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Medical Measures for Secondary Prevention of Urolithiasis

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1. Introduction

The global prevalence of nephrolithiasis has progressively increased over the past several decades [1,2]. Kidney stone disease without treatment is a recurrent illness that represents a major health burden across the globe with associated economic costs.

2. Conservative management of nephrolithiasis

2.1. Role of oral fluid

A conservative approach is key in the management of kidney stones. High oral fluid intake must be administered in all kidney stone formers (KSFs) to reduce urinary saturation with regard to stone-forming constituents. One randomized control trial (RCT) in patients with idiopathic calcium oxalate (CaOx) stones established that increased water intake to sustain urine volume >2 l/d over 5-yr follow up significantly reduced the risk of recurrent kidney stones compared to no treatment [3]. However, the strength of the evidence for the outcome of this study was modest.

The protective role of consumption of soft drinks was examined in a large, fair-quality RCT in men with recurrent kidney stones, and a significant reduction in stone recurrence was observed [4]. However, the strength of evidence was low because only one RCT was considered. Circumstantial evidence of a protective role in reducing urinary CaOx saturation for consumption of sugar-free orange juice, coffee, tea, beer, and wine did not extend to apple juice, grapefruit juice, and sports drinks.

2.2. Role of animal protein and salt: multicomponent dietary interventions

One high-quality study in Italian males with hypercalciuria compared a multicomponent dietary intervention consisting of low sodium (100 meq/d), low animal protein (50–60 g/d) with normal calcium intake (1200 mg/d) to a traditional low-calcium diet (400 mg/d) [5]. The results showed a significantly lower risk of kidney stone recurrence in the multicomponent dietary intervention group. However, this result was not confirmed in

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another study using a high-fiber, low-protein diet [6]. Because of the inconsistent findings in these two studies, it can be argued that the protective effect is not related to low protein consumption but was consequent to imposition of low salt and normal calcium intake.

2.3. Role of fiber intake

At present, there is no established evidence in literature to indicate the role of low dietary fiber versus high dietary fiber in recurrent kidney stone and CSFs [7].

2.4. Role of animal protein, sodium, calcium, and purine intake: single-component dietary intervention

Only one low-quality study demonstrated that there is no difference in kidney stone recurrence between low animal protein intake (<3 servings of fish or meat per week and dairy products <100 g/d) and a control diet [7]. There was circumstantial evidence of a protective role of low sodium, low calcium, and/or low purine intake on kidney stone recurrence.

3. Pharmacological management of nephrolithiasis

Pharmacological treatment is essential in almost all recurrent KSFs and in the management of the majority of non-calcium stone-forming populations, including uric acid, cystine and infection-induced stones, given the lack of knowledge and/or consensus on dietary intervention alone.

3.1. Thiazide diuretic treatment

Thiazide diuretics (TZs) and TZ analogs are customarily used to lower calcium excretion in recurrent calcium KSFs [8]. Results from several RCTs of moderate to high quality have shown that TZs are effective in significantly reducing kidney stone recurrence when compared to a placebo or control (Fig. 1) [7–9]. TZ effectiveness is enhanced by a low-salt diet that attenuates increased urinary calcium excretion, and by adequate potassium supplementation to avoid hypokalemia-induced hypocitraturia [10], with potassium citrate (KCit) advantageous over potassium chloride (KCl) for the latter.

3.2. Alkali treatment

Several moderate-quality studies with and without a placebo control have proved that oral citrate as monotherapy is effective in reducing the risk of kidney stone events (Fig. 1) [7–9,11,12]. There was no significant difference in stone recurrence between the citrate and control groups in only one study [13]. The lack of efficacy of alkali treatment in this study may be related to selection of a high alkali dose that could increase the risk of calcium phosphate (CaP) stones.

3.3. Allopurinol treatment

Few RCTs comparing the effect of allopurinol to placebo or a control in CaOx KSFs showed a lower risk of the stone recurrence [7,14].

3.4. Magnesium treatment

The role of magnesium in calcium KSFs was investigated in only one poorly controlled study, which found a lack of effectiveness for this treatment compared to placebo [7].

3.5. Combined pharmacological treatment

One poor-quality study found that combined TZ and citrate treatment was not significantly different from TZ treatment alone in reducing the risk of stone recurrence [15]. Moreover, stone recurrence did not differ between combined TZ + allopurinol and TZ alone [16].

3.6. Chelating agents in the treatment of cystinuria

Several retrospective, nonrandomized, non–placebo-controlled trials have shown that both D-penicillamine and *α*-mercaptopropionylglycine are effective in decreasing stone events [17]. Both drugs are thiol derivatives and produce a highly soluble disulfide compound with cystine.

3.7. Drug treatment for infection-induced kidney stones

Acetohydroxamic acid is the only drug effective in several RTCs for the treatment of infection-induced kidney stones following surgical removal of stones and antibiotic treatment [8].

4. Recommendations

1. Increased fluid intake must be considered in all KSFs regardless of kidney stone composition. CaOx KSFs should maintain intake of 1000–1200 mg of calcium, 100 mEq/d of sodium, and 0.8 g/kg body weight of animal protein. Circumstantial evidence supports the role of high consumption of fruits, vegetables, and sugar-free beverages in calcium KSFs.
2. Alkali treatment is recommended in recurrent CaOx and CaP KSFs, including those with hypocitraturia or normal urinary citrate, patients with distal renal tubular acidosis, chronic diarrhea, drug or diet-induced hypocitraturia, and those with osteopenia or osteoporosis. Potassium alkali is preferred over sodium alkali treatment, since the latter may negate the protective effect of a rise in urinary citrate by increasing urinary sodium and thus urinary calcium excretion.
3. TZ is indicated in all KSF patients with hypercalciuria. However, whether TZ treatment will be useful in the treatment of normocalciuric patients remains to be explored. TZ combined with KCit is preferred over TZ with KCl to maintain urinary citrate and lower urinary calcium. This combination may act synergistically to increase bone mineral density and thus reduce the risk of the bone fracture.

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Fig. 1.
Pharmacological monotherapy in the treatment of kidney stone disease.