Kidney Stones
Beneficial Roles of Citrus
Executive Summary

Sandy Barros and Filomena Valim

Nephrolithiasis (nef"ro-li-thi'ah-sis) is the formation of stones in the urinary tract commonly referred to as kidney stones. The development of the stones is related to decreased urine volume or increased excretion of stone-forming components such as calcium, oxalate and phosphate. Excessive calcium salts composed of calcium oxalate and/or other calcium salts can crystallize, and precipitate, contributing to the development of kidney stones.

Among Americans adults, the prevalence of nephrolithiasis is 1 in a 1000, with men being almost twice as likely as women to develop stones.

Calcium stones disease is the most common form of nephrolithiasis and represents about 70% of all stone-forming disease. It occurs most often in the third to fifth decade of life.

A high fluid intake is normally the general advice given to patients for the prevention of stone recurrence regardless of stone composition. The increase in fluid intake has been associated with a reduced risk for kidney stone formation. Lowering of the concentration of constituent ions in the urine, through its dilution, causes a decrease of the super-saturation of stone forming salts.

Citrate, the usual form of citric acid in solution, is a well known inhibitor of the formation of calcium oxalate and calcium phosphate stones. Citrate is decreased in 19-63% of patients with recurrent nephrolithiasis. Potassium citrate is the preferred drug for the treatment of hypocitraturia (low citrate in urine) calcium nephrolithiasis. However, because of gastrointestinal adverse effects, there are patients who are not able to tolerate potassium citrate. In such cases, dietary sources of citrate, such as fruit and fruit juices especially those with high citrate content may be considered an option or alternative to pharmacological agents as these juices generally are assumed to deliver an alkali load (increases the net gastrointestinal absorption of alkali).

In a published study it was disclosed that a diet restricted in sodium and animal proteins (low meat) but liberal in calcium and fruit products was more effective than a diet restricted in calcium in preventing stone formation.

However, in another study it was shown that the protective effect of high dietary calcium may have resulted from concurrent increase intakes of protective dietary factors such as fluids, potassium, and magnesium.

In the presence of conflicting reports such as mentioned above, a study was undertaken to ascertain the effect of dietary modification on urinary stones risk, and to determine whether the response depended on the prevailing urinary calcium. The authors found that overall, dietary modification reduced urinary calcium, more so among patients with moderate-severe hypercalciuria (high calcium in urine) than among those with mild hypercalciuria and normocalciuria.

Citrus juices are rich sources of potassium and citrate, and numerous studies have been conducted to evaluate the influence of orange and grapefruit juices as inhibitors of stone forming components have been conducted.

The effect of orange juice consumption on urinary stone risk factors to determine the potential for orange juice to serve as a source of potassium citrate in the management of nephrolithiasis was studied. The authors reported that orange juice is analogous to a liquid preparation of a mixture of potassium citrate and citric acid. Results of the study showed that when compared to potassium citrate treatments at the same equivalent dose of potassium, orange juice delivered an equivalent alkali load and produced a similar rise in urinary pH and urinary citrate. The authors concluded that overall, orange juice should be beneficial in the control of calcarious and uric acid nephrolithiasis.

In a study conducted in 2006 to evaluate the value of orange juice and lemonade with respect to their effects on acid-base balance and reducing stone-forming risk, the author found that orange juice provided alkali load as evidenced by higher net gastrointestinal alkali absorption and higher urinary pH and citrate compared with the distilled water control. These findings were not observed with lemonade. The results suggested that orange juice consumption could result in biochemical modification of stone risk factors, however the short observation term of this study (each phase lasted 1 week) limits the strength of this conclusion and additional research is needed to evaluate orange juice role in long-term prevention of recurrent nephrolithiasis.

The influence of the consumption of grapefruit and orange juices on urinary variables and risk of crystallization leading to stones were studied in 2003. Results of the study showed that grapefruit juice reduced the risk of calcium oxalate stone formation at a level comparable to the effects obtained from orange juice.

The changes in urinary stone risk factors after administration of a soft drink containing grapefruit juice were investigated in 2002. Data showed that a soft drink containing grapefruit juice significantly increased urinary excretion of citrate, calcium and magnesium compared to mineral water. Trinchieri and co-workers concluded that citrus fruit juices could represent a natural alternative to potassium citrate in the management of nephrolithiasis, because they could be better tolerated and more cost-effective than pharmacological calcium treatment.

Potassium citrate has become the gold standard for management of hypocitraturia. However, patient compliance with this form of therapy can, at times, be difficult because of possible gastrointestinal side effects or financial considerations. It has been long known that citrus juices are a natural source of dietary citrate. In a reason study the citrate concentrations of various commercially available fruit juices including citrus juices and other common beverages were measured. Quantitative analysis revealed the highest concentration of citrate among juices was in grapefruit juice, followed in decreasing concentrations by lemon juice, orange juice, pineapple juice, and cranberry juice.

In conclusion, based on the available data, patients with mild to moderate hypocitraturia can benefit from dietary supplementation with citrus based juices. These juices may be an effective alternative to medical management of kidney stones risks, while not requiring large volumes of fluid to be consumed and even providing a more cost-effective alternative or supplementation to medications.

For a more detailed and referenced review of this topic, please continued reading below

Kidney Stones
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Literature Review
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1. Introduction:

Nephrolithiasis (nef"ro-li-thi'ah-sis) is the formation of stones in the urinary tract commonly referred to as kidney stones. The development of the stones is related to decreased urine volume or increased excretion of stone-forming components such as calcium, oxalate and phosphate. Excessive calcium salts composed of calcium oxalate and/or other calcium salts can crystallize, and precipitate, contributing to the development of kidney stones (MedicineNet.com).

Kidney stones may produce no symptoms or may be associated with pain in the abdomen, flank or groin and are a common cause of blood in the urine. The pain associated with kidney stones is usually of sudden on set, very severe and intermittent. It does not improve by change in position, radiating from the back, down the flank, and into the groin (MedicineNet.com).

Among Americans adults, the prevalence of nephrolithiasis is 1 in a 1000, with men being almost twice as likely as women to develop stones.

Calcium stones disease is the most common form of nephrolithiasis and represents about 70% of all stone-forming disease. It occurs most often in the third to fifth decade of life (Clevelandclinicmeded.com).

A high fluid intake is normally the general advice given to patients for the prevention of stone recurrence regardless of stone composition. The increase in fluid intake has been associated with a reduced risk for kidney stone formation (Curhan et al.1996, 1998). Lowering of the concentration of constituent ions in the urine, through its dilution, causes a decrease of the super-saturation of stone forming salts (Honow 2003).

Citrate [usually, the form of citric acid in solution] is a well known inhibitor of the formation of calcium oxalate and calcium phosphate stones. Citrate is decreased in 19-63% of patients with recurrent nephrolithiasis. Potassium citrate is the preferred drug for the treatment of hypocitraturia ([hy-po-si-tra-tu'-re-ah] low citrate in urine) calcium nephrolithiasis. It typically increases urinary citrate and pH, and decreases urinary calcium (Wabner 1993). However,

because of gastrointestinal adverse effects, there are patients who are not able to tolerate potassium citrate. In such cases, dietary sources of citrate, such as fruit and fruit juices especially those with high citrate content, may be considered an option or alternative to pharmacological agents as these juices generally are assumed to deliver an alkali load which increases the net gastrointestinal absorption of alkali (Odvina, 2006).

This paper reviews studies relating the effects of dietary modifications in the management of urinary stone formation, with emphasis in the use of citrus juices due to the fact that they represent natural sources of citrate and potassium.

2. Dietary Modification effects on risks factors for urinary stone formation:

Hypercalciuria ([hy-per-kal-se-u´-re-ah] high calcium in urine) has been reported in about 50% of patients with urinary stones and contributes to calcium-stone formation by increasing urinary saturation and crystallization/precipitation of calcium salts and by inactivating negatively charged urinary inhibitors of stone formation. On the other hand, there is some uncertainty regarding the value of dietary calcium restriction in the management of calcium nephrolithialisis.

A study published by Borghi et.al (2002), disclosed that a diet restricted in sodium and animal proteins (low meat) but liberal in calcium and fruit products, was more effective than a diet restricted in calcium in preventing stone formation. The authors conducted a five-year randomized trial comparing the effect of two diets in 120 men with recurrent calcium oxalate stones and hypercalciuria. Sixty men were assigned to a diet containing a normal amount of calcium (30 mmol (1.2g) per day) but reduced amounts of animal protein (52 g per day) and salt (50 mmol (2.9g) of sodium chloride per day); the other 60 men were assigned to a low-calcium diet, which contained 10 mmol of calcium per day. After five years, 12 of the 60 men on the normal-calcium, low-animal-protein, low-salt diet and 23 of the 60 men on the low-calcium diet had had relapses.

However, a study by Heller et al. (2000) showed that the protective effect of high dietary calcium may have resulted from concurrent increase intakes of protective dietary factors such as fluids, potassium, and magnesium. A total of 21 normal volunteers underwent 2 phases of study in a crossover, randomized design, wherein they consumed constant metabolic diets that matched the estimated highest and lowest quintiles of calcium intake noted within published epidemiological studies.

The authors concluded from published epidemiological studies that a high calcium diet does not alter the propensity for calcium oxalate stone formation in normal subjects despite

increased urinary calcium and unaltered urinary oxalate because of the greater amounts of ingested fluid, potassium and phosphate. However, high calcium intake alone, without additional changes in the diet, poses a modest risk for calcium stone formation.

In the presence of conflicting reports such as mentioned above, Pak and co-workers (2005) undertook a study to ascertain the effect of dietary modification on urinary stones risk, and to determine whether the response depended on the prevailing urinary calcium. In the study 951 patients were broken up into 3 groups, those with moderate-severe hypercalciuria, mild hypercalciuria, and normohypercalciuria. The groups contained 356, 243, and 352 patients respectively.

Each of the three groups participated in both; a random diet (the patients' normal daily diet) for one week followed by a restricted diet limited in calcium, oxalate, sodium and meat products for a second week. During both diets, urine samples were collected in 24-hour pools to measure stone risk factors. The authors found that overall, dietary modification reduced urinary calcium, more so among patients with moderate-severe hypercalciuria than among those with mild hypercalciuria and normocalciuria.

2a. Orange Juice effects on urinary stone risk factors

Citrus juices are rich sources of potassium and citrate, and numerous studies have been conducted to evaluate the influence of orange and grapefruit juices as inhibitors of stone forming components.

Wabner and Pak (1993) looked into the effect of orange juice consumption on urinary stone risk factors to determine the potential for orange juice to serve as a source of potassium citrate in the management of nephrolithiasis. They reported that orange juice is analogous to a mixture of potassium citrate and citric acid delivered as a liquid preparation They studied 8 healthy men 24-42 years of age, and 3 men 40-72 years of age with documented hypocitraturic (low citrate in urine) nephrolithiasis to determine potential control of the disease with potassium citrate treatment.

The three phase study (placebo, potassium citrate and orange juice, with each phase lasting one week) was conducted. In the potassium citrate phase, subjects ingested 20 milli-equivalents (mEq) of potassium citrate 3 times daily with meals; in the orange juice phase subjects drank 400 mL reconstituted frozen orange juice 3 times daily with meals, to provide 60 mEq of potassium each day. When compared to potassium citrate treatments at the same

equivalent dose of potassium, orange juice delivered an equivalent alkali load and produced a similar rise in urinary pH and urinary citrate.

The authors further stated that orange juice, like potassium citrate, reduced urinary undissociated uric acid levels and increased the inhibitor activity (formation product) of bushite (calcium phosphate). However, orange juice increased urinary oxalate and did not alter calcium excretion, whereas potassium citrate reduced urinary calcium without altering urinary oxalate. Wabner and Pak concluded that overall, orange juice consumption should be beneficial in the control of calcarious and uric acid nephrolithiasis.

Odvina (2006) conducted a study to evaluate the value of orange juice and lemonade with respect to their effects on acid-base balance and reducing stone-forming risk. The author found that orange juice provided alkali load as evidenced by higher net gastrointestinal alkali absorption, and higher urinary pH and citrate compared with the distilled water control. These findings were not observed with lemonade. The thirteen subjects in the study were composed of otherwise healthy but stone-forming volunteers between 20 and 65 years of age. During the orange juice phase of the study, each subject was to consume 400 mL of orange juice three times a day. This quantity of juice yielded 100 mEq of citrate and 42 mEq of potassium per day. The same quantity of lemonade (400 mL 3-times/day) providing the same amount of citrate as was ingested daily with the orange juice, was also consumed by subjects during the lemonade phase of the study. Four hundred milliliters of distilled water, 3 times/day, was ingested during the placebo phase of the study. The results suggested that orange juice consumption could result in biochemical modification of stone risk factors. The short observation term of this study (each phase lasted 1 week) limits the strength of this conclusion and additional research is needed to evaluate orange juice role in long-term prevention of recurrent nephrolithiasis.

Coe and co-workers (1992) investigated the stone-forming potential of milk or calcium-fortified orange juice in hypercalciuric adults. The orange juice (OJ) was fortified with calcium-citrate-malate (CCM). Six male and six female, non-stone forming, hypercalciuric adults consumed 600 mg per day as beverage calcium for four consecutive weeks. Both the milk and fortified OJ were well tolerated by male and female participants with few significant ancillary changes occurring over the course of the study. However, the calcium-fortified OJ significantly increased urinary pH (less acidic) relative to milk in both sexes and urinary citrate concentration in women only. Both of these urinary parameters were significantly increased by the calcium-fortified OJ in both sexes relative to the levels prior to the study. The combined pH and citrate effects are recognized as protectants against calcium oxalate stone formation

through the formation of the soluble calcium citrate salt. The data from this study indicated to the authors that either milk or calcium-fortified OJ can be consumed, within the limits of the study, without increasing the risk of stone formation in a calcium-sensitive subpopulation.

2b. Grapefruit Juice effects on urinary stone risk factors:

The influence of the consumption of grapefruit and orange juices on urinary variables and risk of crystallization (leading to stones) were studied by Honow et.al (2003). The study was carried out using nine female volunteers with no history of urolithiasis (formation of urinary tract stones) or other renal disorders. The mean age of the subjects was 29 years (range 26-35). Alkalizing beverages such as orange juice have been shown to be highly effective in the metaphylaxis (the timely mass medication of a group to eliminate or minimize an expected outbreak of disease) of calcium oxalate, uric acid and cystine lithiasis (stone formation). During the study, the subjects received a standardized diet. Fluid intake of 2.75 L (liters) was composed of 2.25 L of neutral mineral water, 0.4 L of coffee and 0.1 L of milk. On the loading days (forth day 0.5 L, fifth day 1.0 L) mineral water was partly substituted for by the juice tested (orange, grapefruit or apple), respectively. The urinary variables were evaluated in 24 h urine sample. The study showed that grapefruit juice reduced the risk of calcium oxalate stone formation at a level comparable to the effects obtained from orange juice.

An increased risk of nephrolithiasis has been associated with the ingestion of grapefruit juice in epidemiological studies-- the Nurses' Health Study and the Health Professionals Follow-up Study (Curhan et al., 1996 & 1998). These two prospective studies dealt with the relation between the consumption of different beverages (17 and 21 respectively) and the risk of symtomatic kidney stones. The authors concluded that the risk of stone formation increased with the consumption of apple and grapefruit juice in the first study and grapefruit juice in the second study. However the authors also stated that "before definitive recommendations can be given to patients who have had kidney stones, additional studies are needed" (Curhan et al., 1996). It should also be pointed out that the results of this study were based on an evaluation of questionnaires without any measurements of urinary composition.

Goldfarb and Asplin (2001) studied the effect of grapefruit juice consumption on urinary chemistry and measures of lithogenicity ([lith-o-gen'-i-ci-ti] stone-forming ability).

Ten healthy men and women between ages of 25 and 40 years participated. Each subject drank 240 mL of tap water at least 3 times daily for 7 days during the control period. This period was followed by a second 7 days experimental period during which they drank 240 mL of grapefruit juice 3 times daily. In each 7-day period urine was collected for 24 hours

during the last 3 days. Urine chemical analysis was performed, and super saturations of calcium oxalate, calcium phosphate and uric acid were calculated and urinary lithogenicity was measured.

Results of the study showed urine volume and creatinine (a breakdown product of muscle metabolism, and a marker of kidney misfunction) excretion were the same during the control and experimental periods. Grapefruit juice ingestion was associated with an increase in mean oxalate excretion and in mean citrate excretion. There was no net change in the super saturation or upper limit of metastability (state of delicate equilibrium) of calcium oxalate, calcium phosphate or uric acid. Crystal aggregation and growth inhibition by urinary macromolecules was not affected by grapefruit juice ingestion.

The authors concluded that offsetting changes in urine chemistry caused by the ingestion of grapefruit juice led to no net change in calculated super saturation. No changes in lithogenicity were demonstrated. The results do not demonstrate an effect of grapefruit juice for increasing lithogenicity. The basis of the observations of the epidemiological studies reported by Curhan et al. 1996 & 1998 remains unexplained.

Trinchieri et al. (2002) investigated changes in urinary stone risk factors after administration of a soft drink containing grapefruit juice. Seven healthy subjects, with no history of kidney stones, were submitted to an acute oral load of a soft drink containing grapefruit juice diluted (10%) in mineral water. After a 7-day wash out period, each subject underwent an oral load with mineral water alone. Urine specimens were collected before and after each oral load. Data showed that a soft drink containing grapefruit juice significantly increased urinary excretion of citrate, calcium and magnesium compared to mineral water. Trinchieri and co-workers concluded that citrus fruit juices could represent a natural alternative to potassium citrate in the management of nephrolithiasis, because they could be better tolerated and more cost-effective than pharmacological calcium treatment.

Potassium citrate has become the gold standard for management of hypocitraturia. However, patient compliance with this form of therapy can, at times, be difficult because of possible gastrointestinal side effects or financial considerations. It has been long known that citrus juices are a natural source of dietary citrate. Haleblian et al. (2008) measured the citrate concentrations of various commercially available fruit juices including citrus juices and other common beverages. Quantitative analysis reveled the highest concentration of citrate among juices was in grapefruit juice, followed in decreasing concentrations by lemon juice, orange juice, pineapple juice, and cranberry juice.

In conclusion, based on the available data, patients with mild to moderate hypocitraturia can benefit from dietary supplementation with citrus based juices. These juices may be an effective alternative to medical management of kidney stones risks, while not requiring large volumes of fluid to be consumed, and even providing a more cost-effective alternative or supplementation to medications.

References:

http://www.MedicineNet.com

Cleveland Clinic website, http://clevelandclinicmeded.com

Curhan GC, Willet WC, Rimm EB, Spiegelman D and Stampfer MJ 1996. Prospective study of beverage use and risk of kidney stones. Am. J. Epidemilogy 143, 240-247.

Curhan GC, Willett WC, Speizer PE and Stampfer MJ 1998. Beverage use and risk for kidney stones in women. Ann. Int. Med 128: 534-540.

Honow R, Laube M, Schneider, Kebler T, and Hesse A. 2003. Influence of grapefruit-, orange- and apple-juice consumption on urinary variables and risk of crystallization. Brit J Nutr, 90: 295-300.

Wabmer. CL, and Pak YC. 1993. Effect of orange juice consumption on urinary stone risk factors. J Urol, 149: 1405-1408.

Borghi L, Schianchi T, Meschi T et al: 2002. Comparison of two diets for the prevention of recurrent stones in idiopathic hypercaluciuria. N Engl J Med, 346: 77-84.

Heller H, Doerner MF, Brinkley et al: 2000. Effect of dietary calcium on stone-forming propensity. J. Urol, 169:470-474.

Pak, CYC, Odvina C, Pearl, MS, Shkhaee K, et al: 2005. Effect of dietary modification on urinary stone risk factors. Kidney Int. 68: 2264-2273.

Odvina CV, 2006. Comparative value of orange juice versus lemonade in reducing stone-forming risk. Clin J Am Soc Nephrol 1: 1269-1274.

Coe FL, Parks JH, and Webb DR, 1992. Stone-forming potential of milk or calcium-fortified orange juice in idiopathic hypercalciric adults. Int Soc Neprol 47: 139-142.

Colditz, CA, 1995. The Nurses's Health Study: a cohort of US women followed since 1976. J Am Med Womens Assoc 50:40-63.

Goldfarb DS, and Asplin JR, 2001. Effect of grapefruit juice on urinary lithogenicity. J Urol, 166: 263-267.

Trinchieri, A, Lizzano R, Bernardine P, et al. 2002. Effect of acute load of grapefruit juice on urinary excretion of citrate and urinary risk factors for renal stone formation. Digest Liver Dis 34 (suppl.2): S 160-163.

Haleblian, G. E. et al 2008. Assessment of citrate concentrations in citrus fruit-based juices and beverages: implications for management of hypocitraturic nephrolithiasis. J Endourol 22 (6): 1359-1366.