Magnesium in kidney stone disease: pathogenesis and treatment

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Summary

Renal stone disease is common in developed countries. Disturbances in the urinary composition of the inhibitor activity against crystal formation is often observed in renal stone formers. One of these inhibitors active against growth of both calcium oxalate and calcium phosphate crystals is magnesium. Patients with recurrent renal stone disease often have a normal magnesium metabolism including a normal urinary excretion of magnesium. In contrast, however, hypercalciuria is common, giving an unfavourable balance between magnesium and calcium in the urine. Such a low urinary magnesium/calcium ratio predisposes for stone formation. Prophylactic treatment with different magnesium compounds have been reported and the experience with magnesium hydroxide is now ten years. The prophylactic effect is good with few stone recurrences and few side-effects.

Résumé

Les maladies de calcul rénal sont assez fréquentes dans les pays développés. Les malades souffrants de calculs rénaux ont souvent des troubles dans la composition urinaire de l'activité inhibitrice contre la formation de cristaux. Un de ces inhibiteurs actif contre la croissance de cristaux d'oxalate de calcium et de phosphate de calcium est le magnésium. Les patients avec une maladie récurrente ont souvent un métabolisme normal de magnésium y compris une excrétion urinaire normale de magnésium. Au contraire, des hypercalcurie sont fréquemment observées, résultant dans une relation défavorable entre magnésium et calcium dans l'urine. Une proportion tellement basse entre magnésium et calcium prédispose la formation de calculs rénals. Le traitement prophylactique avec différentes combinaisons de magnésium a été traité dans la litérature, depuis dix ans on a des expériences avec MgO. L'effet prophylactique est bien avec peu de récurrences de calculs rénals et avec des effets secondaires mineurs.

Zusammenfassung

Die Nierensteinerkrankung ist häufig in entwickelten Ländern anzutreffen. Bei Steinträgern findet sich häufig eine Störung von Inhibitoren der Kristallbildung im Urin. Magnesium ist einer dieser Hemmer des Wachstums sowohl von Calciumoxalat — wie auch von Calciumphosphat-Steinen. Bei Patienten mit rezidivierendem Nierensteinleiden findet sich oft ein normaler Mg-Stoffwechsel, einschließlich einer normalen Mg-Ausscheidung im Urin. Hingegen wird häufig eine Hyperkalziurie beobachtet, so daß sich hieraus ein ungünstiges Mg:Ca-Verhältnis ergibt. Ein derart niedriger Mg:Ca-Quotient im Urin prädisponiert zur Steinbildung. Über die Prophylaxe mit verschiedenen Mg-Verbindungen ist in der Literatur berichtet worden; mit MgO liegen jetzt Erfahrungen über 10 Jahre vor: Der prophylaktische Effekt ist gut bei nur wenigen Steinrezidiven und geringen Nebenwirkungen.

Introduction

Renal stone disease is common and increasing in most developing countries and has partly been proposed to be due to increased well-being in the population. Approximately 5% of females and 10–20% of males will once or more experience a stone. Follow-up studies of unselected stone formers have shown that half on the patients will experience stone recurrence within the next ten years.

Much attention has been directed to attempt to evaluate the possible role of magnesium in patients with renal stone disease. This paper is discussing the connection between magnesium and renal stone disease and has been divided into three parts. Firstly the role of magnesium as an inhibitor in the urine, secondly evaluation of the magnesium metabolism in patients with renal stones and thirdly the effects of magnesium given as prophylactic treatment against stone recurrence.

Magnesium — a urinary inhibitor

The growth of hydroxyapatite or calcium oxalate crystals is normally inhibited in the urine of healthy subjects. The main inhibitors of the crystal formation of calcium oxalate and calcium phosphate are citrate, pyrophosphate and magnesium, whereas glucosaminoglycans, citrate and pyrophosphate play the major role for inhibiting the aggregation of already formed crystals in the urine [11]. Normal urine contains no or just only individual crystals in urine, whereas stone forming patients excrete greater amounts of crystals or large aggregations of these crystals. In renal stone patients, most formed stones are composed of calcium oxalate, calcium phosphate or a mixture of both these compounds. Since naturally occurring inhibitors of this crystal formation and growth may help to protect against stone disease it is important to get more knowledge about these inhibitors. It may then be possible to desing a treatment which increases the excretion of these inhibitory compounds, either those normally excreted or others. Most studies in

this respect involve isolation of urinary components and then a test of these compounds for their inhibitory activity. However, most test systems have the draw-back of measuring the inhibitory effect in diluted urine or artificial solutions, thus making it difficult to draw valid conclusions to the clinical situation.

Already in 1929, *Greta Hammarsten* [16] showed that magnesium could increase the solubility of calcium oxalate **in vitro.** 1973, *Desmars* and *Tawashi* [8] presented another test system where magnesium oxalate was found to have a greater solubility product than calcium oxalate. Other studies have also demonstrated that magnesium decreases the incidence of experimental, calcium oxalate stone formation [4, 10, 25, 35]. *Wunderlich* [41] concluded from studies in their test system than magnesium ions might induce an increase of the solubility of calcium oxalate but did also broaden the *Ostwald-Miers* range, thus favouring the formation of larger crystals. Another test system was used by *Hallson* et al. [15] where a low urinary magnesium was induced in volunteers by giving cellulose phosphate. Magnesium was then added **in vitro** to yield urine samples with normal and high magnesium concentrations. They found a clear inverse correlation between the magnesium concentration and calcium oxalate crystal formation. Recently *Achilles* and *Ulshöfer* [1] measured the effect of magnesium on the relative crystal growth rate of calcium oxalate in artificial urine using a gel crystallization method. The rate of calcium oxalate crystal growth significantly decreased with increasing concentration of magnesium, possibly due to alteration of the calcium oxalate activity product. Most studies on magnesium have thus been made on measurements of crystal growth of calcium oxalate, but *Werness* et al. [40] measured the hydroxyapatite inhibitor activity in diluted urine. Magnesium accounted for 7% of this inhibitor acitivity, citrate for 2% and pyrophosphate for 36%. The difficulty in evaluating results obtained from diluted urine or artificial solutions is well illustrated by the fact that pyrophosphate in these studies accounts for the main inhibitor activity of calcium phosphate crystal formation but accounts for only 10% of the inhibitory activity when measured in whole undiluted urine. In addition, *Bisaz* et al. [3] showed with a quantitative technique to determine the inhibitor activity of calcium phosphate precipitation in whole undiluted urine, that magnesium represented 20% of the total inhibitory activity.

However, it is important to stress that these results apply to measurements in diluted or undiluted urine or artificial systems, which makes it difficult to draw valid conclusions to the clinical situation when dealing with renal stone patients.

Experimental magnesium deficiency

Studies on experimentally induced magnesium deficiency have demonstrated that renal tubular calcium phosphate deposits can be produced in animals [7] where calcium was presented as apatite crystals in the proximal tubular cells [2] or as calcium oxalate monohydrate crystals [34]. In these animal models changes could be found already after 24 hours. Diet containing abundant magnesium protected against this crystal formation. However, these experimentally obtained results provide difficulties when comparison is made to the human stone disease.

Magnesium metabolism in stone patients

As a low urinary excretion of magnesium, according to discussions above, might be associated with a reduced inhibitory activity regarding formation of crystals in the urine, much attention has been attached to determination of the urinary magnesium excretion in stone formers. Most studies including our own [18] have been unable to show a difference in magnesium excretion in renal stone formers in comparison with healthy non-stone forming subjects [23, 32, 37, 43]. However, some studies have shown a low urinary magnesium excretion in stone formers in comparison with controls [24, 39].

Urinary calcium is increased in renal stone formers [27]. In normal subjects a positive correlation is demonstrated in the urinary excretion of both these cations [18]. The role of magnesium in inhibiting the growth of calcium crystals in the urine is then more dependent on the balance between magnesium and calcium than on the absolute amounts of the two ions in the urine. It therefore seems justified to calculate the urinary magnesium/calcium ratio when an attempt is made to evaluate the patients' stone forming propensity. A low value has also been reported to be associated with an increased risk of stone formation [18, 23, 28, 29, 36, 39]. A low magnesium/calcium ratio has also been shown to be an independent risk factor in stone formation irrespective of the urinary calcium excretion [28].

Martinez et al. [30] studied the urinary magnesium in patients with idiopathic hypercalciuria under conditions of basal and restricted diet, fasting and after oral calcium overload. Urinary magnesium increased in absorptive hypercalciuria under free and restricted diet and calcium overload, returning to normal during fasting. In patients with renal hypercalciuria a high magnesium excretion maintained under all conditions. This suggests that in idiopathic hypercalciuria there is an impairment of renal magnesium management dependent on that of calcium because it

normalizes when urinary calcium is normal. *Juuti* [22] studied the effect of seasonal variations of urinary excretion of calcium, oxalate, magnesium and phosphate. However, they could not find any variation in urinary excretion of magnesium affected by season in patients on a free diet whereas this could be found regarding urinary excretion of calcium. If, as experimental studies above indicate, magnesium exerts its influence on calcium oxalate formation by competitive binding of oxalate, a low urinary magnesium level would have the effect on increasing the available oxalate for calcium binding thus increasing the incidence of stone formation.

The possible role of magnesium deficiency playing a part for stone formation in humans has also been considered. As neither serum nor urinary magnesium accurately reflect the magnesium stores in the body, studies have been made measuring the intracellular magnesium concentrations in muscle specimens and the retention of intravenously given magnesium in stone formers. However, no evidence of intracellular magnesium deficiency could be observed in recurrent renal stone formers [18]. Consequently, it seems that the majority of renal stone patients do not exhibit a magnesium deficiency which could be of importance in stone formation.

Magnesium therapy against renal stones

During centuries many modes of prophylactic medical treatment have been used against recurrence of renal stones. Magnesium is one. The *Epsom* salt was already in the 17th century suggested to be effective in renal stone disease and is still recommended for this purpose [14]. 150 years ago *Brande* suggested that magnesium supplements also were effective against uric acid stone disease [5]. During this century and especially the last two decades different kinds of magnesium compounds have been used prophylactic against stone recurrence and often with a significantly reduced recurrence rate [10, 13, 17, 21, 26, 31, 33].

In 1971 *Melnick* and co-workers published their results with magnesium oxide [31]. Ninety-five recurrent calcium oxalate stone formers completed two years of magnesium oxide therapy and 47 completed four years of this therapy. Sixty-eight recurrent stone formers formed a control group. The recurrence rate decreased significantly in the treated group and was more pronounced than in a control group.

Prien and *Gershoff* [33] treated their patients with magnesium oxide and vitamin B_6, altogether 265 renal stone formers. During the follow-up period of six years the stone recurrence rate decreased from 1.3 stones per patient per year before treatment to 0.10 stones per patient per year during therapy. They concluded that magnesium oxide and pyridoxine together in the doses used were effective in reducing the recurrence of calcium oxalate stones.

Brundig and co-workers [6] presented 1981 a short-term treatment study using magnesium chloride. Magnesium chloride was found to be easily absorbed in the intestine and increased the urinary magnesium, kept the calcium excretion unchanged and thus gave a more favourable magnesium/calcium ration in the urine. They also observed a reduced urinary excretion of oxalate. However, they concluded from this short-time study that magnesium chloride in this form cannot yet be recommended as a long-term medical treatment to renal stone patients because of draw-back with gastric intolerance.

Tiselius et al. [38] found in a study with rather few patients during short time no effects on magnesium or calcium excretion in the urine. Thus, the urinary magnesium/calcium ratio remained unchanged.

We have been using magnesium hydroxide as prophylactic treatment to patients with idiopathic recurrent stone disease since 1976 [17, 19–21]. Seventy patients have been treated and these patients had had the renal stone disease on the average eight years before treatment and during this period delivered 0.8 stones per patient per year. Metabolically active stone disease, i. e. at least 2 stones during the previous five years and at least one stone during the last two years, or recently performed difficult operations due to stones, were criteria for inclusion. Analysis of obtained stones showed content of calcium oxalate, calcium phosphate or mostly a mixture of both. Patients were given 500 mg magnesium (20.6 mmoles magnesium) as magnesium hydroxide. During follow-up recurrence has been defined as passage of an earlier unknown stone, removal of a new stone, observed growth of a known stone or formation of new stones on X-ray. The natural history of renal stone disease was at the same time followed in 109 patients not receiving any medical prophylactic treatment against renal stone disease. Both groups were given the same dietary advice, i. e. to avoid excessive dietary intake and to increase water intake. On magnesium treatment the urinary magnesium excretion increased by approximately 1.5–2 mmol/24 h and remained unchanged during the years of follow-up. The urinary calcium excretion remained unchanged, thus giving a more favourable magnesium/calcium ratio in the urine approaching the normal value. Citrate, another inhibitor in the urine, also increased on therapy. The mean stone episode rate decreased from 0.8 to 0.08 stones per patient per year and still 80% of the treated patients remain free of recurrence. In the control group the stone recurrence rate also decreased from

0.5 to 0.2 stones per patient per year but after eight years of follow-up less than 40% of these patients remain free of recurrence. This is significantly different from the figure found in the magnesium treated patients [17].

Ettinger and co-workers presented prophylactic treatment of calcium oxalate stones in clinical trials using allopurinol, magnesium hydroxide or chlortalidon [9]. The patients who had recurrent stone disease received 650 mg or 1300 mg magnesium hydroxide per day. Urinary magnesium increased significantly in both magnesium treated group compared to controls given placebo. Despite this magnesiuria seen with therapy, survival analysis showed both doses were identical to the placebo. No data were presented on possible effects on calcium excretion. The observation time on treatment on the average 15–16 months is unfortunately too short to draw valid conclusions regarding the effect during long term. Few side-effects with magnesium supplementation to renal stone formers have been reported. Some patients might experience minor gastrointestinal discomfort or diarrhoea. Hypermagnesemia has not been reported.

The clinical effects of different magnesium compounds used as prophylactic stone treatment are good. The prophylactic effect is comparable to that observed with thiazides [41]. Since magnesium is a natural occurring substance such a treatment is to be preferable in patients on long-term, sometimes lifelong treatment.

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