Original article

Relationships between enteral nutrition facts and urinary stones in a cohort of pediatric patients in rehabilitation from severe acquired brain injury

Marco Pozzi [a], Federica Locatelli [a], Sara Galbiati [a], Elena Beretta [a], Carla Carnovale [b], Emilio Clementi [a, c, *], Sandra Strazzer [a]

[a] Scientific Institute IRCCS Eugenio Medea, 23842 Bosisio Parini, Lecco, Italy
[b] Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università di Milano, 20157 Milan, Italy
[c] Unit of Clinical Pharmacology, CNR Institute of Neuroscience, Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università di Milano, 20157 Milan, Italy

ARTICLE INFO

SUMMARY

Background & aims: Urolithiasis affects pediatric patients with severe acquired brain injury, in whom the role of several clinical variables and of the presence and composition of enteral nutrition has not been investigated.

Methods: Retrospective chart review on 371 pediatric patients with severe acquired brain injury. We used an essential electronic database to check the association between stones and enteral feeding. We then picked at random paper clinical records until we collected 20 and 20 complete records for patients with/without stones, not matched. With that information, we tested the association of stones with: nutrition facts of enteral formulae (sodium, potassium, calcium, magnesium, phosphorus, proteins, vitamin C); bladder dysfunction, urinary infections, catheterisms, tracheostomy, gallstones, way of feeding; blood and urine exams before stones diagnosis; age, type and severity of injury; prior physical activity, relevant drugs.

Results: All patients with stones were fed enterally. At univariate statistics they were older, weighed more, received bigger volumes of hydration and nutrition; they had worse GCS, more UTIs and they alone received catheterisms; their nutrition mixes were richer in sodium.

In multivariate logistic regression for stone development, UTIs (OR 11.4, 95% C.I. 1.6–83.4) and higher sodium nutrition content (OR 7.5, 95% C.I. 1.6–34.3) were risk factors; higher GCS (OR 0.66, 95% C.I. 0.43–0.99) and higher calcium nutrition content (OR 0.14, 95% C.I. 0.03–0.73) were protective factors.

Conclusions: Besides known risk factors for urolithiasis, including UTIs, catheterisms, worse neurological states, also enteral nutrition was a risk factor, particularly with higher sodium and lower calcium contents. Future studies should test the effect of different sodium/calcium nutrition contents on lithogenesis.

1. Introduction

Urolithiasis is a known issue in adult patients with persistent disease or nutrition problems, or who are in rehabilitation from

injuries [1]. The issue may as well regard pediatric patients; among them children who suffered acquired brain injury (ABI) are at significant risk, being often immobile and requiring enteral nutrition and hydration [2,3] until rehabilitation is completed. The imposition of an enteral nutrition regimen may contribute to urolithiasis, because the fixed contents and volumes it entails prevent the body from adjusting feeding and hydration intake [4]. Stones may be of different nature depending on their ontogeny, for instance: excessive alkalization of the urine leads to the formation of calcium phosphate or calcium oxalate stones; excessive acidification contributes to the formation of cystine or uric acid stones; infection of

the urinary tract by urease-producing bacteria leads to the formation of struvite (triple-phosphate) stones. For each type of stone, appropriate therapies can be chosen [5]. Since the most frequent kidney and bladder stones are made of mineral salts [6] rather than uric acid, the electrolyte content of nutrition mixtures and its balance in the body may be a crucial determinant of urolithiasis. Another factor that is often associated with severe ABI and urolithiasis is the presence of urinary tract infections (UTIs). This does not only regard urease-splitting bacteria, such as Proteus spp., which produce struvite stones [7,8], thus allowing to determine a clear cause−effect relationship, but also calcium-phosphate/oxalate based stones. In the latter case, the precise causal association between UTIs and stones has not been yet elucidated [9], but it is clinically important to acknowledge that UTIs and stones may have a role for reciprocal sustainment, even leading to chronic pyelonephritis [10]. Considering patients who suffered brain injury, both UTIs and nephrolithiasis may be further promoted by a neurogenic bladder dysfunction [7,8], leading to the typical clinical situation of patients who simultaneously present with the three associated components: neurogenic bladder, UTIs, and stones, and may also add a fourth component, which is the need for catheterization.

Risk factors for stone formation like immobility, neurogenic bladder, UTIs, and catheterization are already known and addressed by specific treatments; by contrast, scant work exists on the role of enteral nutrition. Knowing whether specific qualitative or quantitative parameters of nutrition can affect stone formation may help defining the most appropriate nutritional therapy, allowing the correct choice among the many existing nutrition formulae, with different amounts of elements.

2. Methods

Data used for this work were collected retrospectively, from our Institutional electronic clinical database, and from paper clinical records. Following the Italian law, this retrospective collection of anonymized data did not require ethical approval. All procedures described in this work were carried out in accordance with the Declaration of Helsinki. Inclusion criteria for this study were: being admitted to our rehabilitation unit after severe ABI through the years 2007−2016; having had no prior occurrence of kidney stones; having no congenital conditions which may predispose to the development of kidney stones. We initially collected data from the clinical database of the Institute, recording only essential information. It contains admission and discharge dates, diagnoses with dates, and the list of interventions performed with dates. From this database, we collected data on the occurrence of kidney stones (of any size: gravel or stones) and on the requirement of enteral nutrition on the whole population of patients with severe ABI admitted to our rehabilitation unit during the study years. The aim was to verify whether the requirement of enteral nutrition was associated with the occurrence of kidney stones. We then considered a sample of patients who received enteral nutrition, to analyze their clinical characteristics and the nutrition facts of enteral formulae, with the hypothesis that they may have contributed to the formation of kidney stones. In order to perform this analysis, we had to retrieve additional information from the original clinical records, which are paper documents. Considering that data are of retrospective nature, not all patient records contain all information; therefore, we chose to examine clinical records at random from patients who received enteral nutrition and developed kidney stones and from patients receiving enteral nutrition who did not develop stones, until we collected 20 and 20 records with complete data. The expected lack of data was due to the fact that most exams specific for stones were not prescribed as a standard of care for all patients with enteral nutrition. In addition, several clinical data

were not always noted for asymptomatic patients, and the quality and amount of nutrition and hydration were recorded inconsistently through the years. For these reasons, cases and controls were not matched for any demographic or clinical characteristic, which were however controlled in statistical analyses. It must be considered that the present work is retrospective and is severely limited by the issues in data retrieval and case-control matching mentioned above.

From the 40 selected clinical records we collected the following clinical and demographic characteristics of patients: type of ABI (traumatic; non-traumatic), age at ABI, Glasgow Coma Scale score (GCS), physical activity prior to ABI (none; amateur; professional) and mobility status after ABI (if bedridden). At admittance to rehabilitation, we collected: weight; type of enteral feeding device (nasogastric tube; percutaneous endoscopic gastrostomy/jejunostomy), drug therapy. During rehabilitation, we collected data on the presence of: kidney stones, neurogenic bladder dysfunction, requirement for catheterization, urinary tract infections, tracheostomy, gallstones. We collected the results of blood exams (for patients with stones exams were collected prior to the finding), comprising values of Na^+, K^+, Ca^{2+}, Cl^-. We collected the amount of administered water; the type and amount of nutrition administered prior to the finding of stones, from which we obtained the content of sodium, potassium, calcium, magnesium, phosphorus, proteins, vitamin C; elements, except for proteins, were obtained as mg/ml of nutrition and transformed into millimoles per liter (mmol/L), to account for different molecular weights.

We first described differences in the distribution of continuous and discrete variables between patients who developed stones or not, by Mann−Whitney U-test and χ^2 test.

Hypothesizing that several clinical variables may be inter-correlated, such as age and weight, we checked all variables for inter-correlation by Pearson's correlation. In order to use inter-correlated variables in a multivariate statistical model, we had to perform a factor analysis. Factor analysis was conducted using eigenvalue 1 and varimax rotation method; the overall model requirement was Bartlett's test $p < 0.05$ and the required sampling adequacy was >0.7 for the whole model and for every retained variable. Firstly, an exploratory analysis was conducted, then a refined analysis was used to produce the common factors, if the sampling adequacy was met.

We then could apply a multivariate logistic regression model, to test which variables were associated with stone formation. We used a stepwise (p-in <0.05, p-out >0.10) logistic regression model, with the occurrence of kidney stones as a dependent variable. We report in the results the p-values of all variables entered in the first step, and of all the variables that remained in the model up to the last step. The model fit, adjusted R^2 and lack-of-fit at the last step are reported in the results; significant predictors from the last step of the model are reported in the results with their p-values and calculated odds ratios (OR) with 95% confidence intervals (95% C.I.) of increasing the chance of forming stones. For all tests, significance levels were set at p-values <0.05, two-tailed. Analyses were conducted by SPSS v.22 (IBM, Chicago, USA).

3. Results

From the clinical database of the Institute, we observed that 371 patients were admitted to our ABI rehabilitation unit between the years 2007−2016, with an average follow-up duration of 5.3 (S.D. 2.1) months. Of these patients, 191 were capable of oral feeding at admittance, while 180 were fed with enteral nutrition. The proportion of patients who displayed urolithiasis was 0/191 and 26/180 respectively (χ^2 $p < 0.001$), showing a complete association between the use of enteral nutrition and the formation of stones.

The absence of any patient, who developed stones without having enteral nutrition, prevented further statistical calculations. Patients were diagnosed with stones at an average of 25 (S.D. 17) days from admission. A qualitative analysis of stones revealed a predominant calcium phosphate/calcium oxalate composition, with only two cases (7.7%) of struvite stones.

In order to analyze the connection between the presence of stones and clinical-demographic variables we retrieved additional information from the original clinical records. We chose 20 clinical records at random from the 26 of patients receiving enteral nutrition who developed kidney stones and 20 clinical records at random from the 154 of patients receiving enteral nutrition who did not develop stones. As described in Table 1, all 40 patients were bedridden, with impaired consciousness. As compared to other patients, those who developed stones were of older age at ABI and weighed more at admittance to rehabilitation (still being in a normal range of body mass index), and they had more severe brain injuries. Consistent with their higher weight and age, patients with stones received greater daily amounts of hydration and nutrition.

We found a very strong association between the requirement for catheterization and stones. The absence of any patient, who received catheterization without having developed stones, prevented further statistical calculations. The presence of UTIs was also strongly connected with the presence of stones. No significant difference was found regarding other investigated variables, including the use of drugs (details in Supplemental Table), and no significant difference emerged with respect to blood electrolyte levels.

Acknowledging the possibility that homeostatic mechanisms may not allow finding altered electrolyte levels in the blood, we next analyzed possible differences in the electrolyte mixtures administered via nutrition formulae. Patients used many different brands and subtypes of nutrition, which did not allow a purposeful comparison. Therefore, we searched for the nutrition facts of all nutrition regimens and analyzed their distribution with respect to 7 elements: sodium, potassium, calcium, magnesium, phosphorus, vitamin C, proteins. The only element distributed differently in univariate analyses was sodium: patients with stones used nutrition mixes with a higher sodium content.

Before we could carry out multivariate analyses, we checked data for inter-correlations (results not shown), finding two groups of significantly correlated variables. The first group comprised patient age, weight, amount of nutrition per day, and amount of hydration per day. The second group comprised all the nutrition facts. We thus carried out factor analyses to assess the inter-correlations among these variables and make them usable in logistic regression.

The factor analysis of age, weight and amounts of nutrition and hydration administered per day was statistically reliable, with Bartlett's test $p < 0.001$, and the sampling adequacy of the overall model was acceptable (0.79). Individual sampling adequacy was 0.72 for age, 0.75 for weight, 0.92 for the daily amount of nutrition, and 0.87 for the daily amount of hydration, indicating that all variables were adequately represented. Therefore, these 4 variables were assembled in a common factor we named "patient size".

The factor analysis of nutrition facts was statistically reliable, with Bartlett's test $p < 0.001$, but the sampling adequacy of the

Table 1
Clinical and demographic characteristics of patients without and with kidney stones.

Continuous variables		No kidney stones		Kidney stones		p
		Mean	SD	Mean	SD	
Age at ABI	Years	6.9	5.1	10.7	4.9	0.035
Weight at admittance	Kg	23.4	13.7	36.1	17.2	0.018
GCS		10.1	2.2	8.2	2.1	0.004
Blood Na^+	mmol/L	139.4	3.7	138.5	3.2	0.478
Blood K^+	mmol/L	4.37	0.38	4.62	0.58	0.217
Blood Ca^{2+}	mmol/L	9.91	1.07	9.42	0.46	0.271
Blood Cl^-	mmol/L	101.4	4.4	100.3	3.1	0.121
Urine pH		7.0	0.4	7.5	1.0	0.116
Hydration	mL/day	626.5	243.7	893.4	290.1	0.008
Nutrition amount	mL/day	769.4	413.3	977.8	325.5	0.028
Nutrition facts						
Na	mmol/L	71.4	24.2	90.1	27.1	0.048
K	mmol/L	136.6	45.6	153.0	46.2	0.141
Ca	mmol/L	89.8	44.7	87.1	25.3	0.641
Mg	mmol/L	17.4	10.6	18.7	9.8	0.357
P	mmol/L	59.5	17.2	69.4	18.7	0.177
Vitamin C	mmol/L	12.8	4.2	13.1	3.7	0.577
Proteins	g/100 mL	3.3	1.3	4.3	1.6	0.069
Discrete variables		Count	%	Count	%	p
UTI	Yes	2	10	11	55	0.004
Neurogenic bladder	Yes	1	5	5	25	0.101
Catheterization	Yes	0	0	7	35	0.005
ABI etiology	Traumatic	5	25	9	45	0.185
	Non-traumatic	15	75	11	55	
Physical activity before ABI	None	16	80	14	70	0.334
	Amateur	4	20	4	20	
	Professional	0	0	2	10	
Mobility status after ABI	Bedridden	20	100	20	100	1
Feeding	NGT	10	50	7	35	0.350
	PEG-PEJ	10	50	13	65	
Tracheostomy	Yes	10	50	14	70	0.357
Gallstones	Yes	1	5	3	15	0.087

Descriptive statistics are provided for both continuous and discrete variables, with respect to the absence or presence of kidney stones. ABI = acquired brain injury; GCS = Glasgow Coma Scale score; n/a: not available; NGT: nasogastric tube; PEG-PEJ: percutaneous endoscopic gastrostomy/jejunostomy; UTIs: urinary tract infections. Statistics conducted were: χ^2 tests for discrete variables; Mann–Whitney U-tests for comparisons between groups with/without stones.

overall model was unacceptable (0.61). Individual sampling adequacy was unacceptable for sodium (0.56), potassium (0.58), calcium (0.52), and vitamin C (0.62) while it was acceptable for magnesium (0.80), phosphorus (0.90), and proteins (0.76). Therefore, nutrition facts were not assembled in a common factor.

We then carried out a multivariate logistic regression to check whether any variable was associated with the possibility of developing stones. We built a step-wise model with all variables; then, the steps automatically selected only variables that previously resulted significant. The final model ($p = 0.003$, $\Psi_{CS} = 0.39$, lack-of-fit $p = 0.63$) indicated as risk factors: the presence of UTIs, OR 11.4 (1.6–83.4), $p = 0.016$; and a higher nutrition content of sodium, OR 7.5 (1.6–34.3), $p = 0.009$; the model indicated as protective factors: a higher GCS score, OR 0.66 (0.43–0.99), $p = 0.050$; and a higher nutrition content of calcium, OR 0.14 (0.03–0.73), $p = 0.020$; "patient size" had no significant role ($p = 0.068$) in the final model. Results of the full model are available in Table 2.

4. Discussion

Only two studies have previously dealt with possible risk factors for urolithiasis in pediatric patients receiving enteral nutrition, and they adopted an opposite approach. The first one conducted a comparison of patients with urolithiasis, fed orally or by gastrostomy [11]. It found that patients with gastrostomy presented with more acidic urine pH, were more frequently immobile and had lower bone density. However, calciuria and UTIs were not differently frequent among patients and they regarded only a minority of the whole sample of patients with urolithiasis. A second study reported on patients with gastrostomy feeding, who did or did not develop stones [7]. Factors significantly associated with stone formation were the presence of UTIs, being fed by gastrostomy since a short period of time, and the use of topiramate. Of interest, there

Table 2
Results of the multivariate logistic regression model evaluating the risk of stones development.

Independent variables	First step	Last step	
	p-value	p-value	OR (95% C.I.)
Patient size*	0.014	0.068	–
GCS	0.017	0.050	0.66 (0.43–0.99)
Feeding	0.588		
Tracheostomy	0.362		
Gallstones	0.157		
Physical activity before ABI	0.122		
Neurogenic bladder	0.137		
UTIs	0.012	0.016	11.4 (1.6–83.4)
Blood Na$^+$	0.113		
Blood K$^+$	0.197		
Blood Ca^{2+}	0.132		
Blood Cl$^-$	0.112		
Urine pH	0.309		
Nutrition Na	0.015	0.009	7.5 (1.6–34.3)
Nutrition K	0.164		
Nutrition Ca	0.023	0.020	0.14 (0.03–0.73)
Nutrition Mg	0.385		
Nutrition P	0.254		
Nutrition Vitamin C	0.578		
Nutrition Proteins	0.768		

All factors used as independent variables in logistic regression are reported. In the left column "first step" is the whole list of factors. During the following steps, factors were entered ($p < 0.05$) and removed ($p > 0.10$) from the model. The right column "last step" reports the list of factors that were retained in the final model, with their p-values and, when significant, with their odds ratios (and 95% confidence intervals) of increasing the possibility of developing stones. * = The variable "Patient size" was produced by factor analysis. It accounts for: weight at admittance, age at ABI, hydration, and nutrition amount. These four variables could not be used individually, due to inter-correlation.

was no marked difference regarding the mobility capacity of patients.

Our study presents with a yet different approach, we first investigated the association between enteral feeding and stone formation, finding a strong relationship. We observed mostly calcium oxalate stones, as reported in other clinical contexts [7,11]. Then we dealt with patients who were all enterally fed and were with or without stones, in order to identify possible factors associated with urolithiasis, which we found superimposable to what was described previously. We observed a difference in age, and consequently also in weight, and in administered water and nutrition volumes, where patients with stones were older, in accordance with a previous descriptive study [12]. UTIs regarded almost half of our patients with stones, a result that only partially confirms previous observations, as UTIs were usually found with lower prevalence. The role of UTIs as risk factors for stone formation, previously reported in the literature [8–10], was confirmed also in our pediatric sample, by logistic regression. What our study adds in terms of clinical observations is that worse neurological statuses are associated with a higher probability of forming stones, reflected by the role of a better GCS score as protective factor. A possible explanation for this finding may be that the neurological severity after brain injury could be an indicator of future health issues, for instance as severity is connected with the ability to move and to feed independently, or to make conscious requests connected with nutrition or bodily discomfort, all issues potentially linked to nephrolithiasis. We could not investigate the effect of immobility itself on calcium redistribution and stone formation [13], since all patients were bedridden and only received a fixed amount of passive mobilization, both those with and without stones.

The need for catheterization could not be mathematically used as a factor in the logistic regression and thus has no associated OR, although it emerged as a risk factor completely connected with the development of stones. From a clinical perspective, catheterization may be considered as an intervention for urinary pathologies; however, catheterization may as well promote the development of UTIs. Therefore, given the retrospective nature of our data, it is not possible to clarify whether catheterization was among the causes of stones formation or just an associated factor.

Besides clinical aspects, we dealt extensively with the composition of nutritive mixtures, an aspect not investigated before. We focused on the principal electrolytes content and on protein and vitamin C levels, which are also suspected to have a role in lithogenesis [14,15]. The multivariate model we proposed found significant associations with stone formation for the concentration of sodium as a risk factor, and of calcium as a protective factor.

The reciprocal content of sodium and potassium can be a critical regulator of the excretion of all electrolytes, and a lower dietary sodium content has been linked with a lower excretion of calcium [16] and with a lower prevalence of stones in a generally representative population [17]. Therefore, the results of our logistic regression confirm the role of sodium as a promoter of lithogenesis, also in this particular population undergoing rehabilitation. Potassium-rich diets have been associated to a stone-reducing effect [18], such that a restriction of dietary sodium or an increase in dietary potassium is advised in order to prevent urolithiasis [19], rather than calcium restriction. The role of calcium, known promoter of stone formation when highly concentrated in the urine [20], is indeed of complex interpretation as regards nutrition. In the diet of immobile patients with brain injury, dietary calcium may be involved on one side with stones and, on another side, with heterotopic ossification [21,22]; thus, the general attitude is to keep calcium contents low. Calcium intake may however not be determinant even for stone formation, as in a cohort of immobile

pediatric patients, nutrition formulae poor in calcium were observed to associate with higher urine calcium contents, consistent with our observation. A suboptimal calcium intake may in fact trigger a calcium-mobilizing reaction (secondary hyperparathyroidism) and, paradoxically, increase urinary calcium levels [23], and the chance to develop calcium-based stones in connection with osteoporosis. It should be considered that most patients with severe ABI remain immobile for months and the lack of weight loading and mechanical stress may leave the calcium balance in bones unregulated. We could not investigate the effect of physical activity after ABI, as all patients were bedridden. However, among our patients, the two who engaged in professional physical activity prior to ABI were all found to develop stones. Stone development occurred very quickly in our patients, suggesting on the one hand a massive mobilization and turnover of calcium, favoring osteoporosis and calcium loss in the urine in an independent way [9,11]; on the other hand, it fits in well with a potential role for higher dietary sodium content in potentiating calcium loss. As patients in rehabilitation spend several months before regaining mobility and bone loading, it seems promising to investigate more deeply the role of calcium metabolism, whereas nutrition facts may determine the fate of mobilized calcium.

Other nutrition facts that did not obtain a significant association with stones formation need being discussed. Vitamin C can be expected to have positive effects on neurological recovery [24], despite its previous association with the promotion of stones [25]. Although all of our patients received high doses of as compared to average daily intakes, we observed no effects.

Magnesium is a well-known inhibitor of phosphate salts lithogenesis and dietary magnesium intake is inversely correlated with the risk of calcium-phosphate stone formation [26], which may also improve the effect of citrate in reducing stone formation [27,28], however we found no difference in our cohort.

The protein levels in nutrition mixes also seemed to have no role for stone formation in our study, although high protein diets have been linked with both calcium oxalate and uric acid stone formation [29].

In this population, also phosphorus did not result to be associated with stones, although it has been suggested as a possible risk factor [30].

One last remark regards the composition of nutrition mixes. Although several nutrition brands and subtypes are available, a great deal of variability among mixtures could be reduced to a set of elements, known to regulate the formation of stones: sodium, potassium, calcium, magnesium, phosphorus, vitamin C, and proteins. The interesting finding is that, regardless of the nutrition mix chosen, the relative abundances of elements are mostly intercorrelated, although not completely fixed (as shown by factor analysis). Consequently, changing the nutrition mixture used may affect the relative distribution of nutrition elements insufficiently, and specific supplements may thus be necessary to tilt the balance in favor of just one element, to meet specific health requirements.

5. Limitations

The most prominent limitation of this study is the retrospective nature of observations, which implies incompleteness of study data, limits the generalizability of findings and prevents the assessment of potential causality relationships. In particular, there may be an uncertain causal relationship between UTIs and stones in our patients, as records do not allow clarifying which of the two developed first, thus not solving the scientific dilemma of UTIs and non-struvite stones. In addition, as detailed in the methods section, we could not provide a paired case-control set of data. This study had mathematical limitations independent of the study design.

Specifically, we could not test in multivariate models the effect of enteral nutrition and of catheterization on the occurrence of stones, because no patients without stones had either enteral nutrition or catheterization. We also could not test in multivariate models the effect of immobility on the occurrence of stones, since all patients were immobile. This leads to the paradox that very important factors cannot appear in the final logistic regression model. We also did not test all possible macro- or micro-nutrients contained by nutrition mixtures, which may be involved with lithogenesis, such as carbohydrates. One important clinical limitation regards the absence of urinary data (i.e. 24-hour urinary lithogenic risk profile), which could have contributed to the interpretation of results. The present limitations should be considered, together with our novel clinical observations, as a promising starting ground to design future studies of higher quality.

6. Conclusion

Within a cohort of pediatric patients in rehabilitation from severe acquired brain injury, we observed that the use of enteral nutrition was strongly associated with the presence of urinary stones. Among users of enteral nutrition, those at higher risk of stones received catheterisms, had UTIs, had a lower GCS, and received more dietary sodium and less calcium. Future studies on lithogenesis in this specific patient population could benefit from the present findings, while an experimental design testing different nutrition mixes or different element supplements would be required, in order to allow causality statements on the role of single elements for lithogenesis.

Statement of authorship

MP, FL, SG, EC, SS conceived and designed the study; FL, SG, EB acquired and interpreted the data; MP interpreted the data; MP, FL, SG drafted the manuscript; MP, FL, SG, CC, EC, SS reviewed critically the manuscript and approved the final version.

Conflict of interest

All authors declare they have no conflict of interest

Funding sources

References

[1] Raheem OA, Khandwala YS, Sur RL, Ghani KR, Denstedt JD. Burden of urolithiasis: trends in prevalence, treatments, and costs. Eur Urol Focus 2017 Feb;3(1):18–26. https://doi.org/10.1016/j.euf.2017.04.001.

[2] Ost MC, Lee BR. Urolithiasis in patients with spinal cord injuries: risk factors, management, and outcomes. Curr Opin Urol 2006 Mar;16(2):93–9. https://doi.org/10.1097/01.mou.0000193376.07071.ac.

[3] Welk B, Fuller A, Razvi H, Denstedt J. Renal stone disease in spinal-cord-injured patients. J Endourol 2012 Aug;26(8):954–9. https://doi.org/10.1089/end.2012.0063.

[4] Quitadamo P, Thapar N, Staiano A, Borrelli O. Gastrointestinal and nutritional problems in neurologically impaired children. Eur J Paediatr Neurol 2016 Nov;20(6):810–5. https://doi.org/10.1016/j.ejpn.2016.05.019.

[5] Xu H, Zisman AL, Coe FL, Worcester EM. Kidney stones: an update on current pharmacological management and future directions. Expet Opin Pharmacother 2013 Mar;14(4):435–47. https://doi.org/10.1517/14656566.2013.775250.

[6] Spivacow FR, Del Valle EE, Lores E, Rey PG. Kidney stones: composition, frequency and relation to metabolic diagnosis. Medicina (B Aires) 2016;76(6): 343—8. PMID: 27959841.

[7] Johnson EK, Lightdale JR, Nelson CP. Risk factors for urolithiasis in gastrostomy tube fed children: a case-control study. Pediatrics 2013 Jul;132(1):e167—74. https://doi.org/10.1542/peds.2012-2836.

[8] Schwaderer AL, Wolfe AJ. The association between bacteria and urinary stones. Ann Transl Med 2017 Jan;5(2):32. https://doi.org/10.21037/atm.2016.11.73.

[9] Tavichakorntrakool R, Prasongwattana V, Sungkeeree S, Saisud P, Sribenjalux P, Pimratana C, et al. Extensive characterizations of bacteria isolated from catheterized urine and stone matrices in patients with nephrolithiasis. Nephrol Dial Transpl 2012 Nov;27(11):4125—30. https://doi.org/10.1093/ndt/gfs057.

[10] Borghi L, Nouvenne A, Meschi T. Nephrolithiasis and urinary tract infections: 'the chicken or the egg' dilemma? Nephrol Dial Transpl 2012 Nov;27(11): 3982—4. https://doi.org/10.1093/ndt/gfs395.

[11] Smith PJ, Basravi S, Schlomer BJ, Bush NC, Brown BJ, Gingrich A, et al. Comparative analysis of nephrolithiasis in otherwise healthy versus medically complex gastrostomy fed children. J Pediatr Urol 2011 Jun;7(3):244—7. https://doi.org/10.1016/j.jpurol.2011.02.018.

[12] Raj GV, Bennett RT, Preminger GM, King LR, Wiener JS. The incidence of nephrolithiasis in patients with spinal neural tube defects. J Urol 1999 Sep;162(3 Pt 2):1238—42. PMID: 10458475.

[13] Maïmoun L, Sultan C. Effect of physical activity on calcium homeostasis and calciotropic hormones: a review. Calcif Tissue Int 2009 Oct;85(4):277—86.

[14] Gottlieb S. High protein diet brings risk of kidney stones. BMJ 2002;325:408. https://doi.org/10.1136/bmj.325.7361.408/d.

[15] Assimos DG. Vitamin C supplementation and urinary oxalate excretion. Rev Urol 2004;6(3):167. Summer PMID: 16985597.

[16] He FJ, MacGregor GA. Potassium: more beneficial effects. Climacteric 2003 Oct;6(Suppl. 3):36—48. PMID: 15018247.

[17] Cirillo M, Laurenzi M, Panarelli W, Stamler J. Urinary sodium to potassium ratio and urinary stone disease. The Gubbio Population Study Research Group. Kidney Int 1994 Oct;46(4):1133—9. PMID: 7861708.

[18] Ferraro PM, Mandel EI, Curhan GC, Gambaro G, Taylor EN. Dietary protein and potassium, diet-dependent net acid load, and risk of incident kidney stones. Clin J Am Soc Nephrol 2016 Oct 7;11(10):1834—44. https://doi.org/10.2215/CJN.01520216.

[19] Prezioso D, Strazzullo P, Lotti T, Bianchi G, Borghi L, Caione P, et al. Dietary treatment of urinary risk factors for renal stone formation. A review of CLU working group. Arch Ital Urol Androl 2015 Jul 7;87(2):105—20. https://doi.org/10.4081/aiua.2015.2.105.

[20] Coe FL, Worcester EM, Evan AP. Idiopathic hypercalciuria and formation of calcium renal stones. Nat Rev Nephrol 2016 Sep;12(9):519—33. https://doi.org/10.1038/nrneph.2016.101.

[21] van Kuijk AA, Geurts AC, van Kuppevelt HJ. Neurogenic heterotopic ossification in spinal cord injury. Spinal Cord 2002 Jul;40(7):313—26. https://doi.org/10.1038/sj.sc.3101309.

[22] Kraft CT, Agarwal S, Ranganathan K, Wong VW, Loder S, Li J, et al. Trauma-induced heterotopic bone formation and the role of the immune system: a review. J Trauma Acute Care Surg 2016 Jan;80(1):156—65. https://doi.org/10.1097/TA.0000000000000883.

[23] Shetty AK, Carlin J, Mughal MZ. Urinary calcium excretion in enterally fed disabled children. Arch Dis Child 2001 Jul;85(1):58—9.

[24] Shen Q, Hiebert JB, Hartwell J, Thimmesch AR, Pierce JD. Systematic review of traumatic brain injury and the impact of antioxidant therapy on clinical outcomes. Worldviews Evid Based Nurs 2016 Oct;13(5):380—9. https://doi.org/10.1111/wvn.12167.

[25] Ferraro PM, Curhan GC, Gambaro G, Taylor EN. Total, dietary, and supplemental vitamin C intake and risk of incident kidney stones. Am J Kidney Dis 2016 Mar;67(3):400—7. https://doi.org/10.1053/j.ajkd.2015.09.005.

[26] Reungjui S, Prasongwatana V, Premgamone A, Tosukhowong P, Jirakulsomchok S, Sriboonlue P. Magnesium status of patients with renal stones and its effect on urinary citrate excretion. BJU Int 2002 Nov;90(7): 635—9. PMID: 12410738.

[27] Massey L. Magnesium therapy for nephrolithiasis. Magnes Res 2005 Jun;18(2):123—6. PMID: 16100850.

[28] Riley JM, Kim H, Averch TD, Kim HJ. Effect of magnesium on calcium and oxalate ion binding. J Endourol 2013 Dec;27(12):1487—92. https://doi.org/10.1089/end.2013.0173.

[29] Tracy CR, Best S, Bagrodia A, Poindexter JR, Adams-Huet B, Sakhaee K, et al. Animal protein and the risk of kidney stones: a comparative metabolic study of animal protein sources. J Urol 2014 Jul;192(1):137—41. https://doi.org/10.1016/j.juro.2014.01.093.

[30] Chang AR, Anderson C. Dietary phosphorus intake and the kidney. Annu Rev Nutr 2017;37:321—46. https://doi.org/10.1146/annurev-nutr-071816-064607.