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Pears and renal stones: possible weapon for prevention? A comprehensive narrative review

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Abstract. – Urinary stones have been recognized as a human disease since dawn of history and treatment of this condition is reported by Egyptian medical writings. Also, pears have a very long history, being one of the earliest cultivated fruit trees and also known for medicinal use. Urinary tract stone formation represents a common condition and also a significant burden for health care service, due also to possible frequent relapses. Furthermore, urinary stones have been reported to have relationship with different metabolic derangements, and appropriate diet could contribute to avoid or reduce urinary stone formation. Citrate is an inhibitor of crystal growth in the urinary system, and hypocitraturia represents a main therapeutical target in stone formers. Pears contain a significant amount of malic acid, a precursor of citrate, and have antioxidant activity as well. A diet supplemented with pears, and associated with low consumption of meat and salt could impact positively cardiometabolic risk and urinary tract stone formation. However, very few studies evaluated the impact of pears utilization on health, and none on urinary tract stone formation in particular. High content in malate could warrant protection against stone formation, avoiding patients at high risk to be compelled to assume a considerable and expensive amount of pills.

Key words:
Renal stones, Urolithiasis, Prevention, Pears, Organic acids, Fruit, Diet.

Renal stones and pears: a brief of a long history

Urinary stones have afflicted humans since the dawn of history, and gone parallel with the history of civilization, as reported in a recent review[1]. The first known stones were discovered in Egyptian mummies, and the English archeologist E. Smith[1] found a bladder stone from a 4500-5000 year old mummy in El Amrah, Egypt, in 1901. Some relevant paleopathology findings are reported in Table I. Treatments for stones were mentioned in ancient Egyptian medical writings from 1500 b.C., and surgery to treat stones was first described by Sushruta, an Indian surgeon living around 600 b.C., who provided detailed information on urinary stones, urinary anatomy, and surgery for stones in his writings, compiled as the Sushruta Samhita[1]. Medical texts from ancient Mesopotamia, India, China, Persia, Greece, all mentioned such disease. Part of the Hippocratic Oath suggests there were practicing surgeons in ancient Greece to whom physicians were to defer for lithotomies. The Roman medical treatise *De Medicina* by Aulus Cornelius Celsus contained a description of lithotomy[2], and this work served as the basis for this procedure until the 18th century. Also as an anedoctal report, we here report only a short list of a series of historical or distinguished in any field figures documented to be kidney stone formers (Table II).

Pear has a very long history behind as well. In fact, it is one of the earliest cultivated of fruit trees. In 5,000 b.C., Feng Li, a Chinese diplomat, abandoned his responsibilities when he became consumed by grafting peaches, almonds, persimmons, pears and apples as a commercial venture. There are records in China and Europe of pears more than 4,000 years ago reporting that dried pears were used medicinally in those days. Greek mythology refers to the pear as a wholesome, tasty fruit, favourite of gods and heroes, and Homer himself (9th century b.C.) in *The Odyssey* gave confirmation that the pear was cultivated in Greece as early as three thousand years ago. Homer included the pear as one of the 'gifts of the gods'[3]. More than 350 years b.C. the cultivation and the production of the pear was quite widespread in the Magna Graecia, and the ancient greek author Theophrastus mentioned both the

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Table I. Renal stones and some relevant paleopathology findings.

	Geographic area	Date	Finding
Europe	Italy, Sicily	6.500 b.C.	Bladder stone
	Southern France	2.100 b.C.	Bladder stone
	United Kingdom, Yorkshire	2.000-700 b.C.	Bladder stone
	Hungary	Bronze age	Bladder stone
	Germany	500-250 b.C.	Bladder stones (probably)
	United Kingdom, Somerset	450-1.000 a.D.	Bladder stones
	Hungary	VI-VII century a.D.	Bladder stone
	Denmark	1.300-1.500 a.D.	Renal stone
	Italy	Early XIX century	Bladder stone
Africa	Predynastic skeleton	3.900-3.100 b.C.	3 bladder stones
	Abido, Egypt	3.500 b.C.	Bladder stone
	Helouan, Egypt	3.100 b.C.	Renal stones (several individuals)
	Naga-el-Deir, Egypt	2.800 b.C.	4 renal stones
	Mummy, Old Kingdom, Egypt	2.650-2.150 b.C.	Renal stone
	Mummy, XXI dynasty, Egypt	1.069-945 b.C.	Triangular stone located into the naris
	Jebel Moya, Sudan	1.000-100 b.C.	Bladder stones (several individuals)
America	Kentucky	3.500-3.000 b.C.	Renal and bladder stones (3 individuals)
	Illinois	1.500 b.C.	Renal stone
	Arizona	100 b.C.-500 a.D.	Bladder stone (mummy)
	Utah	950-1.100 a.D.	Bladder stone
	Chile	1.000 a.D.	Urethra stone (mummy)
	Arizona	1.100-1.250 a.D.	Bladder stone
	Indiana	1.500 a.D.	Bilateral renal stones
	West Virginia	1.600-1.700 a.D.	Renal stone

wild varieties of pears and the varieties cultivated by men. From Greece the pear spread to Rome, where it was highly regarded. Marcus Procius Cato (234-149 b.C.), known as Cato the Censor, in his famous agricultural manual *De Agri Cultura (De Re Rustica),* wrote extensively on pomological subjects and described six types of pear[3]. In the Roman Empire, the varieties of pears

Table II. Some historical persons or distinguished in any field figures documented to be kidney stone formers.

Emperors, kings, popes, presidents	Politicians, religious persons, statesmen	Artists, philosophers, physicians, scientists, writers	Performers (music, cinema)
Caesar Augustus (63 b.C.-14 a.D.)	Martin Luther (1483-1546)	Epicurus (341-270 b.C.)	Cole Porter (1891-1964)
James I Stuart (1566-1625)	John Calvin (1509-1564)	Michelangelo Buonarroti (1475-1564)	Alfred Hitchcock (1899-1980)
Innocent XI (1611-1689)	Oliver Cromwell (1599-1658)	Michele de Montaigne (1533-1592)	Bing Crosby (1903-1977)
Luois XIV (1638-1715)	Cardinal Jules Mazarin (1602-1661)	Francis Bacon (1561-1626)	Ava Gardner (1922-1990)
Peter the Great (1672-1725)	Samuel Pepys (1633-1703)	William Harvey (1578-1657)	Roger Moore (1927-)
Anna of Russia (1693-1740)	Benjamin Franklin (1706-1790)	Thomas Sydenham (1624-1689)	Burt Reynolds (1936-)
George IV (1762-1830)	Mother Teresa (1910-1997)	Robert Boyle (1627-1691)	Billy Joel (1949-)
Napoleon I (1769-1821)	Indira Ghandi (1917-1984)	Isaac Newton (1642-1727)	Tim Burton (1958-)
Leopold I of Belgium (1790-1865)		Gottfried von Leibnitz (1646-1716)	
Napoleon III (1808-1873)		Antonio Scarpa (1752-1832)	
Lyndon B. Johnson (1908-1973)		Jack London (1876-1916)	

known were about fourty. After the Middle Ages, pears were carried by Spanish missionaries to the New World. Pear strains with fruit of really good eating qualities were not developed until the 18th and 19th centuries in Europe and today more than 5000 varieties are known worldwide. From a geographical point of view, the major areas for the production of pears are three: (a) East, with China being the first world producer; (b) Europe and the Mediterranean basin, with Italy ranking second among the world countries that produce pears; (c) the American continent, with the USA third in the international ranking for the production of pears.

Renal stones: clinical and economic burden

Urinary tract stones formation represents common condition occurring in the great majority of cases in adults, and stone formers are also notorious recidivists so that economic impact of this disease is impressive[4]. In Western countries, calculated yearly incidence was 0.5% and prevalence in the mid-1990 was 5.2%[5]. Scales et al[6] analyzed the prevalence of stone disease in the United States, and identified factors associated with history of kidney stones. They reported a prevalence of 8.8% (10.6% in men, 7.1% in women), with obesity and diabetes strongly associated with history of kidney stones. In order to estimate the economic impact of the disease in the United States, Pearle et al[7] estimated the burden of urolithiasis evaluating the use of health care resources. Almost 2 million outpatient visits for a primary diagnosis of urolithiasis were recorded in the year 2000. Hospital outpatient visits for urinary tract stones increased by 40% between 1994 and 2000, and in the same period physician office visits increased by more than 40% as well. Regarding treatment, shock wave lithotripsy was the most commonly performed procedure, followed by ureteroscopy, and such treatments impact on economic burden. Totally, in 2000 the estimated annual expenditure for individuals with claims for a diagnosis of urolithiasis was almost $2.1 billion. Moreover, since the prevalence of nephrolithiasis was higher among working age adults, the average work loss for treated subjects had been estimated to be 19 hours per person, with additional costs of 3,494 US dollars per person[8]. Data from the United States Nationwide Emergency Department (ED) Sample of patients evaluated between 2006 and 2009, showed that, out of 120 million visits to the ED annually, an average of 1.2 million patients per year were diagnosed with urolithiasis[9]. Overall average rate of admission was higher than 19%. Nonmetropolitan hospitals had the lowest costs, but a consistent number of patients were transferred to other hospitals. In Italy prevalence of male stone formers increased from 6.8% in 1986 to 10.1% in 1998, and in female patients from 4.9% to 5.8%. Incidence was calculated to be 0.4% yearly (0.6% in men and 0.18% in women)[10].

Furthermore, urolithiasis it is very likely to recur. Italian data reported that 27% of stone formers experienced symptomatic stone recurrence after a mean period of 7.5 years, and 28% had recurrent stones at ultrasound examination being patients symptom-free. Recurrence was not influenced by sex, family history of stones and urinary risk factors[11]. More recent data from United States[12] indicate that up to 50% of patients develop recurrence after their initial event. Recently, it has been developed a nomogram in order to predict stone recurrence[13]. Younger age, male sex, white race, family history of stones, prior asymptomatic stone on imaging, prior suspected stone episode, gross hematuria, non-obstructing (asymptomatic) stone on imaging, symptomatic renal pelvic or lower-pole stone on imaging, no ureterovesicular junction stone on imaging, and uric acid stone composition were the risk factors entered in their model. The authors calculated that 10-year recurrence rates varied from 12% to 56% between the first and fifth quintiles of nomogram score.

Urinary tract stones are made of organic and inorganic crystals mixed with proteins, and urolithiasis is not a real diagnosis, but stone formation could be a complication of different underlying diseases. Incidence and prevalence of stones are increasing globally, across sex, race, and age, and it is likely that changes in dietary habits could be a key driving force[14]. In order to determine if kidney stone composition could predict the underlying medical diagnosis, Pak et al[15] studied a large cohort of subjects who underwent a complete ambulatory evaluation and who submitted one or more stones for analysis. The most common kidney stones were composed of calcium oxalate (74.8%), followed by mixed calcium oxalate-calcium apatite (34.8%), and calcium apatite alone (10.5%). The most common medical diagnoses were hypocitraturia (44.3%), absorptive hypercalciuria (36.7%), and hyperuricosuria (28.4%). Calcium apatite and mixed calcium ox-

alate-calcium apatite stones were associated with the diagnoses of renal tubular acidosis and primary hyperparathyroidism. Calcium oxalate stones were associated with chronic diarrheal syndromes, but not with renal tubular acidosis. Pure and mixed uric acid stones were strongly associated with a gouty diathesis, and vice versa. Moreover, there was a very strong association between infection stones and infection, and between cystine stones and cystinuria. Urinary tract lithiasis is rarely the results of hereditary disease such as cystinuria, primary hyperoxaluria, medullary sponge kidney, primary hyperparathyroidism or secondary to well defined disorders such as infections, anatomical defects of urinary tract. In the great majority of cases lithiasis could be classified as idiopathic and in this case dietary habits plays a major role[16]. Nowadays lithiasis of urinary tract is not considered a disease per se, but as a risk factor and a consequence of metabolic syndrome and cardiovascular disease[17]. New approaches to treatment and prevention depend on the identification of frequent modifiable risk factors for kidney stones. Obesity appears to be a major determinant of urinary oxalate excretion[18], and body size was independently associated with the development of incident kidney stones. Aiming to determine if weight, weight gain, BMI, and waist circumference were associated with lithiasis of urinary tract, Taylor et al[19] conducted a prospective study of 3 large cohorts: the Health Professionals Follow-up Study, the Nurses' Health Study I, and the Nurses' Health Study II. They found that obesity and weight gain increased the risk of kidney stone formation. Besides, also diabetes mellitus is a risk factors for development of kidney stones in both sexes[20]. Rule and coworkers evaluated 4,564 stone formers and 10,860 control subjects among residents in Olmsted County, MN, USA[21]. During a mean of 9 years of follow-up, stone formers had a 38% increased risk for myocardial infarction, and this risk remained high (31%) after adjustment for mellitus, chronic kidney disease, hypertension, diabetes, obesity, dyslipidemia, gout, alcohol dependence, and tobacco use and other comorbidities.

Renal stones formation

The milestone in the urinary stone formation is the precipitation of crystal occurring when the concentration of salts exceeds the solubility limit, a phenomenon called '*supersaturation'*. In addition, it is also possible that a deficit of protective substances, defined as crystallization inhibitors, may play a role. As always in medicine, equilibrium represents crucial node (Figure 1).

Pathophysiologic pathways described for kidney stone formation are the following: 1) stones attached to the surface of a renal papilla where interstitial apatite plaques develop (defined as Randall's plaque); 2) stones protruding from the openings of ducts of Bellini; 3) stones forming in free solution in the renal collection system[22]. The main lithogenic risk factors are widely recognized, and include low volume of urinary output, high calcium high oxalate, high uric acid, high phosphate, low citrate, low magnesium and urinary pH alteration. It is known that conditions causing chronic dehydration, such as living in areas with high ambient temperatures, high degree of physical activity and insufficient replacement of water losses, may increase the risk of urolithiasis[23]. Urine dilution is the most important preventive measure for stone recurrence. On the other hand, high fluid intake not only lowers urinary concentration of substances inducing stone formation, but dilutes urinary concentration of inhibitors as well. However an increase in fluid to at least 2500 ml daily is the first step strategy in order to prevent stone[24]. In order to maintain calcium in solution, urine contains inhibitors of crystallization. Inhibitors could be classified in macromolecules and smaller molecules. Osteopontin, prothrombin F1 fragments, inter-α-trypsin inhibitor molecule calgranulin, Tamm-Horsfall glycoprotein, albuminRNA and DNA fragments, and glycosaminoglycans are classified as macromolecular species, while citrate, pyrophosphate, magnesium, and zinc are small molecules[16]. Stone forming inhibitors act on kinetics by interfering with nucleation, growth and aggregation of crystals. Urinary stone formation inhibitors could be also defined as multivalent metallic cations such as magnesium, and small organic and inorganic anions such as citrate and pyrophosphate. However, in clinical practice the effect of inhibitors is evaluated by citrate dosage[5]. At this moment, cit-

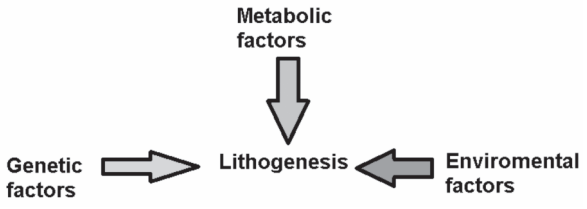

Figure I. Lithogenenesis as a syndrome.

rate is the only natural inhibitor which could be measured in urine, and used in medical treatment. It exhibits a double action, opposing urine crystal formation by both thermodynamic and kinetic mechanisms[25]. Therefore, correction of hypocitraturia represents a main therapeutical target, since citrate binds calcium ions increasing their solubility, and furthermore it binds the crystal surface and inhibits crystal growth and aggregation.

Citrate is an inhibitor of calcium oxalate crystal growth, and a reduction in its urinary excretion is considered a risk factor for urinary tract stone formation. Hypocitraturia has been reported to be the most common urine abnormality with a prevalence of about 60%[26,27]. Potassium citrate has been recognized for long time as a mainstay of medical therapy for nephrolithiasis[28], and in a couple of decades ago its ingestion was suggested as an useful adjunctive treatment for patients with hypocitraturic calcium nephrolithiasis[29]. Urinary excretion of citrate is linked to its plasma levels and renal tubular reabsorption, and citrate salt ingestion determines systemic alkalinization, decreasing renal reabsorption and increasing urinary excretion. On one hand, citrate is absorbed in the gastrointestinal tract and is transformed in the liver forming bicarbonate, on the other ingestion of citrate as citric acid cause consumption of bicarbonate due to the accompanying protons. Only if ingested in the form of a potassium or sodium salt, citrate is converted to alkali without bicarbonate titration, obtaining a systemic alkalinization. This difference is important in stone forming patients, in fact renal citrate excretion is regulated by proximal sodium-dicarboxylase cotransporter. The latter mechanism is activated in case of systemic acidosis. In acidosis states, in fact, citrate is reabsorbed by the cotransporter and incorporated into the Krebs cycle, so that citraturia decreases. On the contrary, alkalosis decreases citrate reabsorption increasing citraturia[30]. Increased excretion secondary to increased synthesis of citrate occurs when citric acid cycle precursors, i.e., malate or succinate, (Figure 2) are infused[31].

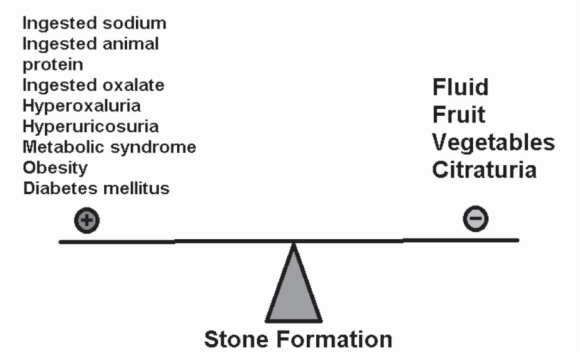

Figure 2. Lithogenesis: promoters *(left)* and inhibitors *(right)*.

Renal stones and metabolism alterations

Alteration of metabolism is frequently associated with renal stones. Obesity and type II diabetes mellitus appear to be risk factors for stone formation[32], and in the case of uric acid nephrolithiasis being diagnosed in overweight patients, diabetes mellitus type 2 (type 2DM) should always be suspected and investigated[33]. Patients with type 2DM defined as stone-forming had a high prevalence of uric acid stones, and shared a key feature of those with gouty diathesis probably due to the passage of unusually acid urine[34]. Urinary pH, in fact, is inversely related to body weight among patients with stones[35]. In subjects with metabolic syndrome, prevalence of uric acid nephrolithiasis is higher as well. Low urinary pH is the major determinant in the development of idiopathic uric acid stones and the two major abnormalities implicated in the development of overly acidic urine are: (i) increased net acid excretion, and (ii) impaired buffering caused by defective urinary ammonium excretion[36]. Patients with recurrent uric acid nephrolithiasis have been shown to have insulin resistance (IR)[37], and in subjects with IR also low urinary citrate excretion could be an increased risk mechanism responsible for calcium stone formation[38]. It has been suggested that patients with normouricosuric uric acid nephrolithiasis had altered renal acidification[39]. Thus, ammonium excretion was altered by insulin-resistant state, and alteration in acid urine pH and hypocitraturia result in uric acid nephrolithiasis.

Furthermore, Stoller et al[40] found that stones contain free and esterified cholesterol. Esterified cholesterol accounted for 14% to 16% of total cholesterol related to stone composition.

Renal stones and diet

Dietary and lifestyle habits can predispose to urinary tract stone formation, and diet may play an important role in the pathogenesis of kidney stones. In fact, the trends in the American diet modifications and stone prevalence between

1974 to 2010 showed that an increase of total calories, fat, protein, fruit and vegetables increased stone prevalence; only citrus fruits were negatively related to kidney stone disease[41].

Animal proteins

Dietary excesses in animal protein and salt are risk factors in calcium oxalate urolithiasis. High protein intake (2 g/kg daily) significantly changes urinary calcium, uric acid, and citrate excretion rates, and similar changes in calcium and citrate are induced by a high sodium intake (310 mmol/day). Moreover, the changes are more pronounced when a high protein is combined with a high sodium diet. These dietary regimens induce a significant decrease in the ability of urines to inhibit calcium oxalate monohydrate crystal agglomeration, which is most marked if diet is combined. The ability of urines to inhibit crystal agglomeration is related to their citrate content. High animal protein and sodium diet intake decreases the ability of urines to inhibit the agglomeration of calcium oxalate crystals providing a physicochemical explanation for the adverse effects of dietary aberrations on renal stone formation[42]. Animal protein-rich diet has been reported to be associated with the highest excretion of undissociated uric acid, reduction in urinary pH and citrate excretion because of the acid load due to high sulfur contents, whereas oxalate excretion was lower than during vegetarian diet. Noori et al[43] performed a randomized controlled trial in recurrent stone formers with hyperoxaluria (urine oxalate > 40 mg/d). A group of patients underwent 8 weeks diet following a calorie-controlled Dietary Approaches to Stop Hypertension (DASH) diet whereas in the second group a 8 weeks low-oxalate diet was prescribed. Authors evaluated change in urinary calcium oxalate supersaturation and changes in 24-hour urinary composition. Urinary oxalate excretion increased in the DASH versus the low-oxalate group, but there was a trend for calcium oxalate supersaturation to decrease in the DASH versus the low-oxalate group in association with an increase in magnesium, citrate excretion and urine pH in the DASH versus low-oxalate group.

Fruit and vegetables

The concept that a vegetarian diet reduces the risk of forming urinary stone has been known for long time, and it is known that vegetable proteins have been shown to have a lower lithogenic potential than animal proteins[44]. As far as in the early 80's, a UK study[45] reported that prevalence of urinary tract lithiasis was 40-60% of that predicted for a group of individuals taken from the general population and matched for age, sex and social class with the vegetarians. Taylor et al[46] evaluated the impact of diet on kidney stone formation examining prospectively patients enrolled in three studies i) Health Professional Follow-up Study (n=45,821 men; 18 years of follow-up), ii) Nurses' Health Study I (n=94,108 older women; 18 years of follow-up), and iii) Nurses' Health Study II (n=101,837 younger women; 14 years of follow-up). Authors focused on eight components: high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and low intake of sodium, sweetened beverages, and red and processed meats, calculating a DASH score. Participants with higher DASH score had higher intakes of calcium, potassium, magnesium, oxalate, and vitamin C, and lower intakes of sodium. A diet with high consumption in fruit and vegetables, moderate consumption in low-fat dairy products, and low in animal protein was associated with a marked decrease in the risk of incident kidney stone. Data from the Women's Health Initiative observational study[47] on about 84,000 postmenopausal women showed that those with no history of kidney stones had higher total dietary fiber, greater fruit intake and greater vegetable intake. In particular, even only a moderate use of fruits (2-3 portions/days) had higher impact on kidney stone preventions (HR=0.75 for intake of 2-3 portions/days respect to 0-1 portion/day). However, in women with history of stones there were no significant protective effects of fiber, fruit or vegetable intake on the risk of kidney stone recurrence. Again, also European data[48] gave further confirmation on the relationship between high intakes of fresh fruit, fiber cereals and magnesium and lower risk of kidney stone compared to patients with high intake of meat. Therefore, the fear of doctors in prescribing a diet rich in fruits and vegetables in stone formers, due to the fact that they are an important source of oxalate, is not understandable. An Italian group[49] studied the effect of diet on urinary stone risk profile in normal adults, and in idiopathic calcium stone formers characterized by hypocitraturia. In normal subjects, the elimination of fruits and vegetables from the diet decreased the urinary excretion of potassium, magnesium, citrate and oxalate, and increased calcium and ammonium. On the contrary, the relative saturation for calcium oxalate and calcium phos-

phate increased. In the hypocitraturic stone formers, the introduction of these foods in the diet increased urinary volume, pH, excretion of potassium, magnesium, and citrate, while it decreased the excretion of ammonium. The relative saturation for calcium oxalate and uric acid decreased. Organic anions are mainly contained in plant foods, in the form of potassium citrate, potassium malate while animal foods supply potassium anions as phosphate or lactate. Organic anions finally yield KHCO3 which is used by the kidneys to neutralize fixed acidity related to the dietary protein level. Failure to neutralize acidity leads to low-grade metabolic acidosis. Therefore, providing a sufficient supply of potassium organic anions through fruit and vegetable intake should be recommended[50]. Moreover dietary calcium influences the bioavailability of ingested oxalate[51]. Compared with diets consumed in the past, actual human diet contains large amount of salt and it is deficient in fruit and vegetables, being the latter rich in potassium and organic anions. This kind of diet could be defined as net-acid-producing one, causing a low-grade systemic metabolic acidosis[52]. Foods' acidity is related to the presence of organic anions such as malate, citrate or lactate. Their metabolism, after absorption in the digestive tract, produces CO_2 and energy[50].

Coffee, and alcoholic, and non-alcoholic beverages

Coffee, both caffeinated and decaffeinated, tea, beer and wine are reported to reduce risk of stone formation, whereas soft drink acidified with phosphoric acid are associated with recurrence of urinary stone formation[23].

Prevention against renal stones: why pears?

A systematic review of PubMed database literature up to July 2014 has been recently published by an Italian group[53], aimed to collect evidence from studies on dietary treatment of urinary stone formation. The main key-point was the mainstay concept of a forced increase in fluid intake. As for hypercalciuria: (i) non recommendation of dietary calcium restriction, (ii) moderate dietary salt restriction, (iii) low-normal protein intake; hyperoxaluria: (i) a diet low in oxalate and/or a calcium intake normal to high (800-1200 mg/day for adults) reduces the urinary excretion of oxalate, whereas a diet rich in oxalates and/or low calcium increase urinary oxalate, (ii) the addition of supplements of fruit and vegetables to a mixed diet does not involve an increased excretion of oxalate in the urine; hyperuricosuria: (i) restriction of dietary protein and purine is suggested although not clearly demonstrated; hypocitraturia: the administration of alkaline-citrates salts is recommended, although compliance to this treatment is limited by gastrointestinal side effects and costs, (ii) high intake of fruit and vegetables increases citrate excretion and involves a significant protection against the risk of stone formation. Again, it has been suggested that a diet rich in vegetables and fruit with high organic anion content, such as citrate and malate, is associated with higher urine pH and prevent formation of stones[54].

We made a search on PubMed library, both using the specific Medical Sub Headings (MeSH) terms and a free term search (Table III). Only 542 hits when using the MeSH term 'pyrus' (but drastically reduced to 42 when adding the term 'humans'), and 931 for 'pear + fruit', reduced to 143 when adding 'humans'. Very few articles were found dealing with 'diseases', whereas the topic of renal stone has not been investigated yet. Thus, we reviewed the available evidence.

Pears and organic acids

Pears are characterized by several advantageous features in their nutritional composition. Fructose is the major sugar, followed by glucose and sucrose[55-56], and potassium is the most abundant mineral, followed by magnesium and calcium[55]. Linoleic acid, palmatic acid, oleic acid, and α-linoleic acid (C18:3) were found to be the most abundant fatty acids, and among essential amino acids leucine, lysine and isoleucine were most prominent while among non-essential amino acids aspartic acid and glutamine were abundant[56].

Even if various amounts of citric, tartaric, and oxalic acids may also be found, the major organic acid in pears is malic acid. Table pears contain more of malic acid, while in some juicy pears, citric acid account for up to 45% of total acids[57]. The acidity level of pears varies from pH 2.6 to 5.4[58]. It has been recently shown that concentration of malic acid was greater than 1,000 mg/kg of fresh pear[556], and European pears have been shown to contain more malic acid than Asian ones (2.5 g/kg *vs.* 0.68 g/kg) and a similar contents of citric acid (0.71 g/kg *vs.* 0.75 g/kg). The malic/citric acid ratio in the Asian pear was on

Table III. PubMed search (update July 31, 2015).

A, Medical Sub Headings (MeSH) terms search.		
MesH	**Results**	**+ add 'humans'**
Pyrus	574	42
Pyrus + chemistry	13	0
Pyrus + biochemistry	10	0
Pyrus + nutritional sciences	0	
Pyrus + nutrition policy	0	
Pyrus + nutrition processes	4	3
Pyrus + disease	0	
Pyrus + cardiovascular diseases	3	3
Pyrus + kidney	0	
Pyrus + kidney calculi	0	
Pyrus + urolithiasis	0	
Pyrus + kidney diseases	0	
Pyrus + citrates	2	0
Pyrus + citric acid	0	
Pyrus + malic acid	1	0
Pyrus + urinary bladder calculi	0	
Pyrus + urinary calculi	0	
Pyrus + urinary bladder calculi	0	
Pyrus + urolithiasis	0	
B, Free search.		
Free terms	**Results**	**+ add 'humans'**
Pear + fruit	931	143
Pear + fruit + chemistry	370	60
Pear + fruit + biochemistry	19	2
Pear + fruit + nutrition	50	19
Pear + fruit + nutritional sciences	6	3
Pear + fruit + nutritional processes	14	11
Pear + fruit + disease	90	20
Pear + fruit + cardiovascular disease	9	8
Pear + fruit + kidney	0	
Pear + fruit + kidney calculi	0	
Pear + fruit + urolithiasis	0	
Pear + fruit + kidney disease	0	
Pear + fruit + citrates	7	2
Pear + fruit + citric acid	11	3
Pear + fruit + malic acid	8	1
Pear + fruit + urinary bladder calculi	0	
Pear + fruit + urinary calculi	0	
Pear + fruit + urolithiasis	0	
Pear + fruit + lithiasis	0	
Pear + fruit + renal stone	0	
Pear + fruit + kidney stone	0	

average lower than in European ones[59]. Malic acid is transformed in citrate and its supplementations induce systemic alkalinization and reduce renal tubular reabsorption of citrate and represent a conservative treatment of calcium renal stone disease[60].

Studies[61] on pears cultivars varieties present in Korea, Japan, and East of Russia showed high concentration of total organic acids, such as malic and citric acid, and the Italian *Pyrus communis* had less total organic acid, but a satisfactory malic and citric acid concentrations.

Pears and antioxidant activity

Chronic metabolic acidosis is often associated with common clinical conditions such as aging and excessive meat ingestion. Body's homeostatic response to these pathologic processes is very

efficient, the serum HCO3- and blood pH are frequently maintained within the "normal" range, on the other hand it causes hypercalciuria and hypocitraturia leading to nephrolithiasis[62]. High intake of fruits and vegetables is beneficial for chronic diseases such as cancer, diabetes, cardiovascular, and neurodegenerative impairments, and this effect is mainly due to the antioxidant capacity derived from the phenolic compounds present in edible plants[63]. Pears have been reported to have a good phenolic profile and antioxidant activity[64], contain high total phenolics and total flavonoids, and have also high anti-inflammatory activity[65]. It is important remember that high concentrations of these elements were present in the pear peel approximately 6-20 times higher than those in the flesh of pear[66]. Experimental animal studies[67] have documented that diets supplemented with fruit peels (pears and apples) exercised a significantly higher positive influence on plasma lipid levels and on plasma antioxidant capacity of rats fed cholesterol-content than diets with fruit pulps. Fruits should be consumed rapidly after purchase and with their peel. In fact, after one week of domestic storage, the ascorbic acid content was found to decrease by 75%, and peeling decreased total phenolics and ascorbic acid of more than 25%[68]. Finally, in animals, pears also exhibit moderate anti-microbial activities against bacteria strains, and anti-inflammatory action[69].

Conclusions

Low consumption of meat and meat products, moderate consumption of ethanol, mostly from wine, and high consumption of legumes, olive oil vegetables and fruits, are the components of the Mediterranean diet and the latter impacts positively cardiometabolic risk, and urinary tract stone formation. Consumption of such a diet favorably affects numerous cardiovascular disorders including dyslipidemia, hypertension, metabolic syndrome, and diabetes, and formation and recurrence of stone in the urinary tract. Although pears could be crucial in such a diet, due to their peculiarities, a very few studies are available in literature. To the best of our knowledge, this is the first comprehensive review on a possible relationship between renal stone disease and potential benefits not only by fruit in general, but specifically by pears. In fact, high content in malic (and also citric acid) warrant effective protection against stone formation at a low coast, and without exposing patients to the potential gastrointestinal side effects of alkaline-citrates salts, and significantly higher costs. It is known that renal colics, both in subjects with or without stones, show a highest risk period during early morning hours[70]. This is possibly due to different factors, such as a morning peak of glomerular filtration rate, urine supersaturation during night time, highest lithogenic risk for calcium oxalate during late night or early morning, altered rhythm of the inhibitory activity of calcium oxalate crystallization in stone formers, and so on[70]. Thus, on one hand, abundant fluid intake could be suggested in people free of congestive heart failure or risk of nocturnal falls– during late evening and before retiring to bed. On the other hand, every time could be the right time for consuming a pear. Surely, more than one peer a day is needed to take the renal stone away. However, in association with appropriate diet and hydration, daily consume of pears could be considered a sort of really healthy and inexpensive diet therapy, avoiding patients to be compelled to increase their amount of pills.

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Conflict of Interests

The Authors declare that they have no conflict of interests.

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