Original Article

Causal associations of inflammatory cytokines and urinary stones: a two-sample Mendelian randomization study

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Background: Prior research has shown potential changes in cytokine and growth factor levels in patients with urinary stones, but the causal relationship remains uncertain. The purpose of this study was to investigate the causal relationship between cytokine and growth factor levels and urinary tract stones.

Methods: This study used a two-sample Mendelian randomization (MR) with 41 circulating cytokines and growth factors datasets alongside urinary stone disease (USD) data. It employed various analytical methods including inverse variance weighted (IVW) analysis, maximum likelihood estimation, MR-Egger regression, weighted median approach, simple median method, and weighted mode to establish causal relationships. Sensitivity analysis included the MR-Egger regression intercept test and Cochrane's Q statistic.

Results: Using the IVW method, an increase in stem cell growth factor β levels was associated with decreased urinary stone risk [odds ratio (OR) =0.9990; 95% confidence interval (CI): 0.9980–0.9999; P=0.04]. Conversely, an increase in interleukin-18 levels elevated the risk of urinary stones (OR =1.0012; 95% CI: 1.0002–1.0022; P=0.01). Various analytical methods consistently supported these findings.

Conclusions: Our findings suggest a causal and unidirectional relationship between interleukin-18, stem cell growth factors, and USD. This indicates that these cytokines may actively contribute to the development or prevention of USD, offering a new avenue for clinical intervention based on cytokines modulation.

Keywords: Inflammatory cytokines; urinary stones; Mendelian randomization study (MR study)

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Introduction

Background

The Mendelian randomization (MR) framework is an epidemiologic method that employs genetic variants as instrumental variables (IVs) to bolster causal interpretations in the relationship between an exposure and an outcome (1). This approach helps reduce lingering confounding and the risk of reverse causality, given that genetic variants are randomly allocated during meiosis and remain constant post-fertilization (2,3). MR relies on genetic variants as tools to infer causality, necessitating that these variants are closely linked to the exposure, not associated with confounders, and influence the outcome only through the exposure, ensuring no direct effect on the outcome bypassing the exposure (4). In this context, we executed an MR analysis to evaluate the links between inflammatory cytokines and urinary stone development. This approach enables the estimation of the influence on traits while minimizing biases arising from confounding factors and reverse causation. Expanding

on this, it is important to highlight that the MR method leverages genetic variants as IVs, offering a more robust inference on causality than observational studies alone. This methodology allows for a deeper understanding of how sleep patterns may directly influence the risk of developing urinary stones, providing insights that could inform preventive strategies or contribute to the development of new treatment approaches based on sleep regulation.

Kidney stone is a very common disease with a high incidence rate. The recurrence rate of urinary stones is estimated to be up to 50% (5). Nephrolithiasis is associated with increased risk of chronic and end-stage kidney disease. Surgical procedures are effective in removing existing kidney stones but do little to prevent their frequent recurrence. The formation of urinary stones may be the result of multiple factors, including metabolic disorders and genetics anatomy and functional abnormalities, nutrition, etc. Numerous epidemiological studies have sought to identify potentially modifiable risk factors that could be adjusted to lower the incidence of urinary stones. These factors include obesity (6), cardiometabolic conditions such as hypertension, dyslipidemia, type 2 diabetes, and glycemic traits (7,8), as well as diet (9), lifestyle (10), and mineral concentrations in blood and urine (11).

Cytokines are low molecular weight (~6–70 kDa) soluble proteins secreted by various cells, including lymphocytes, macrophages, natural killer (NK) cells, mast cells, and stromal cells. Cytokines regulate the maturation, growth, and responsiveness of immune cells, making them vital for health (12,13). A single cytokine can be produced by multiple cell types and can influence various cell types, resulting in a range of biological activities (14). Variations in cytokine levels in different biological fluids such as serum, blood, stool, saliva, and sweat provide essential information for the diagnosis, stage, and prognosis of various diseases. Therefore, Cytokines are critical mediators that oversee and regulate immune and inflammatory responses via complex networks and serve as biomarkers for many diseases, such as atherosclerosis (15), heart disease (16), acquired immunodeficiency syndrome (AIDS) (17), rheumatoid arthritis (18), and other diseases. Cytokines are implicated in urolithiasis by modulating inflammatory responses in the urinary tract, which can influence stone formation and aggregation. Their levels in urine and blood can reflect the extent of inflammation and may serve as biomarkers for stone presence and activity. Investigating the causal relationship between cytokines and urolithiasis is essential to understand the underlying mechanisms of stone formation and identify potential targets for therapeutic intervention and prevention.

Highlight box

Key findings

- This study found a causal relationship between interleukin-18, stem cell growth factor β levels, and urinary calculi. It was demonstrated that elevated interleukin-18 levels significantly increase the risk of developing kidney stones, while increased levels of stem cell growth factor β are associated with a reduced risk.

What is known and what is new?

- Previous research has indicated that cytokines are related to urinary stone formation by modulating inflammatory responses in the urinary tract, which can affect the formation and aggregation of stones. Their levels in urine and blood can reflect the degree of inflammation and may serve as biological markers for the presence and activity of stones.
- This study innovatively employed data from publicly available genome-wide association studies and Mendelian randomization analysis techniques to explore the causal relationship between cytokines and urolithiasis.

What is the implication, and what should change now?

- These findings not only strengthen the critical regulatory role of cytokines in the pathogenesis of urolithiasis but also identify them as promising biomarkers and therapeutic targets, which is crucial for understanding the potential mechanisms underlying stone formation and for identifying potential targets for therapeutic intervention and prevention.

Objective

Therefore, this study employs data from publicly available genome-wide association studies (GWAS) databases and the MR analysis technique to explore the causal relationship between cytokines and urolithiasis. By doing so, it significantly contributes to unraveling the pathophysiological mechanisms underlying stone formation in the urinary tract (19). Understanding these causal links is crucial for developing more targeted and effective treatments, as well as preventive strategies, potentially leading to better clinical outcomes for individuals affected by this condition (20). We present this article in accordance with the STROBE-MR reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-445/rc).

Methods

Study design

In our study, we employed a two-sample MR approach to examine the impact of inflammatory cytokines on the risk of urinary stones using publicly available summary datasets from two GWAS (21). Specifically, we considered various forms of inflammatory cytokines, including chemokines, growth factors, interleukins, and others, as the exposures, while urinary stones served as the outcome of interest (22). To establish IVs, we meticulously selected single nucleotide polymorphisms (SNPs) strongly linked to various forms of environmental pollution (23). The MR framework meets three core requirements: (I) genetic IVs are closely related to exposure (inflammatory cytokines). (II) Genetic IVs are unrelated to potential confounding factors. (III) Genetic IVs can only influence the outcome (urinary stones) through the exposure (inflammatory cytokines). By following these requirements, we aimed to clarify the causal relationship between inflammatory cytokines and the risk of urinary stones.

Summary data resources

Inflammatory cytokines

The dataset for inflammatory cytokines originated from research analyzing genetic variant links to 41 cytokines and growth factors in a Finnish cohort of 8,293 individuals (24). This research integrated findings from the Cardiovascular Risk in Young Finns Study (YFS) and the FINRISK studies, with mean participant ages at 37 years for YFS and 60 years for FINRISK. Cytokine levels were determined using samples of ethylenediaminetetraacetic acid (EDTA) plasma, heparin plasma, and serum from the participants. The analysis included only those cytokine measurements that were within the assay's detectable limits, excluding any cytokine where over 90% of the data were missing (which affected seven out of 48 cytokines).

Urinary stones

Summary statistics from a GWAS meta-analysis of tuberculosis were obtained from the UK Biobank consortium. All urinary stones data, including both male and female European populations, were derived from the same study, involving more than 16 million SNPs (25). For our MR analyses, we utilized SNPs as IVs for urinary stones, referencing GWAS ID: ebi-a-GCST90038631, which includes 3,725 cases and 480,873 controls. The analysis was based on summary statistics accessible from the IEU GWAS database (https://gwas.mrcieu.ac.uk/). We specifically chose SNPs with corresponding summary data [including P values, β effects, and standard errors (SEs)] from research that involved participants of European descent to mitigate population stratification bias. This study is a secondary analysis of publicly available GWAS data. Each original GWAS study received ethical approvals and informed consents were obtained from all participants. As such, no additional ethical approval is required for this secondary analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Selection of IVs

We conducted thorough quality control procedures to pinpoint genetic predictors linked to inflammatory cytokine traits. In the initial stage, we adopted a stringent genome-wide significance threshold of $P<5\times10^{-8}$ to identify SNPs highly associated with inflammatory cytokines and urinary stones. To ensure the MR assumptions were met, we performed a linkage disequilibrium (LD) analysis using data from the European-based 1,000 Genomes Project. SNPs that did not meet the criteria ($R^2<0.001$, clumping distance =10,000 kb) were excluded from further analysis. Due to the uncertainty in the alignment of exposure and outcome in pulmonary embolism GWAS, palindromic SNPs have also been discarded. SNPs with a minor allele frequency (MAF) lower than 0.01 were excluded from the analysis. In cases where SNPs associated with the exposure variable were absent from the outcome GWAS dataset, we utilized proxy SNPs exhibiting high LD ($R^2>0.80$) to ensure comprehensive representation. The strength of the instruments was evaluated by calculating the F statistic using the formula $F = R^2 \times (n - 2)/(1 - R^2)$, where R^2 denotes the variance proportion explained by the IVs and n indicates the sample size. An F statistic below 10 suggests a greater risk of weak instrument bias, thereby necessitating caution in result interpretation.

Statistical analysis

The primary analysis for the MR study used the inverse variance weighted (IVW) method. In order to ensure the reliability of the research results (26), our team also conducted sensitivity analyses, including maximum likelihood estimation, MR-Egger regression, weighted median, simple median, and weighted mode. If the IVW method produced statistically significant results ($P<0.05$),

the outcome was considered positive even if other methods did not reach significance, providing that the direction of the β values was consistent. For assessing autoimmune diseases, odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated, with a significance threshold of P<0.05. Cochran's Q test was used to assess heterogeneity in the IVW and MR-Egger estimates. The MR-Egger regression method was applied to investigate potential pleiotropic bias. To evaluate the stability of the results, a systematic "leave-one-out" analysis was performed, where one SNP was excluded at a time to determine its impact on the overall findings. All analyses were performed in the R software environment (version 4.0.3) using the TwoSampleMR package (version 0.5.5). The use of these rigorous analytical methods is to ensure that the research findings possess reliability and validity.

Results

Selection of genetic instruments

To investigate the relationship between inflammatory cytokines and urinary stones, we conducted a two-sample MR analysis, considering nine environmental pollution characteristics associated with pulmonary embolism (27). We selected robust genetic tools (P values $<5\times10^{-8}$) for the characterization of inflammatory cytokine. To confirm their independence ($R^2<0.01$), it is necessary to excluding palindromic SNPs. The F-statistics of the IVs are all significantly greater than 10, demonstrating that weak instrument bias was not a concern.

Causal effect of inflammatory cytokines on urinary stones risk

Using an IVW method, we discovered that a standard deviation increase in stem cell growth factor β levels reduced the risk of urinary stones (OR =0.9990; 95% CI: 0.9980–0.9999; P=0.04) (*Figure 1A-1D*). Negative correlations between stem cell growth factor β levels and urinary stones were also identified through maximum likelihood, MR-Egger, weighted median, simple median, and weighted mode methods. Additionally, we observed that a standard deviation increase in interleukin-18 levels heightened the risk of urinary stones (OR =1.0012; 95% CI: 1.0002–1.0022; P=0.01) (*Figure 1E-1H*). Positive associations between interleukin-18 levels and urinary stones were further confirmed by the maximum likelihood, MR-Egger, weighted median, simple median, and weighted mode approaches (*Figure 2*).

Sensitivity analyses

The causal effect estimates derived from various methods, including maximum likelihood, MR-Egger regression, and various median and model-based methods, showed alignment in both effect size and direction, affirming the reliability of our results. The lack of substantial evidence for horizontal pleiotropy, indicated by MR-Egger regression intercept P values above 0.05, suggests the IVs were not affected by extraneous factors unrelated to the exposure under study. Cochrane Q statistics, indicating no significant heterogeneity (P>0.05), reinforce the idea that the genetic variants acted consistently across different methods. The stability of effect estimates, confirmed through leave-one-out sensitivity analysis, where no single variant disproportionately affected the results, underscores the robustness of our findings. These analyses collectively validate a consistent and dependable association between inflammatory cytokines and the risk of urinary stones, devoid of significant confounders or influential outliers.

Discussion

Urolithiasis, or urinary stone disease (USD), is a prevalent medical condition characterized by the formation of stones in the urinary system, leading to significant morbidity and healthcare costs. Patients often experience recurrent episodes and severe pain, with current treatment options primarily focused on symptom management and stone removal rather than prevention. The medical community faces challenges in identifying effective preventive measures and understanding the complex etiology of stone formation, which involves dietary, genetic, and environmental factors (28). The prevalence of urolithiasis is on the rise, with a high rate of recurrence. In pediatrics, the majority of stones are primarily composed of calcium, and the incidence is highest among adolescents. Given the morbidity associated with USD, it is crucial to identify the mechanisms of stone formation and significant contributing factors (29). Recent advancements in urolithiasis research have highlighted the significant role of cytokines in stone formation, underscoring a complex interplay between inflammatory processes and stone pathogenesis. Studies increasingly focus on how cytokines influence the urinary environment, potentially altering crystal aggregation and stone development, providing new insights into potential

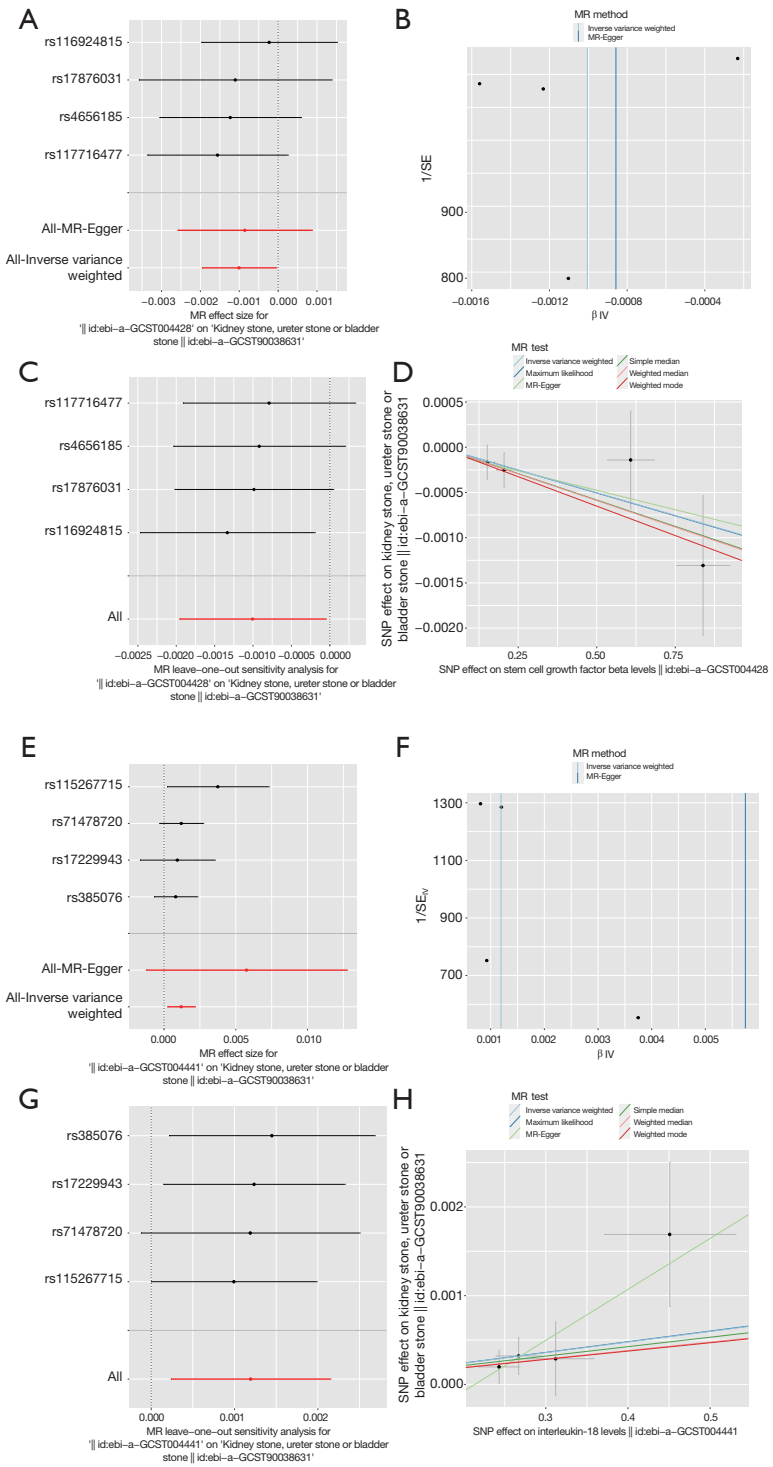

Figure 1 MR analysis of interleukin-18 and stem cell growth factor. (A) Forest map of stem cell growth factor. (B) Funnel plot of stem cell growth factor. (C) Leave-one-out method of stem cell growth factor. (D) Scatter diagram of the effect of SNPs on stem cell growth factor β levels. (E) Forest map of interleukin-18. (F) Funnel plot of interleukin-18. (G) Leave-one-out method of interleukin-18. (H) Scatter diagram of the effect of SNPs on interleukin-18 levels. MR, Mendelian randomization; SE, standard error; IV, instrumental variable; SNP, single nucleotide polymorphism.

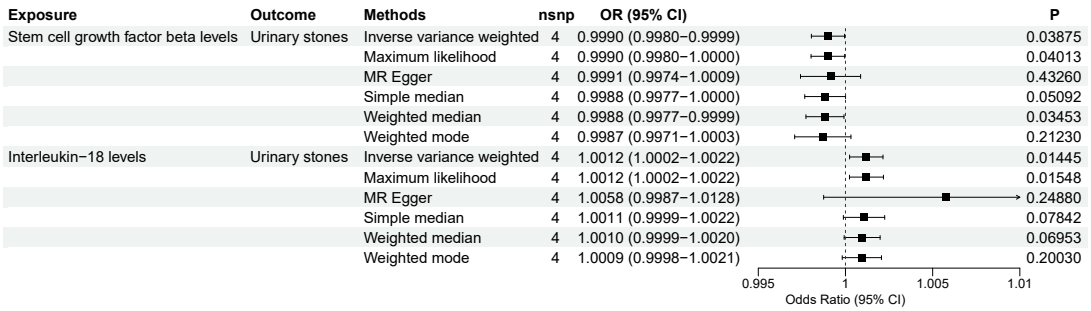

Figure 2 MR analysis of forest map. OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

therapeutic targets and prevention strategies (30). Through our MR analysis in this study, we have identified a causal relationship between cytokines and urolithiasis. This finding underscores the significant role that cytokines play in the formation of urinary stones, providing a potential pathway for intervention and a deeper understanding of the disease's etiology. Cytokines, low molecular weight soluble proteins secreted by various cells such as lymphocytes, macrophages, and mast cells, play a pivotal role in immune responses and serve as crucial components in the immune system's communication network (31). They are key in regulating immune cell growth, maturation, and function, significantly influencing health. These proteins, produced by multiple cell types, have diverse effects on different cells, contributing to their multifaceted biological functions (32). The presence and levels of cytokines in body fluids like serum, saliva, and sweat are critical for diagnosing and assessing the progression and prognosis of numerous conditions. Elevated cytokine levels, as seen in cytokine storm syndromes like those in severe coronavirus disease 2019 (COVID-19) cases, can result in severe outcomes including organ failure and mortality (33). Considering their pivotal function in regulating immune reactions, a wide array of cytokines has been recognized as prospective treatments for different types of cancer (34). Currently, a number of cytokines, such as recombinant interleukin-2 (IL-2), interferon alpha (IFNα), and tumor necrosis factor (TNF), have received clinical approval for use in cancer immunotherapy (35). Thus, cytokine measurement is vital for disease monitoring and tailoring treatments in various conditions, ranging from cancer and heart disease to autoimmune disorders and chronic illnesses, highlighting their importance in clinical diagnostics and therapeutic management. Recent advancements in research have begun to elucidate the role of cytokines in the pathogenesis of urolithiasis, shedding light on the intricate mechanisms through which these signaling proteins influence stone formation. Cytokines, integral to immune response modulation and cellular communication, are now understood to contribute significantly to the inflammatory processes associated with urinary stone development. Their levels in patients with urolithiasis offer insights into the inflammatory state and potential therapeutic targets, highlighting the importance of cytokines not only as biomarkers for disease activity but also as potential modulators in the stone formation process. This burgeoning area of study holds promise for unveiling novel preventive and therapeutic strategies, potentially transforming the management of urolithiasis by targeting cytokine-mediated pathways (36).

MR analysis offers a significant advantage in elucidating the relationship between cytokines and urolithiasis when compared to traditional observational studies. This analytical approach leverages genetic variants as IVs, providing a more robust method for inferring causality by minimizing the confounding and bias often inherent in observational research. The MR method allows researchers to circumvent some of the limitations of traditional studies, such as reverse causation and residual confounding, thereby offering clearer insights into the causal pathways between cytokines and stone formation in the urinary tract. By integrating MR analysis with observational data, researchers can validate findings and gain a more comprehensive understanding of the biological mechanisms at play, enhancing the potential for identifying targeted interventions for urolithiasis prevention and treatment. This combination marks a significant development in the field, propelling forward our understanding of how cytokines influence urolithiasis and opening new avenues for clinical application.

Conclusions

This study systematically establishes a causal relationship

between interleukin-18, stem cell growth factors β levels, and urolithiasis, highlighting the pivotal role of cytokines in the development and prevention of urinary stones. Using a two-sample MR analysis, we demonstrated that elevated levels of interleukin-18 significantly increase the risk of urinary stones, whereas higher levels of stem cell growth factors β are associated with a reduced risk. These findings not only reinforce the critical regulatory role of cytokines in the pathogenesis of urolithiasis but also identify them as promising biomarkers and therapeutic targets.

However, this study has not incorporated a compositional analysis of urinary stones, which represents an important limitation. Investigating the chemical and mineral composition of calculi (e.g., calcium oxalate, uric acid, and phosphate stones) could provide deeper insights into the specific mechanisms by which cytokines influence stone formation and whether their effects vary based on stone type. Future research should address this gap by integrating cytokine data with stone composition analysis to better understand these relationships. Additionally, validating these findings through larger-scale GWAS and further exploring the therapeutic potential of cytokine modulation remain crucial next steps.

By advancing our understanding of cytokine-mediated mechanisms and addressing the role of stone composition, this study lays a foundation for precision medicine approaches, opening new avenues for targeted interventions in urinary stone management and prevention.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-445/rc

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