Introduction

Diet plays a key role in the pathogenesis of kidney stones [1]. In particular, recent findings have advanced knowledge on the protective role of a high calcium diet in the pathophysiology of the formation of calcium oxalate stones (the most common variety). Nonetheless, not much is known about the specific role played by milk intake in the pathogenesis of kidney stones compared with other dairy products, especially cheese.

We performed a retroactive case-controlled study using a questionnaire (using standard household units of weight to make the form user-friendly) to reveal the frequency and customary mean daily intake of food intake, BMI (calculated on weight and height and split into maximum) for the quantitative variables in patients and controls. In addition to food intake, BMI (calculated on weight and height and split into ≤25 or >25 kg/m²), age (≤50 years or >50 years) and gender were taken into consideration. A backwards variable selection method was adopted where p<0.05 (Wald’s test) was minimum threshold.

The odds ratio and 95% confidence limits were calculated for the remaining variables present in the final model. All the analysis was performed using SAS V8.2 software for Windows.

Results

Frequency distributions and elementary statistics carried out to better assess the extent of the differences observed revealed that

Table 1

| Variable          | Patients | Controls |
|-------------------|----------|----------|
| Gender            | Male     | Female   |
| Age               | ≤50      | >50      |
| BMI               | ≤25      | >25      |
| Gender and age    |          |          |
| Gender and BMI    |          |          |
| Age and BMI       |          |          |
| Gender, age, BMI  |          |          |

Conclusions: The odds ratio and 95% confidence limits were calculated for the remaining variables present in the final model. All the analysis was performed using SAS V8.2 software for Windows.

References

1. Brardi S, Verdacchi T, Paoletti G, Giovannelli V, Duranti E (2016) Does Milk Intake Play a Specific Role in the Pathogenesis of Kidney Stones?.

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there were statistical differences in gender (69% in male patients compared with 30% in controls), cheese intake (intake > 100 g/day in 7% of patients and in 25% of controls), milk intake (intake less than 1 cup/day in patients and in 35% of controls), vegetables (more than once a day in 37% of patients and in 70% of controls) and mean age (patients = 54 years; controls = 48 years) (Tables 1,2). Some of these differences may also be ascribable to sample selection, in particular demographics (age and gender). Logistic regression analysis was performed at the end of backwards selection and revealed only two significant results that were retained in the final model, i.e. gender and milk intake, and confirmed that the latter is involved in the formation of kidney stones (Table 3). Nonetheless, in view of the previously mentioned selection bias, the study did not show that also male gender was a significant risk factor: hence, this variable was retained in the model mainly to correct such bias. Formation of kidney stones was 8.6 fold more probable in subjects drinking less than one cup of milk per day compared with those who drank more: uncertainty at 95% confidence limit ranged from a minimum of 2.3 fold to a maximum of 32.6 fold (Table 3). Milk intake was not related to gender and age (Table 3). Correlation between milk intake and other food items showed significant correlations between the former and cheese and vegetables (Table 3). Hence, cheese and vegetable intake was not included in the logistic regression model even if, when taken individually, these are significantly correlated with the formation of kidney stones. Besides, these correlations showed a direct association for both: 72% of the entire study cohort who eats little cheese drinks less than one cup of milk per day, and 75% of the study group that eats a lot of cheese drinks at least one cup of milk per day. Analogously, yet less evidently, 78% of the study population that does not eat many vegetables drinks less than one cup of milk per day compared with 52% of those who eat a lot of vegetables (Table 3).

**Discussion**

Logistic regression analysis performed after the backwards selection only revealed two significant variables that were both retained in the final model, i.e. gender and milk intake (Table 3). The differences between patients and controls in age, and above all gender, may reveal a selection bias and did not show whether also male gender represents a significant risk factor, even if the literature reports that male gender is generally considered a real risk factor of renal stones [2]. Reports in the literature show that the frequency of kidney stones declines markedly after the age of 60 years and there is no longer the known inverse relationship between calcium intake and formation of calculi in subjects over 60 [3]. Therefore, we attempted to reassess the data using the criterion ≤60 years or >60 years, but the age factor was still not significant.

Milk intake was the only dietary factor associated with the formation of kidney stones, yet due to the differences between patients and controls, this factor was not associated with gender or age (Table 3). Our study results agreed with other authors [4,5] and revealed a significant difference between cheese intake in patients and controls that seems to indicate that cheese intake negatively affects kidney stone formation. As milk has one of the lowest calcium content per one hundred grams compared with other dairy products, it is unlikely that this can be explained by a higher daily intake of milk. Diversely, the association between increased urinary uric acid

### Table 1: Elementary statistics of patients with kidney stones and control group and frequency of episodes of colics and kidney stones.

| Variables     | N  | Mean | Median | SD  | Min | Max  | p(t-test) |
|---------------|----|------|--------|-----|-----|------|-----------|
| **Controls**  |    |      |        |     |     |      |           |
| Age (year)    | 20 | 47.85| 50.50  | 8.24| 30.00| 65.00| 0.0324    |
| Weight (kg)   | 20 | 71.00| 71.50  | 9.43| 58.00| 86.00| 0.1846    |
| Height (cm)   | 20 | 167.65| 165.50| 8.07| 155.00| 180.00| 0.1613    |
| BMI (kg/m²)   | 20 | 25.55| 24.83  | 3.66| 20.81| 35.80| 0.8242    |
| **Patients**  |    |      |        |     |     |      |           |
| Age (year)    | 41 | 54.37| 54.00  | 11.96| 33.00| 79.00|           |
| Weight (kg)   | 37 | 76.11| 75.00  | 15.87| 51.00| 120.00|           |
| Height (cm)   | 40 | 171.43| 172.00| 10.42| 150.00| 190.00|           |
| BMI (kg/m²)   | 37 | 25.79| 24.93  | 3.96| 19.20| 38.74|           |

| Number of colics | Frequency | % | Cumulative frequency | Cumulative % |
|------------------|-----------|---|----------------------|--------------|
| None             | 19        | 45.24 | 19 | 45.24 |
| 1 or 2           | 9         | 21.43 | 28 | 66.67 |
| From 3 to 6      | 11        | 26.19 | 39 | 92.86 |
| More than 6      | 3         | 7.14 | 42 | 100.0 |

| Kidney stones   | Frequency | % | Cumulative frequency | Cumulative % |
|-----------------|-----------|---|----------------------|--------------|
| Uric acid       | 1         | 7.69 | 1 | 7.69 |
| Oxalate         | 10        | 76.92 | 11 | 84.61 |
| Mixed (uric acid and oxalate) | 2 | 15.39 | 13 (missing = 28) | 100.0 |
Table 2: Distribution of single variables in patients and controls.

| Variable                  | Control | Patient | Total |
|---------------------------|---------|---------|-------|
|                           | Frequency (%) | Total |
| GENDER (χ²: p = 0.0037)   |         |         |       |
| Female                    | 14 (70.00%) | 13 (30.95%) | 27    |
| Male                      | 6 (30.00%)  | 29 (69.05%) | 35    |
| Total                     | 20       | 42       | 62    |
| MEAT INTAKE (χ²: p = 0.4861) |       |         |       |
| Less than 200 g/day       | 18 (90.00%) | 35 (83.33%) | 53    |
| 200 g/day or more         | 2 (10.00%)  | 7 (16.67%)  | 9     |
| Total                     | 20       | 42       | 62    |
| SALT INTAKE (χ²: p = 0.8138) |       |         |       |
| 1 teaspoonful/day         | 12 (60.00%) | 24 (57.14%) | 36    |
| 2 teaspoonful/day         | 7 (35.00%)  | 17 (40.48%) | 24    |
| > 2 teaspoonful/day       | 1 (5.00%)   | 1 (2.38%)   | 2     |
| Total                     | 20       | 42       | 62    |
| CHEESE INTAKE (χ²: p = 0.0499) |       |         |       |
| < 100 g/day               | 15 (75.00%) | 39 (92.86%) | 54    |
| ≥ 100 g/day               | 5 (25.00%)  | 3 (7.14%)   | 8     |
| Total                     | 20       | 42       | 62    |
| MILK INTAKE (χ²: p = 0.0021) |       |         |       |
| <1 cup/day                | 7 (35.00%)  | 33 (80.49%) | 40    |
| 1 cup/day                 | 8 (40.00%)  | 5 (12.20%)  | 13    |
| > 1 cup/day               | 5 (25.00%)  | 3 (7.31%)   | 8     |
| Total                     | 20       | 41       | 61 (missing = 1) |
| PASTA INTAKE (χ²: p = 0.3440) |       |         |       |
| 80 g/day                  | 11 (55.00%) | 19 (45.24%) | 30    |
| 100 g/day                 | 6 (30.00%)  | 20 (47.62%) | 26    |
| > 100 g/day               | 3 (15.00%)  | 3 (7.14%)   | 6     |
| Total                     | 20       | 42       | 62    |
| SUGAR INTAKE (χ²: p = 0.2810) |       |         |       |
| ≤ 1 teaspoonful/day       | 10 (50.00%) | 12 (30.77%) | 22    |
| 2 teaspoonful/day         | 5 (25.00%)  | 17 (43.59%) | 22    |
| > 2 teaspoonful/day       | 5 (25.00%)  | 10 (25.64%) | 15    |
| Total                     | 20       | 39       | 59 (missing = 3) |
| VEGETABLE INTAKE (χ²: p = 0.0142) |       |         |       |
| ≤ 1 time/day              | 6 (30.00%)  | 26 (63.41%) | 32    |
| > 1 time/day              | 14 (70.00%) | 15 (36.59%) | 29    |
| Total                     | 20       | 41       | 61 (missing = 1) |
| FRUIT INTAKE (χ²: p = 0.4416) |       |         |       |
| ≤ 1 teaspoonful/day       | 2 (10.00%)  | 9 (21.43%)  | 11    |
| 2 teaspoonful/day         | 6 (30.00%)  | 14 (33.33%) | 20    |
| > 2 teaspoonful/day       | 12 (60.00%) | 19 (45.24%) | 31    |
| Total                     | 20       | 42       | 62    |
| WATER INTAKE (χ²: p = 0.4653) |       |         |       |
| ≤ 1 teaspoonful/day       | 4 (20.00%)  | 7 (17.07%)  | 11    |
| 2 teaspoonful/day         | 10 (50.00%) | 15 (36.59%) | 25    |
| > 2 teaspoonful/day       | 6 (30.00%)  | 19 (46.34%) | 25    |
| Total                     | 20       | 41       | 61 (missing = 1) |
excretion and the formation of kidney stones (uric acid, or uric acid and oxalate calcium stones) is well-known [6,7]. Experimental data available are limited. A study conducted on Australian Aborigine children implies that lactose intolerance is linked with kidney stone formation (mainly urate calculi) in determining chronic metabolic acidosis that, in turn, leads to protein catabolism, increased urate excretion and thus formation of calculi [8]. A noteworthy 12-year study by Choi and coworkers on the relationship between dietary risk factors and new cases of gout [9], investigated the above-mentioned relationship in a population of 47,150 men who did not present gout when recruited in the study. Multivariate analysis revealed major inverse correlation only between skimmed milk intake (low fat yoghurt and not other dairy products) and the frequency of gout.

It has been observed that milk protein intake, such as casein and lactalbumin that have uricosuric properties, reduce uricaemia levels [10], whereas a four-week randomised trial of subjects on a dairy product-free diet significantly increased uricaemia levels [11]. According to Choi and coworkers [9], dairy products have a low purine content, thus milk proteins could reduce uricaemic without supplying the purine load contained in other proteins, such

| Table 3: Correlations between milk intake and other dietary items and logistic regression analysis results. |
|---------------------------------|---------------------------------|-----------------|-----------------|
| **Milk vs. Cheese Intake (χ²: p = 0.0026)** | **< 100 g/day** | **≥ 100 g/day** | **Total** |
| <1 cup/day | 38 (71.70%) | 2 (25.00%) | 40 |
| 1 cup/day | 11 (20.75%) | 2 (25.00%) | 13 |
| > 1 cup/day | 4 (7.55%) | 4 (50.00%) | 8 |
| Total | 53 | 8 | 61 (missing = 1) |

| **Milk vs. Vegetable Intake (χ²: p = 0.0913)** | **< 100 g/day** | **≥ 100 g/day** | **Total** |
| <1 cup/day | 25 (78.13%) | 15 (51.72%) | 40 |
| 1 cup/day | 4 (12.50%) | 9 (31.03%) | 13 |
| > 1 cup/day | 3 (9.38%) | 5 (17.24%) | 8 |
| Total | 32 | 29 | 61 (missing = 1) |

| **Milk vs. Gender (χ²: p =0.3550)** | **Female** | **Male** | **Total** |
| <1 cup/day | 16 (59.25%) | 24 (70.59%) | 40 |
| ≥ 1 cup/day | 11 (40.74%) | 10 (29.41%) | 21 |
| Total | 27 | 34 | 61 (missing = 1) |

| **Milk vs. Age (χ²: p =0.3550)** | **≤ 60 year old** | **> 60 year old** | **Total** |
| <1 cup/day | 27 (60.00%) | 13 (86.67%) | 40 |
| ≥ 1 cup/day | 18 (40.00%) | 2 (13.33%) | 20 |
| Total | 45 | 15 | 60 (missing = 2) |

### Analysis of Maximum Likelihood Estimates

| **Variable** | **DF** | **Estimates** | **Standard Error** | **Wald χ²** | **P>χ²** |
|--------------|--------|---------------|--------------------|-------------|----------|
| Intercept | 1 | 0.5404 | 0.3303 | 2.6769 | 0.1018 |
| Milk (<1 cup/day) | 1 | 1.0752 | 0.3402 | 9.9878 | 0.0016 |
| Gender (male) | 1 | 0.8736 | 0.3406 | 6.5808 | 0.0103 |

### Odds Ratio Estimates

| **Point estimate** | **95% Wald Confidence Limits** |
|-------------------|-------------------------------|
| <1 cup/day vs. ≥1 cup/day | 8.598 | 2.263 | 32.594 |
| male vs. female | 5.739 | 1.510 | 21.806 |

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a) χ² statistics:  
DF = 1; Value = 3.6000; Probability = 0.0578  
b) Association of predicted probabilities and observed responses:  
Percent concordant: 72.3; Percent discordant: 10.5; Percent tied: 17.2; Pairs: 820  
Somer’s D: 0.618; Gamma: 0.747; Tau–a: 0.277; C: 0.809
as meat and fish, even if the negative risk of elevated protein intake in kidney stone formation is common knowledge [12]. Nevertheless, the additional nutritional characteristics of milk may produce inverse associations between milk intake and kidney stones. Acids generated by food are excreted in the urine; meat and fish have a high potential renal acid load, as well as many cereals and cheese derivatives. Milk and yoghurt, on the contrary, have a negative potential renal acid load. This fact means they supply alkaline ash [13]. It is common knowledge that citrururia is regulated by the acid–base balance, so intake of substances able to generate acids or alkali can influence such balance [14,15]. Absorption of acid or alkaline foods can therefore represent a critical factor in the regulation and elimination of citrururia, and hypocitrururia, that is crucial in the pathogenesis of kidney stones [14,15], can be caused by reduced intestinal total alkali absorption [14]. It is evident that the potential renal acid load of food influences urine acidity, i.e. its pH [16]. This is very important in the formation of urate kidney stones caused by reduced urine pH values that can increase indissociated uric acid concentrations and lead to the formation of uric acid calculi as well as mixed uric acid and oxalate calcium stones [6]. In our study significant differences were observed between cheese intake of patients and controls and vegetables intake (Table 2). As regards cheese, the previously mentioned protective role of the normally recommended amount of calcium in the diet must be underlined, even if our study does not fully support it. We believe that the higher vegetable intake observed in controls can be explained with the findings by Meschi and coworkers [17]. Surprisingly, we did not find significant differences between patients and controls for some dietary elements that are more closely connected with kidney stone formation, such as daily water intake and meat intake [18] (Table 2). Neither did we observe significant differences when we specifically attempted to see if meat intake was correlated with increased probability of stone formation in all the entire study cohort with BMI < 25 kg/m² as described in the literature [3], but this may have been due to our limited study series. We believe that water intake data are a result of the growing awareness that drinking a lot of water helps prevent kidney stones (Table 2). The non-detection of significant differences in salt and meat, as well as pasta and sugar (Table 2), are linked to cultural factors and the typical Mediterranean diet of our territory. Finally, there were no significant differences in body mass index between patients and controls, and on average the BMI was within normal limits (Table 1).

Conclusions

Further prospective studies are required on the specific relationship between milk intake and kidney stones. Besides, unlike Taylor et al. [19], we didn’t allow non-dairy calcium sources such as calcium supplements or vitamin D neither we took into account the specific type of fruit or vegetables consumed [20]. Nevertheless, we believe that increased milk intake can be recommended in patients where kidney stones are directly or indirectly linked to oversaturation of urine with uric acid, as it not only supplies a higher amount of dietary calcium, but also possesses a peculiar uricosuric action as well as reduced potential renal acid load.

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