Kidney Stone and Cardiovascular Disease

Shahram Taheri M.D.

Associate of Prof.

Isfahan University of Med. Sci,

Introduction

Nephrolithiasis is a worldwide public health problem affecting between 5% and 9% of the European population and almost 12% of the North American society nowadays.

Urinary stone disease (USD) is a disorder of mineral metabolism in which crystals, most commonly calcium oxalate and calcium phosphate, deposit in the kidneys.

Introduction

The rising prevalence of obesity and diabetes in aging populations, two well-established risk factors for USD, are projected to contribute to an additional $1.24 billion/year in US treatment costs by 2030.

A positive association between USD and adverse cardiovascular events (e.g., myocardial infarction) has been reported, with vascular calcification (VC) as the link between the two diseases.

International Journal of
Molecular Sciences

MDPI

Review

Crosstalk between Renal and Vascular Calcium Signaling: The Link between Nephrolithiasis and Vascular Calcification

Chan-Jung Liu [1], Chia-Wei Cheng [1], Yau-Sheng Tsai [2,3] and Ho-Shiang Huang [1,*]

[1] Department of Urology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan 704302, Taiwan; dragon2043@hotmail.com (C.-J.L.); imjohnny7639@gmail.com (C.-W.C.)
[2] Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan 704302, Taiwan; yaustsai@mail.ncku.edu.tw
[3] Center for Clinical Medicine Research, National Cheng Kung University Hospital, Tainan 704302, Taiwan
* Correspondence: hshuang54@yahoo.com.tw; Tel.: +886-6-2353535 (ext. 5251); Fax: +886-6-2766179

Received: 27 February 2021
Accepted: 26 March 2021
Published: 30 March 2021

Abstract: Calcium (Ca^{2+}) is an important mediator of multicellular homeostasis and is involved in several diseases. The interplay among the kidney, bone, intestine, and parathyroid gland in Ca^{2+} homeostasis is strictly modulated by numerous hormones and signaling pathways. The calcium-sensing receptor (CaSR) is a G protein–coupled receptor, that is expressed in calcitropic tissues such as the parathyroid gland and the kidney, plays a pivotal role in Ca^{2+} regulation. CaSR is important for renal Ca^{2+}, as a mutation in this receptor leads to hypercalciuria and calcium nephrolithiasis In addition, CaSR is also widely expressed in the vascular system, including vascular endothelial cells (VECs) and vascular smooth muscle cells (VSMCs) and participates in the process of vascular calcification. Aberrant Ca^{2+} sensing by the kidney and VSMCs, owing to altered CaSR expression or function, is associated with the formation of nephrolithiasis and vascular calcification. Based on emerging epidemiological evidence, patients with nephrolithiasis have a higher risk of vascular calcification, but the exact mechanism linking the two conditions is unclear. However, a dysregulation in Ca^{2+} homeostasis and dysfunction in CaSR might be the connection between the two. This review summarizes renal calcium handling and calcium signaling in the vascular system, with a special focus on the link between nephrolithiasis and vascular calcification.

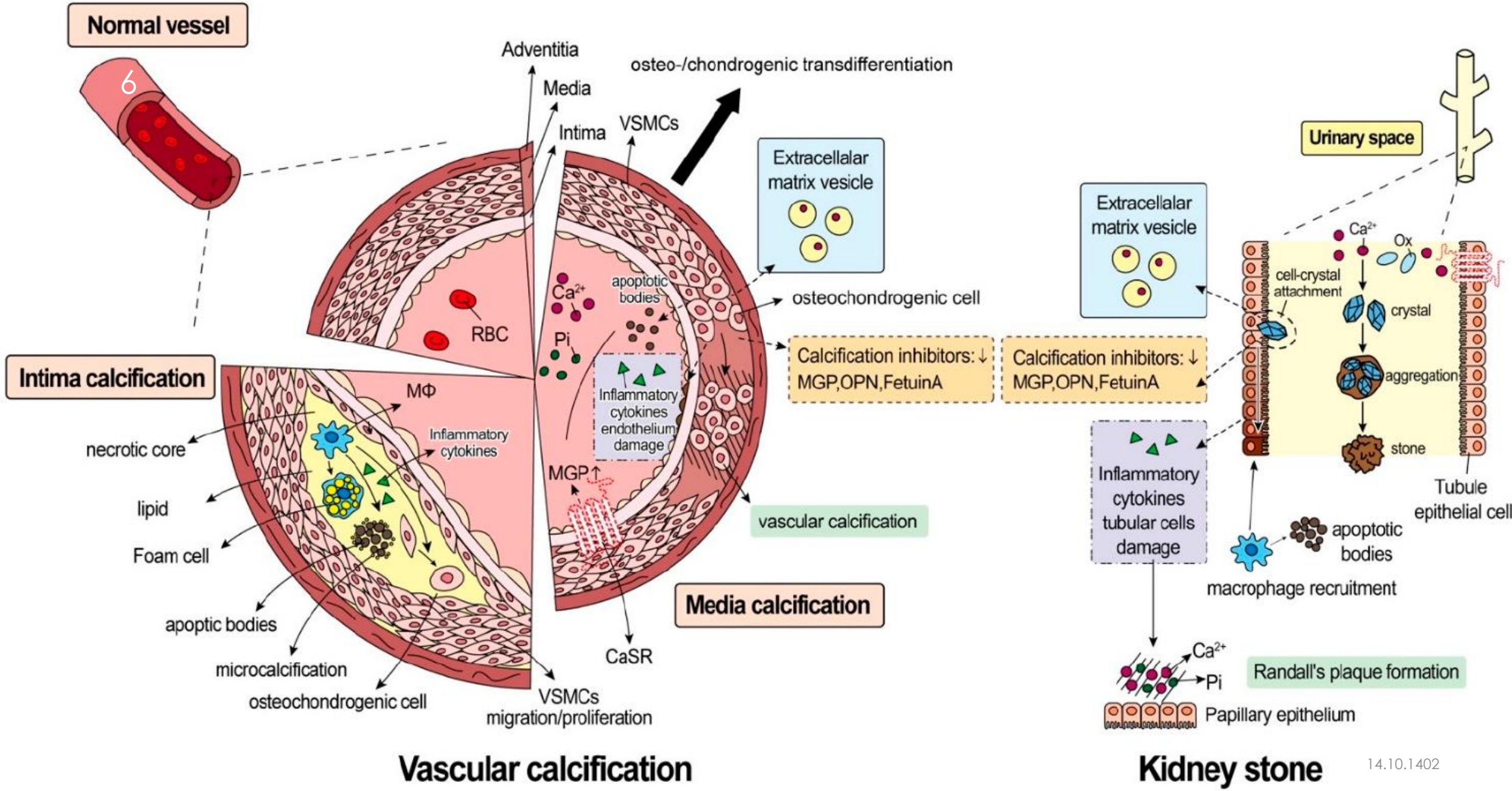

Normal vessel
Adventitia
Media
Intima
VSMCs
osteo-/chondrogenic transdifferentiation
Extracellalar matrix vesicle
osteochondrogenic cell
Calcification inhibitors: ↓ MGP,OPN,FetuinA
RBC
Ca2+
Pi
apoptotic bodies
Inflammatory cytokines endothelium damage
MGP↑
vascular calcification
Intima calcification
MΦ
Inflammatory cytokines
necrotic core
lipid
Foam cell
apoptic bodies
microcalcification
osteochondrogenic cell
VSMCs migration/proliferation
CaSR
Media calcification
Vascular calcification
Urinary space
Extracellalar matrix vesicle
Calcification inhibitors: ↓ MGP,OPN,FetuinA
Ca2+
Ox
cell-crystal attachment
crystal
aggregation
stone
Tubule epithelial cell
Inflammatory cytokines tubular cells damage
apoptotic bodies
macrophage recruitment
Ca2+
Pi
Randall's plaque formation
Papillary epithelium
Kidney stone

Figure 2. Crosstalk between vascular calcification and nephrolithiasis. The process of vascular calcification is demonstrated on the right while that of kidney stone formation is depicted on the left. The molecular characteristics shared by these two distinct diseases are highlighted by the same-colored block. **Vascular calcification** can be categorized into intimal calcification and media calcification. 1. Intimal calcification is frequently associated with atherosclerosis. Macrophage (Mφ) digests lipoproteins and converts them to cholesterol-rich foam cells. Initially, foam cells can be phagocyted by adjacent vascular smooth muscle cells (VSMCs) and release apoptotic bodies. In addition to an increase in the number of apoptotic bodies, there is an accumulation of apoptotic body debris, which results in the formation of a necrotic core. Vesicles in the necrotic core release microcalcification of calcium phosphate as nucleation nidus. 2. Medial calcification is largely related to osteo-/chondrogenic transdifferentiation, which indicates the change in phenotype of VSMCs into osteo-/chondroblasts like cells. Transdifferentiation can be induced by high phosphate (Pi) or calcium (Ca^{2+}) levels. The osteo-/chondroblast-like cells actively promote media calcification by reduced activities of calcification inhibitors (e.g., matrix Gla protein (MGP), osteopontin (OPN), and fetuin A), apoptotic body release, calcifying extracellular matrix vesicle release, and inflammatory cytokine release. The activation of CaSR on VSMCs can stimulate MGP release, which can ameliorate vascular calcification. The mechanism of **kidney stone** formation remains largely unknown. However, the supersaturated urinary stone promoters, e.g., Ca^{2+} and oxalate (Ox), can gradually form crystals, and aggregated crystals could interact with tubule epithelial cells and cause epithelial damage. The cell-crystal interaction could cause calcifying extracellular matrix vesicles release and inflammatory cytokines release, with the assistance of reduced activities of calcification inhibitors (e.g., MGP, OPN, and fetuin A). Mφ recruitment and polarization are also found to occur in the crystal-attached areas. Finally, Ca^{2+} and Pi combine to form hydroxyapatite, which is deposited on the renal papilla and referred to as Randall's plaque.

6. Conclusions and Perspectives

Owing to more advanced animal and molecular studies, the process of renal Ca^{2+} signaling has become clearer over the years. In addition, the pathogenic link between vascular calcification and nephrolithiasis has been further corroborated by a growing body of evidence. As calcium is the main component in these two distinct conditions, a dysfunction in calcium homeostasis might be the mechanism connecting the two. Although calcium dysregulation cannot be used to explain the mechanisms in all patients, knowledge of the Ca^{2+} signaling can aid in the discovery of the optimal drug targets. Currently, vascular calcification or nephrolithiasis occurs due to a lack of effective medications. Consequently, therapeutic strategies targeting the CaSR might reduce the progression of vascular calcification and nephrolithiasis.

International Journal of
Molecular Sciences

MDPI

Review

Endothelial Dysfunction: An Intermediate Clinical Feature between Urolithiasis and Cardiovascular Diseases

Javier Saenz-Medina [1,2,*], Mercedes Muñoz [3], Claudia Rodriguez [3], Ana Sanchez [3], Cristina Contreras [3], Joaquín Carballido-Rodríguez [4] and Dolores Prieto [3]

1 Department of Urology, Puerta de Hierro-Majadahonda University Hospital, 28222 Majadahonda, Spain
2 Department of Medical Specialities and Public Health, Faculty of Health Sciences, King Juan Carlos University, 28933 Móstoles, Spain
3 Department of Physiology, Pharmacy Faculty, Complutense University, 28040 Madrid, Spain; mmpicos@ucm.es (M.M.); claudrod@ucm.es (C.R.); aasanche@ucm.es (A.S.); criscont@ucm.es (C.C.); dprieto@ucm.es (D.P.)
4 Department of Urology, Puerta de Hierro-Majadahonda University Hospital, Autonoma University, 08193 Bellaterra, Spain; carballidojoaquin@gmail.com
Correspondence: javier.saenz@salud.madrid.org

Received: 11 December 2021
Accepted: 11 January 2022
Published: 14 January 2022

Endothelial dysfunction (ED) is an early pathogenic feature of cardiovascular morbidities, consisting of impaired vasodilation, angiogenesis and barrier function [4]. It has been related to metabolic diseases such as diabetes mellitus, obesity or metabolic syndrome; all of them also associated with cardiovascular diseases [5]. The key role of oxidative stress and inflammation in the pathogenesis of ED is well established [4].

Recently, ED has been linked to urolithiasis through clinical and experimental studies [6–9]. The aim of this review is to summarize the current knowledge and the latest findings on the pathogenic mechanisms underlying endothelial dysfunction in urolithiasis, paying special attention to the role of the reactive oxygen species (ROS) as an underlying mechanism.

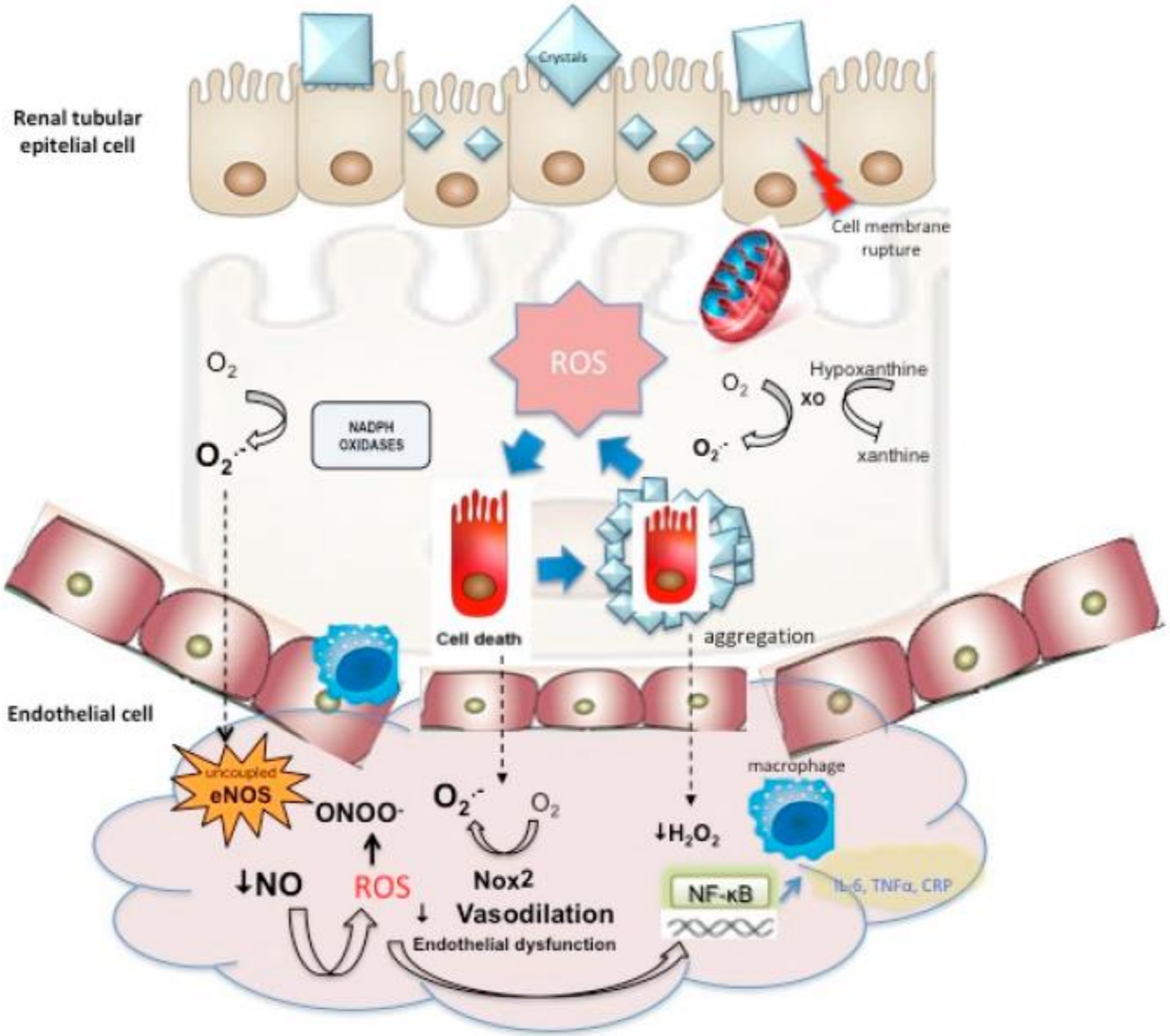


Figure 1. Interaction between oxidative stress-mediated epithelial cell injury, cell death, and stone formation with endothelial dysfunction triggered by impaired endothelium-dependent vasodilation augmented ROS and inflammatory response.

Journal of *Personalized Medicine*

MDPI

Article

Vascular Calcification Is Associated with Fetuin-A and Cortical Bone Porosity in Stone Formers

Fernanda Guedes Rodrigues [1,2], Rodrigo Fernandes Carvalho Azambuja Neves [3], Milene Subtil Ormanji [4], Priscila Ligeiro Gonçalves Esper [4], Melissa Gaspar [3], Rosa Maria Rodrigues Pereira [5], Lucio R. Requião-Moura [3,4], Martin H. de Borst [2,†] and Ita Pfeferman Heilberg [1,4,*,†]

Received: 2 June 2022

Accepted: 5 July 2022

Published: 10 July 2022

1 Nutrition Post Graduation Program, Universidade Federal de São Paulo (UNIFESP), São Paulo 04023-062, Brazil; f.guedes.rodrigues@umcg.nl

2 Department of Nephrology, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, The Netherlands; m.h.de.borst@umcg.nl

3 Hospital do Rim, Fundação Oswaldo Ramos, São Paulo 04038-002, Brazil; roazambuja@hotmail.com (R.F.C.A.N.); memel_gt@yahoo.com.br (M.G.); lucio.requiao@gmail.com (L.R.R.-M.)

4 Nephrology Division, Universidade Federal de São Paulo (UNIFESP), São Paulo 04023-062, Brazil; milene.ormanji@gmail.com (M.S.O.); priscila82@gmail.com (P.L.G.E.)

5 Rheumatology Division, Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo 04023-062, Brazil; rosamariarp@yahoo.com

* Correspondence: ita.heilberg@gmail.com

† These authors contributed equally to this work.

14.10.1402

Abstract: Background: Nephrolithiasis has been associated with bone loss and vascular calcification (VC), reflecting abnormal extraosseous calcium deposition. Fetuin-A (Fet-A) acts as a potent inhibitor of ectopic mineralization. The aim of the present study was to evaluate the prevalence of VC in stone formers (SF) and non-stone formers (NSF) and to investigate potential determinants of VC among SF, including circulating levels of Fet-A and bone microarchitecture parameters. Methods: Abdominal aortic calcification (AAC) was assessed using available computed tomography in SF and in age-, sex-, and BMI-matched NSF (potential living kidney donors). Serum Fet-A was measured in stored blood samples from SF. Bone microarchitecture parameters were obtained as a post hoc analysis of a cross-sectional cohort from young SF evaluated by high-resolution peripheral quantitative computed tomography (HR-pQCT). Results: A total of 62 SF (38.0 [28.0–45.3] years old) and 80 NSF (40.0 [37.0–45.8] years old) were included. There was no significant difference in AAC scores between SF and NSF. However, when dividing SF according to mean AAC score, below <5.8% (n = 33) or above ≥5.8% (n = 29), SF with higher AAC presented significantly higher BMI and tibial cortical porosity (Ct.Po) and significantly lower serum HDL, klotho, Fet-A, and eGFR. Urinary calcium did not differ between groups, but fractional excretion of phosphate was higher in the former. Upon multivariate regression, BMI, serum Fet-A, and tibial Ct.Po remained independently associated with AAC. Conclusions: This study suggests an association between reduced circulating Fet-A levels and increased bone Ct.Po with VC in SF.

antioxidants

MDPI

Article

Urolithiasis Develops Endothelial Dysfunction as a Clinical Feature

Javier Sáenz-Medina [1,2,*], María Martinez [3], Silvia Rosado [4], Manuel Durán [2], Dolores Prieto [5,†] and Joaquín Carballido [6,†]

1 Department of Urology, Puerta de Hierro-Majadahonda University Hospital, 28222 Majadahonda, Spain
2 Department of Medical Specialities and Public Health, Faculty of Health Sciences, King Juan Carlos University, 28933 Móstoles, Spain; manuel.duran@hospitalreyjuancarlos.es
3 Department of Nephrology, Clinic University Hospital Valladolid, 47003 Valladolid, Spain; mariamartinezmanrique@gmail.com
4 Biobank, Health Research Institute "Puerta de Hierro Segovia de Arana", 28222 Madrid, Spain; srosado@idiphim.org
5 Department of Physiology, Pharmacy Faculty, Complutense University, 28040 Madrid, Spain; dprieto@ucm.es
6 Department of Urology, Puerta de Hierro-Majadahonda University Hospital, Autonoma University, 08193 Bellaterra, Spain; joaquinalberto.carballido@salud.madrid.org
* Correspondence: javier.saenz@salud.madrid.org

14.10.1402

A cross-sectional study was performed between 27 urolithiasic patients, matched for age and sex, and 27 healthy patients. All of them were recruited from the outpatient clinic of the Urology Department of Puerta de Hierro University Hospital.

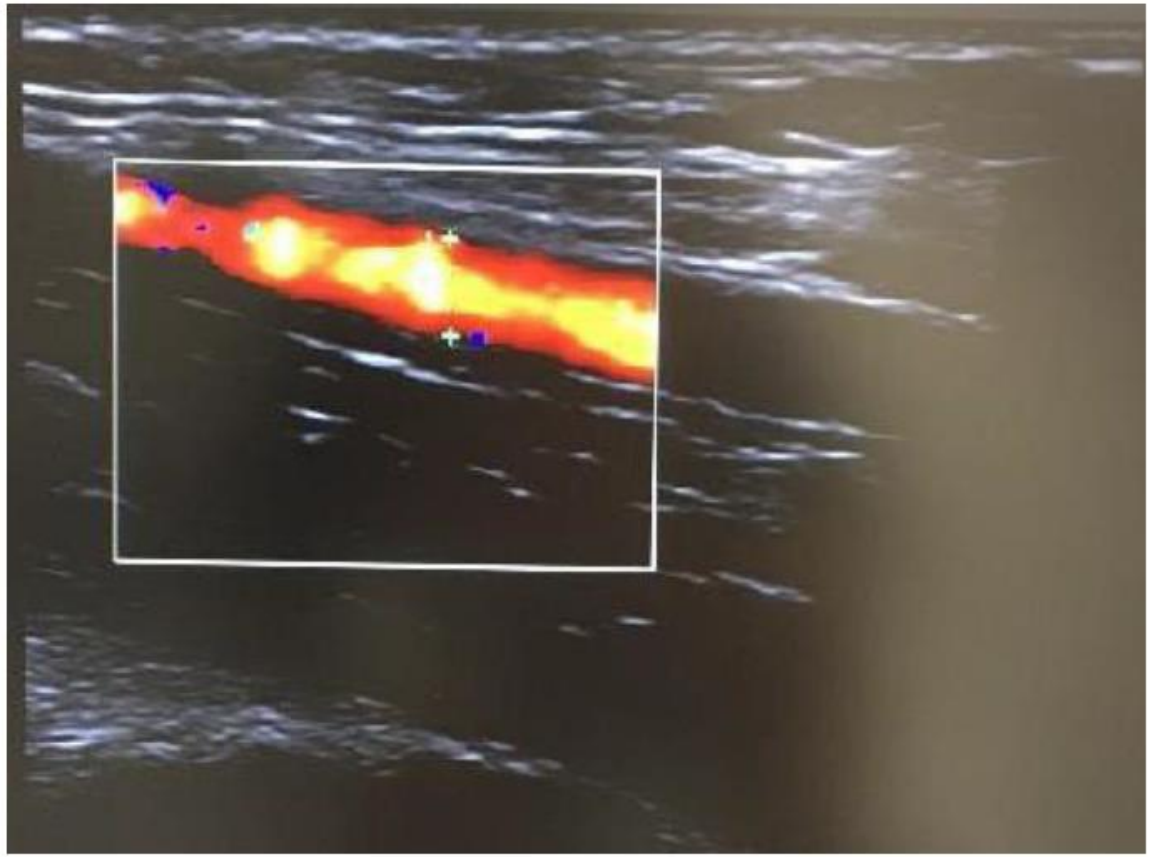
Every patient was evaluated through a clinical history and physical examination. Clinical data, previous pathologies, and blood analysis were collected to exclude patients with metabolic, respiratory, cardiovascular, hepatic, or renal disorders. Patients in treatment with drugs, which could affect the endothelial function, were also discarded. Abdominal echography, as a routinary part of the checkup, demonstrated the absence of urolithiasis in the control group.

2.2. Assessment of Endothelial Function

After the urological and physical evaluation, endothelial function was evaluated using the Celermajer method by a blinded vascular radiologist [8] with high-resolution Doppler ultrasonography. Measurement of the brachial artery diameter was carried out before and after 5-min ischemic compression with a blood pressure cuff inflated around the forearm. Measurement of maximal post ischemic compression artery diameter was taken one minute after cuff release and related with precompression data. The difference between both lumen diameters expressed as the percentage change was considered as the endothelium-dependent vasodilatation (FMD increase %).

Table 3. Endothelial function features (mean ± SEM).

	Patients	Control	*p*
Basal lumen diameter (mm)	4.33 ± 0.15	3.94 ± 0.11	0.0491
Lumen diameter after FMD (mm)	4.71 ± 0.17	4.73 ± 0.12	0.9301
FMD (% increase)	8.95 ± 1.51	20.81 ± 2.34	0.00010448



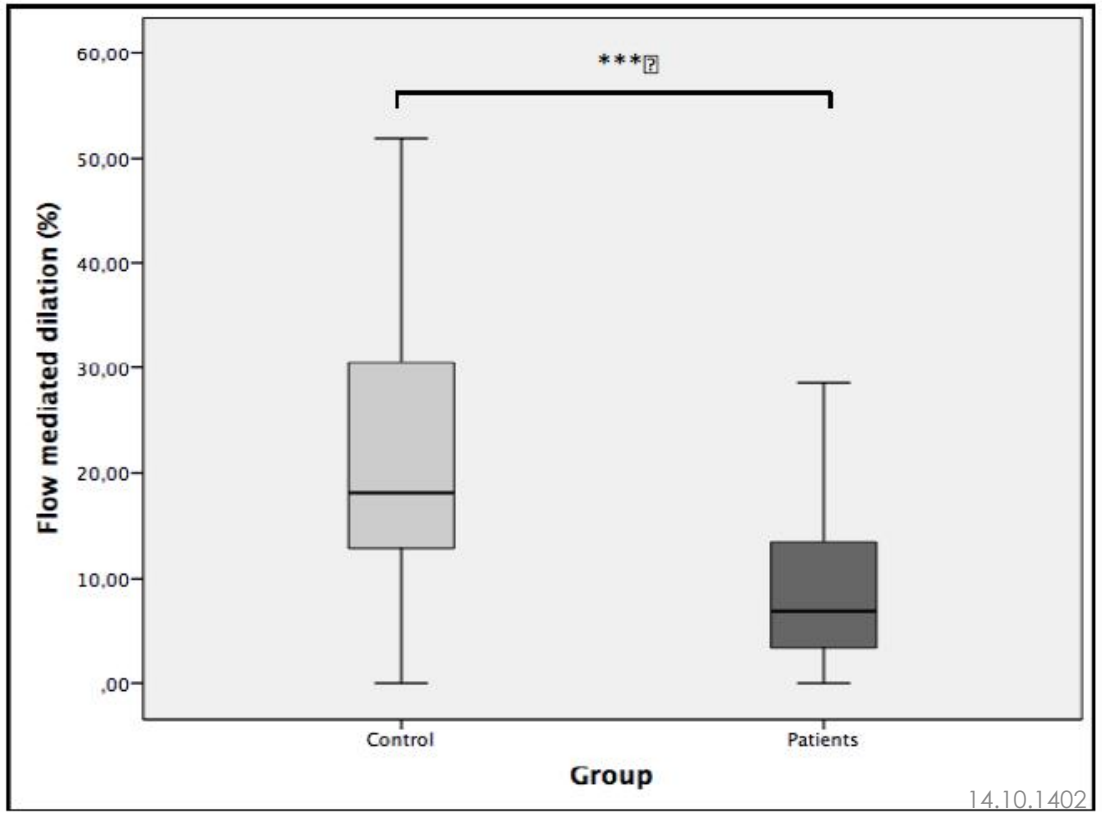


Table 6. Inflammation, oxidative stress, and endothelial dysfunction markers (mean ± SEM).

	Patients	Control	*p*
CRP (mg/L)	5.3 ± 1.6	3 ± 0.9	0.2432
IL-6 (pg/mL)	1.7 ± 1.2	18.8 ± 13.8	0.23
MDA (ng/mL)	157.8 ± 15.3	199.57 ± 29.6	0.23
VCAM-1 (ng/mL)	95.4 ± 5.1	90.1 ± 4.8	0.47
ADMA (ng/mL)	92.8 ± 31.8	75.6 ± 30.2	0.71

The correlation analysis for the study of the behavior of the different molecules in relation with FMD in lithiasic patients, did not show statistical significance in any of them, although a negative correlation trend was observed in IL-6, MDA, and VCAM-1 (Figure 2).

5. Conclusions

We can conclude that ED constitutes an important disorder in urolithiasis patients that should be regarded as a sentinel symptom of a cardiovascular morbidity, and a strong predictor of future cardiovascular events.

Original Article

Ectopic biomineralization in kidney stone formers compared to non-stone formers

Adrian M. Fernandez[1], Benjamin A. Sherer[1], Stuart A. Gansky[2], Jorge D. Mena[1], Sudarshan Srirangapatanam[1], Scott V. Wiener[1], Thomas Chi[1], Sunita P. Ho[2], Marshall L. Stoller[1]

[1]Department of Urology, University of California San Francisco, San Francisco, CA, USA; [2]Department of Preventative and Restorative Dentistry, University of California San Francisco, San Francisco, CA, USA

Contributions: (I) Conception and design: AM Fernandez, BA Sherer, SP Ho, ML Stoller; (II) Administrative support: JD Mena, S Srirangapatanam, SV Wiener; (III) Provision of study materials or patients: SP Ho, T Chi, ML Stoller; (IV) Collection and assembly of data: AM Fernandez, BA Sherer, JD Mena, S Srirangapatanam, SV Wiener; (V) Data analysis and interpretation: AM Fernandez, BA Sherer, SA Gansky, JD Mena, S Srirangapatanam, SP Ho, ML Stoller; (VI) Manuscript writing: All Authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sunita P. Ho, PhD. Department of Preventative and Restorative Dentistry, University of California San Francisco, 513 Parnassus Ave, San Francisco, CA 94143, USA. Email: Sunita.Ho@ucsf.edu; Marshall L. Stoller, MD. Department of Urology, University of California, San Francisco, 400 Parnassus Ave, San Francisco, CA 94143, USA. Email: Marshall.Stoller@ucsf.edu.

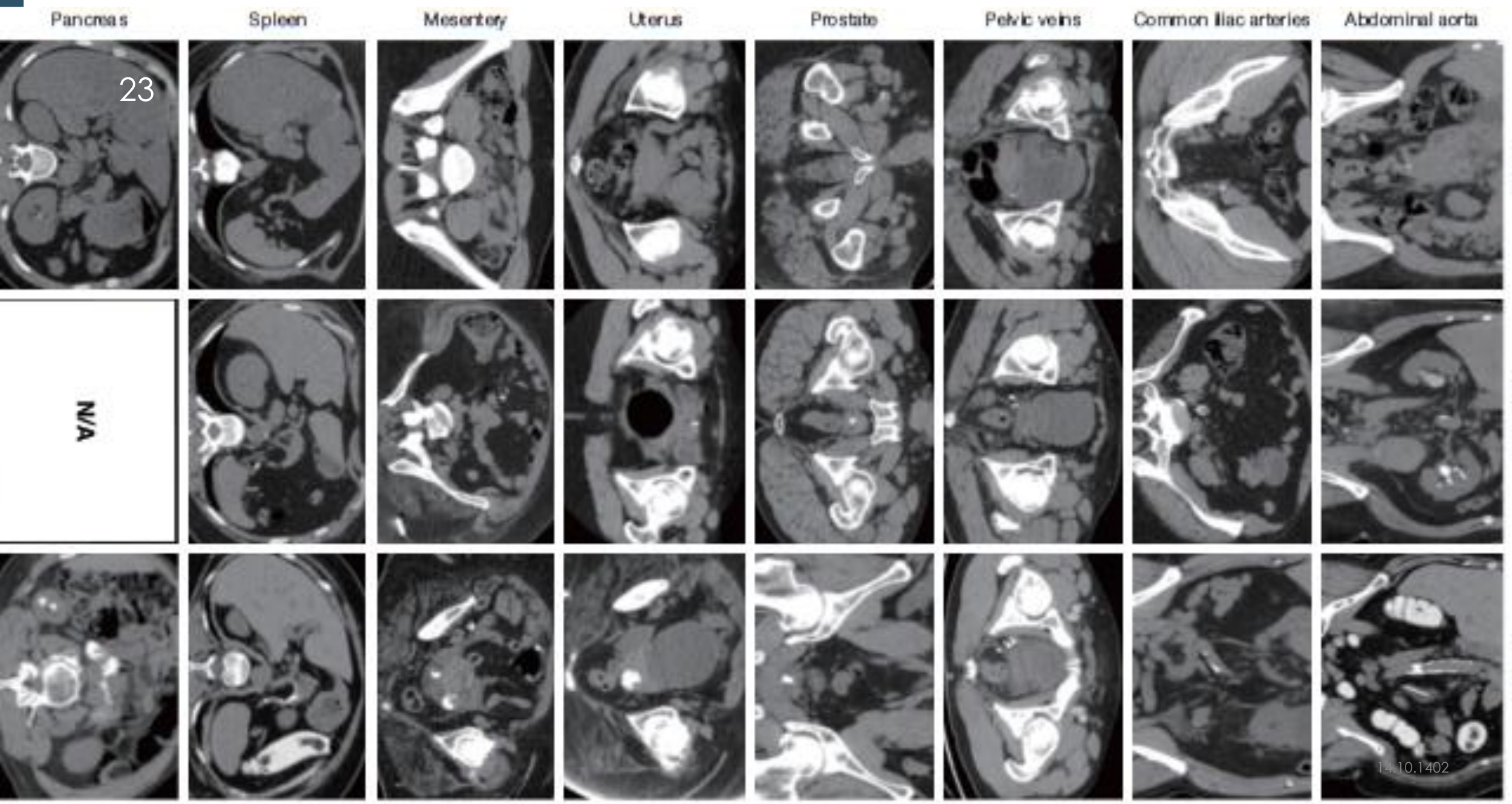
Transl Androl Urol 2020;9(5):2129-2137 | http://dx.doi.org/10.21037/tau-19-927 14.10.1402

Methods

The presence and quantity of biominerals at eight non-renal anatomic locations were determined by a retrospective analysis of clinical non-contrast X-ray computed tomography (CT) scans (GE Healthcare, 2.5 mm continuous slices, approximately 20 mGy per scan) of the abdomen/pelvis obtained from known SFs and a matched cohort of NSFs (renal transplant donors). Non-renal, non-osseous sites evaluated included the abdominal aorta, common iliac arteries, pelvic veins (phleboliths), prostate or uterus, mesentery, pancreas (pancreatic vessels), and spleen (splenic vessels). These anatomical sites were chosen because they were captured consistently within the field of view of the CT of the abdomen and pelvis, a routine diagnostic imaging test used for evaluating both SFs and NSFs.

Table 1 Patient characteristics

Characteristic	Stone formers (n=190)	Non-stone formers (n=190)	P value
Female, n [%]	105 [55]	105 [55]	1
Male, n [%]	85 [45]	85 [45]	1
Age at CT	48.5±0.7	49±0.9	0.728
Body mass index	30.6±0.7	27.3±0.3	<0.001
Diabetes mellitus, n [%]	27 [14]	0	<0.001
Hypertension, n [%]	61 [32]	13 [7]	<0.001
Hyperlipidemia, n [%]	59 [31]	27 [14]	<0.001
Smoking, n [%]	51 [27]	43 [23]	0.405
Hyperparathyroidism	1	0	0.317


Pancreas
Spleen
Mesentery
Uterus
Prostate
Pelvic veins
Common iliac arteries
Abdominal aorta
Mild
N/A
Moderate
Severe

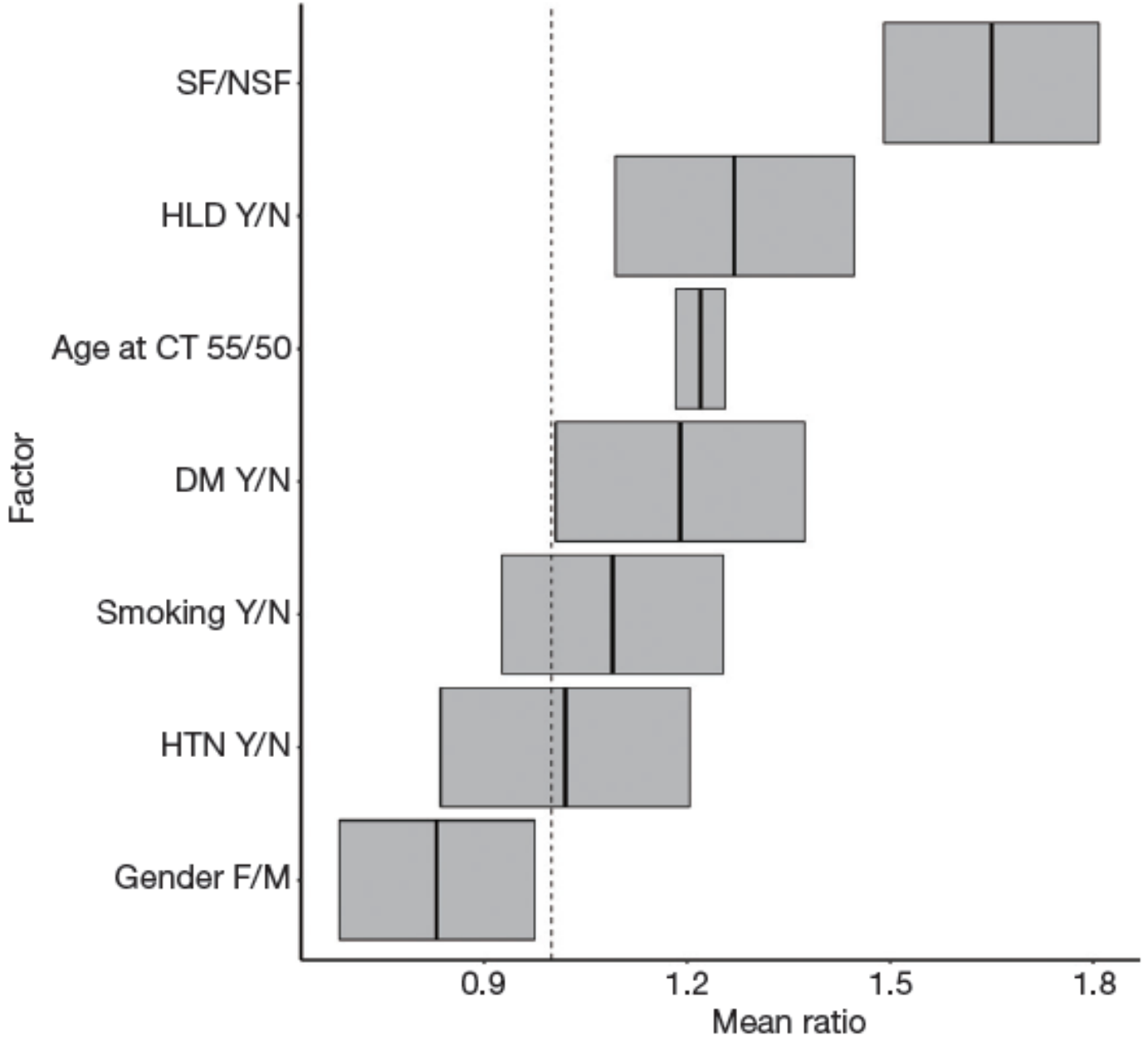


Figure 2 Predictors of calcification include nephrolithiasis, male gender, and hyperlipidemia.

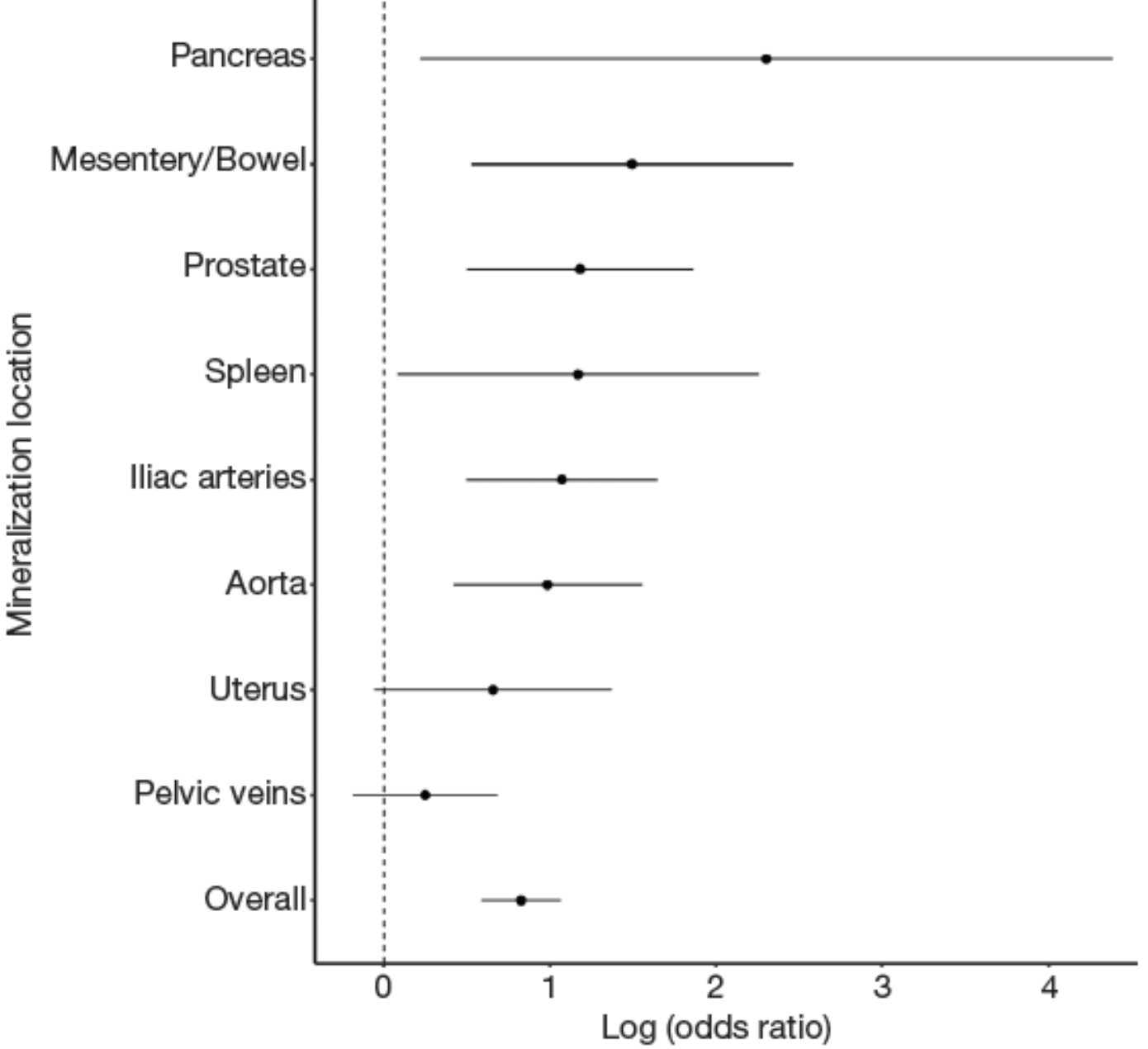


Figure 3 SFs have increased calcification at many anatomic locations and overall.

RENAL FAILURE
2023, VOL. 45, NO. 1, 2183727
https://doi.org/10.1080/0886022X.2023.2183727

Taylor & Francis
Taylor & Francis Group

CLINICAL STUDY

OPEN ACCESS Check for updates

Vascular calcification on the risk of kidney stone: a meta-analysis

Linxi Huang[a]*, Junjie Hu[b]*, Cheng Xue[c], Jiarong Ding[a], Zhiyong Guo[a] and Bing Yu[b]

[a]Department of Nephrology, Changhai Hospital, Naval Medical University (Second Military Medical University), Shanghai, China; [b]Department of Cell Biology, Center for Stem Cell and Medicine, Naval Medical University (Second Military Medical University), Shanghai, China; [c]Division of Nephrology, Kidney Institute of CPLA, Changzheng Hospital, Naval Medical University (Second Military Medical University), Shanghai, China

ABSTRACT

Background: The association between vascular calcification (VC) and kidney stone is still inconclusive. Therefore, we conducted a meta-analysis to estimate the risk of kidney stone disease in subjects with VC.

Methods: To identify publications from related clinical studies, we performed a search on PubMed, Web of Science, Embase, and Cochrane Library databases from their inceptions until 1 September 2022. According to obvious heterogeneity, a random-effects model was used to calculate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Subgroup analysis was conducted trying to dissect the effects of VC in different segments and population regions in predicting kidney stone risk.

Results: Seven articles were included with a total number of 69,135 patients, of which 10,052 have vascular calcifications and 4728 have kidney stones. There was a significantly higher risk of kidney stone disease in participants with VC versus control (OR = 1.54, 95% CI: 1.13–2.10). Sensitivity analysis confirmed the stability of the results. VC can be separated into abdominal, coronary, carotid, and splenic aortic calcification while pooled analysis of abdominal aorta calcification did not indicate a significant higher kidney stone risk. An obvious higher risk of kidney stone was observed in Asian VC patients (OR = 1.68, 95% CI: 1.07–2.61).

Conclusion: Combined evidence of observational studies suggested patients with VC may be associated with an increased risk of kidney stone disease. Despite the predictive value was relatively low, it is still worth noting that patients with VC are under the threat of kidney stone disease.

Study or Subgroup	Calcification Events	Calcification Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Shavit 2015	22	41	35	70	16.0%	1.16 [0.53, 2.51]	2015
Tanaka 2017	33	52	259	387	18.2%	0.86 [0.47, 1.57]	2017
Stern 2019	61	104	136	290	20.2%	1.61 [1.02, 2.53]	2019
Schoenfeld 2021	304	605	368	739	22.6%	1.02 [0.82, 1.26]	2021
Li 2022	409	1113	618	3403	23.0%	2.62 [2.25, 3.04]	2022
Total (95% CI)		**1915**		**4889**	**100.0%**	**1.37 [0.79, 2.37]**	
Total events	829		1416				

Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 58.39$, df = 4 ($P < 0.00001$); $I^2 = 93\%$

Test for overall effect: Z = 1.13 (P = 0.26)

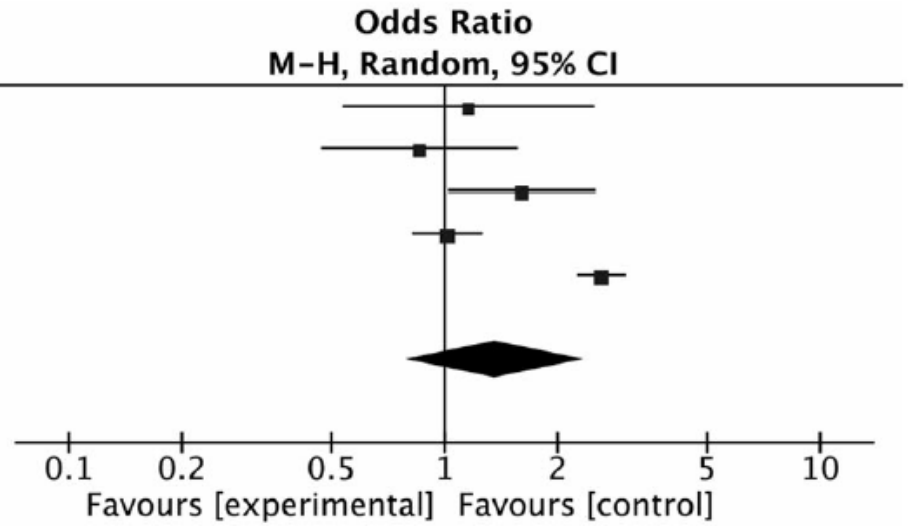


Figure 5. Pooled odds ratio of kidney stone disease in patients with abdominal aortic calcification compared with healthy control.

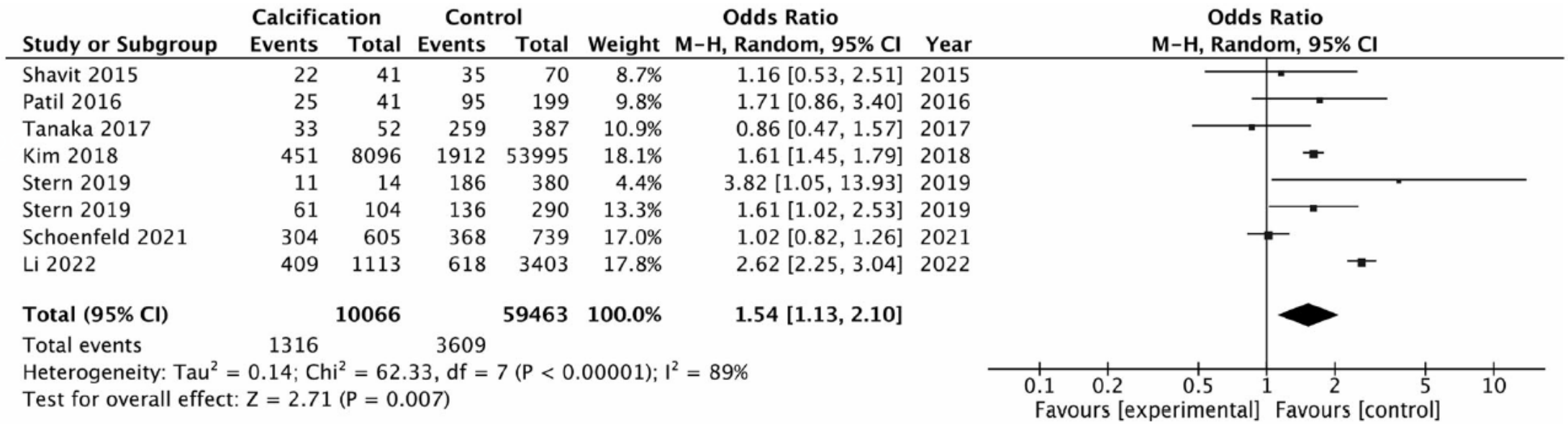
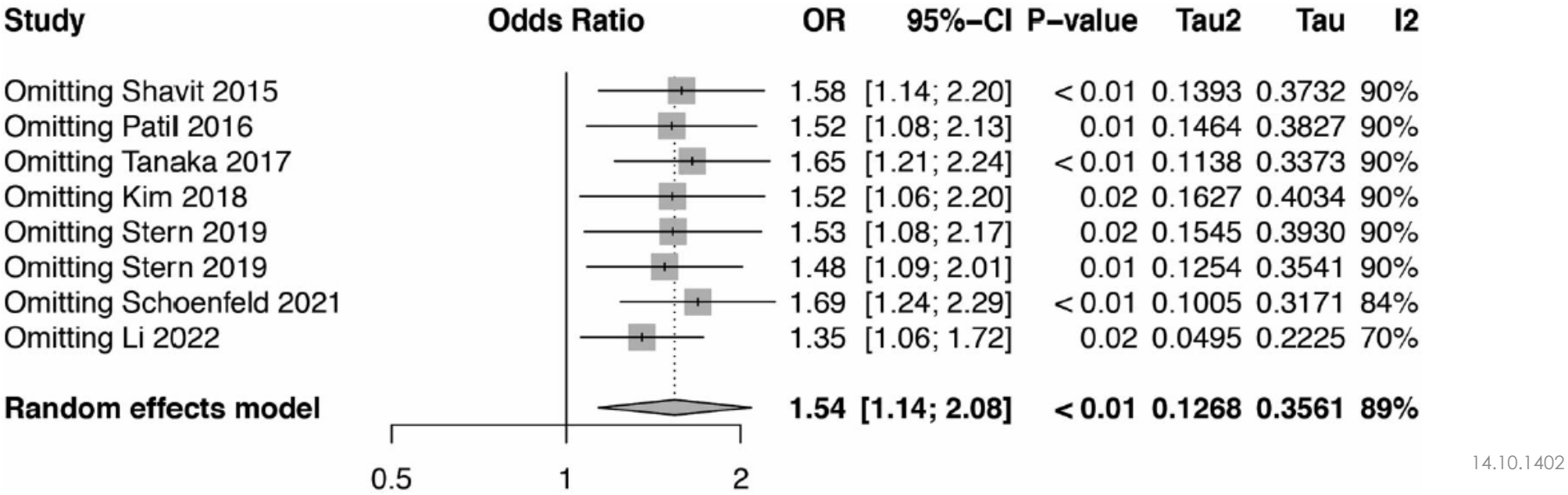


Figure 2. Pooled odds ratio of kidney stone disease in patients with vascular calcification compared with healthy control.



14.10.1402

Figure 3. Forest plot of sensitivey analysis.

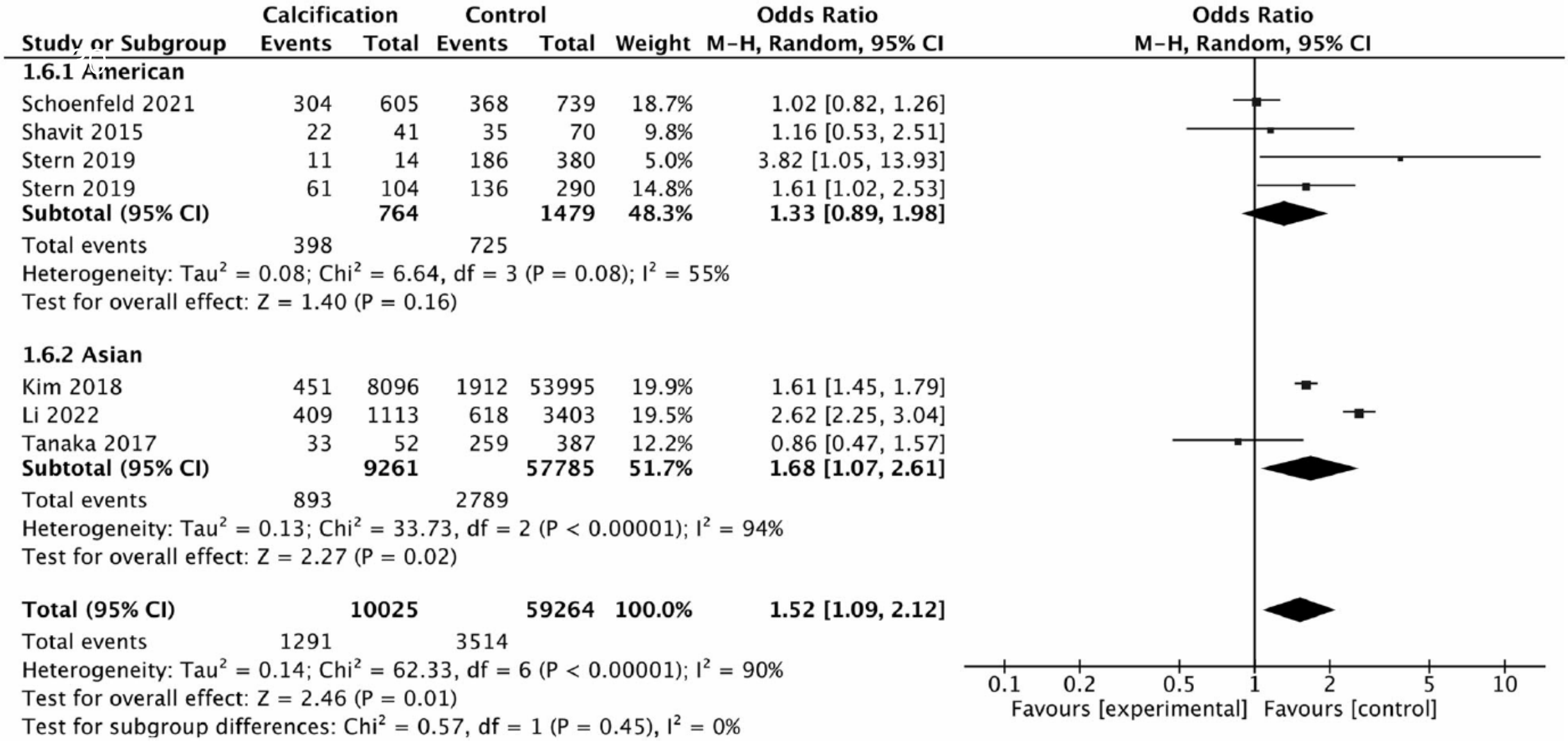


Figure 6. Pooled odds ratio of kidney stone disease in patients from different regions.

Published in final edited form as:
JAMA. 2013 July 24; 310(4): 408–415. doi:10.1001/jama.2013.8780.

History of kidney stones and risk of coronary heart disease

Pietro Manuel Ferraro, MD[1,2], **Eric N Taylor, MD, MSc**[2], **Brian H Eisner, MD**[3], **Giovanni Gambaro, MD, PhD**[1], **Eric B Rimm, ScD**[2], **Kenneth J Mukamal, MD, MPH, MA**[4], and **Gary C Curhan, MD, ScD**[2,5]

[1]Division of Nephrology – Renal Program, Department of Internal Medicine and Medical Specialties, Columbus-Gemelli Hospital, Catholic University of the Sacred Heart, Rome, Italy

[2]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

[3]Department of Urology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Design, setting, and participants—Prospective study of 45,748 men and 196,357 women in the United States without a history of CHD at baseline who were participants in the Health Professionals Follow-Up Study (HPFS, 51,529 men aged 40–75 years followed since 1986), Nurses' Health Study (NHS) I (121,700 women aged 30–55 years followed since 1976) and II (116,430 women aged 25–42 years followed since 1989). The diagnoses of kidney stones and CHD were updated biennially during follow-up.

Main outcome measure—CHD was defined as fatal or non-fatal myocardial infarction (MI) or coronary revascularization. The outcome was identified by biennial questionnaires and confirmed through review of medical records (fatal and non-fatal MI).

Results—Out of a total of 242,105 participants, 19,678 reported a history of kidney stones. After up to 24 years of follow-up in men and 18 years in women, 16,838 incident cases of CHD occurred. After adjusting for potential confounders, among women, those with a reported history of kidney stones compared with those without had an increased risk of CHD in NHS I (incidence rate (IR) 754 vs 514/100,000 person-years; multivariate HR 1.18, 95% CI 1.08 to 1.28) and NHS II (IR 144 vs 55/100,000 person-years; multivariate HR 1.48, 95% CI 1.23 to 1.78); there was no significant association in men (IR 1,355 vs 1,022/100,000 person-years; multivariate HR 1.06, 95% CI 0.99 to 1.13). Similar results were found when analyzing the individual end-points (fatal and non-fatal MI, revascularization).

Conclusions—Among two cohorts of women, a history of kidney stones was associated with a modest but statistically significant increased risk of CHD; there was no significant association in a separate cohort of men. Further research is needed to determine whether the association is sex-specific.

Published in final edited form as:

J Urol. 2016 April ; 195(4 Pt 1): 971–976. doi:10.1016/j.juro.2015.10.001.

Coronary Artery Calcium Score and Association with Recurrent Nephrolithiasis: The Multi-Ethnic Study of Atherosclerosis

Purpose—Subclinical coronary artery calcification is an established predictor of cardiovascular events. While a history of kidney stones has been linked to subclinical carotid atherosclerosis, to our knowledge no study has examined its relationship with coronary artery calcification. We studied the association between kidney stone history and prevalent coronary artery calcification in MESA (Multi-Ethnic Study of Atherosclerosis).

Materials and Methods—MESA is a multisite cohort study of participants 45 to 84 years old without known cardiovascular disease at baseline from 2000 to 2002. Computerized tomography was done in 3,282 participants at followup in 2010 to 2012 to determine coronary artery calcification and kidney stone history was assessed by self-report. Coronary artery calcification scores were categorized as none—0, mild—1 to 99, moderate—100 to 399 or severe—400 or greater. Cross-sectional analysis was performed adjusting for demographic and dietary factors related to kidney stones.

Results

- The prevalence of kidney stone disease history was approximately 9%, mean ± SD participant age was 69.5 ± 9.3 years, 39% of participants were Caucasian, 47% were men and 69% had detectable coronary artery calcification (score greater than 0).

Results

- No difference in the score was seen between single stone formers and non-stone formers.
- Recurrent kidney stone formation was associated with moderate or severe calcification on multivariable logistic regression vs none or mild calcification (OR 1.80, 95% CI 1.22–2.67).

Results

- When coronary artery calcification scores were separated into none, mild, moderate and severe calcification, recurrent stone formation was associated with a higher score category on multivariable ordinal logistic regression (OR 1.44 per category, 95% CI 1.04–2.01).

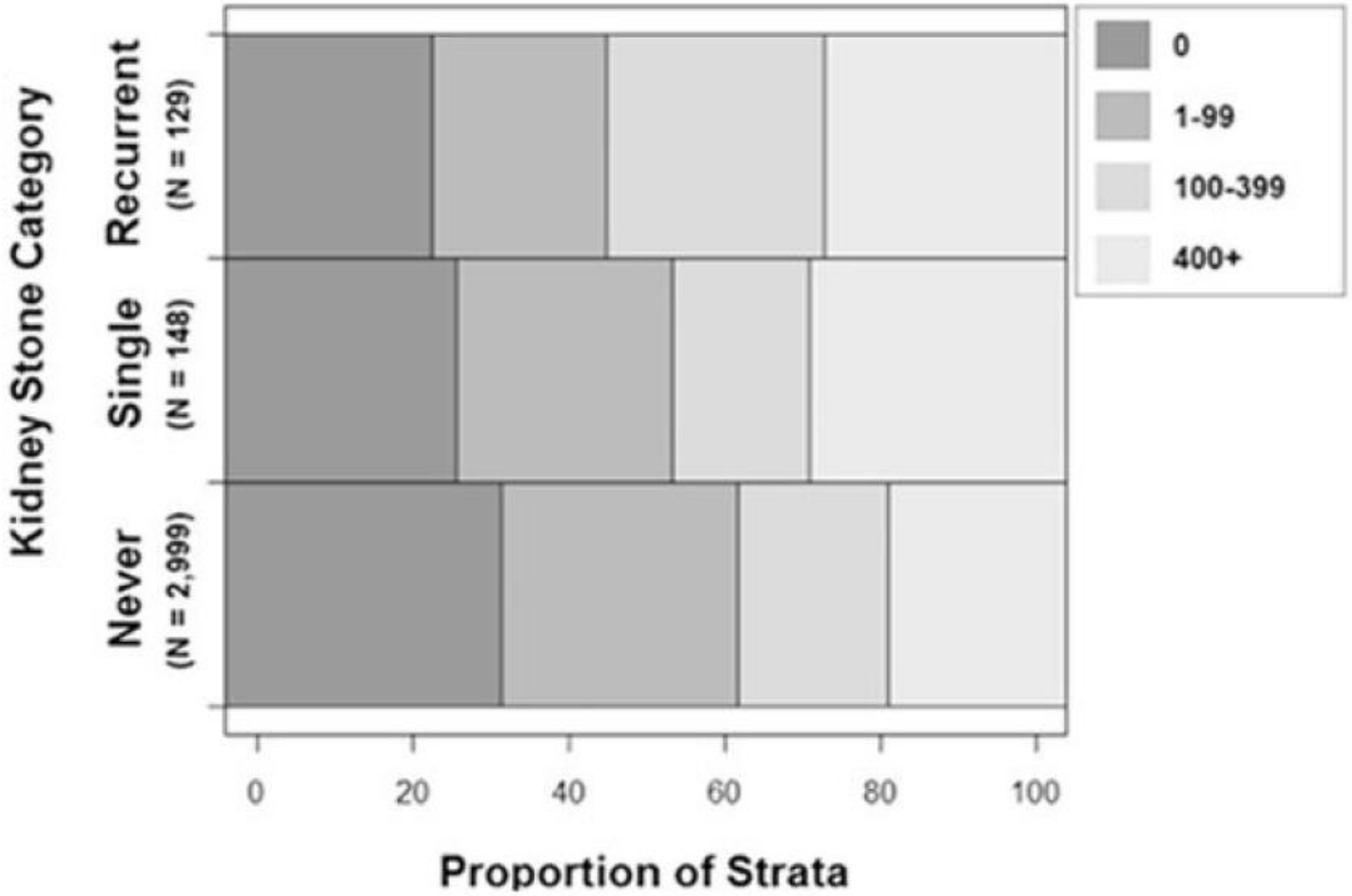


Figure.

CAC score categories by kidney stone history (0, 1, or 2 or more)

Neurological Sciences (2021) 42:4521–4529
https://doi.org/10.1007/s10072-021-05113-5

ORIGINAL ARTICLE

Association between kidney stones and risk of developing stroke: a meta-analysis

Min Yuan[1] · Huang-Yan Zhou[2] · Fan Hu[1] · Shi-Ying Liu[1] · Wei Rao[1] · Ling-Feng Wu[1] · Hong-Bing Nie[1] · Wen-Feng Cao[1]

Received: 12 August 2020 / Accepted: 2 February 2021 / Published online: 19 February 2021

Abstract

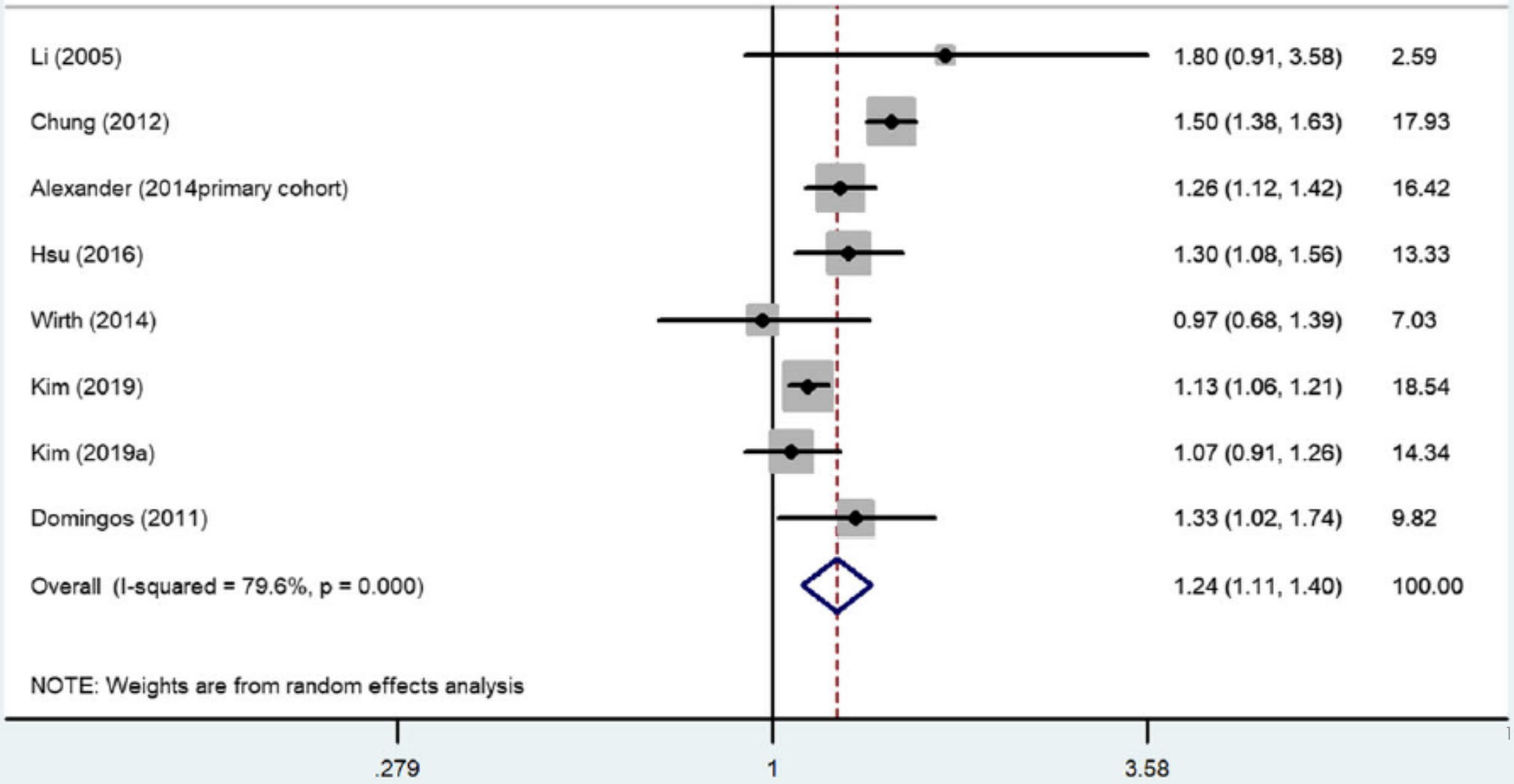
Background Many studies have described the relationship between kidney stones and stroke, but the results are controversial, so we conducted this meta-analysis to estimate the relationship between kidney stones and the risk of developing stroke.

Methods Studies were marked with a comprehensive search of PubMed, EMBASE, Google, and ISI Web of Science databases through 25 March 2020. Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted, and a random-effects model or fix-effects model was used to compute the pooled combined risk estimate. Heterogeneity was reported as I^2. We performed subgroup and sensitivity analysis to assess potential sources of heterogeneity.

Results Eight studies of seven articles involving 3,526,808 participants were included in the meta-analysis. Overall, kidney stones were associated with a moderate risk of stroke incidence (HR, 1.24; 95% CI, 1.11–1.40; I^2=79.6%; p=0.000). We conducted a sensitivity analysis by removing the studies that had a high risk of bias. Heterogeneity subsequently decreased significantly, while an increased risk of stroke in patient with kidney stones was again demonstrated (HR, 1.16; 95% CI, 1.11–1.23; I^2=28.7%; p=0.000). Stratifying analysis showed that the results were more pronounced for ischemic stroke (HR, 1.14; 95% CI, 1.08–1.22; I^2=15.6%; p=0.00) and the follow-up duration ≥10 years (HR, 1.18; 95% CI, 1.10–1.27; I^2=31.6%; p=0.003).

Conclusions Our meta-analysis suggests that patients with kidney stones may have a modestly increased risk of developing stroke, especially in ischemic stroke. More large-scaled and clinical trials should be done to identify the relative impact of kidney stones on stroke outcomes in the future.

Fig. 2 Random-effects analysis of fully adjusted studies for the association between kidney stones and stroke risk



Concluding Remarks

- Nephrolithiasis is a worldwide public health disorder of increasing incidence, especially in industrialized countries in which diet factors have been pointed out as responsible of the higher urolithiasis prevalence.

Concluding Remarks

- Cardiovascular disorders have been independently associated to urolithiasis disorders and lithiasic patients present a higher incidence of cardiovascular diseases, myocardial infarction and stroke with relative risks between 1.20 and 1.24.

Concluding Remarks

- Oxidative stress has been pointed out as an important factor in lithogenesis and a trigger factor for the vascular complications of low-chronic inflammation diseases such as obesity, diabetes or hypertension.
- Endothelial dysfunction is the preclinical stage of atherosclerosis and is also highly associated with cardiovascular morbidities.

Concluding Remarks

- Oxidative stress and inflammation play an important role in the pathogenesis of endothelial dysfunction.
- In addition, endothelial dysfunction has been related to urolithiasis, so it may be considered as an intermediate and changeable feature between urolithiasis and cardiovascular disorders.

Concluding Remarks

- Special attention must be paid for some concomitant comorbidities associated with urolithiasis.
- Active treatment of hypertension or hyperlipidemia with angiotensin receptor blockers or statins allows to take advantage to prevent endothelial dysfunction through their pleiotropic effects and prevent the cardiovascular morbidity.

Concluding Remarks

- On the other side, further studies are needed to clarify the mechanisms linking urolithiasis and endothelial dysfunction evidenced by epidemiological studies.