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Kidney Stones: A Fetal Origins Hypothesis†

Sarah A. Howles, MA, MRCS(Eng)[1,2], **Mark H. Edwards, MRCP**[3], **Cyrus Cooper, FMedSci**[3,4], and **Rajesh V. Thakker, MD, FRCP, FMedSci**[1,2,*]

[1]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom

[2]Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom

[3]MRC Lifecourse Epidemiology Unit, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom

[4]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

Abstract

Kidney stones are common with a multifactorial aetiology involving dietary, environmental and genetic factors. In addition, patients with nephrolithiasis are at greater risk of hypertension, diabetes, metabolic syndrome, and osteoporosis although the basis for this is not fully understood. All of these renal stone associated conditions have also been linked with adverse early life events, including low birth weight, and it has been suggested that this developmental effect is due to excess exposure to maternal glucocorticoids *in utero*. This is proposed to result in long-term increased hypothalamic-pituitary-axis activation and there are mechanisms through which this effect could also promote urinary lithogenic potential. We therefore hypothesise that the association between renal stone disease and hypertension, diabetes, metabolic syndrome and osteoporosis may be related by a common pathway of programming in early life which, if validated, would implicate the developmental origins hypothesis in the aetiology of nephrolithiasis.

Keywords

Kidney Stones; Low Birth Weight; Fetal Origins; Osteoporosis; Metabolic Syndrome

Introduction

Renal stone disease, also known as nephrolithiasis or urolithiasis, represents a major clinical and economic health burden with approximately 20% of men and 10% of women manifesting symptoms by 70 years of age(1). The incidence of nephrolithiasis is increasing

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*Corresponding author and address for reprints: Professor RV Thakker, Academic Endocrine Unit, Nuffield Department of Clinical Medicine, Oxford Centre for Diabetes, Endodrinology and Metabolism, University of Oxford, Churchill Hospital, Headington, Oxford, OX3 7LJ, United Kingdom. rajesh.thakker@ndm.ox.ac.uk. Telephone: 01865 857501..

S.A.H. is a Wellcome Trust Clinical Research Training Fellow. M.H.E. is an Arthritis Research UK Clinical Research Training Fellow.

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and in untreated patients the chance of formation of new stones over the following 5 years is greater than 50%(1). Renal calculi which consist of calcium oxalate, calcium phosphate, urate, cysteine or struvite (magnesium ammonium phosphate), form as crystals when their solubility product in urine is exceeded. Thus, a major risk factor for stone formation is urinary salt concentration with hypercalciuria being the most common metabolic abnormality in stone formers(2). Urinary pH also influences the risk of stone formation, with increased urinary pH promoting the formation of calcium phosphate stones and decreased urinary pH promoting the formation of uric acid stones(3). In addition, increased urinary ceruloplasmin concentrations have been observed in stone-forming patients and ceruloplasmin has been reported to promote lithogenesis in *in vitro* studies; the mechanisms underlying this observation are unclear(4). However, other urinary constituents such as citrate, osteopontin, uromodulin, inter-α-trypsin molecule(3), and human urinary trefoil factor 1(5) inhibit stone formation. Indeed, oral citrate therapy to increase urinary citrate which binds to calcium and acts to inhibit urinary crystal nucleation and aggregation reduces the risk of stone formation in patients with low urinary citrate excretion(3). In this article, we explore the possibility that prenatal effects may influence the balance of these urinary constituents to increase an individual's lifetime risk of developing renal stone disease, and propose a novel hypothesis for kidney stone formation that involves a fetal origin with an adverse intrauterine environment.

Nephrolithiasis Association With Hypertension, Type 2 Diabetes, Metabolic Syndrome, And Osteoporosis

Patients with metabolic diseases that result in increased urinary solute loads have a higher risk of nephrolithiasis(3). Such diseases include primary hyperoxaluria, enteric hyperoxaluria, primary hyperparathyroidism, autosomal dominant hypocalcaemic hypercalciuria, and Dents disease(3). Epidemiologic studies have also reported that hypercalciuria and nephrolithiasis are associated with low bone mineral density (BMD), osteoporosis, and fractures(6); and features of the metabolic syndrome, such as hypertension and type 2 diabetes(7,8). In addition, hypertensive patients are at risk of hypercalciuria, which may be due to increased dietary sodium, a genetic predisposition, or chronic hyperaldosteronism that may be associated with hypocitraturia(7). Obesity and insulin resistance have also been linked to hypercalciuria(9,10), hyperuricosuria(9), and increased urinary acidity(7) and it has been reported that uric acid stones may be more common in those with the metabolic syndrome(7).

Fetal Developmental Planning Is Implicated In The Development Of Hypertension, Type 2 Diabetes, Metabolic Syndrome And Osteoporosis

An adverse intrauterine environment has been associated with components of the metabolic syndrome(11-13), impaired bone health(14), and coronary heart disease(15). This is consistent with the hypothesis of fetal origins of disease. Catch-up growth in the postnatal period is also predictive of these diseases, thereby suggesting the importance of relative growth restriction(15). The increased risk of these adult chronic diseases with adverse early environment was initially considered to be related to maternal-fetal malnutrition, and more recently to increased circulating maternal glucocorticoid levels during pregnancy which may cause an adverse *in utero* environment that results in long-term constitutive activation of the fetal hypothalamic-pituitary-axis (HPA); these alterations may also involve epigenetic mechanisms(16). The prenatal environment has been established to have major influences on the development and function of the HPA axis, with effects on the susceptibility to metabolic and neurological dysfunction(16). For example, several animal models have shown the effects of maternal and fetal environment on offspring stress responsiveness and

behaviours, and maternal stress during pregnancy has been reported to increase HPA activity in rat, guinea pig and primate offspring. Furthermore, offspring of non-human primates given dexamethasone have alterations in their HPA axis(17), and administration of glucocorticoids to pregnant rats, sheep and non-human primates leads to smaller progeny at birth(18). However, outcomes are variable and depend on the nature of the maternal exposure (e.g. stress, glucocorticoid exposure, or undernutrition), the timing within pregnancy, and the duration and intensity of the insult. In addition, interspecies variations in outcomes have been shown and this likely relates to temporo-spatial differences in fetal brain and neuroendocrine development, which may be associated with phases of rapid brain growth(19).

Human studies, which are invariably observational, reveal that maternal stress is associated with a range of neuroendocrine differences in the offspring. Specifically self-reported maternal anxiety during late pregnancy was associated with higher awakening salivary cortisol concentrations in their children at 10 years of age(20) and markers of anxiety at 16 weeks of gestation were associated with greater salivary cortisol responses to vaccination in offspring aged 5 years(21). Although the results of observations of women following catastrophic experiences in pregnancy are not always consistent, evidence has emerged that women in their second or third trimester during the Chernobyl disaster had offspring with higher salivary cortisol levels at the age of 14 years(22). There is also evidence that high levels of maternal circulating glucocorticoids may lead to low birth weight(16,23). As maternal stress has been linked to both low birth weight and offspring HPA activation, this may be the basis for the association between low birth weight and higher fasting plasma cortisol levels in humans(16,24). Furthermore, an inverse relationship between birth weight and plasma aldosterone in humans has been established(25). Maternal circulating glucocorticoid excess may alter development and function of the fetal adrenal cortex by suppressing fetal adrenocorticotropic hormone (ACTH), which affects development of the adrenal transitional zone, the future zone fasiculata, and the functional maturation of the adrenal definitive zone, the future zona glomerulosa(26). In addition, mineralocorticoid receptor activation by glucocorticoids, is normally prevented by 11β-hydroxysteroid dehydrogenase type 2 which converts cortisol to inert cortisone and 11-dehydrocorticosterone(16); however, in states of mineralocorticoid excess, this system may become overwhelmed. Thus, these alterations in cortisol and mineralocorticoid activity may have multiple effects on adult physiology, including blood pressure(25).

Hypothesis: *In Utero* Environment Influences Risk Of Developing Renal Stone Disease

Low birth weight and fetal developmental programming may contribute to the risk of kidney stone disease, for the following three reasons. First, premature infants with very low birth weight have been reported to have either nephrocalcinosis or nephrolithiasis with higher urinary calcium excretion which could not be explained by the greater use of dexamethasone and furosemide, as these disorders had occurred in individuals who had not received these drugs(27). The longer-term implications of these occurrences remain to be elucidated. Second, maternal protein restriction in rats resulting in an adverse intrauterine environment, led to progeny with higher urinary calcium excretion(28). Third, the association between nephrolithiaisis and hypertension, type 2 diabetes, metabolic syndrome and osteoporosis, all of which are linked to low birth weight, suggests a shared aetiology during early development with multiple effects on the adult phenotype (Table 1). A possible mechanism for this association may involve exposure in low birth weight infants to higher levels of maternal glucocorticoids that results in persistent HPA activation and increased mineralocorticoid activity. This may result in a form of chronic hyperaldosteronism, which has been reported to lead to hypercalciuria in humans and rats(29,30) as well as lowering

urinary pH(31). These factors would contribute to increasing the risk of calcium and urate containing stones, respectively. Further evidence of the link between corticosteroids and renal stone disease, comes from a study that reported a 50% rate of nephrolithiasis in patients with Cushing's syndrome; there was also an association with hypercalciuria, hyperuricosuria and hypocitraturia. Following successful treatment of the Cushing's syndrome, patients became normocalciuric and normouricosuric although 30% continued to have nephrolithiasis(32).

Testing The Hypothesis

We hypothesise that an individual's lifetime risk of developing renal stone disease is inversely related to their birth weight. The mechanism proposed is through the *in utero* exposure to excess maternal glucocorticoids leading to long-term activation of the HPA and greater mineralocorticoid activity resulting in lifelong alterations in the lithogenic potential of the individual's urine.

This hypothesis of the contribution of fetal developmental programming to the risk of renal stone disease could be tested by undertaking epidemiological studies in birth cohorts that have combined information on: birth weight, post-natal growth and development, renal stone disease prevalence rates, and relevant plasma and urinary biochemical measurements. Such a cohort would need to include individuals in late adult life and in whom a history of symptomatic renal stone disease could be confirmed. The specific urinary measurements, in these individuals, would assess excretion of calcium, citrate, urate and pH, which are established determinants of renal stone disease; osteopontin, uromodulin, inter-a-trypsin molecule, and human urinary trefoil factor 1, as inhibitors of renal stone formation; and ceruloplasmin, as a potential promoter of lithogenesis. In addition, urinary cortisol and steroid metabolites would be measured to assess glucocorticoid and mineralocorticoid activity. The specific plasma measurements would assess osteocalcin, β-crosslaps and parathyroid hormone concentrations, as these have recently been identified as indicators of increased lithogenic risk(33). In addition, plasma cortisol, ACTH, aldosterone and renin would be measured to assess for glucocorticoid, mineralocorticoid and HPA activity. Analyses of these data would then be undertaken to examine for an association between low birth weight and lifetime risk of renal stone formation, as well as for associations between the measurements obtained from the urinary and plasma samples and birth weight. Such studies, which would aid in the understanding of the aetiology of the developmental origin of renal stone disease, are currently not possible as epidemiological birth cohorts with data on renal stone disease and the relevant urinary and plasma measurements are not available and hence a prospective study is required. However, such a prospective study could be facilitated by collecting the required data on renal stone disease and associated urinary and plasma measurements and combining this with birth weight data already collected by established epidemiological cohorts, for example the Hertfordshire Cohort Study(34) and the Southampton Women's Survey(35). The Hertfordshire Cohort Study already provides data on birth-weight and growth during early postnatal life, diet, blood pressure, fracture history and bone mineral density, as well as indices of socioeconomic status during childhood and adulthood(34); recalling participants, the majority of whom are in their seventh and eighth decades of life, from this cohort to ascertain the occurrence of renal stone disease as well as measurements of relevant urinary and plasma markers for nephrolithiasis would facilitate an analysis for association between the occurrence of renal stone disease and the parameters of fetal and early postnatal development. The Southampton Women's Survey provides further data on maternal nutrition, physical activity and other lifestyle characteristics as well as body composition prior to conception(35), and recall and assessment for renal stone disease, and urinary and plasma studies of the participating offspring, for whom growth data to the age of four years is available, would facilitate the association studies. Thus, prospective

studies, which gather data related to renal stone disease from the established birth-cohorts are likely to be the most efficient way of testing the hypothesis of fetal programming in renal stone disease.

Conclusion

In conclusion, fetal developmental programming has been implicated in hypertension, type 2 diabetes, metabolic syndrome, and osteoporosis. We propose that early prenatal environment also influences the lifetime risk of developing renal stone disease and that this may involve constitutive HPA activation with excess glucocorticoid and mineralocorticoid activity. Validation of this hypothesis and an understanding of the precise mechanisms that underlie it may help to identify individuals at risk of the condition, give further insight into pathogenesis and lead to novel interventions in early life to modify the risk of developing the debilitating condition of recurrent renal stone disease.

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Table 1
Association of low birth weight with nephrolithiasis-related conditions

Condition	Population	Outcome Measure	Value (confidence interval)	Reference
Type II diabetes mellitus[a]	Meta-analysis of 25 studies including Northern European, Asian, and Northern American populations	Odds ratio of association of birth weight with type II diabetes mellitus, adjusted for adult body mass index	0.70(0.65,0.76)/kg	(11)
Hypertension[a]	Systematic review of 80 studies including Western and Northern European, northern and southern American, African, Middle Eastern and Asian populations	Mean difference in systolic blood pressure per kg increase in birth weight	Approximately −2mmHg/kg	(12)
Metabolic syndrome[a]	Meta-analysis of 11 studies including Western and Northern European and Northern and Southern American populations	Odds ratio of association of low birth weight with metabolic syndrome (birth weight <2.5kg vs >3.4kg)	2.53(1.57,4.08)	(13)
Bone health[a]	Meta-analysis of 6 studies including Northern European, East Asian, Northern American and New Zealand populations Meta-analysis of 5 studies including Northern European, East Asian, Northern American and New Zealand populations	Increase in lumbar spine bone mineral content per kg increase in birth weight Increase in hip bone mineral content per kg increase in birth weight	1.49g/kg (0.77,2.21) 141g/kg (0.91,1.91)	(14)
Nephrocalcinosis[a]	Taiwanese infants born <34 weeks and <1500g	Comparison of mean birth weight of children with renal calcification compared to those without calcification	p=0.004	(27)
Hypercalciuria[b]	*4 week old rats exposed to either a normal or low protein diet during pregnancy*	*Comparison of renal calcium clearance after maternal exposure to a normal or low protein diet during pregnancy*	*p*<0.01	(28)

[a] Human studies

[b] rodent studies (in italics)