Primary hyperparathyroidism and nephrolithiasis

Hyperparathyroidie primaire et lithiases

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Abstract

Calcifications in the kidneys may occur in the parenchyma (nephrocalcinosis), pelvis renis (nephrolithiasis) or ureters (ureterolithiasis). Several factors may protect against stone formation or promote precipitation of stones. Most stones contain calcium, and the hypercalciuria seen in primary hyperparathyroidism is a contributing factor to stone formation in the kidneys and urinary tract. In early case series, renal stone formation was frequent, whereas the proportion of patients with symptomatic renal stones has declined in recent years. However, a substantial proportion of patients present with asymptomatic nephrocalcinosis or nephrolithiasis. Before diagnosis and treatment of primary hyperparathyroidism, renal stone events are more frequent than in the general population. However, even after surgical cure, an increased rate of renal stone events may be seen. This may to some extent be the result of stones or calcifications already present at the time of diagnosis or sequelae to prior stones such as infections or ureter strictures.

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1. Introduction

Many factors may contribute to stone formation in the renal pelvis (nephrolithiasis) or ureters (ureterolithiasis) or to calcifications in the kidney parenchyma (nephrocalcinosis). However, protective factors also exist [1]. Most stones are calcium containing. This narrative review will focus on calcifications in the kidney parenchyma (nephrocalcinosis), renal pelvis (nephrolithiasis) and ureters. The main factor behind the calcifications is believed to be the increased calcium excretion in the urine [2]. However, other factors may also contribute such as dehydration brought about by nausea and the osmotic diuretic effect of the high calcium levels.

2. Basal physiology

Fig. 1 shows the normal calcium fluxes and an example of primary hyperparathyroidism. Usually calcium is absorbed in...
the intestine, deposited and resorbed from the skeleton and filtered in the glomerulus in the kidney. A large re-absorption of calcium takes place in the kidney (see Table 1 for a hypothetical example).

In primary hyperparathyroidism, more calcium is re-absorbed from the skeleton through the effects of parathyroid hormone (PTH) on the osteoclasts. However, an increased calcium absorption in the intestine may also play a role as PTH activates the one-alpha-hydroxylase enzyme, which increases the levels of activated vitamin D (1,25-dihydroxy-vitamin D), which in turn may increase intestinal calcium absorption thus further contributing to the calcium load in the kidney. In the kidney, PTH may increase calcium re-absorption, but as PTH only works in parts of the tubuli, e.g. through stimulation of TRPv5 in the distal tubulus [1], the increased filtration of calcium in the glomerulus may overpower the capacity for calcium absorption further downstream in the tubuli leading to an increased net excretion although the calcium/creatinine clearance ratio if increased (Table 1).

Under normal circumstances, total plasma calcium is around 2.20–2.55 mol/l with an ionised plasma calcium of 1.18–1.32 mmol/l. This is because approximately 50% of the total calcium is “free”. Calcium is filtered in the glomerulus as other ions. At a glomerular filtration of 90 ml/min and a “free” ionised plasma calcium of 1.20 mmol/l. The filtration is thus 155.5 mmol of calcium per day (or 6221 mg). With an excretion of 4%, the total daily excretion is around 249 mg in the urine (Fig. 1). The normal urine calcium excretion is around
This relationship may be particularly interesting as patients with primary hyperparathyroidism may tend to weigh more than the general population [10].

3. Epidemiology

The prevalence of renal stones in primary hyperparathyroidism has declined from as much as 80% in early series to between 7 and 20% in more recent series [11,12]. However, these estimates are based on clinical stone events – which in the early series earned the disease its eponym of “stones, bones, abdominal groans, throes and psychiatric moans”. In more recent series, where systematic screening of patients presenting with largely asymptomatic primary hyperparathyroidism has been performed, a prevalence of 25% (95% CI: 19–31%) of either nephrocalcinosis (10%) or nephrolithiasis (15%) of all patients evaluated for primary hyperparathyroidism has been observed [13]. As expected, calcium excretion was higher in patients with calcifications than in those without [13], but otherwise no correlations was present with plasma calcium, plasma phosphate, plasma 25-hydroxy-vitamin D, plasma 1,25-dihydroxy-vitamin D. No reduction in renal function was seen in the patients with renal calcifications [13]. The absence of a relationship with biochemical parameters underlines the importance of fluxes of calcium and parameters of renal calcium handling not necessarily mirrored in plasma levels of calcium.

An increased risk of clinical renal stone events may be seen as early as 10 years before the diagnosis of primary hyperparathyroidism is made [14]. This indicates that the disease may have been present many years prior to its diagnosis. A significant increase in the presence of renal stone events is seen in the time leading up to the diagnosis of primary hyperparathyroidism [14]. However, this is biased by the fact that the renal stone events lead to the disease being diagnosed (a form of “Berkson Bias”). After surgical cure, the risk of recurrent clinical renal stone events taper only gradually [14], possibly as a consequence of stones left over from before the diagnosis, infections, ureter stenoses, etc. Although the disease of primary hyperparathyroidism is cured, damage left from it may thus still impact the occurrence of new stone events.

4. Treatment

The treatment of renal stone events follows current guidelines for management of renal stones in general. Current guidelines emphasize surgical treatment for primary hyperparathyroidism in the presence of renal stones [15]. Current evidence only suggests a gradual decrease in renal stone events after surgery [14]. Actually, surgery does not reduce the risk of renal stones compared to non-surgically managed cases [16] – as mentioned probably related to damage done by the disease not necessarily corrected by surgery such as ureter strictures and leftover renal stones. It should be mentioned that the study cited [16] was done on patients with relatively high plasma calcium levels as compared to the often asymptomatic patients of current series. The treatment may thus be tailored in individual cases.
Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References

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