the international
JOURNAL OF ARTIFICIAL ORGANS

Official Journal of the
EUROPEAN SOCIETY FOR ARTIFICIAL ORGANS

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Reprinted from
Vol. 30 / no. 12, 2007 / pp. 1109-1115

WICHTIG EDITORE
MEDICAL PUBLISHER

The International Journal of Artificial Organs / Vol. 30 / no. 12, 2007 / pp. 1109-1115

Artificial Kidney and Dialysis

High doses of water increase the purifying capacity of the kidneys

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ABSTRACT: Background: *In previous studies we were successful in demonstrating that the administration of water over a short period of time increases the transport capacity in the excretory tract of rabbit ureters by increasing urinary volume in the ureter from 0.3 ml/min to 10 ml/min. This phenomenon may explain the effect of water therapy performed in thermal spas, where the administration of 1-2 liters of mineral water is performed in 30-60 minutes.*
Objectives: *The aim of the present study is to investigate if this increased transport capacity can act also in the renal tubular apparatus to modify the excretion of some endogenous substances.*
Materials and Methods: *We evaluated daily renal clearances in ten subjects under basal conditions during supplemental administration of 25 ml/kg of mineral water over a 24-hour period and during the administration of the same amount of water over a 30-minute period.*
Results: *Subjects who drank a water load of 25 ml/Kg over 30 minutes showed a higher diuresis than that observed in those who drank the same amount over a 24-hour period. Creatinine and urea clearance at 24 hours were significantly higher in subjects who drank the water load over 30 minutes. Serum magnesium levels and folic acid levels were also significantly higher in subjects who drank the water load over 30 minutes.*
Conclusions: *Water administration over a short period of time seems to modify the daily excretion of some endogenous metabolites. (Int J Artif Organs 2007; 30: 1109-15)*

KEY WORDS: Renal clearances, Fluid transport capacity, Water therapy

INTRODUCTION

Mineral water has always been a fundamental part of the therapy for kidney stones and urinary infections (1, 2). It may seem strange, however, that to date there are very few studies published in international journals on this subject. The mechanism by which water acts on the urinary tract is still to be completely defined and the potential differences between different waters has still to be studied.

There are a few obvious considerations: normally urinary volume is approximately 1000 ml/day, corresponding to 0.27-0.34 ml/min in each ureter. This flow does not allow efficient removal of solutes and debris, which can therefore promote the formation of kidney stones, and even a two- to three-fold increase in diuresis is still not sufficient to flush the urinary tract. However, by administering the same amount of water in 60 to 90 minutes, the flow in each ureter reaches 10 to 12 ml/min, which is sufficient to flush out the urinary tract (3, 49).

To better understand the effect of a water load on the urinary tract, we have to go back to 1842 when Hopkins postulated the “law of the sixth power.” According to this rule, if the liquid flow doubles, the load capacity, or ability to carry solutes, increases 64 times (2^6). According to some authors the load capacity is, in fact, to the fourth or fifth power, but this law is commonly accepted. Our group has studied the effect of distilled water and of different solutions on an experimental model, and we have also studied the effect of forced diuresis on animal models (3-5).

Another important factor is the quantity of solutes dis-

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solved in the water. Mineral water, with few solutes, stimulates the osmoceptors and baroceptors in the urinary tract, activating peristaltic movements and assisting in the elimination of debris. In an experimental model in rabbits, we found that an increase in intraureteral pressure promotes the elimination of sand and of little metal spheres placed in the ureter. We used both distilled water and saline solution, and we found that distilled water causes more elimination compared to saline. This can be explained by the fact that distilled water forms hypotonic urine, which stimulates osmoceptors in the urinary tract.

Presently, we know that forced diuresis reduces the risk of stone formation, especially if the water is consumed over a short period of time. We also know that the use of water with a low solute content promotes ureteral peristalsis, flushing out the urinary tract. The next step is to study the effect of mineral water on different renal indices in healthy volunteers and to evaluate how the drinking speed (24 hours or 30 minutes) influences these indices.

The fact that forced diuresis over a short period of time enormously amplifies the transport capacity in the excretory tract by increasing urinary volume in the ureter from 0.3 ml/min to 10 ml/min made us wonder what happens in the nephron when the urinary flow is increased 20 to 30 times.

The present study was designed to evaluate the effects of mineral water on various renal and excretory parameters in healthy subjects and to assess whether the ingestion of a substantial dose of this water gives different results according to the mode of ingestion.

MATERIALS AND METHODS

We enrolled 20 healthy volunteers (doctors, nurses and students), age range 18 to 60 years. All subjects were informed regarding the aims of the trial and the length of the study. Informed consent was obtained from all participants, according to the regulations of the local Ethics Committee.

To understand if water has a real purifying effect when consumed in elevated quantities and to obtain an exact measure of this purifying effect, we prepared a complex protocol aimed at eliminating all possible interferences when examining the potential therapeutic effects of water, a substance which is inert from a pharmacological point of view.

The study was conducted in the city of Siena, in April 2006, when the maximum temperature was 18°C and the minimum night time temperature was 9°C. Participants were kept on standard diet (1g of proteins per kg of body weight, 30 cal/kg and a standard diet for all participants so as to maintain a standard water input from food, while water ingestion was 100 ml/kg in 24 hours) for 4 days before the trial. During this time participants did not undertake any physical activity and did not go to work.

After a 4-day induction period, subjects were randomly assigned to 2 groups of 10 people each and the following parameters were measured: 1. creatinine clearance; 2. urea clearance; 3. serum uric acid; 4. urinary uric acid; 6. serum and urinary sodium; 7. serum and urinary potassium; 8. serum and urinary magnesium; 9.serum folic acid; 10. hematocrit. We chose these parameters because in our previous studies they were the only ones which had been modified by water therapy (6, 7).

Ten subjects were asked to drink 25 ml/kg body weight over 24 hours for two consecutive days, in addition to the amount of water required by the diet. After 48 hours, the above-mentioned measurements were repeated.

After another 24 hours of the standard diet, the same 10 subjects were asked to drink 25 ml/kg body weight of water over 30 minutes. Water was administered in the morning, in a fasting state, and the participants drank nothing else during the whole day. After 48 hours, the blood and urine tests were repeated.

The other 10 subjects performed the inverse test: they drank 25 ml/kg of water over 30 minutes while fasting in the morning for two consecutive days and after 48 hours blood and urine samples were taken. After another 24 hours of standard diet, they performed the first part of the test, increasing water intake by 25 ml/kg over 24 hours for two days and then repeating the blood and urine tests. This complicated cross-over design was developed in agreement with our statisticians and was aimed at eliminating potential errors due to residual hyperhydration resulting from the first intake or from the ingestion of foods with high water content. This allowed us to identify true alterations in the parameters examined.

Water with a low mineral content was used. This water had already been used in previous trials; it is palatable and therefore well accepted by participants. This is an essential condition when administering a water load over a short period of time.

Statistical analysis was performed using the Mann-Whitney-Wilcoxon (MWW) test to compare the difference between the median in the two groups and the differences in the three parts of the test.

RESULTS

We did not find any side effects or intolerance to the water load ingested over 30 minutes. None of the participants abandoned the study.

Our first analysis showed that there were no statistically significant differences in the baseline parameters between the two groups. This was confirmed by applying the MWW test to the median of all the parameters studied; the hypothesis of equality between the parameters was accepted in all cases. Having accepted the equivalence between the two groups, a second, more detailed analysis was performed to examine the possible differences between the two phases in each group and between the two groups in each phase. The first analysis did not offer any relevant evidence for our study. Therefore we will report and analyze only the results of the comparison between the two groups in each phase of the study.

It is important to note that we compared corresponding phases according to the order in which the water was consumed. Therefore, phase 1 corresponds to the ingestion of water over 24 hours for the first group and over 30 minutes for the second group, and the inverse is true for phase 2. Table I shows the results of this statistical analysis; we have included only variables which present significant differences in at least one phase of the study. Median baseline, phase 1 and phase 2 values are reported for each group. For each measurement, the value of significance of the hypothesis of equality between medians is reported (obtained using the MWW test). The two columns correspond to the two alternative hypotheses: the left column hypothesis that the median of the first group (24 hours+30 minutes) is inferior to the median of the second group (30 minutes+ 24 hours); in the right column the opposite hypothesis is tested.

The results in the table below can be represented graphically.

A significant difference in diuresis emerges during the second phase of the study (Fig. 1). In fact, the group that drank water in 30 minutes had a higher diuresis compared to the 24-hour group (median values 2300 mL vs. 1625

TABLE I - ANALYSIS OF THE DIFFERENCES BETWEEN CORRESPONDING PHASES IN THE TWO GROUPS

Variable	Median		Level of significance	
	Group 1 (24h+30')	Group 2 (30'+24h)	G1 < G2	G1 > G2
BASELINE				
Diuresis	1575.0	1600.0		N.S.
Serum urea	31.5	33.5	N.S.	
Urea clearance	58.6	54.4		N.S.
Serum creatinine	0.90	0.85		N.S.
Creat. clearance	158.5	115.5		N.S.
Serum magnesium	1.95	1.90		N.S.
Serum folic acid	7.0	7.0	N.S.	
PHASE 1	24 H	30 MIN		
Diuresis	2300.0	2100.0		N.S.
Serum urea	28.5	32.5	**	
Urea clearance	65.1	59.9		N.S.
Serum creatinine	0.80	0.90	**	
Creatinine clearance	137.0	165.5	N.S.	
Serum magnesium	1.90	2.05	*	
Serum folic acid	8.0	7.0		N.S.
PHASE 2	30 MIN	24 HRS		
Diuresis	2300.0	1625.0		**
Serum urea	25.5	33.5	*	
Urea clearance	70.5	39.3		***
Serum creatinine	0.80	0.90	*	
Creatinine clearance	166.5	119.0		*
Serum magnesium	1.90	1.95	N.S.	
Serum folic acid	9.0	5.5		***

Levels of significance observed (p-values): * = $0.05 < p < 0.10$; ** = $0.01 < p < 0.05$; *** = $p < 0.01$; N.S. = Nonsignificant ($p > 0.10$). The cells highlighted in gray correspond to the alternative hypothesis with a level of significance above 0.5.

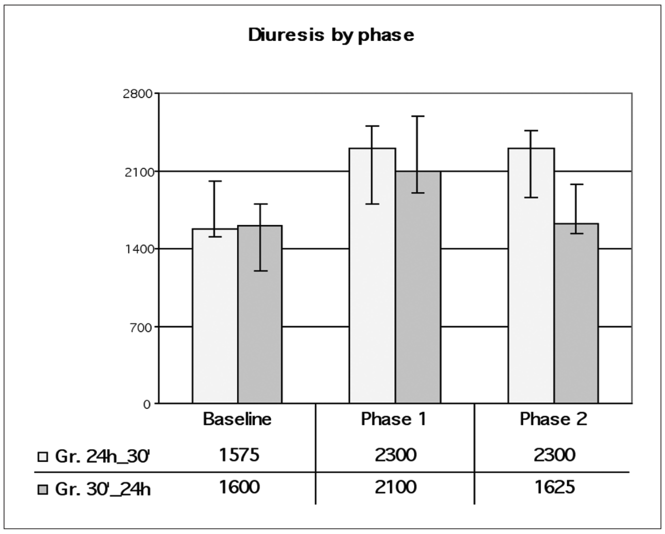

Fig. 1 - *Behaviour of median and level of significance of diuresis in baseline in phase 1 and phase 2.*

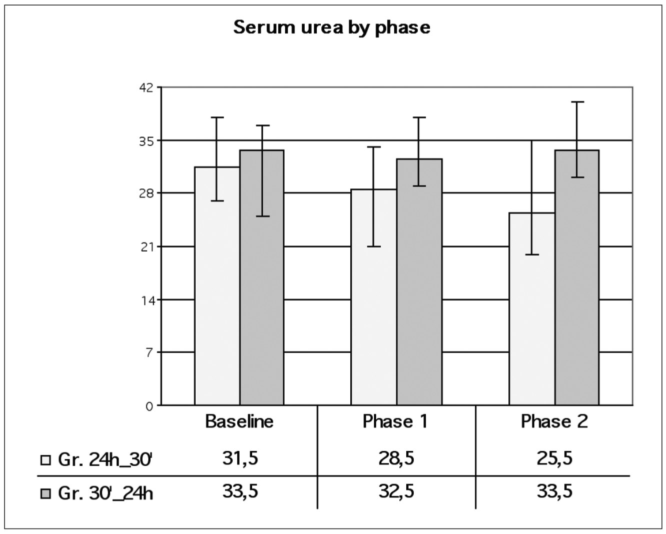

Fig. 2 - *Behaviour of median and level of significance of serum urea in baseline in phase 1 and phase 2.*

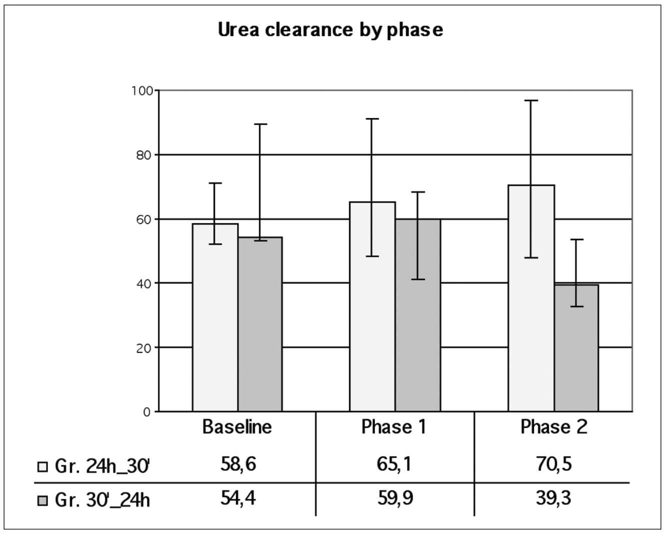

Fig. 3 - *Behaviour of median and level of significance of urea clearance in baseline in phase 1 and phase 2.*

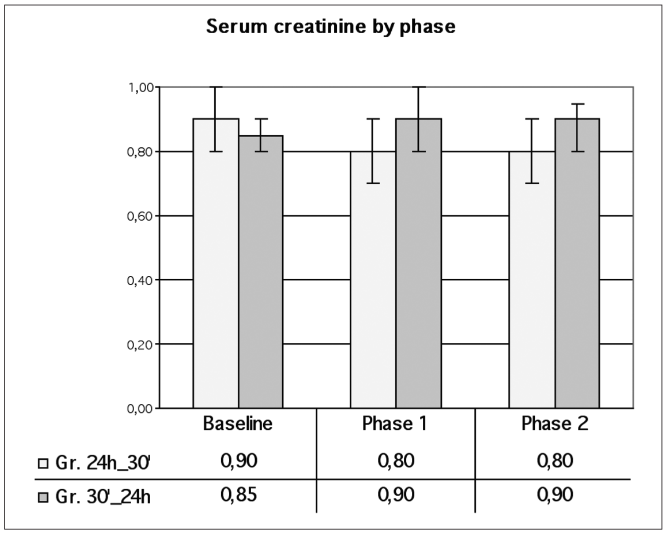

Fig. 4 - *Behaviour of median and level of significance of serum creatinine in baseline in phase 1 and phase 2.*

mL, significance between 0.01 and 0.05).

No clear difference between treatments was found in relation to serum urea (Fig. 2). Although Group 2 tended to have higher values during both phases of the trial, this does not allow us to identify an effect associated with the speed of water intake.

The evidence on urea clearance is interesting (Fig. 3). Although baseline levels are similar in the two groups, from the table and this graph it can be seen that the second phase strongly influences this parameter. The group that drank water in 30 minutes had a clearance of 70.5, which is much higher than the value of 39.3 for the other group. Since the difference between these two groups is significant for any value of $p \leq 0.01$, it may therefore be stated that the rapid ingestion of water increases urea clearance.

Even though we found significant differences in serum creatinine between the two groups, the same consideration made for urea applies equally to this parameter (Fig. 4). The results show that Group 2 had significantly higher

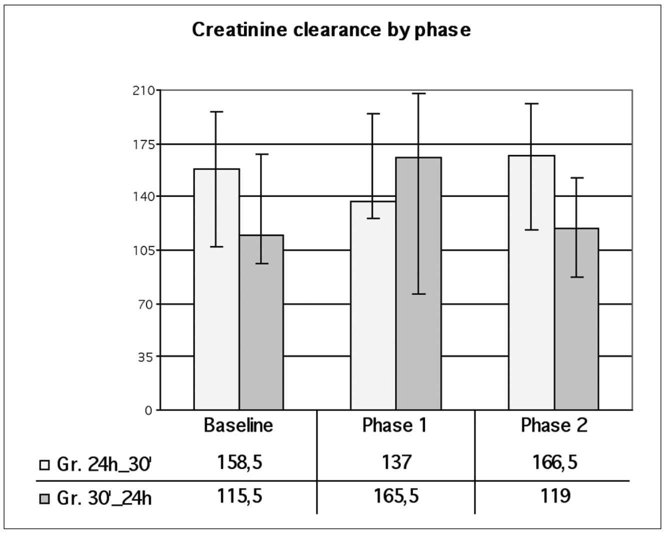

Fig. 5 - *Behaviour of median and level of significance of creatinine clearance in baseline in phase 1 and phase 2.*

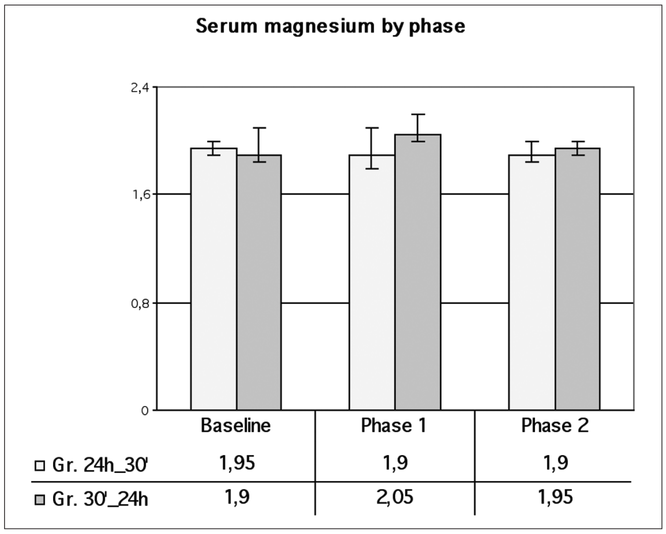

Fig. 6 - *Behaviour of median and level of significance of serum magnesium in baseline in phase 1 and phase 2.*

creatinine values compared to Group 1 during both phases of the trial.

Results for the creatinine clearance rate were similar to that of urea clearance (Fig. 5). The different intake speed of water seems to have a signficant effect on this variable: after phase 2, the group which had drunk the water in 30 minutes had a significantly higher creatinine clearance compared to the other group. The level of significance was between 0.05 and 0.1, while median values were 166.5 and 119.

Group 2 (30 minutes) had a significantly higher serum magnesium level compared to Group 1 (24 hours) during phase 1 of the study, with a level of significance between 0.05 and 0.1 and median values of 2.05 and 1.90 (Fig. 6).

In analyzing the variation of folic acid, a strong significance emerged between the two groups during phase 2 of the study (Fig. 7). Specifically, the group which drank the water over 30 minutes had a higher level of folic acid (median 9) compared to the group that drank the water over 24 hours (median 5.5). The hypothesis that this variable is higher when water is ingested in 30 minutes instead of 24 hours can be accepted with a level of significance of less than 0.01.

CONCLUSIONS

In a recent work, we successfully demonstrated the mechanism by which water therapy works for kidney

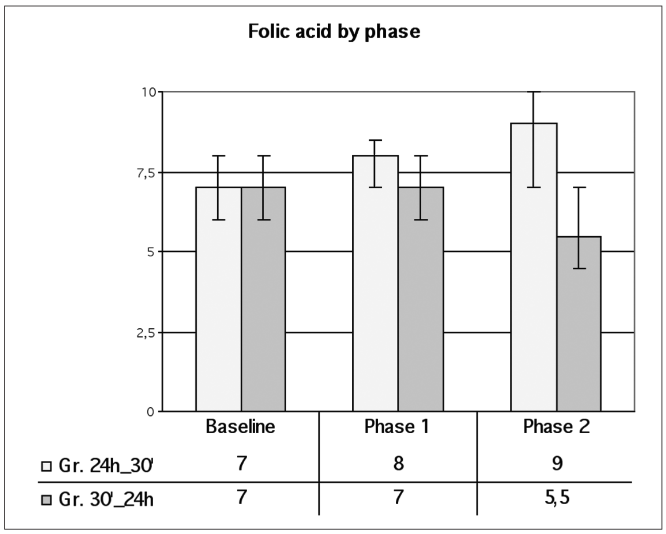

Fig. 7 - *Behaviour of median and level of significance of folic acid in baseline in phase 1 and phase 2.*

stones using *in vitro*, animal and mathematical models. We further demonstrated the utility of 1000 to 1500 mL of water, taken in a short period of time, to flush out the urinary tract.

Forced diuresis has always been medically viewed as the best means for preventing and often treating renal stones, as is demonstrated by the longstanding success of thermal spa therapies. However a rational explanation for this phenomenon has never been given and no one has ever explained why certain waters have a greater effect than others.

It is commonly thought that forced diuresis promotes a general flushing of the urinary tract, cleaning it out and thus promoting the elimination of any substances deposited there and preventing further deposition.

The model of the human ureter is more complex than a river bed. The organic material which forms the walls of the urinary tract is not a rigid or semi-rigid tube and has peristaltic activity (3, 4). A water load implies a considerable increase in ureteral peristalsis, both in the number of contractions and in their length, due to the probable presence of osmoceptors and/or baroceptors in the calices. This causes an increase in intraureteral pressure from 5-15 cm/H_2O to 50-80 cm/H_2O (3, 4). On the other hand, peristalsis can only increase the transport and erosion capacity.

We wondered if this friendly "tsunami" (as it has been defined (5)) obtained with the rapid ingestion of 25 ml/Kg of water in 30 to 40 minutes, cleaning out the urinary tract, also causes parenchimal alterations in the nephronic function. In other words, does the flushing effect take place even in the nephron, and can this produce an increase in renal clearances?

To be precise, we know that healthy individuals who drink a supplemental amount of 25 ml/Kg over 24 hours do not modify their clearances compared to baseline values. But what comes of this supplement if it is drunk over a short time, resulting in a diuresis of 10 to 20 ml/min?

The present study showed that:

- There is a significant difference in diuresis (at 24 hours) in a subject who drinks a water load of 25 ml/Kg over 24 hours and over 30 minutes. In the second case, diuresis is higher.
- Creatinine and urea clearances at 24 hours are significantly higher in healthy subjects who drink a water load over 30 minutes compared to those who drink it over 24 hours.
- Serum magnesium levels and folic acid levels are significantly higher in subjects who drink a water load over 30 minutes compared to 24 hours.

What results from this complex study is that a water load of 25 ml/kg of mineral water drunk over 30 minutes results in an increase in creatinine and urea clearances.

The data regarding folic acid and magnesium are useful. We know that in 1996 the FDA began to recommend that many foods be enriched with folic acid, since there was found to be a greater risk of cancer, a higher probability of neonatal neuropathies, depression and, obviously, constant anemia in the populations who lack it (6-8). In the last decade, the kidney has proved fundamental in maintaining magnesium homeostasis. Not only is it important to maintain normal magnesium levels in renal insufficiency, but renal calculi are often associated with low magnesium levels.

All of this shows that the ancient Romans were right in publicizing thermal spa therapy as a detoxifying therapy. For thousands of years, a huge number of people have undergone thermal therapies, the most important of which is drinking a water load in a short time. In the morning, on an empty stomach, patients drink several glasses of water, directly from the source, generally exceeding the suggested intake of 25 ml/Kg in 30 minutes. Some patients may ingest 4000-5000 mL of water in 60 to 90 minutes without experiencing any difficulties. This obviously induces massive diuresis, even over 50 ml/min, causing lively peristalsis and a drastic increase in transport force, with effective cleaning of the urinary tract.

This study shows that even in the renal parenchyma something important happens and clearance of some catabolites is increased. We may hypothesize that several other small and medium-sized molecules including toxic substances, medications or catabolites may behave similarly to the molecules studied here, and that these may be the subject of future studies. This study, as in other previous ones (9-16), shows that mineral water has therapeutic effects: these effects are so clear that when this water is drunk on an empty stomach, it produces an effect similar to that of a thermal therapy. At the same time, we can conclude that millennia of thermal therapy now have a scientific basis that is in agreement with the ancient Roman doctors who prescribed thermal and water therapies as a cornerstone of their treatment. In our opinion, it is of fundamental importance to understand that to increase the elimination of catabolites and exogenous substances through the kidney, we must administer a mineral water load over a short period of time.

ACKNOWLEDGEMENTS

We thank the Rocchetta Spa for supplying the mineral water to carry out the experiment and for the financial support to complete the study.

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