INTRODUCTION

It is intriguing that despite marked abnormal urinary factors, most humans will not form stones. Alternatively, some patients develop stones despite normal urinary composition. The key element, therefore, appears to be inhibition of the steps in calculogenesis (nucleation, crystal growth, aggregation, and crystal/stone retention). Urolithiasis will not develop if any one of these steps is blocked. Despite this simple fact, it is unclear exactly why many people form stones. Numerous molecules have been identified that inhibit crystallization in vitro but many stone formers have normal levels of these substances; others will continue to develop stones despite replacement of these known inhibitors. The formation of urinary calculi requires a complex combination of factors, both promoting and inhibiting stone formation. Fortunately, there are many patients who can be helped because of our existing knowledge about two specific urinary inhibitors: citrate and magnesium. This chapter will discuss the in vitro and in vivo evidence regarding citrate and magnesium as inhibitors of urinary stone disease.
CITRATE

Background

Citrate is the most well-studied inhibitor of calcium-based stones. It is therefore appropriate to detail the investigations leading to this discovery and outline the proof of its use in the treatment and prevention of urolithiasis.

Sabatini is credited as first discovering the ability of citrate to bind to calcium in the 1930s (1). Hypocitraturia was noted in two patients with urinary stones by Boothby and Adams in 1934 but the significance of this report was not fully appreciated (2). Hypocitraturia was again noted by Kissin and Locks in 1941 who first postulated that citrate replacement might treat and/or prevent calcium-based calculi (3). Howard first described the clinical use of citrate as an alkalinizing agent for the treatment of noncalcium stones in 1954 (4).

Scientific interest in urinary citrate was rekindled in the early 1980s as numerous studies verified hypocitraturia in stone patients (5–7). Citrate replacement therapy for prevention of calcium-based nephrolithiasis was introduced in 1981 by Butz and Dulce (8). They noted that a combination of sodium citrate and potassium citrate lowered urinary calcium levels and raised urinary citrate concentrations. Dissolution of existing calcium-based stones with potassium citrate was reported by Pak and colleagues in 1983 (9). These reports spurred countless investigations and led to the approval of potassium citrate by the United States Food and Drug Administration in 1985.

Chemistry

Citrate is a tricarboxylic acid (Fig. 1) and is entirely ionized above a pH of 6.5 at 37 °C (10,11). Citrate is almost entirely absorbed by the gastrointestinal tract (12). Plasma concentrations range from 0.05 to 0.3 mM (13). Assuming a normal glomerular filtration rate of 125 mL/min, citrate is filtered at rates ranging from 6.25 to 37.5 μmol/min. Approximately 75% is reabsorbed by the proximal convoluted tubule (Fig. 2) (14). Ten to 35% (by volume) of oral citrate is excreted in the urine unchanged and is dependent on the renal acid/base status. Renal tubular cells can additionally extract citrate from the peritubular fluid at a rate of 0.5 to 3 μmol/min (11). Therefore, the citrate concentration in the renal cortex can exceed that of peripheral serum.

Urinary citrate excretion is strongly dependent on the acid-base status of renal tubular cells. When the cells are in an acidotic state, as much as 95% of the filtered citrate is sequestered by proximal tubular mitochondria as an additional source of energy in the Krebs cycle (also known as citric acid cycle and tricarboxylic acid cycle) (11,15).

Fig. 1. Chemical composition of citrate.