Fad diets and their effect on urinary stone formation

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Abstract: The influence of unhealthy dietary habits on urinary stone formation has been widely recognized in literature. Dietary advice is indeed the cornerstone prescription for prevention of nephrolithiasis as well. However, only a small amount of medical literature has addressed the influence of popular or fad diets, often self-prescribed for the management of obesity and overweight or for cultural beliefs, on the risk of kidney stones. Thereby in this paper we analyze the current knowledge on the effects of some popular diets on overall lithogenic risk. High-protein diets, like Dukan diet, raise some concerns, since animal proteins are able to increase urinary calcium and to decrease urinary citrate excretion, thus leading to a high overall lithogenic risk. Low-carbohydrate diets, like Atkins diet or zone diet, may have a protective role against kidney stone formation, but there are also evidences stating that this dietary approach may rise calciuria and decrease citraturia, since it is generally associated to a relatively high intake of animal proteins. Vegan diet can be harmful for urinary stone disease, especially for the risk of hyperuricemia and micronutrient deficiencies, even if only few studies have addressed this specific matter. On the other side, the benefits of a lacto-ovo-vegetarian diet on kidney stone prevention have been largely emphasized, provided that the intake of calcium and oxalate is balanced. Traditional Mediterranean diet should exert a protective effect on nephrolithiasis as well, even if specific studies have not been carried out yet. High phytate and antioxidant content of this diet have however demonstrated to be beneficial in preventing the formation of new or recurrent calculi. Anyway, at the current state of knowledge, the most effective dietary approach to prevent kidney stone disease is a mild animal protein restriction, a balanced intake of carbohydrates and fats and a high intake of fruit and vegetables. Other fundamental aspects, which are often neglected in fad diets, are a normal intake of milk and dairy products and salt restriction. All these nutritional aspects should be greatly taken into account when patients who are willing to undergo fad or commercial diets ask for dietary advice.

Keywords: High-protein diet; low-carbohydrate diet; vegan diet; vegetarian diet; Mediterranean diet; Dukan diet; Atkins diet; zone diet; nephrolithiasis

The importance of diet in nephrolithiasis onset and prevention has been widely recognized in medical literature. Nowadays dietary advice, alongside with adequate fluid intake and pharmacologic therapy, where indicated, is the cornerstone prescription in the medical management of kidney stone disease (1-5).

However, the dietary habits of kidney stone formers often do not fit together with the principles of an anti-lithogenic diet (6,7), even if a new attention for the quality of diet has risen among the general population in Western countries in the last decades, leading to minor but significant changes in the daily intake of fat, fruit and vegetables (8,9). There is also some evidence that dietary habits have changed even in calcium stone formers in the last 25 years (10,11).

People have become more and more conscious of the importance of nutrition in the prevention and treatment

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of many diseases, especially in the obesity, diabetes and cardiovascular prevention field. Therefore, many different diets have been proposed in the last years and have gained popularity among general population. Some of these diets, such as the Mediterranean and the hyperproteic diet (e.g., Dukan diet), have been extensively studied in medical literature, so that a large amount of evidences on their risks and benefits is nowadays available. Some other diets have poorer scientific basis, even if there are reliable hypothesis explaining their possible effects on human health.

The purpose of this paper is therefore to review the present knowledge about the effects of fad diets on kidney stone risk factors and kidney stone formation, highlighting their differences with the correct dietary prescriptions for nephrolithiasis prevention.

High protein diets

Raising the daily intake of protein is one of the most popular dietary treatments for obesity, sometimes also associated to an important reduction in carbohydrate consumption. Several studies have addressed the efficacy of this prescription, showing that an elevated protein intake rises total energy expenditure through a higher thermic effect of feeding and promotes premature satiety during meals (12,13). The resulting decrease in the intake of other macronutrients, such as carbohydrates and lipids, leads to an improvement in many parameters of the metabolic syndrome (for example, reduction in total serum cholesterol and better glucose tolerance) and ultimately to a weight loss (14,15). The most common prescription is to eat at least 25% of total energy requirements as proteins, which means at least 1.6 g/kg of ideal body weight, while the usual recommended dietary allowance for protein is 0.8 g/kg (16). These prescriptions are the basis of many fad commercial diets, such as the Dukan diet, consisting in a first phase of exclusive protein intake, followed by various phases of mild progressive reintroduction of other nutrients such as fibers and carbohydrates (17).

There are some concerns about the adverse effects of these diets, especially for the progression of chronic kidney disease and the increase in cardiovascular risk (16,18,19), and some studies have also doubted their efficacy in glucose tolerance control and weight loss (16).

From a urinary point of view, it has been demonstrated a long time ago that the main effect of a high protein intake is a rise in urinary calcium excretion, independent from other dietary factors such as salt intake (20,21). These results have

been confirmed in a large number of studies, showing a significant rise in the global lithogenic risk (22-25). On the other side, shifting from an ad libitum protein intake to a recommended daily allowance (RDA) protein intake results in a net 32% decrease in the levels of calcium excretion (25). Dietary proteins, especially of animal origin, actually lead to a high potential renal acid load (PRAL), a decrease in urinary pH and a state of mild chronic metabolic acidosis (26). Therefore some researchers claim that hypercalciuria comes from high bone reabsorption due to this high acid load (24), while others show that there are no proofs to support this hypothesis, thus claiming that it might have a renal origin (25). In fact, neutralization of the dietary acid load with potassium citrate therapy is not able to prevent the hypercalciuric effect of a high animal protein diet (27).

There are also other urinary factors driving the risk for kidney stones in high protein diets. For example, a significant reduction in urinary citrate levels has been demonstrated (22,23). These modifications may be due to the lower content of citrate in diet, since high protein diets usually do not include large amounts of fruit and vegetables, but they may also be linked to the high levels of PRAL and to urinary acidification (28).

Moreover, it has also been shown that a high animal protein intake in diet may determine a rise in the urinary oxalate excretion in about 30% of patients with idiopathic calcium nephrolithiasis, while other subjects do not exhibit any hyperoxaluric response at all. This susceptibility is independent from vitamin B6 deficiency and seems to be related to yet unknown genetic factors (29).

The connection between high protein intake and the risk for kidney stone onset or recurrence has also been demonstrated in a large epidemiologic study carried out in male healthy subjects on their usual diet and prospectively followed up for four years. Men in the highest quintile for animal protein consumption (>77 g/day) actually showed a higher multivariate relative risk for incident kidney stones (1.33 *vs.* 1.00, P trend 0.05) than men in the lowest quintile (<50 g/day) (30). The same group of authors carried out other two similar studies on larger cohorts of healthy females, but they failed to demonstrate a similar relationship between animal protein intake and kidney stone risk (31,32).

Therefore, the real-life risk for developing kidney stones during or after a high protein diet may be slightly lower than what suggested by clinical studies carried out on randomized controlled conditions. The reason for this discrepancy may be due to dietary questionnaires that do not discern between red meat, poultry and fish proteins.

It is well known, for example, that fish proteins have a low sulphur content and are associated with a high content in n-3 fatty acids, eicosapentaenoic acid and alkaline potassium, which may actually protect against the calciuric effect of proteins (33). However, intervention studies have shown that a reduction in animal protein intake is really effective in preventing kidney stone relapse, either alone or combined with a reduction in salt intake and an increase in fruit and vegetable intake (34,35). Therefore, a mild protein restriction is generally recommended in all anti-lithogenic diets (2,3). Subjects who undergo high protein diets, like Dukan diet, for obesity or overweight management should be aware that nephrolithiasis is a potential side effect and subjects with a known history of stone disease should not undergo these diets at all.

Low carbohydrate diets

Diets with a very low content in carbohydrates have gained great popularity for weight loss in the last decades. The most studied one is Atkins diet, which consists of a normocaloric, very low carbohydrate, normal/high protein and high fat intake. Some variants of Atkins diet emphasize the benefits of animal protein, so they may overlap to high protein diets described above. Two renowned randomized studies published about 10 years ago compared Atkins diet with the usual low-fat low-calorie diet for obesity, showing that weight loss was higher in the Atkins diet group after 6 months, but was similar to the usual diet group after 1 year (36,37).

Severe carbohydrate restriction leads to a progressive depletion of glycogen stores and associated bound tissue water. Therefore, it is plausible, but not properly demonstrated yet, that the weight loss is due to tissue dehydration and not to fat store losses (38). Moreover, the depletion of glycogen produces ketotic acidosis, which has some effects on brain functioning, leading to appetite suppression and reduced production of excitatory neurotransmitters. Atkins diet has actually proven to be effective in controlling drug-refractory forms of epilepsia in children (39). The risk of severe ketoacidosis and the poor rate of adherence among patients are the main medical concerns in prescribing this diet, even if there are some evidences stating that it may improve glucose tolerance and cardiovascular risk factors (36,37,40).

Other popular diets, such as zone diet, include only a mild carbohydrate restriction (40% of total energy intake), with a proportionally higher-than-recommended intake of fats

and proteins (30% of total energy intake each). In zone diet every meal and snack should have a composition of 40% in carbohydrates, 30% in proteins and 30% in fats, especially rich in omega-3 polyunsaturated fatty acids. The rationale of this approach is that this formula is the best way to limit insulin secretion, which is seen as the main detrimental factor in the onset of overweight, obesity and metabolic syndrome (41,42). Some studies have actually claimed that zone diet is effective in decreasing insulin and homocysteine levels and has anti-inflammatory properties (43), while others have demonstrated that its efficacy on weight loss is limited, especially if compared to Atkins diet (44).

The effects of low carbohydrate diets on urinary stone risk factors have not been extensively studied and results in literature are partially conflicting. Some studies carried out in renal stone patients and in healthy subjects have addressed the effects of an acute oral load of simple carbohydrates, such as glucose or xilitol, on the urinary profile of lithogenic risk, showing that it can result in an increase in calciuria (45,46). Xilitol ingestion is also associated to a rise in the urinary excretion of phosphate and oxalate, thus increasing lithogenic risk (46). Moreover, a habitual high dietary intake of sucrose is associated to a high risk of kidney stone onset or recurrence in a large epidemiologic study carried out in healthy women (31). High insulin levels, indirect marker of a high carbohydrate consumption or metabolic syndrome, have actually been correlated to high calcium excretion (47), even if more recent research denies that euglycemic hyperinsulinemia has a significant effect on urinary calcium excretion (48).

All these evidence seem to indirectly support the assumption that low-carbohydrate diets are protective against kidney stones. As a matter of fact, even from a physio-pathological point of view, carbohydrates are the main carbon donors in the endogenous liver synthesis of glyoxylate and therefore of oxalate. However, the only study who specifically addressed the effects of Atkins diet in nephrolithiasis showed that it is associated to a high lithogenic risk. The shift from usual diet to Atkins diet in healthy subjects actually leads to an average 61% rise in urinary calcium and a 41% decrease in urinary citrate compared to baseline levels (22). It should be pointed out that in this study the low-carbohydrate diet was associated to a high-protein intake, as documented by the average 56 mEq/day increase in net acid excretion, so probably the harmful effects of proteins, which are consistent with what is reported above, can mask the effects of carbohydrate reduction.

To our knowledge, there are no studies in literature addressing the effects of zone diet on lithogenic risk. However, one of the main components of zone diet, i.e., n-3 fatty acid or fish oil supplementation, has been extensively studied. Kidney stone formers generally have higher levels of plasma arachidonic acid content, which has been linked to hypercalciuria and hyperoxaluria (49,50). Several studies have demonstrated that fish oil or n-3 fatty acid supplementation can reduce plasma arachidonic acid levels, with a concomitant reduction in urinary calcium and oxalate and lower levels of calcium oxalate supersaturation index (49-53). However, a large epidemiologic study carried out on healthy subjects has denied any correlation between fatty acid intake and the onset or prevention of nephrolithiasis (54).

Thus, current knowledge supports neither the prescription nor the avoidance of low-carbohydrate diets in nephrolithiasis and their real effect on lithogenesis is still poorly known. More studies are needed to address this specific matter; in the meanwhile, a mild carbohydrate restriction with a normal intake of n-3 fatty acids seems a reasonable prescription for those who want to avoid kidney stones (2).

Lacto-ovo-vegetarian and vegan diets

Vegan diet has been defined as a diet with no intake of animal derivatives, where only vegetal derivatives are allowed. On the other side, vegetarian diet is a diet where only meat and fish are prohibited, while eggs and milk derivatives are allowed (55). These diets have gained great popularity in Western countries in the last decades, especially for cultural or religious reasons. A large number of scientific studies have supported these diets, highlighting many benefits especially on cancer prevention (56), cardiovascular disease and death prevention (57) and treatment of type 2 diabetes mellitus (58). On the other side, the main nutrition concern about these diets is the insufficient intake of vitamin D, vitamin B12, n-3 fatty acids, iron and zinc, which may result in clinical deficiencies (59). These concerns are particularly emphasized for vegan diet, where deficiencies are more frequent with possible reflections on an unfavorable cardiovascular risk profile (60).

Vegetarian diets have been recognized as protective against kidney stone disease a long time ago (61), and the prevalence of nephrolithiasis in vegetarians has been esteemed in about half that of free diet (62). Fruit and vegetables, the main components of vegetarian diets, actually have a low content in proteins and sodium chloride and a high content in lithogenesis inhibitors such as magnesium, citrate and alkaline potassium. Some studies have addressed the impact of the switch from an omnivorous diet to a vegetarian diet on urine chemistries, actually demonstrating a rise in the urinary excretion of potassium, magnesium and citrate and a decrease in the excretion of calcium, thus reducing the supersaturation indexes for calcium oxalate and calcium phosphate (63-66). Vegetarian diet also has a high alkalinizing power on urines, leading to a higher urine pH, resulting in a lower risk for uric acid stones (67). Vegan diet instead has been associated to a high prevalence of severe hyperuricemia, which is the strongest and most common risk factor for hyperuricosuria and uric acid nephrolithiasis (68).

The positive effects of a high fruit and vegetable intake on lithogenic risk have also been assessed in large epidemiologic studies evaluating the urinary chemistries and the risk of kidney stone formation in Dietary Approaches to Stop Hypertension (DASH)-style diet. DASH diet has been specifically designed for managing hypertension and cardiovascular risk and encompasses a high intake of fruit and vegetables, a moderate intake of low-fat dairy products and a low intake of salt and animal proteins. Subjects who spontaneously follow diets that fit with DASH diet recommendations actually have a lower risk of incident kidney stones [multivariate relative risk 0.55 (95% CI, 0.46-0.65) for men, 0.58 (95% CI, 0.49-0.68) for older women and 0.60 (95% CI, 0.52-0.70) for younger women] and higher urinary volume and urinary citrate than other subjects that do not eat according to DASH recommendations (69,70). These effects are most likely due to the high intake of fruit and vegetables, although we cannot fully recognize the effects of other foods, since these diets are not strictly vegetarian. High intakes of potassium and phytate, which are considered reliable indexes of fruit and vegetables consumption, are actually associated to a lower risk of incident nephrolithiasis in groups with different age and sex (30-32).

Despite these well demonstrated positive effects, vegetarian diets have not been extensively prescribed for nephrolithiasis prevention or treatment. Fruits and vegetables, especially if eaten in large amounts, are actually the main dietary sources of oxalate and a high dietary oxalate load may result in hyperoxaluria, especially in subjects with idiopathic calcium nephrolithiasis (71). Moreover, an oxalate load may raise the fractional intestinal absorption of calcium, thus promoting a mild hypercalciuria (72). Vegetarian diet has actually been associated to hyperoxaluria

and hypercalciuria in a famous clinical study published more than twenty years ago (73), and has been considered detrimental for stone formers ever since.

More recent investigations have actually pointed out that vegetarian diet does not increase oxalate excretion and lithogenic risk per se, but the global calcium/oxalate dietary content should be taken into account to define lithogenic risk. As a matter of fact, a balanced intake of calcium and oxalate can promote chelation in the intestinal tract, so that a smaller fraction of the two substances is excreted in urine. It is also important that the dietary intake of other substances able to chelate calcium, such as phytate, is low, making calcium available for chelation with oxalate. Therefore, the ability of a vegetarian diet to promote or prevent nephrolithiasis also depends on its composition in calcium, oxalate and phytate and on the timing of their ingestion (74). Simultaneous intake of high-oxalate foods and high-calcium foods is the best way to limit the absorption of both substances (75). On the other side, simultaneous ingestion of calcium and substances with a high chelating power, such as fibres or rice bran, may result in a rise of lithogenic risk due to the higher excretion of oxalate, that leads to higher levels of calcium oxalate supersaturation index, even if stone recurrence rate is prospectively not affected (76,77).

It should also be noted that only a few vegetables have demonstrated to significantly raise oxalate excretion, if eaten regularly, such as spinach, rhubarb, beets and tomatoes (78). Moreover, even a massive dietary oxalate load results in a relatively mild increase in oxaluria (79): hyperoxaluria is indeed determined more frequently by genetic than environmental factors, and it generally affects only a small portion of calcium stone formers (4,80). Finally, both vegan and lacto-ovo-vegetarian diets have shown not to significantly affect calcium metabolism, bone turnover and calcium excretion on a short-term period, even if their effect for a long-term period is still poorly known (81).

Therefore, current evidence shows that a balanced lacto-ovo-vegetarian diet is generally not detrimental for kidney stone prevention and can on the contrary be protective, provided that there is an adequate and simultaneous intake of calcium and oxalate and that there is not an excessive intake in fibres. On the other side, the effects of vegan diet in kidney stone disease are not fully understood; the risks of micronutrient deficiencies and of hyperuricemia may outweigh benefits for kidney stone prevention. Thus, at the present state of knowledge, vegan diet should not be recommended for kidney stone prevention.

Mediterranean diet

The traditional Mediterranean diet is characterized by a high intake of olive oil, fruits, vegetables and cereals, a moderate intake of fish, poultry and wine, and a low intake of dairy products, red meat and sweets (82). It is not properly a "fad" diet like the others discussed above, which have gained popularity for cultural or commercial reasons, but it should be instead considered an "evergreen" model of a healthy way of eating, recognized worldwide as one of the cornerstones of nutrition.

Mediterranean diet, as a matter of fact, has been extensively studied, especially in recent years. A huge amount of evidence has shown that it has protective effects against cardiovascular disease (83), hypertension (84), metabolic syndrome (85), cancer (86,87), neurological diseases like stroke and cognitive decline (88) and kidney function (89). Mediterranean diet has also been linked to biochemical and genic parameters of a successful aging (90).

However, the epidemiologic and biochemical impact on urinary stone risk factors of this diet has not been studied yet in literature, even if our research group has published a 5-year trial demonstrating the efficacy of normal calcium, low salt, low protein diet very close to a traditional Mediterranean diet (35). There are indeed no studies, at the current state of knowledge, comparing Mediterranean diet with the usual Western diet focusing on urine composition and the risk of stone relapse. Nevertheless, the composition of the traditional Mediterranean diet highly fits with the main dietary recommendations for nephrolithiasis prevention, such as the low intake of animal proteins and the high intake of fruits and vegetables. For many aspects, Mediterranean diet is very similar to DASH diet, which has proven to be effective in the prevention of kidney stone onset and relapse (69,70).

An aspect of Mediterranean diet that has been particularly emphasized is the high content of antioxidant substances, such as beta-carotene and vitamin E. These substances have been overall associated with a better health-related quality of life, both from a mental and physical point of view (91). In the nephrolithiasis field, there are some evidences stating that low levels of antioxidants such as alpha-carotene, beta-carotene and beta-cryptoxanthin are associated in general population to a history of kidney stones, thus indicating a possible protective role of these substances in stone prevention (92). There are also reports showing that antioxidants may prevent renal cell injury and stone formation in idiopathic calcium nephrolithiasis

(93,94). Moreover, a high dietary intake of vitamin E has been able to prevent calcium oxalate crystal deposition in the kidneys, thus confirming the hypothesis that a diet rich in antioxidant substances, such as vitamin E, may be protective against nephrolithiasis (95).

Mediterranean diets usually encompass a high intake of cereals, nuts and legumes. These foods have a high content of phytate and their consumption has been associated to a high urinary excretion of phytate (96). There are some reports in literature stating that a high urinary phytate excretion may exert a protective role against the formation of renal calculi, especially against the regrowth of calcium oxalate dihydrate fragmented calculi (97,98). Therefore, a Mediterranean-style diet may be important in preventing calcium stone relapse.

Additional nutritional aspects in nephrolithiasis

There are at least other two nutritional aspects that are generally poorly considered in fad popular diets, but that are a basic part of any diet prescription in nephrolithiasis: salt and calcium intake.

There are many reports in literature demonstrating that a dietary sodium chloride load results in a linear increase in calcium excretion, thus affecting global lithogenic risk, in cohorts of healthy subjects, idiopathic calcium stone formers and post-menopausal osteoporotic women (99). A 3.5 g increase in sodium chloride intake may result in a 1.63-fold increase in the relative risk for hypercalciuria, while healthy subjects with a daily salt intake higher than 10 grams have 21.8% prevalence in hypercalciuria, compared to 3.9% prevalence in those with a lower intake (100). Moreover, the levels of calcium excretion are generally higher in stone formers than in healthy subjects with the same sodium intake, so that a 6 g/day rise in salt intake may result in an 80 mg/day increase in urinary calcium (1). Salt-induced calcium excretion also exhibits an additive effect with animal protein-induced hypercalciuria (21). Finally, sodium chloride ingestion is also associated with a reduction in the urinary excretion of citrate (101).

The strong connection between salt intake and nephrolithiasis has also been demonstrated by Curhan & coll. in a large epidemiologic study on healthy middle-aged women, highlighting a higher risk for calcium stone onset or recurrence in those who have a daily salt intake in the highest quintile (31). However, the same authors failed to demonstrate an analogue correlation in younger women and in men (30,32).

Nevertheless, some renowned intervention studies have shown that reducing salt intake is a really effective prescription for diminishing calciuria and the risk for kidney stone relapse in idiopathic calcium nephrolithiasis (35,102,103). The same results have been obtained assessing the effects of DASH-style diet, whose primary recommendation is the reduction of salt intake, on nephrolithiasis onset and recurrence (69). Therefore, dietary salt reduction is nowadays one of the fundamental prescriptions in nephrolithiasis prevention (1-5).

The second issue often neglected in fad diets is calcium intake. Given that hypercalciuria is the most common risk factor for nephrolithiasis, it was believed in the past that stone formers should eat a low-calcium diet, poor in milk and dairy products. However, since the early 1990s a large amount of clinical evidence has pushed against the prescription of low-calcium diets in nephrolithiasis, and Martini *et al*. in 2002 definitely demonstrated that dietary calcium diminish, rather than increase, stone risk (104). As a matter of fact, a high dietary calcium intake is able to reduce oxalate intestinal absorption, and consequently urinary excretion, since oxalate and calcium may complex together to form unabsorbable aggregates (105-107). Low-calcium diet seems to be suitable for nephrolithiasis prevention only when it is associated with a very low intake of oxalate (108).

These findings have also been confirmed by the large epidemiologic studies carried out by Curhan & coll, showing that people in the highest quintile of milk and dairy product consumption are at the lowest risk for kidney stone onset (30-32). Moreover, a normal-calcium low-salt low-animal protein diet has proven to be a better approach for kidney stone prevention than a simple dietary calcium restriction in a renowned prospective intervention study (35). So, nowadays low-calcium diets are no longer recommended for nephrolithiasis.

Conclusions

Different diets generally have different effects in outlining the overall lithogenic risk. When prescribing a new diet or giving dietary advice, physicians and nutritionists should also take into account its effect on kidney stone formation. Many popular fad diets, such as high-protein diet, low-carbohydrate diet and vegan diet, may raise the overall lithogenic risk. On the other side, lacto-ovo-vegetarian and traditional Mediterranean diets seem to be at least not harmful, or even protective against kidney stone formation. Anyway, a dietary approach with low salt, low animal

protein and high fruit and vegetable intake, together with a normal and balanced consumption of milk, dairy products, carbohydrates and fats, is the best way to prevent kidney stone onset and relapse at the current state of knowledge.

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Footnote

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