

# Whey protein and albumin effects upon urinary risk factors for stone formation

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**Abstract** Protein supplements are consumed for an expected increase in muscle mass and improved exercise performance, but as their impact on lithogenic parameters are unknown, we aimed to evaluate the effects of Whey protein (WP) and Albumin upon the risk factors for nephrolithiasis. WP or Albumin supplements (one scoop/day) were administered for 3 days to 18 healthy volunteers, with 1-week washout period between them. Serum and 24-h urine samples were collected at baseline and after completing each intervention. All participants were asked to replicate their baseline diet during the subsequent urine collection. After WP or albumin, mean protein equivalent of nitrogen appearance (PNA) was significantly higher ( $p < 0.001$ ), as the result of the consumption of each of the supplements, but mean urinary calcium, phosphorus, sodium, potassium, uric acid, citrate, oxalate, magnesium, creatinine, pH, and urinary saturation indices did not differ from baseline. However, individual increases higher than 50% in urinary calcium were observed in 39% of the individuals and variable decreases in urinary pH in 44 and 67% of them, respectively, after WP or Albumin. Increases higher than 50% in urinary sodium occurred in one-third of them after Albumin. A short-term consumption of WP or albumin by healthy subjects, under controlled diet, did not significantly change the mean lithogenic parameters.

Nevertheless, the wide individual variation and relevant increases/decreases observed for urinary calcium, sodium, and pH suggest the need of a closer surveillance of these parameters and adequacy of diet in case of supplementation by stone formers.

**Keywords** Albumin · Hypercalciuria · Kidney stones · Nephrolithiasis · Whey protein

## Introduction

The consumption of high amounts of animal protein contributes to changes in urinary composition, which may lead to hypercalciuria, hyperuricosuria, hypocitraturia, and hyperoxaluria [1–4]. Reductions of urinary citrate and pH and increases in urinary sulfate, ammonium, and calcium induced by a high-protein diet were observed in rats [5]. A short-term dietary protein restriction significantly reduced urinary calcium, phosphate, hydroxyproline, uric acid, and oxalate and increased citrate in nephrolithiasis patients [6]. In a prospective study by Borghi et al. [7], a low-animal-protein and salt with normal calcium diet reduced the risk of stone recurrence by means of decreasing urea, sulfate, oxalate, and calcium excretion. On the other hand, two small randomized trials have not shown an impact on stone recurrence following a low-protein diet although the authors recognized imperfect adherence [8, 9]. Lately, Ferraro et al. [10] examined intakes of dairy, nondairy animal, and vegetable protein and risk of incident kidney stones and concluded that it may vary by protein type.

Consumption of whey protein (WP) or albumin supplements has been a common practice especially among healthy individuals with moderate or even mild physical activity. WP corresponds to 20% of the protein amount in

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milk and is generated during cheese manufacturing, while albumin is a protein derived from the egg white. Both are considered as high-quality proteins, which contain all essential amino acids, that may favor the increase of muscle mass and improve performance [11, 12], although still subject to debate [13, 14]. Studies focusing on the potential effects of protein supplements, available over the counter, upon the risk of kidney stones are scarce. Experimental data have suggested that WP induces a decrease in urinary citrate and pH, and an increase in urinary calcium [15]. A clinical study found higher plasma urea after albumin consumption but urinary parameters were not evaluated [12]. Only one study determined urinary oxalate after WP and found it to be unaltered [16].

This study sought to evaluate the effect of WP and albumin consumption on the risk factors for nephrolithiasis in healthy subjects.

## Methods

### Subjects and study design

Twenty-eight (28) healthy volunteers, aged 20–45 years old, without any clinical evidence of heart, liver, endocrine or kidney disease or abnormal renal function, history of nephrolithiasis, or report of use vitamins/supplements were recruited since November 2012 through April 2014 for the present randomized crossover study. The protocol was composed of three phases: Baseline (control), followed by Albumin and Whey Protein supplementation, comprising 3 days each. During the Baseline period, the individuals were instructed to consume their regular unrestricted diets and asked to complete a 3-day food diary. In order to minimize diet variability among periods and potential effects upon urinary parameters, all subjects were asked to replicate their diet during the two subsequent supplementation periods, separated from each other by a 1-week wash out interval. The amount of protein provided by each of the supplements was 27 g, in the form of whey protein (isolate whey protein—red fruits flavor, ISOFORT®), with sodium (48 mg), calcium (139 mg), and 108 kcal/scoop contents; or albumin (pure albumin vanilla flavor, Schraiber®), with sodium (435 mg), calcium (22 mg), and 136 kcal/scoop contents.

All participants were subjected to an anthropometric evaluation, including weight and height measurement to calculate body mass index (BMI) in all phases and assessment of body composition through bioelectrical impedance at baseline and at the end of study.

Diet compliance during supplementation was assessed by the nutritionist through the dietary recall and nutrient intake calculated with a computer program developed in

our Department, with food tables from the US Department of Agriculture. Oxalate intake was calculated based on data from <http://regepi.bwh.harvard.edu/health/Oxalate/files>. Protein intake was also estimated by the protein equivalent of nitrogen appearance (PNA) formula [17].

### Laboratory testing and analytical procedures

All subjects underwent blood drawing and collection of 24-h urine samples obtained on the last day of the baseline and supplementations periods. Serum creatinine, albumin, and urea were determined in the blood specimens; creatinine, urea, sodium, potassium, calcium, phosphorus, magnesium, uric acid, citrate, oxalate, and pH were determined in the urinary samples.

Creatinine was determined according to the modified Jaffe's reaction by an isotope dilution mass spectrometry traceable method; albumin, phosphorus, calcium, and magnesium by a colorimetric method; urea, uric acid, citrate, and oxalate by an enzymatic method and sodium/potassium by ion-selective electrode. All biochemical parameters were measured in a Beckman Clinical Chemistry Analyzer (AU480-America Inc., Pennsylvania, USA) and urine pH by pHmeter (Micronal São Paulo, Brazil). The ion-activity product with respect to calcium oxalate supersaturation (AP(CaOx) index), calcium phosphate supersaturation (AP(CaP) index), sodium urate supersaturation, AP sodium urate, uric acid supersaturation, and AP uric acid were calculated [18, 19]. The ion-activity products for CaOx (APCaOx) corresponding to the solubility (SP) and formation products (FP) are  $0.23 \times 10^{-8}$  and  $2.0 \times 10^{-8}$  (mol/L)<sup>2</sup>, respectively. AP(CaOx) index was accordingly formulated with the aim of approximately reflect 108. APCaOx. This means that the SP and FP levels expressed in terms of AP(CaOx) index are  $\sim 0.23$  and  $\sim 2.0$ . For uric acid and sodium urate, SP and FP values given in the literature are approximately  $2 \times 10^{-9}$  and  $5 \times 10^{-9}$  (mol/L)<sup>2</sup>; for sodium urate  $4.8 \times 10^{-5}$  and  $7.2 \times 10^{-4}$  (mol/L)<sup>2</sup>, respectively. There is no real value corresponding to AP(CaP) index, because this is a simplified expression of the risk of forming urine supersaturated with any CaP-crystal phase. For OCP, that approximately can be derived from AP(CaP) index, and the corresponding levels for SPOCP and FPOCP are  $8.3 \times 10^{-48}$  and  $2.5 \times 10^{-45}$  (mol/L)<sup>8</sup>, respectively.

### Statistical analysis

Results were expressed as median and interquartile range and non-parametric test was employed (Wilcoxon's rank sum test). A *p* value less than 0.05 was regarded as statistically significant. It was estimated that this sample size would provide >80% power to detect changes in primary endpoints. The software G. Power 3.1.4 was used for the

sample calculation. Statistical data were analyzed with IBM SPSS Statistics 19 and Statistica (StatSoft, Tulsa, OK, USA).

## Results

Of the 28 participants, 9 were lost to follow-up after baseline and 1 after the first intervention, so that 18 subjects, who were mostly health care professionals recruited from our hospital staff, aged 21–38 years old (14 female/4 male,  $23.5 \pm 5.3$  years old, 16 Caucasian/2 Asian), completed the study protocol. The Baecke questionnaire, validated in the Brazilian population, was used to calculate the level of physical activity, as previously reported [20]. Intense physical activity was reported by 3 individuals, mild/moderate physical activity by 12 and 3 was sedentaries. As shown in Table 1, the median consumption of all nutrients except for oxalate, which was slightly lower after albumin, was similar among all periods. PNA was significantly higher reflecting the effect of each supplementation period compared to baseline. There has been no statistical difference between body weight, BMI, or serum albumin among all periods (Table 2). Creatinine was slightly lower ( $p < 0.01$ )

for both albumin and WP vs baseline. Urea was slightly higher, almost reaching statistical significance, after albumin ( $p = 0.053$ ) and WP ( $p = 0.058$ ) compared to baseline. Percent lean mass, which detected by electric bio-impedance at the end of the study, did not differ from baseline, 70 (66–78) vs 72 (65–78)% (data not shown in tables).

As shown in Table 3, there has been no significant change in the median value of any urinary parameter after each of the supplements compared to baseline, except for urea ( $p < 0.001$ ). There was a slight nonsignificant increase in AP uric acid after each intervention period compared to baseline. The remaining urinary supersaturation parameters were not statistically different except for a slightly lower AP(CaP) index ( $p = 0.049$ ) after albumin administration.

Individual values of all urinary parameters are presented in Fig. 1 where upper/lower limits for stone risk at the various parameters are displayed. The number of subjects who crossed each of the classic arbitrary limits was not very high given they were not stone formers but healthy volunteers, exhibiting normal or slightly altered baseline values. However, a percentage of increment or decrement (calculated taking into account each baseline value) revealed that 7/18 volunteers presented an increase in urinary calcium higher than 50% after either

**Table 1** Nutrient intake at baseline, after albumin, and whey protein supplementation

Nutrients	Baseline	Albumin	Whey protein
Energy (kcal/kg/day)	31 (26–37)	32 (22–33)	33 (26–36)
Protein (g/kg/day)	1.34 (0.97–1.58)	1.21 (0.87–1.58)	1.31 (0.87–1.68)
Protein + supplement (g/kg/day)	1.34 (0.97–1.58)	1.62 (1.29–2.01) <sup>c</sup>	1.72 (1.25–2.14) <sup>c</sup>
PNA (g/kg/day)	1.06 (0.90–1.20)	1.23 (1.04–1.37) <sup>b</sup>	1.25 (1.17–1.37) <sup>c</sup>
Calcium (mg/day)	751 (481–1017)	745 (469–937)	747 (520–937)
Oxalate (mg/day)	59 (40–71)	55 (40–68) <sup>a</sup>	54 (40–68)
Phosphorus (mg/day)	1072 (808–1244)	975 (840–1186)	1149 (840–1244)
NaCl (g/day)	8.82 (6.47–12.94)	10.53 (8.53–14.76)	8.38 (5.88–11.41)
Potassium (mEq/day)	48 (43–59)	49 (43–59)	54 (43–64)
Magnesium(mg/day)	192 (159–200)	186 (146–205)	200 (160–228)

Data expressed as median (interquartile range)

PNA protein equivalent of nitrogen appearance

<sup>a</sup> $p < 0.05$ ; <sup>b</sup> $p < 0.01$ ; <sup>c</sup> $p < 0.001$  vs baseline

**Table 2** Anthropometric and serum biochemistry parameters

Anthropometric parameters	Baseline	Albumin	Whey protein
Weight (kg)	66.6 (54.0–73.6)	66.6 (54.0–72.6)	67.4 (53.8–72.8)
BMI (kg/m <sup>2</sup> )	23.4 (20.7–29.2)	23.6 (20.8–29.6)	23.7 (20.9–29.5)
Serum biochemistry parameters			
Creatinine (mg/dL)	0.74 (0.65–0.93)	0.67 (0.63–0.88) <sup>a</sup>	0.68 (0.62–0.83) <sup>a</sup>
Urea (mg/dL)	26 (23–32)	30 (26–37)	29 (27–34)
Albumin (mg/dL)	4.45 (4.20–4.60)	4.50 (4.30–4.70)	4.40 (4.10–4.60)

Data expressed as median (interquartile range)

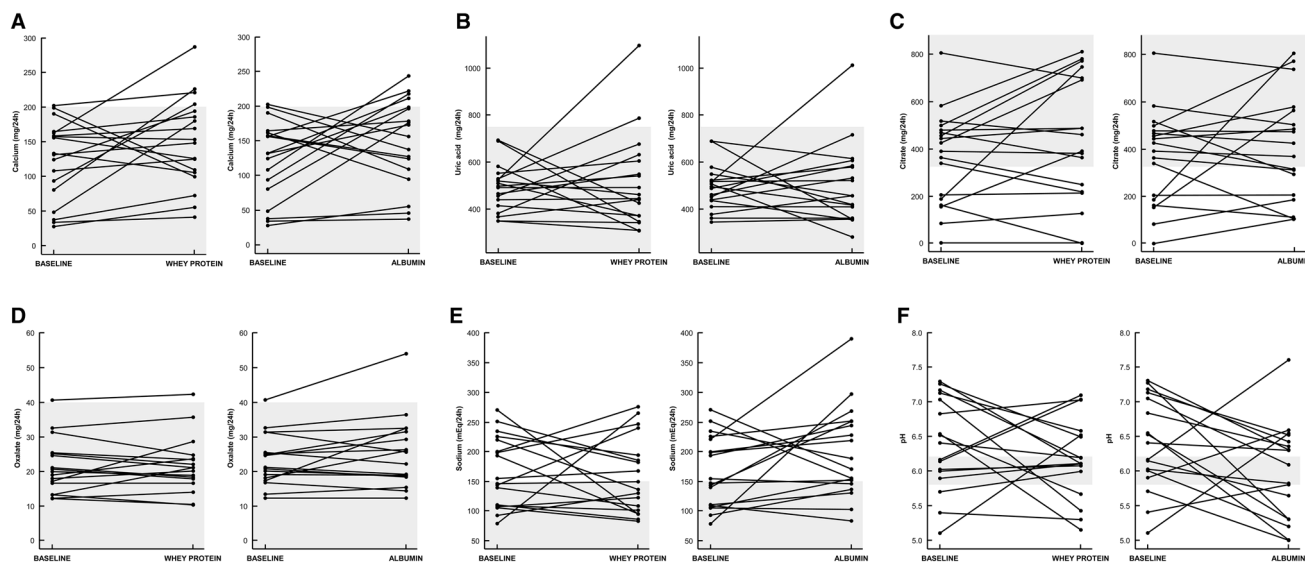
<sup>a</sup> $p < 0.01$  vs baseline

**Table 3** Urinary parameters

Urinary parameters	Baseline	Albumin	Whey protein
Volume (mL/24 h)	1580 (1060–2120)	1750 (1400–2180)	1850 (1280–2020)
Urea (g/24 h)	18 (16–20)	22 (21–26) <sup>b</sup>	23 (21–26) <sup>c</sup>
Calcium (mg/24 h)	132 (80–162)	165 (109–198)	151 (105–194)
Phosphorus (mg/24 h)	545 (480–658)	585 (443–757)	597 (410–768)
Sodium (mEq/24 h)	150 (110–220)	179 (145–251)	143 (100–194)
Potassium (mEq/24 h)	42 (35–53)	44 (36–56)	47 (35–62)
Uric acid (mg/24 h)	493 (437–526)	458 (364–585)	451 (370–603)
Citrate (mg/24 h)	407 (185–477)	396 (205–562)	424 (218–700)
Oxalate (mg/24 h)	21 (17–25)	26 (19–31)	21 (18–25)
Magnesium (mg/24 h)	60 (44–78)	80 (56–90)	66 (63–82)
pH	6.46 (6.00–7.13)	6.20 (5.30–6.52)	6.10 (5.90–6.52)
Creatinine (mg/24 h)	1150 (1033–1295)	1161 (994–1517)	1165 (1005–1504)
AP-levels			
AP (CaOx)	0.60 (0.08–1.46)	0.58 (0.16–2.05)	0.56 (0.22–0.94)
AP (CaP)	3.16 (0.002–68.8)	0.93 (0.0001–221.7) <sup>a</sup>	1.30 (0.0007–42.9)
AP uric acid	3.62 <sup>-10</sup> (0.27 <sup>-10</sup> to 47.9 <sup>-10</sup> )	4.94 <sup>-10</sup> (0.16 <sup>-10</sup> to 78.8 <sup>-10</sup> )	6.64 <sup>-0</sup> (0.67 <sup>-10</sup> to 35.1 <sup>-10</sup> )
AP sodium urate	0.72 <sup>-4</sup> (0.27 <sup>-4</sup> to 4.90 <sup>-4</sup> )	0.89 <sup>-4</sup> (0.11 <sup>-4</sup> to 2.81 <sup>-4</sup> )	0.64 <sup>-4</sup> (0.11 <sup>-4</sup> to 2.17 <sup>-4</sup> )

Data expressed as median (interquartile range); supersaturation in terms of ion-activity products (AP) for calcium oxalate (CaOX), calcium phosphate (CaP), uric acid, and sodium urate

<sup>a</sup> $p=0.049$ ; <sup>b</sup> $p=0.002$ ; <sup>c</sup> $p<0.001$  vs baseline



**Fig. 1** Each point corresponds to individual values of urinary calcium (a), uric acid (b), citrate (c), oxalate (d), sodium (e), and pH (f) at baseline and after whey protein or albumin supplementation.

Parameters outside of the gray zone represent values with increased risk for kidney stone formation

WP or albumin. Uric acid excretion increased more than 50% in 4/18 subjects after WP and in only 2/18 after albumin. Urinary oxalate increased and urinary citrate decreased by more than 50% in 2/18 and 1/18 individuals, respectively, after both supplements. Sodium excretion increased more than 50% in only 2/18 subjects after

WP and in 6/18 after albumin. Finally, there has been a wide variation in urinary pH values, decreasing in 8/18 (44%) subjects with WP and in 12/18 (67%) after albumin.

## Discussion

The consumption of protein supplements such as WP and albumin, among others, has risen among athletes due to the potential effects of these substances upon increase of muscle mass [11, 12]. The acid load resultant from a higher protein intake may increase or not urinary calcium [2, 21], among other effects. As recently shown [10], non-dairy animal protein was associated with a slightly but significantly higher risk of kidney stones among men but not women while dairy animal protein was protective among younger women. In addition, while increases in urinary calcium were only associated with dairy protein consumption, changes in opposite directions in urinary citrate were observed in association with dairy and nondairy animal protein [10]. To the best of our knowledge, no clinical study has examined the effects of WP or albumin supplementation on nephrolithiasis risk.

In the present study, we observed that the consumption of one scoop of either WP or albumin (27 g of protein) for 3 days did not produce changes in the median values of urinary calcium, phosphorus, sodium, potassium, uric acid, citrate, oxalate, magnesium, creatinine, and pH nor induced an elevation in the median values of urinary crystallization indexes in healthy subjects. Nevertheless, individual relevant changes in urinary profiles have been disclosed.

The compliance to the replication of diet has been ascertained by the observed significant increase solely in protein intake assessed by PNA and urinary urea, induced by the consumption of each of the supplements, given that the other nutrient intakes were not statistically different between interventions and baseline period. Although we cannot exclude a certain degree of dietary variability underlying the individual changes of urinary parameters, the collection of dietary logs after both periods of supplementation must have minimized such effects. Statistical difference concerning lower median oxalate intake after albumin supplementation was clinically irrelevant for an oxalate intake already shown to be low at baseline.

In the current series, the rise of protein intake to up to 1.72 g/kg/day considering the amount provided by each of the supplements (27 g) did not increase mean urinary calcium, contrasting with some studies [2, 22], but corroborating with others [23, 24]. Controversial data from all these intervention studies may be ascribed to the populations studied, the starting protein and calcium intakes of the subjects, the overall acid/base balance of the diet, and the amount, duration, and type of protein used. Reddy et al. [2] observed increases in mean urinary calcium under a low-carbohydrate high-protein diet that provided more than 2 g/kg of protein per day, whereas Tracy et al. [23] compared the effect of 3 animal protein sources (fish, beef, or chicken) on urinary stone risk and found no statistical

differences for urinary calcium among them. The lack of an increase in median urinary calcium following WP or albumin in the present series might have also been a consequence of the milder level of protein overload. However, individual values of urinary calcium were highly variable, showing increases by more than 50% in 39% of the subjects. On the other hand, Nguyen et al [4] have observed that increases up to 2.26 g/kg/day and did augment urinary calcium in stone formers but not in controls, suggesting that the former seem to be more sensitive to the calciuric action of protein. Additionally, significant correlations between urea and calcium outputs have been previously detected only among stone formers with hypercalciuria [25], indicating that the effects of consuming protein supplements in these patients, may increase the risk of forming stones.

In the current series, median urinary excretion of uric acid, phosphorus, and oxalate were not significantly different after WP or albumin. Individual increases of 50% in uric acid and oxalate were disclosed in only 10 or 20% of the subjects following supplementation. These data differ from some reports [1, 26] who observed higher uric acid excretion but agree with Reddy et al. [2], who did not observe a significantly higher uricosuria in healthy subjects even after a much higher protein overload.

The effect of dietary protein on urinary oxalate is controversial, with some studies showing an increase [1, 4, 6] and others not [27]. Knight et al. [16], employing an equivalent amount of WP (30 g) compared to our study, also did not demonstrate statistical differences in oxaluria [16]. In another study in healthy subjects, mean oxalate excretion following a high-protein diet (1.8 g/kg/day) was 20% higher only among females [1]. The low oxalate content in the diet might have accounted for the lack of increase in oxaluria in some of these studies, as according to Knight et al. [26], increased protein intake on controlled oxalate diets does not increase urinary oxalate excretion. Nevertheless, once again, except for one study [27], the findings among stone formers have been distinct from the aforementioned, evidencing increases in urinary uric acid and oxalate levels induced by protein intake [4, 6].

In the present study, although median urinary pH was numerically lower after each intervention, it did not reach statistical difference from baseline and significant decreases in median urinary citrate were not observed after either WP or albumin. These findings contrast with studies reporting a decrease for both parameters [2, 26] and only for citruria in stone formers [4, 6]. Current individual values of citruria did not show important declines but noteworthy, urinary citrate excretion was already low at baseline in several samples. Citrate content is not available in the Nutritional Composition Tables, and therefore, we could not determine the intake of citrate provided by the diet. It is possible that the consumption or not of some citrus fruits might have

influenced urinary citrate excretion as previously shown by our group [28]. However, the daily consumption of potassium did not differ between periods so that the alkali feeding must have been similar. Although individual values of urinary pH were highly variable, they did decrease in roughly half of the patients after WP and in 67% of them after albumin. Inasmuch as urine pH-measurements were restricted to the 24 h urines, it is likely that in many subjects, periods with low pH might increase the risk of abnormal CaOx crystallization indirectly and not reflected in the calculated supersaturation indices. Such effects can be expected by decreased inhibitory power as a result of reduced dissociation of inhibitory substances and by establishing high local levels of supersaturation with CaOx as a consequence of calcium phosphate dissolution [29].

Median urinary sodium was unaltered by WP, whereas it was numerically higher but without statistical significance after albumin, with one-third of the subjects showing increases around 50%. The high content of sodium in albumin supplement (435 mg/scoop) might have accounted for such increase in sodium excretion, a well-known undesired effect for patients with stone disease [30, 31] as well as for those with other co-morbidities.

With respect to the risk of urinary crystallization of uric acid and calcium salts in urine, we found non-statistical increase in uric acid supersaturation after both intervention periods compared to baseline. AP(CaP) after albumin disclosed a wide range of values and the statistically significant increase is probably without clinical significance. There were no significant changes in CaOx supersaturation unlike the findings reported by Knight et al. [26] suggesting that people may respond to a protein load in different ways. Moreover, the pH used for calculating AP uric acid as measured in 24-h urine does not take into account the diurnal variation of pH, and it cannot be excluded that peaks of supersaturation with uric acid might have occurred closer to meals; effects that we were unable to disclose.

In the present series, percent lean body mass, evaluated by electric bio-impedance, did not change after the consumption of either supplements vs baseline, in agreement with others [13, 14] although contrasting with the data obtained after longer periods [32]. We observed an increase of marginal statistical significance for plasma urea after albumin, as observed by other investigators [12]. Surprisingly, serum creatinine was slightly lower after both interventions, in contrast with clinical data in overweight and obese adults under WP supplementation [32] who found it unchanged and experimental data showing increases in plasma creatinine after WP [33]. Weight loss could not explain such findings given that neither body weight nor lean body mass changed. It is possible that hyperfiltration due to the protein overload has occurred. Anyway, in other intervention study in which a post-exercise similar

WP dose was given to elderly individuals [34], values of serum creatinine were also reported to be lower. We did not observe changes in median serum albumin, confirming previous clinical data [32].

Limitations of the present study included the short-term period of intervention what could have precluded an adaptation of the body, the absence of ammonium and sulfate determination and the lack of a double-blind design, which was due to the fact that albumin supplements available on the market would be easily distinguished from WP due to its distinct taste. Some of the subjects from the present series had basic variables at levels that made conclusions during supplementation periods more difficult to interpret. In several samples, urinary citrate excretion was low already at baseline as aforementioned, and the lack of correspondence between citrate excretion and urine pH might have been explained by the shortcoming of measuring pH only as an average during the 24-h period. However, the study also has major strengths: although the number of subjects was small due to the rigors that the present design imposed on its participants, the sample size was still bigger than in most other studies and considered adequate to provide statistical power to our results. In addition, as compliance to the replication of diet has been presently ascertained, the effect of the supplements alone could be analyzed more properly.

It must be emphasized that the present applied protocol does not reflect what happens in the milieu of sports people, body builders, and “abusers” who do not increase their daily protein intake only by 30% in their habitual diet when using supplements and do not take one protein supplement alone but rather a combination of them and the load of protein supplements is planned to be taken for months. The goal of the present study was to unmask potential problems with these two protein supplements at a commonly used dose in order to guide future studies. We are aware that studies with longer periods of observations and higher doses of supplementation are warranted to better clarify this relationship, and further research among stone formers is still needed in order to predict accurately the effects on specific metabolic profiles presented by these patients, since a particular sensitivity of stone formers to dietary protein intake, distinct from healthy subjects, has been previously suggested [4]. Notwithstanding the urgent need of these studies, the ethical issues and the experimental problems highlighted above are still very difficult to avoid.

In conclusion, present findings suggest that consumption of WP or albumin supplements by healthy subjects in habitual doses (one scoop/day) during 3 days, under conditions of a normal level of protein intake, did not induce changes in the median values of lithogenic urinary parameters. Of note, relevant increases by more than 50% in urinary calcium excretion were presented by 39% of the

individuals and variable decreases in urinary pH in 44 and 67% of them, after WP or albumin, respectively. Increases higher than 50% in urinary sodium occurred in one-third of them after albumin. Therefore, healthy people should be aware of the amount of protein consumption provided by their self-selected diet when consuming such protein supplements, to avoid triggering urinary risk factors for stone formation. Moreover, the current study suggests a note of caution to be taken by stone formers willing to consume such supplements, and apart from tailored dietary recommendations, a concomitant closer surveillance of urinary calcium, sodium, pH, and other urinary parameters must be advised.

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#### Compliance with ethical standards

**Informed consent** All procedures performed in the present study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** All authors declare that they have no conflicts of interest.

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