.3 (1.0)	25 (0.1)	27.6 (0.4)	
≥75th percentile	18.3 (0.9)	25.1 (0.4)	22.7 (0.4)	
Education level				0.110
Elementary and/or junior high school graduated	24.7 (0.7)	29.3 (0.2)	27.6 (0.1)	
Senior high school and/or college graduated	75.3 (0.7)	70.7 (0.2)	72.4 (0.1)	
Lifestyle				
High-risk drinking	13.8 (0.4)	10.5 (0.1)	18 (0.4)	0.019
Smoking status				0.026
Current	25.6 (0.8)	16.9 (0.0)	27.2 (0.3)	
Former	33.0 (0.6)	20.2 (0.1)	27.7 (0.6)	
Never	41.4 (0.2)	62.9 (0.1)	45.1 (0.3)	
Physical activity	45.4 (0.2)	43.8 (0.5)	47.3 (1.7)	0.208
Waist circumferences (cm)	82.1±0.4[b]	81.3±0.1[b]	88.2±0.0	0.040
BMI (kg/m^2)	22.9±0.1[b]	23.6±0.0[b]	25.8±0.0	0.020
Dental visit experience	53.4 (1.3)	57.8 (0.1)	55.5 (1.1)	0.293
Tooth brushing, times per day				0.133
0	4.3 (1.1)	3.5 (0.0)	4.4 (0.2)	
1	19.7 (0.5)	24.9 (0.3)	28.4 (0.8)	
2	34.9 (0.3)	35.6 (0.1)	36.9 (0.2)	
≥3	41.1 (1)	36 (0.4)	30.2 (0.3)	
Dental floss use	9.2 (0.2)	24.3 (0.1)	21.8 (1.0)	0.134
Interdental brush use	16.2 (0.4)	18.5 (0.1)	20.4 (0.3)	0.080
Mouthwash use	23 (0.6)	24.2 (0.0)	19.6 (0.3)	0.056
Electric toothbrush use	3.5 (0.1)	4.7 (0.1)	5.1 (0.3)	0.476
Clinical				
Number of remaining teeth	25±0.13[a)b)]	26.8±0.0	26.5±0.2	0.012
Number of permanent teeth with caries	0.81±0.0	0.61±0.0	0.74±0.0	0.053
Periodontitis	51.1 (1.3)	30.3 (0.5)	30.6 (1.3)	0.112
Metabolic				
SBP (mmHg)	120.4±0.2	118.1±0.1	122.6±0.3	0.155
DBP (mmHg)	73.8±0.4[b)]	75±0.0[b)]	78.6±0.0	0.048
Fasting blood glucose (mg/dL)	120±0.8[a)b)]	100.8±0.1	102.3±0.3	0.016
HbA1c (%)	6.4±0[a)b)]	5.69±0.0	5.72±0.0	0.024
Total cholesterol (mg/dL)	186.0±0.1[b)]	191.3±0.1[b)]	196.4±0.2	0.021
eGFR	118.2±0.4[a)b)]	101.6±0.2[b)]	91.1±0.0	0.010
Triglyceride (mg/dL)	125.7±1.8[b)]	127.3±0.0[b)]	182.5±1.8	<0.001
HDL cholesterol (mg/dL)	53.6±0.3[b)]	51.9±0.13[b)]	46.0±0.2	0.013
LDL cholesterol (mg/dL)	115.0±0.0[b)]	117.2±0.1[b)]	120.6±0.3	0.035
AST	22.9±0.1[b)]	22.5±0.0[b)]	27.3±0.1	0.018
ALT	21.8±0.3[b)]	21.0±0.0[b)]	31.1±0.2	0.033
Haemoglobin (g/dL)	14.2±0.0[b)]	13.9±0.0[b)]	14.7±0.0	0.041
hs-CRP (mg/L)	1.3±0.0	1.1±0.0	1.6±0.0	0.108
HTN	11.6 (1.1)	11.0 (0.1)	13.8 (0.6)	0.120
DM	42.7 (1.3)	14.0 (0.1)	15.3 (0.5)	0.061
Dyslipidaemia	7.9 (0.2)	9.8 (0.1)	14.0 (0.6)	0.088

Data are expressed as weighted mean ± standard error (SE) or weighted percentage (SE).
BMI, body mass index, SBP, systolic blood pressure, DBP, diastolic blood pressure, HbA1c, haemoglobin A1c, eGFR, estimated glomerular filtration rate, HDL, high-density lipoprotein, LDL, low-density lipoprotein, AST, aspartate transaminase, ALT, alanine transaminase, hs-CRP, high-sensitivity C-reactive protein, HTN, hypertension, DM, diabetes mellitus.
[a)]*P*<0.05, analysis of variance with the Bonferroni post-hoc test compared with normouricemia.
[b)]*P*<0.05, analysis of variance with the Bonferroni post-hoc test compared with hyperuricemia.

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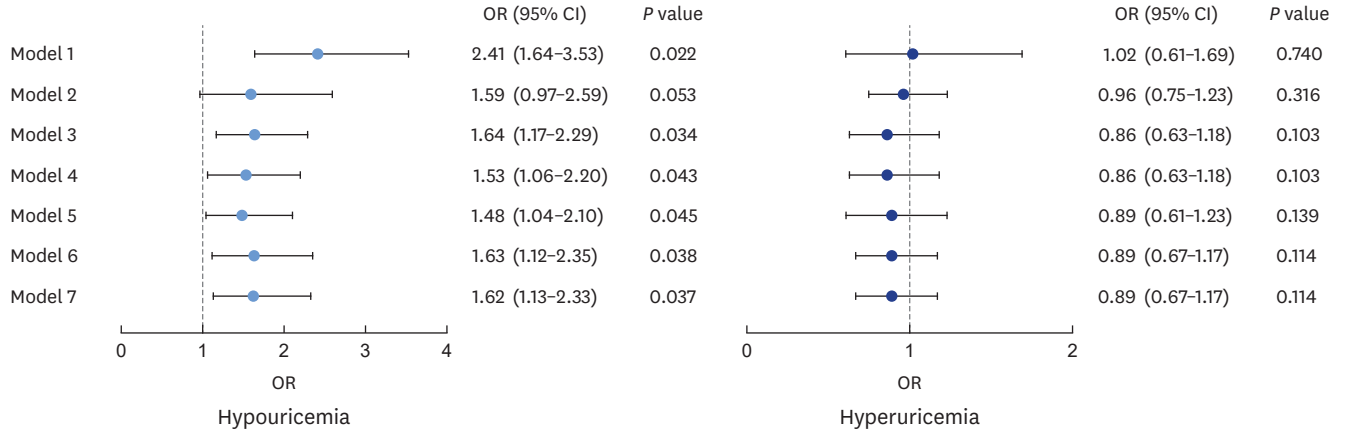

Figure 2. Associations of hypouricemia and hyperuricemia with periodontitis assessed by logistic regression models. Model 1: unadjusted model; model 2: sex- and age-adjusted; model 3: adjusted for all variables in model 2 and body mass index, high-risk drinking, smoking, and physical activity; model 4: adjusted for all variables in model 3 and hypertension, diabetes mellitus, and dyslipidaemia; model 5: adjusted for all variables in model 4 and the estimated glomerular filtration rate and alanine transaminase; model 6: adjusted for all variables in model 5 and haemoglobin and C-reactive protein levels; model 7: adjusted for all variables in model 6 and interdental brush use and mouthwash use.
OR: odds ratio, CI: confidence interval.

Although the exact mechanism is not fully understood, there are some potential explanations for the association between hypouricemia and periodontitis. First, UA is a potent antioxidant that neutralises reactive oxygen species. The production of reactive oxygen species by polymorphonuclear cells in response to periodontal pathogenic bacteria can induce and activate various inflammatory mediators, such as matrix metalloproteinases and proinflammatory cytokines, subsequently leading to periodontal tissue injury and disturbance in local bone homeostasis, an important pathological process in periodontitis. Thus, reduced antioxidant capacity under hypouricemic conditions may play a role in the development of periodontitis. Whether UA exhibits an antioxidant or pro-oxidant effect depends on the surrounding environment. Although UA has pro-oxidant properties in a hydrophobic milieu, it has antioxidant activity in hydrophilic environments, such as biological fluids, including blood, saliva, and gingival crevicular fluid [29]. Previous studies have also reported that UA is an important antioxidant in human saliva and that salivary UA levels correlate with SUA levels [30,31]. Second, low SUA levels could potentially reflect malnutrition, and SUA levels correlate with protein intake and BMI [12]. Purine-rich foods such as red meat and seafood are major sources of exogenous UA and have high protein content. The known association between poor nutritional status and unfavourable dental status [32] may explain, at least partially, the relationship of hypouricemia with the risk of periodontitis. Third, alterations in genes involved in purine metabolism could cause an impaired immune response, and this systemic condition may promote the progression of periodontitis. Fourth, some investigators have suggested that proinflammatory cytokines could decrease SUA levels through the inhibition of renal UA reabsorption in critically ill patients [33]. Thus, the production of various proinflammatory cytokines in periodontitis might lead to hypouricemia, although no data to support this have been presented. As discussed above, plausible immune-metabolic mechanisms by hypouricemia might promote the progression of periodontitis have been suggested, such as oxidative stress, malnutrition, an impaired immune response, pathological bone remodelling, and dysbiosis.

In the new classification of periodontitis based on stage and grade, grade is an emerging issue that should be considered as an important factor in diagnosing and treating periodontitis because it provides supplemental information about disease progression,

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the risk of further progression, possible poor outcomes of treatment; and the risk that treatment may negatively affect the general health of the patient [34]. The progression of periodontitis or treatment outcomes may be related to the host's systemic condition, and periodontitis that is not properly treated may exacerbate existing systemic disease. As host susceptibility plays an important role in the pathogenesis of periodontitis, the need for host modulation therapy in addition to conventional periodontal treatment is being increasingly recognised. Host modulation predominantly refers to efforts to manipulate the immune response or inflammatory reaction in ways that prevent or ameliorate tissue damage [2]. In particular, host modulation therapy strategies targeting anti-inflammatory and antioxidant agents may serve as an excellent therapeutic approach to reach the level of clinical benefit [35]. Maintaining an appropriate concentration of UA is a type of host modulation therapy. It has anti-inflammatory and antioxidant effects, and can be helpful in the treatment of periodontitis by controlling SUA and increasing systemic immunity.

The epidemiology and clinical aspects of hypouricemia have not been extensively studied. The prevalence of hypouricemia was 0.6% in this study, while that reported in previous epidemiological studies ranged from 0.19 to 0.58% [36-38]. Thus, it is assumed that the overall prevalence of hypouricemia in the general population is less than 1%, although it varies slightly according to the study design, the characteristics of the study population, and the definition of hypouricemia. In this study, the eGFR in hypouricemic subjects was significantly higher than that in non-hypouricemic subjects. Even though hyperuricemia is regarded as a significant contributing factor for the development of chronic kidney disease, it is unclear whether hypouricemia may result in reduced kidney function or may play a protective role against renal impairment. Renal hypouricemia, a genetic disorder characterised by defective renal UA reabsorption due to mutations in the *SLC22A12* and *SLC2A9* genes, has been reported to be associated with exercise-induced acute kidney injury [39]. Thus, it has been suggested that hypouricemia of any cause may lead to deterioration in renal function. This hypothesis was supported by the study of Wakasugi et al. [36], which described an association between hypouricemia and decreased renal function. However, contradictory results have also been reported [37,40]. The causes of hypouricemia are complex, multifactorial, and largely unknown, and the underlying mechanism by which hypouricemia affects kidney function has not yet been fully elucidated. The results of this study showed that hypouricemic subjects had significantly higher serum blood glucose levels and HbA1c than non-hypouricemic subjects, suggesting a potential association between hypouricemia and hyperglycaemia. A previous observational study demonstrated that SUA levels decreased with an increasing duration of DM because hyperglycaemia could lead to uricosuria, which supports the findings in this paper.

The potential limitations of this study merit consideration. First, due to its cross-sectional nature, the causal relationship between hypouricemia and periodontitis should be interpreted carefully; thus, further prospective or experimental studies are needed to validate these results. Second, the KNHANES did not include detailed information regarding the diagnosis of gout or medications that affect SUA levels, such as xanthine oxidase inhibitors, uricosuric agents, pyrazinamide, and aspirin; hence, these variables could not be fully adjusted in this study. Third, hyperuricemia was defined as SUA levels ≥7 mg/dL for men and ≥6 mg/dL for women, and hypouricemia was set at SUA levels <3 mg/dL for men and <2 mg/dL for women. The definitions of hyperuricemia and hypouricemia have been diverse in previous studies, and there are no established criteria for hyperuricemia and hypouricemia. The relationship among hypouricemia, hyperuricemia, and periodontitis may vary according

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to their definition. Many studies have adopted the definition of hypouricemia as SUA levels <2 mg/dL for both men and women; however, as SUA levels in men are higher than those in women, it may be inappropriate to apply the same standard for both sexes. Fourth, because SUA levels were measured only once in the KNHANES, it was impossible to distinguish between transient and persistent hypouricemia in this study.

In conclusion, hypouricemia was independently associated with a higher risk of periodontitis in a representative national sample of Korean adults. Although the overall prevalence of hypouricemia is less than 1% in Korean adults, more attention needs to be given to periodontitis screening in hypouricemic subjects. The present study sheds light on the epidemiological and pathophysiological significance of hypouricemia in oral health. However, due to the potential limitations of this study, further studies are warranted to confirm the causal relationship between hypouricemia and periodontitis and to explore the exact mechanism by which hypouricemic status contributes to the pathological process of periodontitis.

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