

Association between the atherogenic index of plasma and kidney stones: a nationally representative study

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Abstract

Purpose The atherogenic index of plasma (AIP) is a novel comprehensive lipid index. We aimed to investigate a possible relationship between AIP index and kidney stones in US adults.

Methods This cross-sectional study was conducted among adults with complete AIP index and questionnaire records on kidney stones from the National Health and Nutrition Examination Survey (NHANES) spanning from 2007 to 2018. The AIP index served as the exposure variable, defned as the logarithm of the ratio between triglycerides (TG, mmol/L) and high-density lipoprotein cholesterol (HDL-c, mmol/L). Self-reported history of kidney stones was utilized as the outcome variable. The independent relationship between AIP index and the risk of kidney stones was fully assessed.

Results A total of 14,833 participants were included in this study, with an average AIP index of -0.07±0.01. The proportion of kidney stones progressively increased with higher AIP index tertile intervals (7.33% vs. 9.97% vs. 12.57%, *P*<0.001). Furthermore, AIP index was found to be independently associated with the risk of kidney stones after adjusting for confounding factors (OR=1.32, 95% CI 1.08–1.61, *P*=0.006). Restricted cubic spline (RCS) analysis confrmed the robustness of our results. There was no signifcant interaction observed based on subgroup analysis stratified by age, gender, race, body mass index (BMI, kg/m²), smokers, diabetes, hypertension, and cardiovascular disease (*P* for interaction > 0.05).

Conclusions The AIP index may be a potential epidemiological tool to quantify the role of dyslipidemia in the risk of kidney stones in US adults.

Keywords Atherogenic index of plasma, Dyslipidemia, Kidney stones, NHANES, Population-based study

Introduction

Kidney stones is a prevalent urological disorder formed by the accumulation of inorganic substances (such as crystalline salts) and organic components (such as

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urinary macromolecules) within the renal parenchyma or pelvicalyceal system $[1]$ $[1]$. The prevalence and incidence of kidney stones have signifcantly risen in recent decades, with global estimates ranging from 2 to 20% $[2-5]$ $[2-5]$ $[2-5]$. Common symptoms of kidney stones include lower back pain, hematuria, frequent urination, urgency to urinate, and dysuria. Kidney stones can cause serious complications such as ureteral blockage, urinary tract infections, and ultimately, end-stage renal failure $[6]$ $[6]$. Surgical intervention is often required for the treatment of kidney stones, imposing signifcant fnancial burdens, and escalating public health concerns [[1,](#page-7-0) [7\]](#page-7-4).

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Emerging research suggests that dyslipidemia plays a crucial role in the development of kidney stones, independent of other components of metabolic syndrome such as diabetes and obesity $[8-10]$ $[8-10]$. Specific alterations in lipid profles may serve as potential indicators of unique abnormalities in urine physicochemical properties and the risk of stone formation. The AIP index is a newer and more efective lipid marker, introduced by Dobiásová and Frohlich in 2001 [\[11](#page-7-7)]. It is calculated as the logarithmic transformation of TG to HDL-c ratio [[11\]](#page-7-7). Unlike TG or HDL-C levels alone, the AIP index combines both TG and HDL-C levels, providing a comprehensive refection of the ratio as well as the size of lipoprotein particles, making it a more accurate indicator of dyslipidemia pathogenicity and specifcity [\[12](#page-7-8), [13](#page-7-9)]. Previous studies have demonstrated a strong association between AIP index and various diseases, including cardiovascular diseases, diabetes, metabolic syndrome, and non-alcoholic fatty liver disease [[14–](#page-7-10)[17\]](#page-8-0).

However, to our knowledge, there have been no studies exploring the relationship between AIP index and kidney stones. This cross-sectional study utilized data from the NHANES database to investigate the relationship between the AIP index and the risk of kidney stones.

Materials and methods

Data source

This population-based study utilized data from the NHANES, conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention [\[18,](#page-8-1) [19\]](#page-8-2). NHANES employed a randomized, stratifed, multi-stage survey with nationwide representation. Participants underwent physical examinations, health and nutrition questionnaires, and laboratory assessments. The NHANES study protocol was approved by the Ethics Review Board of the National Center for Health Statistics, and detailed design can be accessed at [https://www.cdc.gov/nchs/nhanes/.](https://www.cdc.gov/nchs/nhanes/) The current study fnally consisted of 14,833 eligible participants, obtained by merging data from the NHANES cycles: 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018 (59,842 participants). All participants were aged 20 years or older, not pregnant, had complete data of AIP index, and provided comprehensive questionnaire records on kidney stones.

Exposure and outcome defnitions

The AIP index, as an exposure variable, is defined as the logarithm base 10 of the ratio between TG and HDL-c, both measured in mmol/L $[20]$ $[20]$ $[20]$. The history of kidney stones, which served as the outcome variable, was assessed by posing the question, "Have you or the sample person (SP) ever had a kidney stone?" (ID: KIQ026). Participants who responded "yes" were classifed as individuals with kidney stones, whereas those who responded "no" were categorized as individuals without kidney stones. The reliability of self-reported kidney stone history has been established in previous studies [\[4](#page-7-11), [5,](#page-7-2) [21](#page-8-4)–[24\]](#page-8-5).

Covariate defnitions

Demographic data (age, gender, and race) was obtained. It also included various potential covariates such as annual household income, educational level, physical activity, smokers, diabetes, hypertension, cardiovascular disease, BMI, alanine transaminase (ALT, U/L), aspartate transaminase (AST, U/L), gamma-glutamyl transferase (GGT, U/L), glycohemoglobin, fasting plasma glucose (FPG, mmol/L), total cholesterol (TC, mmol/L), lowdensity lipoprotein cholesterol (LDL-c, mmol/L), serum creatinine (Scr, μmol/L), serum uric acid (SUA, μmol/L), and the estimated glomerular fltration rate (eGFR, ml/ $min/1.73$ m²). BMI was classified into three categories: < 25, 25–29.9, and \geq 30 kg/m², representing normal weight, overweight, and obesity. The eGFR was calculated using the CKD-EPI creatinine equation, considering factors such as age, gender, race, and Scr [[25\]](#page-8-6). Smokers were identifed as current and former smokers. Self-reported diabetes and hypertension were also defned, and the presence of cardiovascular disease was determined based on self-reported history of heart attack, stroke, congestive heart failure, coronary artery disease, or angina. Detailed measurement procedures for all variables in this study were publicly available in the NHANES database.

Statistical analysis

All statistical analyses followed Centers for Disease Control and Prevention guidelines, incorporating a complex multistage cluster survey design, and combining fasting subsample weights from six cycles. Continuous variables were reported as mean with standard error (SE), and categorical variables as percentage. Weighted Student's t-test and chi-squared test were used to compare continuous and categorical variables among multiple groups. Weighted Pearson correlation analysis assessed the association of AIP index with other covariates. Weighted logistic regression models were employed to investigate the associations between TG, HDL-c, TG/HDL, and AIP index and the risk of kidney stones. Three Models were used: Model 1 without covariates adjusted, Model 2 with adjustments for age, gender, and race, and Model 3 with adjustments for multiple covariates including age, gender, race, annual household income, education level, physical activity, smokers, diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, glycohemoglobin,

FPG, TC, LDL, Scr, SUA, and eGFR. RCS analysis was used to further elucidate the correlation between AIP index and the risk of kidney stones. Subgroup analyses were performed based on age $\left(< 60 / \geq 60 \right)$ years), gender (female/male), race (white/no white), smokers (ye/ no), BMI (normal weight/overweight/obesity), diabetes (yes/no), hypertension (yes/no), and cardiovascular disease (yes/no). The Empower software ([http://www.](http://www.empowerstats.com) [empowerstats.com](http://www.empowerstats.com)) and R software [\(http://www.R](http://www.R-project.org)[project.org](http://www.R-project.org)) were used for all statistical analyses. A *P* value < 0.05 was considered statistically signifcant.

Results

Baseline characteristics of study population

The study finally included 14,833 participants who met the inclusion criteria. Among the entire participant cohort, a total of 1,421 individuals were found to have kidney stones. The average age of the participants was 47.59 ± 0.25 years, and 48.76% of them were male. General characteristics and clinical indicators were compared between the non-kidney stone and kidney stone groups (Table 1). The kidney stone group had higher values in terms of age, male, smokers, diabetes, hypertension, cardiovascular disease, obesity, glycohemoglobin, FPG, TG, Scr, and SUA compared to the non-kidney stone group (*P*<0.05). However, the kidney stone group exhibited signifcant decreases in moderate physical activity, HDL-c, and eGFR (P <0.05). Significant differences in race distribution were also observed between the groups (*P*<0.001). Importantly, the kidney stone group had higher AIP levels than the non-kidney stone group (*P*<0.001).

Clinical features of the participants according to the tertiles of AIP index

Participants were divided into three groups based on their AIP index levels: tertile I, tertile II, and tertile III (Table [2\)](#page-4-0). Compared to the tertile I-AIP group, the tertile II-AIP, and tertile III-AIP groups showed signifcant increases in age, male, annual household income under \$20,000, smokers, prevalence of diabetes, hypertension, cardiovascular disease, obesity, ALT, AST, GGT, glycohemoglobin, FPG, TG, TC, LDL-c, Scr, and SUA (*P*<0.001). Education level above high school and HDL-c exhibited signifcant decreases (*P*<0.001). Signifcant diferences in race were also observed among the tertile groups (*P*<0.001). No diferences in moderate physical activity were observed between groups. Importantly, as AIP levels increased, the prevalence of kidney stones showed a gradual increase (7.33% vs. 9.97% vs. 12.57%, *P*<0.001).

Correlation of AIP index with clinical parameters

Weighted Pearson correlation analysis revealed signifcant correlations between the AIP index and various variables (Table [3](#page-5-0)). Specifcally, the AIP index was positively correlated with age, male, race, annual household income under \$20,000, smokers, prevalence of diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, glycohemoglobin, FPG, TG, TC, LDL-c, Scr, and SUA, and kidney stones. On the other hand, the AIP index was negatively correlated with education level above high school, HDL-c, and eGFR. After adjusting for age, gender, and race, except for moderate physical activity, AST, and Scr, the AIP index remained signifcantly correlated with the other variables.

Associations between the AIP and kidney stones

Table [4](#page-5-1) presents the association between the AIP index and the risk of kidney stones. The unadjusted models showed that TG, TG/HDL-c, and AIP index were positively associated with an increased risk of kidney stones $(P<0.001)$, while HDL-c was negatively associated with the prevalence of kidney stones $(P<0.001)$. After adjusting for age, gender, and race, these associations remained statistically signifcant (*P* < 0.05). Further adjustment for multiple covariates revealed that only HDL-c and AIP index were related to the risk of kidney stones. The results indicated a 32% increased risk of kidney stones per unit increase in AIP index (OR=1.32, 95% CI 1.08–1.61, *P*=0.006). Classifcation of AIP index into teritles showed that higher AIP teritles levels were associated with a higher prevalence of kidney stones compared to the lowest teritles in the fully adjusted model (*P* for trend < 0.001). Furthermore, the results of RCS analysis also confrmed a positive correlation between AIP index and kidney stones (Fig. [1](#page-6-0)), with no signifcant threshold efect observed (*P* for nonlinear > 0.05).

Subgroup analyses

Subgroup analyses were performed to investigate the relationship between AIP index and the risk of kidney stones in various population. Subgroups were stratifed by various factors, including age $\left(< 60 / \geq 60 \right)$ years), gender (female/male), race (white/no white), smokers (yes/no), BMI (normal weight/overweight/obesity), diabetes (yes/ no), hypertension (yes/no), and cardiovascular disease (yes/no). Figure [2](#page-6-1) illustrates the results of these analyses, which revealed no signifcant interactions among the subgroups (P for interaction > 0.05). However, there is a trend towards a stronger association between AIP index and kidney stones in individuals with diabetes.

Table 1 Baseline characteristics of study population in NHANES from 2007 to 2018, weighted

Values for categorical variables are given as weighted percentage (standard error); for continuous variables, as weighted mean±standard error. Weighted Student's t-test and chi-squared test were used

Abbreviations: *BMI* body mass index, *ALT* alanine transaminase, *AST* aspartate transaminase, *GGT* gamma-glutamyl transferase, *FPG* fasting plasma glucose, *TG* triglyceride, *TC* total cholesterol, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *Scr* serum creatinine, *SUA* serum uric acid, *eGFR* estimated glomerular fltration rate, *AIP index* atherogenic index of plasma

Discussion

To our knowledge, this is the frst population-based study to explore the relationship between AIP index and the risk of kidney stones. Our research indicated that AIP index is associated with the risk of kidney stones in the US population ($OR = 1.32$, 95% CI 1.08– 1.61, *P*=0.006). Compared to simple TG, HDL-c, and TG/HDL-c, the AIP index is a promising epidemiological tool that can quantify the role of dyslipidemia in the risk of kidney stones.

Previous studies have shown that serum lipid profles also afect urinary metabolite profles and stone composition. Patients with low HDL-c or high TG exhibit signifcantly increased levels of urinary sodium, oxalate, and uric acid, as well as lower pH values [\[8](#page-7-5), [26\]](#page-8-7). Additionally, lipid-lowering medications, such as atorvastatin, have been shown to signifcantly alter urinary citrate, uric acid, and urinary pH levels [[27\]](#page-8-8). Masterson et al. propose that metabolic syndrome may partially explain the impact of dyslipidemia on the formation of kidney

Values for categorical variables are given as weighted percentage (standard error); for continuous variables, as weighted mean±standard error. Weighted Student's t-test and chi-squared test were used

stones, as dyslipidemia is one of the diagnostic criteria for metabolic syndrome [\[28](#page-8-9), [29\]](#page-8-10). Dyslipidemia is also closely associated with insulin resistance. Additionally, elevated levels of AIP index have been suggested as indicative of insulin resistance [[30](#page-8-11)]. Insulin resistance can impair ammonia excretion and increase renal tubular uptake of citrate, contributing to high urinary acidity and reduced citrate levels, respectively, which are major risk factors for uric acid and calcium stone formation [\[31](#page-8-12)]. Moreover, evidence suggests that dyslipidemia, which mediates infammation, is an independent risk factor for increased stone formation [\[21](#page-8-4), [32](#page-8-13), [33](#page-8-14)]. Some scholars also suggest that the accumulation of atherosclerotic plaques may lead to calcifcation, subsequently eroding into the Bellini collecting ducts, further increasing the likelihood of stone growth [[34](#page-8-15)]. It is evident that dyslipidemia can have a multifactorial impact on the formation of kidney stones.

In this study, we observed a correlation between high TG levels, low HDL-c levels, TG/HDL-c, and AIP index with the formation of kidney stones. However, it is worth noting that, after adjusting for various confounding factors, only HDL-c and AIP index maintained this correlation. Previous studies have shown that AIP index, the logarithmic ratio of TG to HDL-C, not only quantifes lipid metabolism, but also shows signifcant associations with small dense low-density lipoproteincholesterol (sdLDL-C) and glucose metabolism [[35,](#page-8-16) [36](#page-8-17)].

 $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{2}$

Table 4 Logistic regression analysis results of AIP index and kidney stones, weighted

Adjusted model 2: age, gender, and race were adjusted

Adjusted model 3: additionally adjusted for annual household income, education level, physical activity, smokers, diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, glycohemoglobin, FPG, TC, LDL, Scr, SUA, and eGFR

OR odds ratio, *95% CI* 95% confdence interval

Fig. 1 RCS results of AIP index and the risk of kidney stones (**a** no covariates adjusted; **b** adjusted for age, gender, race, annual household income, education level, physical activity, smokers, diabetes, hypertension, cardiovascular disease, BMI, ALT, AST, GGT, glycohemoglobin, FPG, TC, LDL, Scr, SUA, and eGFR)

0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4

Fig. 2 Subgroup analysis results based on age, gender, race, smokers, BMI, diabetes, hypertension, and cardiovascular disease

Other studies have also demonstrated that AIP index is a simple and useful tool for identifying insulin-resistant patients at higher cardiovascular risk, proving more efective than the conventional visceral adiposity index [[36,](#page-8-17) [37](#page-8-18)]. Therefore, consistent with previous research fndings, we also believe that the AIP index, as a novel comprehensive lipid indicator, may have clinical signifcance that surpasses the impact of individual TG and HDL-c levels and the simple ratio of the two on kidney stone formation $[38, 39]$ $[38, 39]$ $[38, 39]$. The AIP index is anticipated to serve as a quantifable marker that connects metabolic syndrome and obesity to the risk of kidney stones. Moreover, the comparative efficacy of the AIP index versus other metabolic indicators, such as the triglycerideglucose index (TyG), requires further investigation.

This study used a nationally representative sample that adequately represented the various ethnic groups in US adults [\[24](#page-8-5)]. However, it is important to recognize the limitations of our study. Firstly, the cross-sectional design used does not allow us to establish a cause-and-efect relationship between the AIP index and the risk of kidney stones. Prospective cohort studies and intervention trials are needed to determine if such a relationship exists. Secondly, although adjustments were made for some common confounding factors in this study, it did not consider the history of diseases like metabolic syndrome and nonalcoholic fatty liver disease, the use of medications such as lipid-lowering drugs that afect lipid levels, or dietary habits including water and meat consumption, which could lead to biased findings. Thirdly, given that our research is an exploratory preliminary analysis of existing data, we were unable to gather detailed information on kidney stones, such as their quantity and composition, which limited further analysis. Lastly, our study was conducted using a sample from the US population, so further research is needed to confrm the generalizability of our fndings.

Conclusion

In a nationally representative study of an adult population in the United States, we uncovered a compelling correlation between the AIP index and a heightened susceptibility to kidney stones.

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Authors' contributions

Z.W. and B.L. wrote the main manuscript text. L.Z., F.T., and Y.P. prepared fgures and tables. S.Z. reviewed the manuscript.

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Availability of data and materials

Data was collected from the NHANES database, which is a publicly accessible and free resource [\(https://www.cdc.gov/nchs/nhanes/](https://www.cdc.gov/nchs/nhanes/)).

Declarations

Ethics approval and consent to participate

This study involving human participants were reviewed and approved by the Ethics Review Board of the National Center for Health Statistics. The patients/ participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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