Calcium nephrolithiasis, metabolic syndrome and the cardiovascular risk

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Sakhaee et al. [1] in this issue have investigated whether the risk of the common calcium nephrolithiasis is associated with the metabolic syndrome (MS). This question is interesting since it deals with a more general problem on whether calcium nephrolithiasis is a ‘systemic disorder’ [2, 3] and entails a cardiovascular (CV) risk.

The concept of nephrolithiasis as a systemic disease was first addressed by Baggio and Gambaro [4] after the finding that idiopathic calcium oxalate stone formers have a lower plasma concentration of gamma-linolenic acid and a higher concentration of arachidonic acid (AA) than healthy controls and that supplementation with fish oil lowers urinary calcium and oxalate [5]. It was suggested that stone formers have a systemic imbalance between the essential fatty acid (EFA) omega-3 and the omega-6 pathways which causes higher phospholipid AA level responsible for hypercalciuria and hyperoxaluria. Although a subsequent study could not confirm these results since reduced levels of AA were found in stone formers’ red blood cell membranes, it was observed that these levels were relatively higher in hyperoxaluric stone formers compared to normo-oxaluric patients [6]. In a subsequent study, higher plasma AA was again observed in stone formers, as well as higher serum PGE2, 25-vitamin D and 1,25 vitamin D [7]. Elevated urinary levels of bone turnover markers were also found in the stone formers [7].

Supplementation with fish oil in the same study induced a reduction in AA, 1,25 vitamin D and hydroxyproline suggesting that phospholipid AA levels influence an array of calcium disturbance mechanisms, including bone loss and kidney stone formation. However, although stimulating the omega-3 cascade can induce a urinary milieu which is less supportive of lithogenesis, the same favourable outcome was also achieved by stimulating the omega-6 pathway [8] suggesting that the relationship between EFA and renal stones could be more complex, possibly explaining why, in large prospective cohorts, no relationship between renal stone episodes and omega-6 and omega-3 EFA intake was demonstrated [9].

One should also expect that a systemic disorder in AA metabolism could also lead to alterations in the CV system, namely to atherosclerosis, but this was not investigated.

In addition to the AA metabolism disorder, it has been reported that patients with kidney stones suffer from other non-renal manifestations like metabolic bone disease, MS and CV disease. They will be discussed separately.

With respect to metabolic bone disease, it is evident that stone patients have a larger risk of being exposed to this disorder [10], although the pathogenetic link is still controversial [11].

Several papers have suggested an association between nephrolithiasis and MS [12], but which stones are passed by patients affected by MS is not clear. They certainly have a significant risk to form uric acid stones since a reasonable pathophysiological link with MS and allied conditions has been discovered [13]: in fact, some of the MS features (high blood glucose—type 2 diabetes, obesity), possibly because of the insulin-resistance, have an abnormally low urine pH which favours uric acid crystallization. However, whether they also pass an increased number of calcium stones is unknown. The article by Sakhaee et al. [1] leaves this question largely unanswered.

The authors have indirectly addressed this issue by investigating the urinary calcium stone risk in patients with MS, with and without previous renal stones. Their data could suggest that calcium oxalate stones are also very common in MS patients. However, the finding that, in the non-stone-forming group, an association exists between urinary stone risk factors and number of features of MS, while this is lost in stone formers, may indicate that actually the calcium stone-driving mechanisms are not triggered by MS. On the other hand, the ‘clinical’ relevance of the association between urinary calcium stone risk factors with the MS in non-stone formers is questionable; indeed, these subjects have not (yet?) formed stones. Thus, the study of Sakhaee et al. [1] may support the idea that the association between MS and nephrolithiasis is largely driven by uric acid stones rather than by an increased propensity of patients with MS to form calcium stones.

Two recent papers have described the relationship between renal stones and CV disease. Rule et al. [14], in
5081 incident stone formers and 14,144 matched control subjects (identified from the Olmsted County general population between 1984 and 2003), found that stone formers have a 38% increased risk for myocardial infarction (MI). Interestingly, the risk for MI in stone formers remained elevated even when adjusted for other risk factors like hypertension, diabetes, obesity, dyslipidaemia and even chronic kidney disease (CKD). It is highly likely that calcium nephrolithiasis may be responsible for this association.

The relationship between nephrolithiasis and CV diseases was further confirmed by Domingos and Serra [15] through a study performed in over 23,000 adult individuals from the 4th Portuguese National Health Survey. They showed that stone formers have a higher prevalence of MI [odds ratio (OR), 1.338; P < 0.05] and stroke (OR, 1.330; P < 0.05) compared with non-stone formers. After adjustment for the presence of diabetes and hypertension, nephrolithiasis remained, at least in women, an earlier and independent risk factor for MI later in life. The authors did not analyse their data according to stone composition; however, since uric acid stones are relatively rare in females [16], their findings suggest that calcium nephrolithiasis may be responsible for the reported association.

The observations on the increased CV morbidity in (calcium) stone formers are of great interest, but are not, in our opinion, conclusive. Firstly, earlier reports did not observe any increased risk [17]. Secondly, it is surprising that there are no data on survival which one should expect to be decreased in a population at higher CV morbidity. Finally, it is not clear whether the association between renal stones and CV morbidity is related to the chemical nature of stones since this issue has not been addressed in the two recent studies [14, 15]. We may suppose that the association was with calcium stones, but this hypothesis requires further epidemiological–clinical studies.

The idea of an increased CV risk in calcium nephrolithiasis could be strengthened by the understanding of the mechanism(s) involved (Figure 1).

The rebuttal of the hypothesis of a link between MS and calcium nephrolithiasis rules out that MS is involved in the higher CV risk reported in (calcium) stone formers. It has been suggested that the increased risk for CKD in individuals with kidney stones [18, 19] would lead to a larger threat for CV disease, but the data of Rule et al. [14] suggest that this is not the case since the association between renal stones and MI was maintained even after adjustment for CKD.

Hypertension, one of the most important CV risk factors, has been recognized to be a significant predictor of kidney calcium stones [20, 21]. Hence, such a relationship could explain why calcium stone formers have an increased CV morbidity.

A further mechanism has been recently proposed. As observed, reduced bone mass is a frequent finding in calcium stone formers [10]. A number of reports have disclosed an inverse relationship between bone density and abnormal arterial stiffness partly related to vessel calcifications. It is well known that abnormal arterial stiffness is a strong predictor of CV mortality. Fabris et al. [22] have shown a higher pulse wave velocity in stone formers suggesting an increased stiffness of small arteries and a preclinical atherosclerosis condition. Multivariate analysis, adjusted for age, gender and body mass index, disclosed an inverse relationship between arterial stiffness and bone mineralization.

A bone-vessel liaison which leads to atherosclerosis has been discovered in a number of conditions (hypertension, primary hyperparathyroidism, osteoporosis, CKD, uraemia) [23]. The data of Fabris et al. [22] extend to calcium nephrolithiasis so that this paradigm may help to explain the increased CV morbidity of renal stone formers.

Considering the prevalence of calcium nephrolithiasis in the general population, up to 10–15%, the association of renal stones with CV diseases is an important topic to be clarified. Unfortunately, at the moment, we have much more doubt than certainties. It is unquestionable that further studies are necessary to establish a clear relationship between nephrolithiasis and CV risk and to disclose the potential mechanism(s).

Conflict of interest statement. None declared.

(See related article by Sakhaee et al. Metabolic syndrome and the risk of calcium stones. Nephrol Dial Transplant 2012; 27: 3201–3209.)

References

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Urinary angiotensinogen as a biomarker of chronic kidney disease: ready for prime time?

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In recent years, there has been an explosion of research directed at the identification and characterization of biomarkers of health and disease, driven to a great extent by advances in proteomic analysis and other technologies. Since urine sampling is relatively non-invasive and accessible, and since urine contains substances derived primarily from tubular secretion, kidney disease has been a major focus of biomarker research. But what really is a biomarker? Strictly speaking, a biomarker should be indicative of a biological process, and if it is to be adopted for clinical use, it should satisfy three criteria, as recommended by the Institute of Medicine of the National Academies of Science [1]. First, the biomarker must have analytic validity, in that testing should be reliable and reproducible across laboratories and clinical settings, and with sufficient sensitivity and specificity for the condition under consideration. Second, the biomarker must undergo qualification, with a determination that it is associated with the disease and that interventions targeting the biomarker can impact hard clinical endpoints. Finally, the biomarker must be evaluated for its utilization: in order to consider the use of the biomarker as a surrogate endpoint...