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ORIGINAL RESEARCH ARTICLE

Renal lithiasis and cardiovascular risk

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ABSTRACT

Renal lithiasis (RL) is a common disease whose prevalence has increased in recent years. It is now considered a systemic pathology, not limited to the kidney and urinary tract, but largely related to diabetes mellitus, obesity, arterial hypertension, hyperuricemia, hypercholesterolemia, and chronic kidney disease, all cardiovascular risk factors that are often linked to severe events such as stroke, coronary heart disease, or acute myocardial infarction. Numerous cross-sectional studies and meta-analyses have demonstrated the association between these two entities. In this review we will attempt to demonstrate the mechanisms involved in the pathophysiology of RL and its relationship with cardiovascular disease. As mechanisms involved, three associations are mentioned. The first refers to oxidative stress and inflammation. The second association refers to the presence of lithogenic mechanisms that contribute to vascular calcification. The last theory is the already known association of obesity, metabolic syndrome, diabetes and HT, all risk factors for the development of RL as well as cardiovascular disease, remembering that RL is the cause, in 8%, of the development of chronic kidney disease, another risk factor for cardiovascular disease and death. In conclusion, the theory that RL is not a disease limited to the kidney and urinary tract, but a systemic disease, with a risk of cardiovascular events so severe that they can lead to death, is confirmed.

Keywords: lithiasis; kidney stones; cardiovascular risk; cardiovascular events; risk factors

1. Introduction

Renal lithiasis (RL) is a common disease nowadays, due to the progressive increase in its prevalence in recent years. This can be seen reflected in different studies, the most recognized being the one carried out with the National Health and Nutrition Examination Survey (NHANES) database in the United States, where an increase in prevalence from 3.8% in NHANES I (1976 to 1980) to 8.8% in NHANES III (2007–2010) was observed[1]. In epidemiological terms it can be said that not only its prevalence has changed, but also the way it is distributed by sex. NHANES III found a predominance of men (10.3%) with respect to women (6.7%), a ratio of 1.5:1, similar to other series[2], although a greater balance by sex, as observed by Serio and Fraioli in Italy with a ratio of 1.25:1[3] or a population-based study in the city of Buenos Aires, where the male/female ratio was 1.19:1, published in 2006[4].

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RL is currently considered a systemic pathology, not limited only to the kidney and urinary tract, but largely related to diabetes mellitus (DM), obesity, arterial hypertension (AHT), hyperuricemia, hypercholesterolemia and chronic kidney disease (CKD), all known cardiovascular risk factors that are often linked to severe events such as stroke, coronary heart disease (CHD) or acute myocardial infarction (AMI). Historically, as early as 1973 Knute Westlund described an association between urolithiasis and CAD while Elmfeldt, three years later, observed the presence of AMI in 16.1% of patients with LR vs. 7.8% in patients without LR (p 0.01)[5,6].

The aim of the present study was to relate LR to cardiovascular events and to evaluate possible relationships or causes between them.

2. Renal lithiasis and cardiovascular events: Facts and associations

Numerous cross-sectional studies and meta-analyses have demonstrated the association between these two entities. Liu et al.[1] developed a meta-analysis, including 6 studies published between 2005 to 2014, with a total of 49,597 patients with LR and incidence of cardiovascular events defined as CAD (fatal or nonfatal AMI and/or myocardial revascularization) or stroke. These patients were compared with 3,558,053 controls, with a median follow-up of 8 to 9 years. Statistical analysis showed that the risk of having a stroke, CAD or AMI was 40%, 19% and 29% higher, respectively, in patients with a history of LR versus controls, although the risk of AMI was only significant among women. Although the included studies had heterogeneity between 60% and 95%, the variance between studies was small. The strength of this meta-analysis is based on the sample size and the fact that only prospective studies were included. Among the limitations, we highlight the impossibility of obtaining homogeneous models, probably due to differences in the characteristics of the population, in the follow-up periods, as well as in the size of the different samples. We could also include as a limitation the greater number of women affected, which could be explained by the larger female population in the sample.

In 2015, a group from Taiwan conducted a longitudinal study with a cohort of 80,546 patients taken from a database between 2000 and 2010, of whom 40,773 had LR; these were matched with the same number of controls by propensity score risk index (Propensity Score) with a 1:1 ratio. A 10-year follow-up was performed. At the end of the study, a higher incidence of AMI and stroke was observed in lithiasic patients compared to controls, 11.79% vs. 8.94% per 10,000 person-years, p: 0.003 for AMI and 31.41 vs. 22.45 per 10,000 person-years $p < 0.001$ for stroke. Applying the Cox regression model, the presence of LR was associated with an increased risk of total cardiovascular events of 38%, of AMI of 31% and of stroke of 39%. In a sub-analysis, a higher risk of AMI was found among men (HR 1.35; 95%CI 1.11–1.65 p: 0.003) compared to women (HR 0.93; 95%CI 0.62–1.38, p: 0.702). Although the data found in this last study are striking, we must consider that it was carried out in an Asian population that is not reliable to extrapolate to our population. Among the limitations, it should be clarified that the diagnoses were extracted from a database without standardized criteria, which entails a potential classification bias[7].

The association of HTN with renal lithiasis is well known, but not all published studies report the risk of lithiasis in hypertensive patients, so Madore et al. conducted two prospective studies to clarify the role of HTN and nephrolithiasis. In the first study, the investigators used data collected from the Health Professionals Follow-up Study (HPFS), a longitudinal study of cardiovascular disease and cancer in men. Cross-sectional analysis of baseline responses to mailed questionnaires revealed an age-adjusted Odds Ratio (OR) of 1.31 (95%CI 1.30 to 1.32) between HTN (defined as systolic >139, or diastolic >89 mm Hg) and nephrolithiasis. Follow-up data over 8 years suggested that a history of nephrolithiasis corresponded with an increased

tendency to develop HT (multivariate adjusted OR: 1.29, 95%CI: 1.12–1.41). At 8-year follow-up, patients with HT did not have a higher incidence of new stones (multivariate adjusted OR: 0.99, 95%CI = 0.82–1.21)[8]. Looking, in the second study, at middle-aged women who were enrolled from the Nurses Health Studies II data, a similar pattern was found. Prospective analysis over 12 years revealed only an increased risk of developing HTN in women with a history of nephrolithiasis[9]. Like the men studied in HPFS, hypertensive women were not at increased risk of developing nephrolithiasis. These studies confirm, as in previous studies, the increased presence of ETS in patients with nephrolithiasis. However, they also suggest that it is not hypertension, per se, that increases the risk of nephrolithiasis. In an attempt to link the underlying pathophysiological mechanisms in a single pathway connecting bone mineral loss, kidney stone formation and vascular calcifications, Fabris et al. compared arterial stiffness (an independent predictor of cardiovascular events] and bone mineral density in subjects with kidney stones secondary to idiopathic hypercalciuria, with the aim of simultaneously analyzing the independent relationship between calcium kidney stones, arterial stiffness and bone metabolism. For this purpose, 42 patients with idiopathic hypercalciuria and recurrent nephrolithiasis and 42 non-lithiasic patients, matched for age and sex, had their carotid-radial and carotid-femoral pulse wave velocity and augmentation index measured and defined abnormal arterial stiffness (AAR) if any of the above was above the 90th percentile of the distribution pool. From the results, AAR was obtained in 24% of the total sample. All the arterial stiffness measures considered were higher and significant in patients with lithiasis compared to controls, even after multivariate adjustment; the prevalence of AAR among lithiasis patients was 32% vs. 12% in controls (*p*: 0.01) suggesting arterial compliance among hypercalciuric patients, predisposing them to greater cardiovascular risk through a systemic mechanism involving both central and peripheral arteries. Among the limitations of the study, it is worth mentioning that the control group was composed of healthy professionals, which reduces the generalizability of the results[10].

The latest published study is from a group in Seoul, which performed a cross-sectional study of the presence of coronary artery calcifications (CAC) and nephrolithiasis, using the Agaston index as a screening test for cardiovascular disease. They included 62,091 patients, of whom only 2363 had LR. The prevalence of CAC was higher in patients with nephrolithiasis (19.1% vs. 12.8% *p*: 0.001). The Agaston index was higher in patients with RL than in patients without nephrolithiasis (25 vs. 19). These results remained unchanged even after adjusting for confounding factors, including metabolic alterations related to nephrolithiasis. The limitations of this study include the absence of temporal association due to the cross-sectional nature of the study, the lack of studies of metabolic disorders that predispose to litho formation, and the type of population used, which cannot be generalized[11].

3. Renal lithiasis and cardiovascular events: mechanisms involved

As mechanisms involved, three associations stand out in the literature. The first one refers to oxidative stress and inflammation. There are two main pathways for kidney stone formation according to Randall[12] known as Randall's type 1 and type 2 plaques. In type 1, stone formation begins with the deposition of calcium phosphate (PCa) or calcium oxalate (OxCa) in the basement membrane of the loop of Weller[13] or in the interstitium in association with the vasa recta[14], while type 2 begins with the crystallization of salts in the collecting ducts. There is evidence of the presence of inflammatory molecules associated with plaques, especially in type 1 Randall's plaques, including osteopontin,[15] collagen[16] and zinc, suggesting that localized inflammation would start early[17]. According to this theory, it is proposed that the injury and inflammation would be a consequence of the exposure of epithelial cells to the crystals. Several experimental studies have shown that exposure of the renal epithelium to high concentrations of OxCa or PCa crystals generates the release of renin and angiotensin II,[18] activates the enzyme NADPH oxidase[19,20] and this promotes the release

of reactive oxygen substances (ROS)[21]. A variety of transcriptional and growth factors including NFkB and fibroblast growth factor B are also involved in this mechanism[22]. In turn there is generation of secondary mediators such as prostaglandins, isoprostanes and phospholipase A2[17], which increase the production of chemotactic substances such as crystallization modulators, including osteopontin, and prothrombin fragments[23,24] (**Figure 1**).

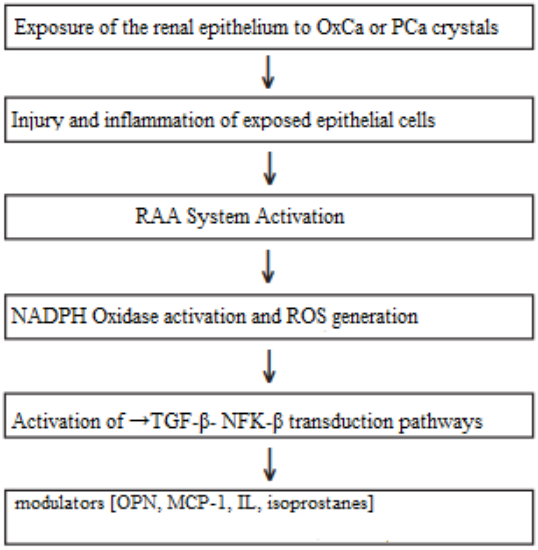

Figure 1. Signaling pathways associated with renal lithiasis formation[25].

With regard to cardiovascular disease, the mechanisms that generate tissue damage such as hypertension[26], DBT mellitus[27], atherosclerosis[28] among others, generate increased oxidative stress with release of the enzyme NADPH oxidase and reactive oxygen species[29]. A decrease in nitric oxide is produced by oxidative stress and, as a consequence, signaling pathways such as NFkB MAPK are activated, generating greater inflammation, which can culminate in AMI, stroke and peripheral vascular disease, among others (**Figure 2**)[28]. In Khan's theory[25], who considers the formation of lithium as a metabolic alteration and not as a physical-chemical event, proposes that disorders associated with oxidative stress are a continuum. The stress introduced by one disorder can promote the other under the right circumstances.

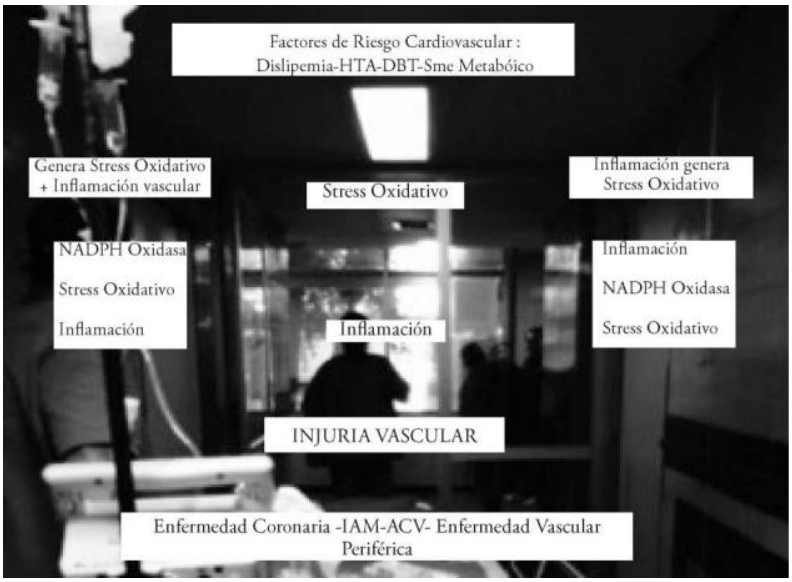

Figure 2. NADPH oxidase generation in different inflammatory vascular disorders[28].

The second association refers to the presence of lithogenic mechanisms that contribute to vascular calcification. This relationship is based on the fact that lithogenesis, as well as vascular calcifications, present similar characteristics, which can be summarized in 4 analogies: 1) deposits of calcium minerals in plaques, such as atheromatous plaques in vessels and Randall's plaques in the kidney; 2) need for inhibitors of calcifications, since it is postulated that these would be the consequence of a functional deficit of inhibitors, rather than an active process; 3) bone-related proteins present in both plaques[30] and finally; 4) inflammatory reaction and injury. Among these common mechanisms we can find the presence of Matrix Gla Protein (MGP). This protein is a potent inhibitor of vascular calcifications and can be found in high concentrations in the renal tubular epithelium, as well as in lung, bone and heart[31]. It is overexpressed (up regulation) after exposure to OxCa and ethylene glycol, a precursor of oxalate. Several previous studies have shown that this protein is not only an important biomarker associated with atherosclerosis, but that it is also associated with crystal formation in the kidney[32]. Considering the aforementioned analogies, Kenjiro Kohri's group studied the MGP gene variants and their relationship with renal lithiasis, taking as study population 122 patients with a history of renal lithiasis, with an average age of 55 years; and 125 control patients with no history or family history of renal lithiasis, who underwent genetic analysis of MGP polymorphisms, finding a significant association between single nucleotide polymorphism 11 (SNP11), rs4236, and risk of renal lithiasis[33]. This result, similar to that described by Simon et al. in a study that evaluated vascular calcifications and risk of AMI related to the presence of genetic polymorphisms of MGP, relates SNP11 with vascular calcifications and renal lithiasis[34]. To confirm these findings the group of Bin Gao et al. analyzed genetic polymorphisms of MGP in a larger population of 354 patients with renal lithiasis and 374 control patients without history of renal lithiasis, finding in the LR group again that the SNP11 polymorphism (rs4236) alters the function of MGP increasing the risk of renal lithiasis[35]. These studies were performed in patients of Asian ethnicity, therefore they have limitations when generalizing their results due to the different racial and genotypic differences in Europe and America.

Regarding the third association between renal lithiasis and cardiovascular disease, we mention metabolic alterations as common factors in the pathogenesis of the development of both pathologies (**Figure 3**). In this last theory, an already known association is made between obesity, metabolic syndrome, DBT and HT; all risk factors for the development of renal lithiasis as well as cardiovascular disease[36,37].

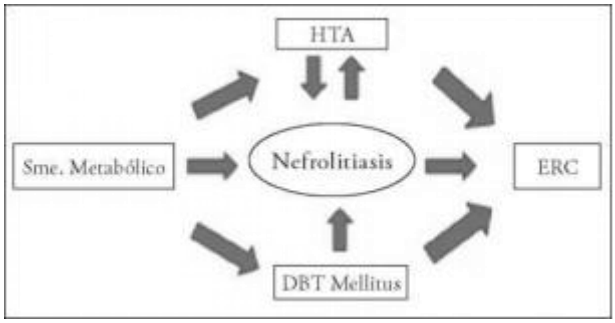

Figure 3. Common risk factors in the development of nephrolithiasis and cardiovascular disease.

Hypertension, diabetes and metabolic syndrome not only produce oxidative stress, renal injury and inflammation, but also produce changes in the urinary environment that promote crystallization[25]. In the case of diabetes, these changes specifically promote uric acid nephrolithiasis, since it is known that there is a mechanism that produces hypocitraturia and decreased pHu, which favors greater precipitation of uric acid salts[37,38]. Just as the aforementioned risk factors can generate the development of renal lithiasis and cardiovascular disease, on the other hand, renal lithiasis is the cause of 8% of the development of chronic kidney disease, another risk factor for cardiovascular disease and death[37].

4. Conclusions

Considering all of the above, the theory is confirmed that when we speak of RL we are not only referring to a disease limited to the kidney and urinary tract, but rather to a systemic disease, with involvement and risk of cardiovascular events, so severe that they can lead to death. This previously known association, with pathophysiological mechanisms in common, including metabolic, inflammatory and genetic mechanisms, not yet fully clarified, makes us consider lithiasic patients as patients at high cardiovascular risk and raises the question of how to proceed with young lithiasic patients, given that the studies have been performed in populations aged 45 years and older.

The common risk factors of patients with renal lithiasis and cardiovascular disease, both oxidative stress and inflammation, as pathophysiological mechanisms of systemic diseases, will surely be complemented with genetic studies to clarify and prevent the high cardiovascular risk of patients with nephrolithiasis.

Conflict of interest

The authors declare no conflict of interest.

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