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Aortic Calcification in Patients with Nephrolithiasis: A Cross-Sectional Case-Control Study

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Abstract

Background: Nephrolithiasis is a common condition that has been linked to various systemic diseases. Recent studies have suggested that young patients with nephrolithiasis are at increased risk of developing premature atherosclerosis. This study aims to investigate the relationship between nephrolithiasis and systemic disease by examining the association between aortic calcification and the severity of kidney stone disease.

Methods: This study employed a matched case-control design involving 144 patients with kidney stones and 144 non-stone formers. All participants underwent non-contrast abdominal and pelvic CT scans. The Agatston score was used to quantify the severity of aortic calcification. The data were analyzed and compared between the two groups. Quantitative data were analyzed using Pearson's chi-square test. Non-parametric data were analyzed using the Mann-Whitney test.

Results: The Agatston score was measured in both case and control groups, with mean values of 316±734 and 231±706, respectively. However, the difference between the two groups was not statistically significant (P = 0.122). Notably, a significant correlation was observed between Agatston score and stone size (P = 0.014). The value of the correlation coefficient is 0.23, which shows the increase in severity of aortic calcification with increasing stone size. A comparison of the Agatston score between male kidney stone formers patients aged 45 years or younger and controls revealed a statistically significant difference, with a p-value of 0.049, indicating more pronounced aortic calcification in the patient group.

Conclusion: These results suggest that there may be a shared pathophysiological mechanism underlying both nephrolithiasis and atherosclerosis.

Keywords: Atherosclerosis, Nephrolithiasis, Radiology

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Introduction

Nephrolithiasis, a common condition affecting millions worldwide, has been linked to various systemic diseases, including cardiovascular disorders, hypertension, and metabolic syndrome (1-3). This association suggests that nephrolithiasis may be a systemic condition with implications beyond the kidneys (4). The underlying mechanisms re-

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↑What is "already known" in this topic:
Recent studies have implicated nephrolithiasis as a systemic disorder associated with several medical conditions, including osteoporosis and vascular calcification.

→What this article adds:
Our research reveals a substantial association between stone size and Agatston score, a widely used metric for assessing aortic calcification. The results of this study provide further evidence that nephrolithiasis and vascular calcification share a common pathophysiological mechanism, which is influenced by similar risk factors.

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main unclear, but recent studies have shown that young patients with nephrolithiasis are at increased risk of developing premature atherosclerosis (5).

Vascular calcification (VC) is a well-established cardiovascular risk factor that predicts future cardiovascular events and is associated with diabetes mellitus and reduced bone density (6, 7). Abdominal aortic calcification (AAC) is commonly observed in patients with risk factors for coronary artery disease (7, 8), and high-resolution computed tomography (CT) scans can help assess the risk of cardiac-related events.

Reduced bone density is a common finding among kidney stone formers (KSFs) (9), and extra-osseous calcium deposition and bone demineralization may play a role in the development of nephrolithiasis and VC (10). The "Agatston score" (AS) is a widely used method for evaluating coronary artery calcification using CT scans (11). Interestingly, this score has also been employed to assess aortic calcification in some studies (12).

This study aimed to investigate the relationship between the severity of aortic calcification, as measured by the Agatston score, and the severity of kidney stone disease.

Methods

Subjects and Setting

This is a cross-sectional case-control study. Prior to any intervention, all participants provided written informed consent. The study included all patients with kidney stones who were referred to the urology department from July 2017 to February 2021. However, only patients with calcium stones were included in the analysis. Patients with coexisting diseases, such as primary hyperparathyroidism, sarcoidosis, intestinal malabsorption, and renal tubular acidosis, were excluded from the study.

A total of 144 kidney stone former (KSF) patients aged 25 to 65 years old were included in the study. After obtaining informed consent, a non-contrast abdominal and pelvic CT scan was performed for all patients. All KSF patients were consulted by a nephrologist. If necessary, laboratory tests such as calcium, phosphorus, Parathyroid hormone, Arterial Blood Gas, Blood Urea Nitrogen, creatinine, serum electrolytes, and urine PH were performed to investigate the patients. In case of suspicion of sarcoidosis, patients were evaluated with a chest X-ray. As a control group, a total of 144 age- and sex-matched non-stone formers were selected from the list of patients admitted to the emergency department due to trauma. These patients had undergone non-contrast abdominal CT scans as part of their diagnostic procedures. Following informed consent, they were included in the study. Demographic and clinical variables, including age, sex, weight, smoking history, and other comorbidities such as cardiovascular events, diabetes, hypertension, peripheral vascular disease, and cerebral vascular accident, were collected.

Computerized Tomography (CT) Imaging for Measurement of AS and stone size

The CT images, viewed in both soft tissue and bone windows, were assessed for aortic calcification. A blinded radiologist measured the AAC using the Agatston method with a 3D slicer (a platform for subject-specific image analysis, visualization, and clinical support). Calcified plaques from the origin of the celiac axis to the level of the aortic bifurcation were identified using threshold segmentation with a density greater than 130 HU. Manual selection was then used to exclude non-plaque regions that were incorrectly segmented. For each plaque, the total number of pixels was attributed to the area of the plaque. Subsequently, the highest density within each plaque was determined and a density factor was assigned: 1 for 130-199 HU, 2 for 200-299 HU, 3 for 300-399 HU, and 4 for ≥ 400 HU. Finally, we calculated AS by multiplying the area of each plaque by its density factor and then summed the results of all segmented plaques (8). Manual CT-based stone size measurements were performed using multi-planar image reformatting with a bone window setting. The stone burden was characterized by the total volume of all stones in the scan.

Outcomes

In this study, the outcome of interest is aortic calcification (measured by the Agatston score). The exposure is kidney stone disease, and the predictor variables are age and sex. The potential confounders are factors that could affect the relationship between kidney stone disease and aortic calcification, such as risk factors for atherosclerosis, lifestyle factors, and medical comorbidities. The effect modifiers are age, sex, and stone size. Overall, the study aims to investigate the relationship between kidney stone disease and aortic calcification and to identify potential predictors and confounders that may influence this relationship.

Statistical analysis

To assess the severity of aortic calcification, patients were classified into four groups based on their Agatston scores: mild (1-100), moderate (101-400), severe (>400), and no aortic calcification (0). Additionally, the size of the kidney stones was categorized into three groups: less than 20 millimeters (mm) (n = 32), 20-30 mm (n = 52), and more than 30 mm (n = 60), as well as cases without any stones (n = 144).

Statistical analysis was conducted using SPSS version 22 statistical software (IBM Corp., Armonk, NY, USA). Quantitative data were analyzed using Pearson's chi-square test. Non-parametric data were analyzed using the Mann-Whitney test. A *P*-value less than 0.05 was considered statistically significant.

Results

In this study, all participants were within the age range of 25 to 65 years. The mean age was 47.81 ± 13.66 years for kidney stone formers (KSFs) and 47.11 ± 10.74 years for non-stone formers. The gender distribution was relatively balanced, with 62.5% of KSFs and 66.6% of non-stone formers being male. Importantly, there were no significant differences between the two groups with respect to age, gender, or other clinical and demographic features (Table 1).

The Agatston score (AS), used to evaluate aortic calcification, was 316 ± 734 for kidney stone formers (KSFs) and 231 ± 706 for non-stone formers. There was no significant difference in the Agatston score between the two groups (*P*

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Table 1. Comparison of clinical and demographic features between two groups

Variable	Case (N=144)	Control (N=144)	*P*-value
Gender (Male/Female)	90/54	96/48	0.601
Age (Mean±SD)	47.81±13.66	47.11±10.74	0.640
BMI* (Mean±SD)	26.6± 2.5	26.2± 2.9	0.422
Smoking history	30	27	0.100
Diabetes mellitus	13	11	0.151
Hypertension	25	23	0.226
Cardiovascular events	5	3	0.111

* Body mass index

Table 2. Comparison of Agatston score severity based on different stone sizes

Agatston score severity	Stone Size				Total (%)	*P*-value
	No stone	<20mm	20≤size≤30	>30 mm		
No Calcification	96 (55.8%)	22 (12.8%)	32 (18.6%)	22 (12.8%)	172 (100.0%)	
Mild	12 (35.3%)	2 (5.9%)	8 (23.5%)	12 (35.3%)	34 (100.0%)	
Moderate	20 (55.6%)	4 (11.1%)	6 (16.7%)	6 (16.7%)	36 (100.0%)	
Severe	16 (34.8%)	4 (8.7%)	6 (13.0%)	20 (43.5%)	46 (100.0%)	0.014
Total (%)	144 (50.0%)	32 (11.1%)	52 (18.1%)	60 (20.8%)	288 (100.0%)	

Table 3. Association between gender, age, and Agatston score in KSFs* and the control group

Age	Gender	Number	Agatston Score (Mean ± SD)	*P*-value
<=45 years	Male	Case: 46	117±495	0.049
		Control: 54	1±4	
	Female	Case: 16	60±169	0.350
		Control: 14	0±0	
>45 years	Male	Case: 44	584±1040	0.392
		Control: 42	466±1093	
	Female	Case: 38	353±617	0.795
		Control: 34	402±709	

* KSF: Kidney Stone Former

= 0.122).

The relationship between stone size and aortic calcification severity was examined using Spearman's correlation coefficient. The analysis showed a significant correlation between stone size and aortic calcification severity, with a correlation coefficient of 0.23 (P = 0.014). This suggests that as stone size increases, the severity of aortic calcification also increases. The categorized Agatston score severity was used to assess the severity of aortic calcification (Table 2).

The study also examined the association between gender, age, and Agatston score (AS) in kidney stone formers (KSFs) and the control group (Table 3). Male KSF patients aged 45 years or younger exhibited more severe aortic calcification rates compared to those in the control group, with a *P*-value of 0.049.

Discussion

The results of our study provide evidence supporting the vascular theory of nephrolithiasis, which suggests that kidney stones may be a manifestation of a systemic disorder that affects not only the kidneys but also other organs and tissues (1, 13, 14). The findings of our study demonstrate a significant correlation between stone size and Agatston score (AS), which is a measure of aortic calcification. This suggests that larger kidney stones may be associated with increased vascular calcification.

Our results are consistent with previous studies that have reported an association between nephrolithiasis and vascular calcification. For example, Shavit et al. (1) conducted a retrospective analysis of CT scans and found that patients with kidney stones (KSFs) had a higher severity score for aortic calcification compared to non-stone formers. They also reported that the average CT bone density was lower in KSFs compared to the control group. These findings suggest that augmented calcium depositions in kidneys and blood vessels may be an underlying mechanism in nephrolithiasis.

Stern et al. (13) found that patients with kidney stones (KSFs) had insignificantly higher rates of aortic and splenic calcification compared to healthy individuals. However, KSFs were more likely to have intermediate or severe aortic calcification than non-stone formers.

Hormonal changes that occur after menopause provide sufficient explanation for osteoporosis, urolithiasis, and arteriosclerosis (15, 16). However, the development of aortic calcification in men between 20 and 40 years old cannot be fully explained by hormonal changes. Instead, other factors such as diet and lifestyle may play a more significant role.

For example, the increased incidence of urolithiasis and atherosclerosis in young adults may be related to the convergence toward Western diet (17-19). Other studies have suggested that male sex and cholesterol levels may be significant risk factors for high vascular calcification in young adults (20-22), while others have proposed that psychological factors and emotional stresses may also play a role (23, 24).

Matrix protein plays a crucial role in stone formation. Osteopontin is the primary matrix of urinary calcium stones (25) and is also involved in arterial neointima formation and dystrophic calcification, which often accompanies arteriosclerosis (26). A recent study found an association between recurrent kidney stone formation and subclinical carotid atherosclerosis, suggesting that nephrolithiasis and

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atherosclerosis may share a common mechanism (27).

The findings of our study support the idea that nephrolithiasis and vascular calcification have the same pathophysiology and common risk factors. We found a strong relationship between stone size and the aortic calcification score, which suggests that these two conditions may be related.

Limitations of the study

The study relied on patients who presented to a single hospital and were diagnosed with kidney stones. This may not be representative of all patients with kidney stones. Also, this study was done only on one breed, and different breeds were not examined. The authors used a single imaging modality (CT scan) to assess aortic calcification. This may not be the most accurate or sensitive method for assessing aortic calcification.

Conclusion

Our study demonstrates a significant correlation between the severity of aortic calcification and the size of kidney stones. Specifically, patients with kidney stones greater than 3 cm in diameter exhibited more severe aortic calcification compared to those with smaller stones and non-stone formers. Furthermore, our findings suggest that men aged 25 to 45 years with kidney stones may be at increased risk of developing more severe aortic calcification, which is consistent with the idea that nephrolithiasis and atherosclerosis share a common pathophysiology. These results support the notion that nephrolithiasis should be considered a systemic condition rather than a localized issue and highlight the importance of considering the potential cardiovascular implications of kidney stones in patients.

Authors' Contributions

Amir Reza Abedi: conception and design, Writing - review & editing

Saeed Montazeri: conception and design, Writing - original draft, Data curation

Morteza Sanei Taheri: analysis and interpretation of data, Writing - original draft

Seyyed Ali Hojjati: analysis and interpretation of data, Writing - review & editing

Morteza Fallah-karkan: conception and design, Writing - original draft, Data curation

Reza Soleimani: analysis and interpretation of data, Writing - original draft

Amir Alinejad Khorram: analysis and interpretation of data, Writing - original draft

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

All authors are accountable for all aspects of the work.

Ethical Considerations

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Ethical Code No. IR.SBMU.UNRC.1397.21).

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Conflict of Interests

The authors declare that they have no competing interests.

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