V Edition of the Clinical Cases Contest on

non-surgical clinical management of Kidney Stones

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Title: KIDNEY STONES IN DENT'S DISEASE: WHAT ROLE COULD PHYTATES PLAY?

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1. Abstract

Dent's Disease (DD) is an X-linked tubulopathy and a rare cause of recurrent urinary lithiasis. The CLCN5 mutation (DD 1) is the most common, followed by the mutation on OCRL1 (DD 2). Proteinuria and hypercalciuria are the main urinary characteristics. Kidney stone formation is related to hypercalciuria, so thiazide diuretics, usually in combination whit citrates, are the main treatment. The problem is the alkalinization of the urinary pH, which increases the risk of phosphate calcium-based lithiasis. Phytates reduce calcium-oxalate crystallization without altering urinary pH, leading to a minor risk of lithiasis. We present the initial results of the treatment with phytates (Lit-Control®) in three cases of DD. Patients had stable pH levels during the treatment, without side effects. In addition, 24-hour urine analysis showed a diminution of calciuria, so, pending mid and long-term results, phytates are likely to be an effective and safe option in the management of these patients.

2. Introduction

Dent's Disease (DD) is an X-linked tubulopathy and a rare cause of recurrent urinary lithiasis. It was first described in 1962 by Gentil et al, who reported two cases of children presenting with non-nutritional rickets and tubular dysfunction that could not be classified within the classic Fanconi Syndrome, characterized by aminoaciduria, phosphaturia, bicarbonaturia, metabolic acidosis, glucosuria, rickets or osteomalacia, and growth retardation. Subsequently, additional cases with similar but phenotypically distinct features were reported. The term "Dent's Disease" was first suggested in 1990, and the CLCN5 gene, responsible for most cases, was identified in 1995[1].

Although its current prevalence remains unknown, by 2010 approximately 250 families had been documented with the disease. Its manifests in males, typically over the age of 10 years, while female carriers manifest milder symptoms, often limited to proteinuria with hypercalciuria or nephrolithiasis. Patients are typically

characterized by low molecular weight proteinuria (LMWP), hypercalciuria, and at least one of the following: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, or chronic kidney disease (CKD)[2].

Clinical suspicion is crucial for diagnosis, and management is primarily symptomatic. The treatment aims to reduce hypercalciuria and, consequently, the incidence of nephrolithiasis, nephrocalcinosis, and the risk of progression to CKD. The management of recurrent lithiasis does not differ significantly from that of the general population, with therapeutic decisions guided by the number and location of stones and metabolic evaluation of patients to minimize lithogenic risk.

Phytates are the most abundant inositol phosphate found in nature, present in high concentrations in cereals, legumes, and seeds. Since the 1990s, their direct relationship with renal lithiasis has been recognized, as they reduce calcium oxalate crystallization without altering urinary pH[3].

3. Clinical Case description

a. Patient information

We present the cases of three patients diagnosed with DD, presenting with renal lithiasis and followed up at our center.

The first case (***case 1***) is a 47-year-old male with two maternal cousins with nephropathy and two nephews with DD. Initially diagnosed with Cacci-Ricci syndrome, he had bilateral nephrocalcinosis, multiple caliceal microlithiasis, recurrent infections, renal colic, proteinuria, and CKD, so a genetic test was done. In 2019, hemizygous mutation in the CLCN5 gene, responsible for DD type 1, was confirmed.

Urologically, he experienced his first episode of obstructive pyelonephritis in 2004, requiring several interventions over the years, including the placement of ureteral stents (JJ catheters and nephrostomies), one ureterolithotomy, two Retrograde IntraRenal Surgeries (RIRS), four Extracorporeal ShockWave Lithotripsies (ESWL), and multiple hospital admissions for colic or infections. He is under nephrological follow-up for stage 4 CKD with a glomerular filtration rate (GFR) of 15 ml/min. Current treatment includes potassium citrate (1080 mg every 8 hours) and bicarbonate (3 g every 48 hours) for hypercalcemia, hypercalciuria, hypocitraturia and metabolic acidosis.

The second case (***case 2***) is a 36-year-old male with mild intellectual disability, under follow-up since 2010 and diagnosed with proteinuria at the age of 17. Renal biopsy performed as part of the diagnostic workup showed no significant findings, but genetic testing revealed a mutation in the OCRL1 gene, responsible for DD type 2.

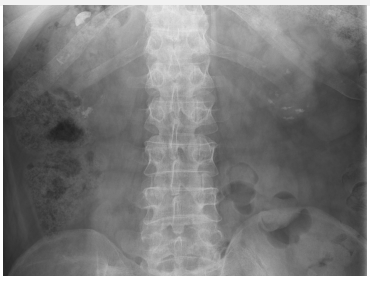
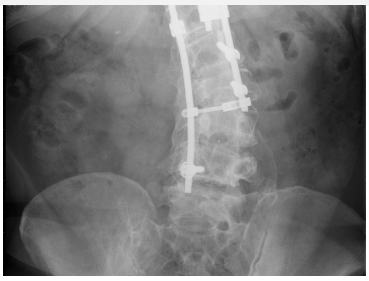
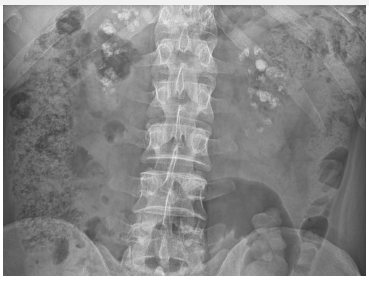
Since 2018 he has undergone multiple interventions for renal lithiasis, including one ESWL, one RIRS, one Endoscopic Combined IntraRenal Surgery (ECIRS), and the placement of JJ catheters on two occasions. He has a functional left solitary kidney and is being followed by Nephrology for stage 3b CKD. Current treatment includes potassium citrate 1080 mg every 8 hours and hydrochlorothiazide (25 mg/day) to manage hypercalciuria, with normal citraturia levels.

The third and final case (***case 3***) is a 28-year-old male, nephew of the first patient. Diagnosed at the age of 10, genetic testing in 2004 confirmed a mutation in the CLCN5 gene, with his mother identified as a heterozygous carrier.

His history of lithiasis began in 2013 with his first episode of renal colic. Since then, he has experienced several episodes, none of which required invasive treatment as the stones were spontaneously expelled. He maintains a normal GFR, although he is monitored by nephrology. Current treatment includes potassium citrate 1080

mg (two tablets every 8 hours) and hydrochlorothiazide (25 mg/day) for hypercalciuria, with normal citraturia levels.

b. Diagnosis

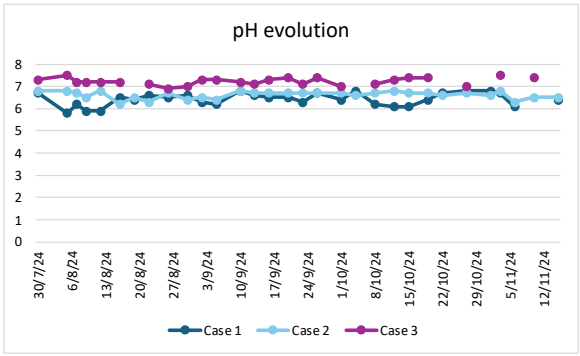
CASE 1, ♂ 47 yr.	CASE 2, ♂ 36 yr.	CASE 3, ♂ 28 yr.
Cristallographic analysis		
90% calcium phosphate 10% protein	90% calcium phosphate	80% calcium phosphate
Last 24-hour urine collection		
Proteinuria 2.26 g/24 h Albuminuria 0.9 g/24 h Calciuria 2.16 mmol/24 h Hypocitraturia 0.7 mmol/24h	Albumin/creatinine 168 mg/g Protein/creatinine 1246 mg/g Hypercalciuria 10.6 mmol/24 h Phosphaturia Citraturia 3 mmol/24h	Proteinuria 1.57 g/24 h Albuminuria 0.32 g/24 h Hypercalciuria 6.6 mmol/24 h Citraturia 2.69 mmol/24h
Last blood test		
Cr 395umol/L, GFR 15ml/min	Cr 161umol/L, GFR 47ml/min	Cr 120umol/L, GFR 70ml/min
Last imaging test		
		
Bilateral litiasis & microlithiasis	*Right renal microlithiasis*	*Bilateral litiasis & nephrocalcinosis*

c. Treatment

We initiated in all three patients treatment with phytates (Lit-Control® pH Balance every 12 hours), and intensive monitoring of the therapy was performed using the Lit-Control® pH meter. The utility of the pH meter lies in its ability to provide rapid, simple, and reliable monitoring of treatment, benefiting both patients and healthcare professionals. We requested the most intensive urinary pH monitoring possible (at least three times per week) and a clinical and metabolic evaluation after four months of treatment.

d. Evolution and progress

The pH values of the three patients were analyzed between July 30 and November 15, 2024 (107 days), and a metabolic study, which included a 24-hour urine collection, was performed at the end of the follow-up.



Over the 107 days of monitoring, ***case 1*** recorded 79 measurements, ***case 2*** recorded 48, and ***case 3*** recorded 28. Initial pH values were 6.7, 6.8, and 7.3, respectively. The median (IQR) pH for ***case 1*** was 6.4 (6.6–6.15), for ***case 2*** was 6.6 (6.7–6.5), and for ***case 3*** was 7.2 (7.33–7.1).

e. Clinical results

None of the patients experienced any clinical side effects of the treatment. During the follow-up, even though it was a short period of time, none of them had colic, infection or kidney stone complications. Initial treatment will be given for 6 months, and its effectiveness will be evaluated with 24-hour urine analysis, ultrasound, and X-ray at the end of this period. To make an initial assessment of the effect of phytates on hypercalciuria, a 24-hour urine collection was performed after 4 months of medical treatment with Lit-Control® pH Balance in the two cases where hypercalciuria had been detected.

Case 2, with a 24h volume of 2835cc presented a frank decrease in calcium levels, with a calcium of 6.5 mmol/24h (2.3 mmol/L) and previous values of 10.6 mmol/24h and 3.5 mmol/L. In ***case 3***, with an initial calcium of 6.6 mmol/24h and 2.8 mmol/L, with a volume of 2680cc, the decrease was less (6.5 mmol/24h and 2.4 mmol/L).

4. Discussion

DD is a rare X-linked recessive tubulopathy. Its true prevalence is unknown, likely due to incomplete penetrance, variable expressivity, and the absence of family history in some affected individuals. The disease is characterized by impaired protein reabsorption and disruption of acidification, predisposing patients to proximal tubular dysfunction, nephrolithiasis, nephrocalcinosis, and CKD.

Most patients have mutations in the CLCN5 gene (Xp11.22), responsible for DD type 1. This gene encodes a protein consisting of 746 amino acids and weighing 83 kDa, known as ClC-5, a voltage-gated chloride channel regulator[4]. ClC-5 is primarily located in the proximal tubule, in the loop of Henle and in the intercalated cells of the collecting duct. Along with the H+-ATPase pump, ClC-5 facilitates endocytic reabsorption of albumin and low molecular weight proteins, and participates in acidification processes[5]. This inability to acidify urine predisposes these patients to the formation of calcium phosphate stones, associated with alkaline pH levels, as evidenced in our three cases (median (IQR) pH of 6.4 (6.6–6.15), 6.6 (6.7–6.5), and 7.2 (7.33–7.1)).

It is estimated that approximately 60% of DD cases are due to mutations in CLCN5, 15% are attributed to mutations in OCRL1, and the remaining 25% are linked to mutations in other genes. The OCRL1 gene (Xq26) is responsible for DD type 2. Mutations in OCRL1 result in reduced levels of the encoded protein of inositol polyphosphate 5-phosphatase, critical for cellular homeostasis. When DD type 2 is associated with extrarenal manifestations, it constitutes Lowe syndrome, with neurological (cognitive and behavioral disturbances), ocular (congenital cataracts and glaucoma), and muscular (growth retardation) sequelae[6].

The most characteristic and early finding in DD is LMWP. Diagnosis requires three criteria: 1) LMWP, 2) hypercalciuria, and 3) at least one of the following: hypophosphatemia, rickets, osteomalacia, renal failure, or hematuria[2]. When these criteria are met, genetic testing confirms the disease in approximately 75% of cases.

Although the mechanism remains unclear, calcium accumulation in the urine leads to nephrolithiasis and nephrocalcinosis. Nephrocalcinosis, observed in three out of four patients, is associated with more severe forms of lithiasis and CKD. Up to 50% of patients develop urinary stones, typically composed of calcium oxalate or calcium phosphate. Hypercalciuria and concomitant nephrolithiasis appear to be more frequent in CLCN5 mutations[5].

CKD is the most significant consequence of DD, typically manifesting between the ages of 30 and 50[5]. Between 35% and 100% of CKD patients progress to end-stage renal disease.

Clinical suspicion is critical for diagnosis, especially in patients with a family history of nephrolithiasis or related syndromes, as well as those with proteinuria detected on urinalysis. In addition to basic blood and urine tests

and ultrasonography, abdominal-pelvic CT scans are useful for diagnosing lithiasis, and genetic studies are crucial for identifying the aforementioned mutations.

Currently, no curative treatment is available for DD, and management focuses on symptom control. For renal lithiasis, the choice of technique depends on the number and location of stones and the presence of complications such as ureterohydronephrosis. There is no standardized approach. Medical management primarily targets hypercalciuria to reduce the incidence of nephrolithiasis and nephrocalcinosis and delay CKD progression. Thiazide diuretics, -usually in combination with citrates- are the main treatment[2], as they significantly reduce urinary calcium excretion when combined with dietary modifications. However, their primary side effect -hypokalemia- requires close monitoring.

In this study, we administered phytates (Lit-Control® pH Balance) to our three patients. Phytates are compounds found in various plant seeds, and their levels in the body depend primarily on dietary intake. In addition to being potent natural antioxidants, phytates exhibit significant inhibitory properties against calcium oxalate and calcium phosphate crystallization, protecting against pathological calcifications in tissues[3]. In the case of renal stones, phytates inhibit crystallization both at the intrapapillary level and in the urine.

Both in vitro and in prospective studies, phytates have shown equal or greater efficacy compared to citrate salts (e.g., potassium citrate) in inhibiting calcium oxalate crystallization. It should be noted that the prospective study mentioned above only analyses calcium oxalate formers[7,8].

Citrate salts are prescribed to our patients not only to correct hypocitraturia, but also to manage hypercalciuria (preferably at urinary pH <5.5) and to prevent hypokalemia caused by thiazides. Since the predominant stones in our patients were calcium phosphate, associated with urinary pH >6.5, the pH elevation induced by citrates may promote lithiasis formation. In all our three cases, we see alkaline pH and with that, an increased risk of kidney stone disease. By contrast, we are also unable to acidify our patients' urine, as the tubulopathy entails an inability to manage pH imbalances, thereby posing a significant risk of inducing a systemic acidosis.

This is where phytates emerge as an interesting treatment option. They do not alter urinary pH, potentially reducing both calcium phosphate stones and struvite stones or the risk of infections. This maintenance of pH levels has been observed in our patients during the follow-up. Although Dent's disease is a rare disease, the metabolic alterations like hypercalciuria and the inability to acidify are similar to those observed in other tubulopathies. This makes the findings of this study a valuable example for the management of other entities such as distal tubular acidosis, improving the treatment of a much larger population with this inability to manage pH disorders.

On the other hand, stone formation is directly related to hypercalciuria. In DD patients, the mechanism underlying hypercalciuria remains unknown. A prospective, randomized study showed that three months of phytate treatment in patients with hypercalciuria secondary to bone resorption significantly reduced urinary calcium levels ($p<0.005$) and increased bone resorption[9]. Further studies are required to determine the prevalence of hypercalciuria due to idiopathic bone resorption, and also to assess its impact on hypercalciuria in DD patients. In our patients, we found a slight decrease in calciuria in one case and a more significant decrease in another case. Since we do not know the mechanism of hypercalciuria in our patients, it is difficult to determine exactly how we can explain these differences and how these patients will progress, but the results are consistent with the existing evidence and are very promising.

To conclude, as a hypothesis, phytates may also play a specific role in DD type 2. In this entity, decreased inositol polyphosphate 5-phosphatase activity disrupts the regulation of phosphatidylinositol (IP6, IP5, IP4, IP3…) levels on cell surfaces and internal membranes. Phytates (IP6) may help increase the levels of phosphatidylinositol in the cells of affected patients, offering a potential therapeutic avenue.

5. Conclusions and recommendations

In DD we found an increased risk of kidney stone formation mainly due to hypercalciuria and alkaline pH. Phytates, calcium and phosphate oxalate crystallization inhibitors that don't modify pH levels, have a very good adverse effect profile and improve calciuria, may be a safe and effective alternative in the treatment of these patients. Studies with larger patient populations and longer follow-up are needed before they can be recommended as routine and standardized treatment, but the fact that these metabolic alterations are shared with other tubulopathies would allow us to improve not only the treatment of DD but also that of patients with tubulopathies such as distal tubular acidosis.

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