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ORIGINAL RESEARCH

Effect of Dietary Magnesium on the Association Between Serum Uric Acid and Female Infertility

Xiaoqin Xin[1], Qi Zhang[2], Jing Xu[1], Jungao Huang[3]

[1]Department of Clinical Laboratory, Ganzhou People's Hospital, Ganzhou, Jiangxi, People's Republic of China; [2]Department of Obstetrics and Gynecology, Ganzhou Maternal and Child Health Hospital, Ganzhou, Jiangxi, People's Republic of China; [3]Department of Medical Genetic, Ganzhou Maternal and Child Health Hospital, Ganzhou, Jiangxi, 341000, People's Republic of China

Correspondence: Jungao Huang, Email jungaohuang@sina.com

Background: Few studies have evaluated the correlation between serum uric acid (SUA) levels and the prevalence of female infertility in the general population, and the effect of magnesium intake on this correlation has not been investigated.

Methods: All participants aged 18–45 years at baseline were enrolled from the National Health and Nutritional Examination Surveys (NHANES) 2013–2018. The continuous variable of SUA was divided into quartile (Q1: ≤3.7 mg/dL, Q2: 3.7–4.4 mg/dL, Q3: 4.4–5.1 mg/dL, Q4: ≥5.1 mg/dL). Multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). Dietary magnesium was divided into two groups based on the median number of participants (low magnesium intake, <243 mg/day; high magnesium intake, ≥243 mg/day).

Results: A total of 3185 female participants were included in the final analysis, 10.58% of whom were infertile. In the full adjustment model, SUA was positively associated with female infertility (OR=1.13, 95% CI: 1.01–1.27). Compared to the lowest quartile (Q1), female participants with the highest SUA levels (Q4) had an increased risk of infertility by 62% (OR=1.62, 95% CI: 1.1–2.4). Moreover, we found an interactive effect of magnesium intake on the association between SUA and infertility in adjusted models (interaction likelihood ratio test: P=0.029), implying that high magnesium intake may ameliorate the association between SUA and female infertility.

Conclusion: This study is the first to report an interactive effect of dietary magnesium intake on the relationship between SUA and female infertility.

Plain Language Summary: Infertility affects approximately 15% of reproductive-aged couples worldwide. Few studies have evaluated the correlation between serum uric acid (SUA) levels and the prevalence of female infertility in the general population. The role of magnesium on infertility through its effects on uric acid has not been investigated. We found SUA was positively associated with female infertility in the present study and an interactive effect of magnesium intake on the association between SUA and infertility existed, which implied that high magnesium intake may ameliorate the association between SUA and female infertility. The study casts a light on how magnesium affects infertility, hinting at the importance of supplementing with magnesium in various ways.

Keywords: serum uric acid, infertility, dietary, magnesium

Introduction

Infertility, defined as the failure to achieve conception within 12 months of unprotected intercourse or therapeutic donor artificial insemination,[1] affects approximately 15% of reproductive-aged couples worldwide.[2] The World Health Organization has listed infertility as a global public health problem.[3] Infertility not only affects physical health but also psychological status, such as psychological anxiety and depression.[4,5] Recently, it has been reported that changing lifestyles or dietary patterns can decrease the risk of infertility in women.[6,7]

Uric acid (UA) was considered a major end-product of purine metabolism and is catalyzed by xanthine oxidoreductase (XOR). It also reflects the metabolic state of the body and maintains its oxidation level under physiological

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conditions.[8] However, excessive accumulation of uric acid can damage multiple systems, including the reproductive system.[9] Serum uric acid levels have been reported as important markers of oxidative stress and inflammation in the body.[10,11] Oxidative stress may lead to oocyte aging, which manifests as a gradual decline in the number and quality of oocytes.[12] In addition, previous studies have found that serum uric acid (SUA) accumulation is associated with sexual dysfunction.[13] Several studies had shown that SUA levels in polycystic ovarian syndrome (PCOS) patients are significantly higher than those without PCOS individuals.[14,15] Therefore, it is reasonable to hypothesize that elevated SUA levels are associated with fertility.

It is well established that magnesium (Mg) is an important nutrient for the human body and plays an important role in prevention and treatment of a variety of diseases. Magnesium can reduce the formation of reactive oxygen species (ROS) in living organisms such as ·OH, H2O2, and ·O2- and improve the antioxidant system.[16] In addition, Kong et al found that Mg can up-regulate the transcription level of antioxidant enzyme genes.[17] Helena et al believed that magnesium supplementation and dietary education should be promoted among women of childbearing age.[18] Notably, a study of 5168 participants indicated that daily Mg intake was inversely associated with uric acid levels.[19] Thus, increasing the consumption of foods rich in magnesium may exert a positive effect on the body and could be a preventive strategy to reduce the risk of hyperuricemia. However, few studies have explored the effect of Mg intake on the association between UA and female to infertility. Therefore, in the present study, we aimed to explore whether SUA is positively associated with infertility and whether magnesium can alleviate this association.

Materials and Methods

Study Population

This study used data from the National Health and Nutrition Examination Survey (NHANES, 2013–2018). The NHANES is a research program approved by the Centers for Disease Control and Prevention (CDC) that uses complex multistage sampling techniques to provide a large amount of data on the nutrition and health status of the general population in the United States. Data collection consisted of questionnaires, home interviews, and physical examinations at a mobile examination center to collect blood and urine samples. All methods were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained from all participants. Three consecutive cycles of NHANES data from to 2013–2014, 2015–2016, and 2017–2018 (n=29,400) were included in this study. First, we included women of reproductive age between 18 and 45 years (n=8214). Pregnant participants (n=141) and those with missing SUA (n=847), infertility (n=3584), dietary Mg intake (n=139), and other key covariates (n=318) were excluded. Finally, 3185 subjects were included in the present study (Figure 1).

Measurements of Serum Uric Acid

Serum samples were collected from the study population and stored at −30 °C until they were shipped to the CDC for testing. SUA was measured using the Beckman Coulter UniCel®dx800 timing endpoint method, and the system monitored the change in absorbance at 520 nm, which is proportional to the concentration of uric acid in the sample. The detailed uric acid testing procedures are provided in the NHANES Laboratory Procedure Manual.[20]

Magnesium Intake

Dietary Mg intake data for the 24-h period were collected via a dietary recall interview at mobile examination centers. Using estimated food volumes, nutrient intake was calculated at the individual level using a revised nutrient database that converted the intake of specific foods to the intake of individual nutrients. Daily magnesium intake was defined as high (≥243 mg/day) or low (<243 mg/day), based on the median of the population.

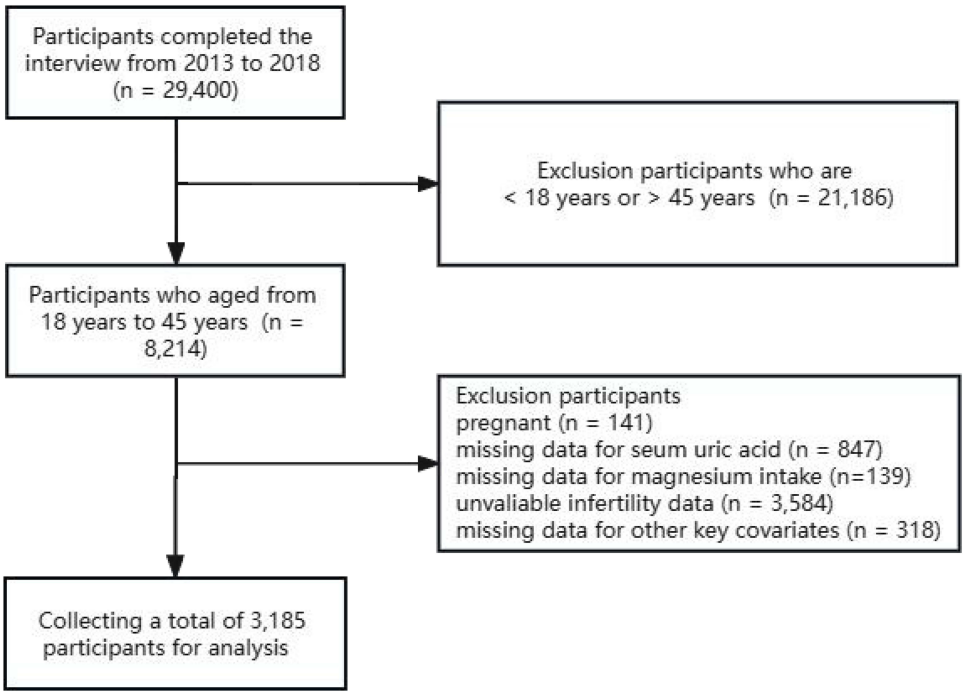

Figure 1 Flow chart of the enrollment of participants.

Assessment of Infertility

The outcome of infertility was defined based on two questions from the NHANES Reproductive Health Questionnaire (RHQ): (1) RHQ074, "Have you tried to get pregnant for at least a year without getting pregnant?" (2) RHQ076, "Have you ever had to see a doctor or other healthcare provider because you could not conceive of baby?" Women who answered "yes" to either of these two questions were considered to have a history of infertility.

Covariates

The following categorical covariates were included in our analyses: age (<35 years or ≥35 years), race/ethnicity (Mexican American, other Hispanics, non-Hispanic white, non-Hispanic black, or other race), poverty income ratio (PIR) (PIR<3, PIR ≥3), marital status (living with partner, married, divorced or widowed, never married), BMI (<25 kg/m^2, 25–30 kg/m^2, ≥30 kg/m^2), menstrual cycle regularity (yes or no), pesticide exposure (yes or no), physical activity (light work activity, moderate work activity, or vigorous work activity), diabetes (yes or no), hyperlipidemia (yes or no), and hypertension (yes or no). Continuous covariates included dietary factors such as magnesium intake (mg), folate (mg), fiber (g), calcium (mg), vitamin D (mg), serum total cholesterol (TC) (mg/dL), triglycerides (mg/dL), serum urea nitrogen (mg/dL), and serum cotinine. Dietary data for the 24-h period were collected via dietary recall interviews at mobile examination centers. Menstrual cycle regularity and pesticide exposure were defined based on the responses to the items in the questionnaire. Diabetes was diagnosed according to American Diabetes Association criteria. High blood pressure was defined as a systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 110 mmHg. Hyperlipidemia was classified as total cholesterol >200 mg/dL, triglycerides >200 mg/dL, high-density lipoprotein <40 mg/dL in women, high-density lipoprotein <50 mg/dL in men, or low-density lipoprotein >130 mg/dL.[21]

Statistical Analysis

Continuous variables of SUA were divided into quartiles from lowest (Q1) to highest (Q4). Means with standard deviations (SDs) or medians (interquartile range) were expressed as continuous variables, and proportions were used for categorical variables. Multivariate logistic regression models were used to evaluate the relationship between SUA levels and infertility in the women. The chi-squared test was used for categorical variables and the linear regression

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model was used for continuous variables to calculate the differences between the groups. Crude model adjusted for none; adjusted model adjusted for sex and race/ethnicity; full-adjusted model adjusted for sex, race/ethnicity, marital status, PIR, BMI, serum cholesterol, blood urea nitrogen, serum cotinine, menstrual cycle regularity, dietary factors (magnesium, folate, fiber, vitamin D, calcium), physical activity, pesticide exposure, history of diabetes, hypertension, and hyperlipidemia. A stratified multiple regression analysis was conducted based on dietary magnesium intake, and the likelihood ratio test was used to evaluate the interaction. All analyses were performed using the statistical software package R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.3, with p values < 0.05 as statistically significant.

Results

Baseline Characteristics of the Study Population

Among the 3185 participants, 337 (10.6%) were infertile. The characteristics of the participants are presented according to whether they were infertile (Table 1). The median SUA was 4.5±1.1 mg/dL. The presence of infertility showed significant differences in baseline characteristics, such as age, PIR, marital status, BMI, SUA, serum triglycerides, total

Table 1 The Characteristics of the Study Population by Infertility

Variables	Total (n = 3185)	Non-Infertility (n = 2848)	Infertility (n = 337)	P value
Age, n (%)				< 0.001
<35	1918 (60.2)	1778 (62.4)	140 (41.5)	
≥35	1267 (39.8)	1070 (37.6)	197 (58.5)	
Race, n (%)				0.128
Mexican American	577 (18.1)	520 (18.3)	57 (16.9)	
Non-Hispanic Black	681 (21.4)	607 (21.3)	74 (22)	
Non-Hispanic White	1052 (33.0)	924 (32.4)	128 (38)	
Other Hispanic	340 (10.7)	315 (11.1)	25 (7.4)	
Other Race	535 (16.8)	482 (16.9)	53 (15.7)	
PIR, n (%)				0.014
PIR < 3	2010 (68.4)	1811 (69.2)	199 (62.4)	
PIR ≥ 3	927 (31.6)	807 (30.8)	120 (37.6)	
Marital status, n (%)				< 0.001
Living with partner	403 (12.7)	361 (12.7)	42 (12.5)	
Married	1229 (38.6)	1028 (36.1)	201 (59.6)	
Divorce or widow	325 (10.2)	286 (10)	39 (11.6)	
Never married	875 (27.5)	826 (29)	49 (14.5)	
Unknown	353 (11.1)	347 (12.2)	6 (1.8)	
BMI, (kg/m^2) n (%)				< 0.001
BMI < 25	1128 (35.8)	1039 (36.8)	89 (26.8)	
BMI 25–30	754 (23.9)	697 (24.7)	57 (17.2)	
BMI ≥ 30	1273 (40.3)	1087 (38.5)	186 (56)	
Uric acid (mg/dL), Mean (SE)	4.5 ± 1.1	4.5 ± 1.1	4.8 ± 1.1	< 0.001
Triglycerides (mg/dL), Median (IQR)	92.0 (65.0, 140.0)	90.0 (64.0, 137.0)	107.0 (72.0, 158.0)	< 0.001
Total cholesterol (mg/dL), Mean (SE)	178.3 ± 35.0	177.6 ± 35.0	184.1 ± 34.7	0.001
Urea nitrogen (mmol/L), Mean ± SD	4.0 ± 1.4	4.0 ± 1.4	4.0 ± 1.3	0.719
Serum cotinine (ng/mL), Median (IQR)	0.0 (0.0, 1.5)	0.0 (0.0, 1.2)	0.1 (0.0, 16.1)	0.043
Dietary Factor				
Magnesium (mg), Median (IQR)	243.0 (174.0, 324.0)	242.5 (174.0, 323.0)	245.0 (172.0, 338.0)	0.856
Folate (μg), Median (IQR)	303.0 (202.0, 441.0)	303.5 (203.0, 442.0)	294.0 (186.0, 435.0)	0.409
Fiber (gm), Median (IQR)	13.2 (8.5, 19.3)	13.3 (8.7, 19.2)	12.2 (7.8, 19.3)	0.063
Calcium (mg), Median (IQR)	775.0 (499.0, 1103.0)	777.5 (498.8, 1103.0)	761.0 (499.0, 1096.0)	0.96

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 3185)	Non-Infertility (n = 2848)	Infertility (n = 337)	P value
Vitamin D (mg), Median (IQR)	2.5 (0.8, 5.1)	2.5 (0.8, 5.0)	2.8 (0.9, 5.2)	0.388
Regular menstrual cycle, n (%)				0.909
No	327 (10.3)	293 (10.3)	34 (10.1)	
Yes	2858 (89.7)	2555 (89.7)	303 (89.9)	
Pesticide exposure, n (%)				0.017
No	2889 (90.7)	2596 (91.2)	293 (86.9)	
Yes	287 (9.0)	245 (8.6)	42 (12.5)	
Unknown	9 (0.3)	7 (0.2)	2 (0.6)	
Physical activity, n (%)				0.533
Light	1804 (56.6)	1611 (56.6)	193 (57.3)	
Moderate	826 (25.9)	746 (26.2)	80 (23.7)	
Vigorous	555 (17.4)	491 (17.2)	64 (19)	
Diabetes, n (%)				< 0.001
No	2930 (92.0)	2638 (92.6)	292 (86.6)	
Yes	235 (7.4)	193 (6.8)	42 (12.5)	
Unknown	20 (0.6)	17 (0.6)	3 (0.9)	
Hyperlipidemia, n (%)				0.003
No	1465 (46.0)	1336 (46.9)	129 (38.3)	
Yes	1720 (54.0)	1512 (53.1)	208 (61.7)	
Hypertension, n (%)				< 0.001
No	2659 (83.5)	2403 (84.4)	256 (76)	
Yes	526 (16.5)	445 (15.6)	81 (24)	

Abbreviations: BMI, body mass index; PIR, poverty income ratio.

cholesterol, serum cotinine, hyperlipidemia, hypertension, and diabetes. Compared to the non-infertility group, infertile participants were more likely to be older and obese, with lower values of triglycerides, uric acid, total cholesterol, and serum cotinine.

Association Between SUA and Female Infertility

The results of multivariate regression analysis are presented in Table 2. SUA levels were positively correlated with the risk of female infertility in the crude model (OR=1.21, 95% CI: 1.11–1.32, P<0.001). After adjusting for sex and race, this correlation remained significant (OR=1.21, 95% CI: 1.11–1.33, P<0.001). Furthermore, serum UA was positively associated with female infertility even after adjusting for all potential covariates in the fully adjusted model (OR=1.13,

Table 2 Relationship Between Serum Uric Acid and Risk of Infertility

Uric Acid	Event (%)	Crude Model		Adjusted Model		Full-adjusted Model	
		OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Uric acid (mg/dL)	337 (10.6)	1.21 (1.1–1.32)	<0.001	1.21 (1.1–1.33)	<0.001	1.13 (1.01–1.27)	0.031
Quartiles (mg/dL)							
Q1 (≤3.7)	65 (8.3)	1 (Ref)		1 (Ref)		1 (Ref)	
Q2 (3.7–4.4)	62 (8.7)	1.13 (0.79–1.61)	0.516	1.23 (0.84–1.81)	0.278	1.21 (0.81–1.81)	0.353
Q3 (4.4–5.1)	99 (11.4)	1.5 (1.08–2.07)	0.014	1.73 (1.22–2.43)	0.002	1.57 (1.08–2.28)	0.018
Q4 (≥ 5.1)	111 (13.6)	1.73 (1.26–2.39)	0.001	1.91 (1.36–2.69)	<0.001	1.62 (1.1–2.4)	0.015
Trend test			<0.001		<0.001		0.008

Notes: Crude model: adjusted for none. Adjusted model: adjusted for sex and race/ethnicity. Full-adjusted model: adjusted for sex, race/ethnicity, marital status, PIR, BMI, serum cholesterol, blood urea nitrogen, serum cotinine, menstrual cycle regularity, dietary factors (magnesium, folate, fiber, vitamin D, calcium), physical activity, pesticide exposure, disease history of diabetes, hypertension and hyperlipidemia.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; Ref, reference.

Table 3 Interactive Effect of Dietary Magnesium Intake and Serum Uric Acid on Infertility

Models	Low Mg Intake (< 243 mg/day) n=1590		High Mg Intake (≥ 243 mg/day) n=1595		P for interaction
	OR (95% CI)	P value	OR (95% CI)	P value	
Crude model					0.051
Uric acid (mg/dL)	1.34 (1.17–1.54)	<0.001	1.12 (0.98~1.27)	0.097	
Adjusted model					0.027
Uric acid (mg/dL)	1.36 (1.18~1.57)	<0.001	1.09 (0.96~1.25)	0.184	
Full-adjusted model					0.029
Uric acid (mg/dL)	1.36 (1.16~1.6)	<0.001	1.07 (0.92~1.24)	0.366	

Notes: Crude model: adjusted for none. Adjusted model: adjusted for sex and race/ethnicity. Full-adjusted model: adjusted for sex, race/ethnicity, marital status, PIR, BMI, serum cholesterol, blood urea nitrogen, serum cotinine, menstrual cycle regularity, dietary factors (magnesium, folate, fiber, vitamin D, calcium), physical activity, pesticide exposure, disease history of diabetes, hypertension and hyperlipidemia.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.

95% CI: 1.01–1.27, P=0.031). When SUA was converted into a categorical variable, the p-trend remained statistically significant in all three models (P<0.05).

Magnesium Intake Affects the Relationship Between SUA and Female Infertility

We found an interactive effect of Mg intake on the correlation between SUA levels and infertility (interaction likelihood ratio test: P<0.05) (Table 3). In adjusted models, the correlation between SUA and infertility was significant in low Mg intake group, and one-unit increment of SUA increased the risk of infertility by 36% (OR=1.36, 95% CI: 1.16 1.6, P<0.001). In contrast, this correlation disappeared in high Mg intake group (OR=1.07, 95% CI: 0.92–1.24, P=0.366).

Discussion

In the present study, multivariate logistic regression analysis showed that elevated SUA levels correlated with an increased risk of female infertility. Furthermore, we report for the first time that there is an interactive effect between dietary intake and SUA on female infertility, suggesting that adequate magnesium intake could attenuate the association between high uric acid levels and infertility. It had been established that SUA was the final product of the metabolic transformation of exogenous purines and endogenous purines. SUA levels can be affected by smoking, exercise, BMI, renal dysfunction, history of hypertension, and diabetes.[22,23] Therefore, our study attempted to account for the potential confounding effects of these factors when assessing the association between SUA and infertility. Our findings showed that SUA levels are positively associated with the risk of female infertility.

Emerging evidence indicates that high SUA levels are commonly linked to multiple health outcomes such as metabolic syndrome, diabetes, cardiovascular disease, kidney disease, and female reproductive disorders.[24–27] So far, few studies have been conducted on the relationship between SUA and female infertility. The evidence from these two retrospective studies is similar to our results. Luo et al reported that high SUA levels were associated with a higher infertility risk among female participants, and this association can vary according to BMI and age.[28] Another population-based study indicated that participants with elevated SUA levels had a higher infertility risk (Q4[≥5.2 mg/dL] vs Q1 [≤3.6 mg/dL]).[29] Our study varied from previous studies in terms of confounding factors and the inclusion or exclusion criteria of the study population. We considered environmental factors, such as pesticide exposure, and dietary factors, which could potentially affect SUA levels and/or infertility.

Therefore, our results are plausible. Previous studies have indicated that high levels of UA could cause monosodium urate (MSU) around the cells through an extracellular sodium reaction, which converts pro-IL-1 produced by MSU to IL-1β, thereby triggering an inflammatory response.[9] Many studies have shown that elevated uric acid levels can act as an inflammatory activator and promote oxidative stress.[30,31] Oxidative stress can result in many female reproductive disorders, such as PCOS.[32] Oxidative stress is mainly caused by an imbalance between ROS production and antioxidant

defense systems, and UA appears to be involved in this process. UA is produced by xanthine oxidase (XO) and xanthine dehydrogenase (XDH), which catalyze purine oxidation. Under specific conditions, such as oxidative stress, XO activity is enhanced. XO is an important source of superoxide radicals, which can use molecular oxygen, reactive superoxide radicals, and hydrogen peroxide to produce UA.[33] Reproductive hormones also influence serum uric acid (SUA) levels. Androgens may increase SUA levels by inducing hepatic metabolism of purine nucleotides and enhancing purine turnover in the kidney.[34] High testosterone levels are positively correlated with elevated SUA levels and PCOS.[14] Some studies have reported a positive relationship between UA accumulation and elevated follicle-stimulating and luteinizing hormone levels.[35] Hyperuricemia may lead to decreased sex hormone binding globulin (SHBG) production by inducing AMPK inactivation in the liver, and it was hypothesized that reduced SHBG levels could be used as a predictor of hyperuricemia.[36] Sex hormone disorders are among the most common causes of infertility. High UA levels may affect infertility by altering sex hormone levels and by inducing oxidative stress.[37]

Our findings showed that the median daily magnesium intake among US female adults was 243 mg/day, which was lower than the recommended amount. The recommended dietary allowance (RDA) for magnesium intake varies from 310 to 320 mg/day in women.[38] Magnesium acts as a cofactor and activator for a variety of enzymes.[39] Magnesium has a protective effect against oxidative stress and can reduce free-radical-mediated oxidative damage.[40] Various experimental studies have also explained the antioxidant and defensive effects of magnesium,[41] implying the importance of magnesium in repairing oxidative damage. Furthermore, Magnesium has been shown to exhibit anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines, such as TNF-αand IL-6, which are often upregulated in response to UA accumulation.[42] By modulating these inflammatory pathways, magnesium can potentially reduce the inflammation triggered by high UA levels, thus protecting against UA-induced infertility. A large-scale population-based study suggested that dietary magnesium intake was inversely associated with SUA levels.[18] In the present study, we found that one-unit increment in SUA increased the risk of infertility by 36% in the low-Mg intake group, and SUA was not associated with infertility in the high-Mg intake group (>243 mg/day), which may encourage people to consume more magnesium.

This study also had some limitations. First, given the characteristics of cross-sectional observational studies, direct causality could not be determined and the observational nature of our data cannot replace the direct mechanistic evidence of the experimental data. Second, the lack of reproductive hormone data prevented further investigation of the association between uric acid and sex hormones, and, given the potential mechanism, future studies need to consider more inflammatory markers. Third, although some potential confounders, such as demographic data, dietary factors, personal life history data, comorbidities, and laboratory data, were adjusted for in the logistic regression models, residual potential factors may remain. Fourth, recall interviews using questionnaires may have been biased. Finally, UA levels in serum samples were measured only once and may not reflect long-term uric acid levels. Urinary uric acid were not available. Therefore, a well-designed prospective cohort study is needed to verify our results.

Conclusion

Our analysis provides further evidence of a positive correlation between SUA levels and female infertility. An interactive effect between dietary magnesium intake and the correlation was reported, suggesting that adequate magnesium intake could attenuate the correlation.

Data and Resource Availability

The data underlying this article will be shared upon reasonable request from the corresponding author.

Ethics Approval and Consent to Participate

The NHANES study was approved by the NCHS Research Ethics Review Board (protocols 98-12, 2005-06, 2011-17, and 2018-01). Patients aged ≥18 years who provided written informed consent upon enrollment were included in the study. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or

integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All information from the NHANES program is available and free for public, so the agreement of Ganzhou Maternal and Child Health Care Hospital medical Ethics Committee was not necessary.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

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