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SHORT REVIEW

Towards solving the riddle of nephrolithiasis: a South Africa perspective

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Introduction

South Africa has a rich tradition in urinary tract stone research. This paper asks what research originating from South Africa has contributed to the understanding of the pathophysiology of nephrolithiasis. Many of these contributions are based on the premise that ethnicity variation accounts for dramatic differences in the prevalence of nephrolithiasis and that South Africa represents an ideal place for investigating this variation. It needs to be noted that many of the papers dealing with this question, as Rodgers has put it, "demonstrate an insensitivity to racial terminology and classifications."[1] We have nevertheless attempted to review these papers to understand what valid science this literature holds and how it can inform further work in the relatively under-investigated field of nephrolithiasis aetiology and pathophysiology.

Earliest work

Vincent Vermooten from the University of the Witwatersrand writing in JAMA in 1937 compared the admission records of white and black hospital patients. An examination of the hospital admission records of 1 091 000 black patients only yielded one black patient with renal tract stones. This compared with 126 000 admissions of white patients where renal calculi were found in the ratio of one in 460 admissions.[2]

Monte Modlin started Groote Schuur Hospital's dedicated kidney stone clinic in 1962.[3] He was a consultant urologist attached to the University of Cape Town. He was to echo Vermooten's finding that the occurrence of renal stones in black South Africans is extremely rare when he stated that: "I have personally never attended a black patient with a renal stone."[4] Modlin is to our knowledge the only South African to have given the prestigious Hunterian lecture in London in 1967. The lecture was titled: "The aetiology of renal stones: a new concept arising from studies on a stone-free population." He started his lecture by recognising the work of John Hunter, regarded by many as a father of the scientific method in medicine. Hunter, in a 1771 paper, asserted a view of the origin of renal calculi which is not too dissimilar from contemporary theories: "I have made many experiments on the formation of different calculi and find that they are formed by crystallisation."[4] Modlin made a detailed study of the 24-hour urine collection of white (n = 103) and black (n = 128) subjects, hoping to find an answer to the apparent low incidence of renal calculi in black subjects. Despite Modlin's extensive study, he stated that: "The important conclusions that could be reached are that factors, other than traditional etiological factors of hypercalcuria and hypocitrateuria, appear important in the genesis of calcium-containing renal stone. It is apparent, therefore, that a different approach to the problem is required."

There is now over the last 15 years more robust epidemiology research, much of it from the USA, which supports Modlin and Vermooten's early notion that there are ethnic differences in stone prevalence. Mente and Honey showed in a cohort of over 1 000 patients that the propensity for the development of calcium nephrolithiasis differed markedly among ethnic groups in North America.[5] Hsi et al. showed in a long term cohort study of over 42 000 patients a difference of six (white patients) vs two (black patients) stone episodes per 1 000 patient years (HR 2.2).[6] However, the cause or these differences remain to be conclusively elucidated. It needs to be noted that there is no contemporary epidemiological study of nephrolithiasis in South Africa. Hence, we are unable to confirm these early findings or to comment if they have changed over time.

Contemporary work

Allen Rodgers, professor emeritus of chemistry at the University of Cape Town has contributed more than anyone else to the understanding of the basic science of urolithiasis in South Africa. Like Modlin and Vermooten, he too has used apparent ethnic differences in stone prevalence as a starting point to attempt to unlock aetiological answers to the pathophysiology of nephrolithiasis.

Rodgers' years of inquiry have included study of a great variety of potential factors which could account for ethnic differences in stone incidence. His papers have looked at amongst others the following: urinary macromolecules inhibitors, physiochemical properties, crystal-cell interaction, diet, genes (AGT Pro11Leu polymorphism).[1]

In a review paper published in 2013, Rodgers concluded that answers to apparent ethnic differences remain elusive when he states: "It is the present author's view that the urinary physicochemical risk factors (calcium, magnesium, oxalate, citrate, phosphate, pH), which have been routinely

determined and cited for years as differentiating between the relative risk in stone-formers and healthy controls, do not convincingly account for racial and ethnic differences in stone occurrence."[1]

Toward solving the riddle

Unpublished work from the Groote Schuur Hospital's Stone Clinic database suggests that 65% of our patients present with a calcium oxalate stone. Hyperoxaluria is of more importance than urinary calcium in the supersaturation that leads to calcium oxalate stones. Oxalate is mainly produced endogenously as an end-product of metabolism in the liver. Dietary contribution is variable among individuals ranging as high as 50% of urinary oxalate.[7] This contribution of dietary oxalate to urinary oxalate was in earlier decades thought to be low and this resulted in oxalate being largely ignored.[8]

Lewandoski et al. published an important paper in 2001 comparing urinary and dietary variables in 11 black and 11 white South African men.[9] Urine analysis showed an intriguing anomaly; black subjects had significantly higher baseline oxalate and lower citrate values than white subjects. Furthermore, the Tiselius risk index and relative supersaturation of calcium oxalate was higher in black subjects. Thus, counterintuitively, black subjects who appear to be clinically immune to stones had greater apparent physiochemical risk.

The Lewandoski et al. trial yielded a further significant finding. The subjects were then fed a controlled lithogenic diet (high in oxalate/low in calcium). Black subjects maintained their base levels of excretion, while white subjects saw a marked 57% rise in oxalate urinary excretion.[9]

Another counterintuitive finding from a separate 2001 dietary study concludes that "South African black subjects have a dietary intake that is traditionally high in oxalate and low in calcium because of widespread lactose intolerance."[10] Hence, black South African subjects would appear to be further at risk for stones from a dietary perspective. Given the presumed changing dietary patterns in South Africa these findings need to be considered with caution.

Lewandoski et al. now focused on gut oxalate absorption as a candidate explanation for these unexpected findings with initially disappointing results. From a 2005 paper he concluded that: "South African black subjects handle dietary oxalate more efficaciously than white subjects and that this occurs via some endogenous mechanism, which has not yet been identified or characterised."[11] While further work from a 2013 paper studying 10 healthy and matched black and white men concluded that: "Intestinal permeability is not a contributory factor in the apparent different handling of dietary oxalate in black and white South Africans."[12]

The next piece of the gut-oxalate puzzle came from work analogous to Marshall and Warren's landmark 1984 Lancet paper linking bacteria to peptic ulcer disease.[13] A 1988 paper identified oxalate degrading bacteria in guinea pigs. The paper concluded that these bacteria may be important in preventing excess absorption of oxalate.[14] Two decades later this idea was taken forward in humans with the published paper reporting that: "colonization with *Oxalobacter formigenes* was associated with a 70% reduction (17% among stone former patients and 38% among control subjects) in the risk of being a recurrent calcium oxalate stone former."[15]

There is now good evidence that colonisation with *O. formigenes* varies internationally. PeBenito et al. showed an 80% colonisation in Tanzania compared to 20% in the USA. Their findings are "consistent with the hypothesis that the rising incidence of kidney stones is associated with the progressive loss of *O. formigenes* colonisation in populations […] due to socioeconomic advances and medical treatments."[16]

Recent work by Magwira el al. from the University of Cape Town has applied this hypothesis to South Africa. Their initial insights were disappointing when they found that: "*O. formigenes* was present only at very low levels in black ($n = 20$) and white ($n = 20$) South African subjects."[17]

However, *O. formigenes* is only one of many oxalate degrading bacteria. Magwira et al. went on to concluded that: "The South African black population harbours a pool of oxalate-degrading lactic acid bacteria, which is more abundant and diverse than that of white South Africans."[16] Rodgers had found similar results from a 2006 paper which showed a 70% carriage of oxalate degrading bacteria (*O. formigenes*) in black subjects compared to 10% in white subjects.[18]

International research into probiotic inoculation with oxalate degrading bacteria as a stone prevention strategy has disappointed. A recent study ($n = 14$ control and $n = 14$ "Oxadrops") concluded that: "dietary oxalate restriction reduced urinary oxalate, but the probiotics (containing lactic acid bacilli) did not further reduce it in patients on a restricted oxalate diet."[19]

Unpublished work from the Groote Schuur Hospital Stone Clinic has supported a growing body of evidence that dietary instructions can effectively reduce urinary oxalate levels in a stone clinic setting.[20] We demonstrated a statistically significant drop in urinary oxalate to within normal levels in a group of idiopathic hyperoxaluric stone formers on general preventive advice and specific oxalate dietary restriction (53.2 mg to 29.6 mg/24 hour, $p = 0.0002$).

Lastly, one additional notable avenue of research has been urinary inhibitors of crystallisation and stone formation. These are urinary macromolecules which reduce stone formation. Rodgers et al. found in a South African cohort that: "urinary albumin from black subjects was superior to that from white subjects with regard to inhibitory activity of calcium oxalate crystallisation."[21]

In conclusion, South Africa has a fine pedigree of basic science urinary tract stone research. Work to date supports the hypothesis that gut oxalate degrading bacteria and macromolecule inhibitors appear to explain South Africa's apparent ethnic differences in stone incidence. These findings deserve validation in further study with a hope to bring preventive strategies to the stone clinic setting.

Conflict of interest

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