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Original Research

Nutraceutical role of citrates in tissue pH balance: analysis and clinical interpretation of results obtained from urinary pH

Abstract

Unbalanced diets with a high protein load, illness, abuse of drugs and ageing are some of the many elements predisposing to alter tissue pH balance. This, poorly compensated for by buffer systems acting to maintain the acid-base balance, can be a harbinger of:

1) calcium phosphate removal from the bones with osteopenia and, later, osteoporosis;

2) symptomatic aggravation of various pre-existing conditions typically characterized by the presence of pain (arthritis, headache, myalgia and so on);

3) the genesis of new diseases.

The scientific literature clearly reports that the administration of citrates, or carbonates, support physiological pH tissue balance and alkalizes urinary pH.

In addition, this effect, could reduce the risk of osteopenia and the perception of pain. Non-allopathic medicine describes a situation that is even more severe, secondary to that described above. Wit the progression of impaired balance, the body, probably in an attempt to limit the damage to skeleton structures, could bring about the storage of excess acid in the extracellular matrix by preventing its further elimination in urine, which would then be paradoxically alkaline.

The aim of our study was to demonstrate that, even in this case, the administration of citrates can normalize urinary pH, making it acidic. This urinary normalization would be the result of the release of stored acid from connective tissue. This release would also lead to balance tissue pH and this would be monitored through observing the typical symptoms of patients with osteoarthritis, myalgia, headache and migraine, the incidence of which should be significantly reduced.

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Introduction

In 2008, Welch *et al.*, in the conclusions of their important trial in the British Journal of Nutrition [1], declared: "A more alkaline diet, high fruit and vegetable intake and lower consumption of meat was significantly associated with a more alkaline urine pH before and after adjustment for age, BMI, physical activity and smoking habit and also after excluding for urinary protein, glucose, ketones, diagnosed high blood pressure and diuretic medication". This statement was (and this is as true now as it was then) quite detrimental to the perceived scientific depth of that journal, primarily because a large section of allopathic medicine denied the existence of any alkalizing effect related to the intake of food and/or dietary supplements. The scientists who regard this effect as a hoax emphasize that blood pH is almost numerically unchangeable. They also rightly point out that minimal pH fluctuations could probably be deadly in a very short time. Therefore, even if we had in place foods or supplements that were truly alkalizing, they would be extremely dangerous. The supporters of "alkaline medicine", meanwhile, point out that the observation of pH variations, in an anti-acidosis context, should not be carried out using blood, but derived and interpreted from urinary pH analysis. Urinary pH reflects the effort of an organism to maintain constant (or within very tight margins) blood pH, which is an essential condition for a healthy life.

The two steps of tissue pH unbalance

According to non-allopathic medicine, the incorrect intake of food, use of medications or drugs, smoking, chronic degenerative diseases, environmental pollution, over-training and psycho-physical distress are elements that displace the pH balance towards a mild acidification of tissue, interstitial fluid and the extracellular matrix. If this becomes chronic, the systems that act to maintain a correct pH balance will perform less effectively, and so, to avoid exhaustion, will draw from bone tissue substances with buffering effects, especially calcium phosphate (this is more soluble at lower pH), causing osteopenia. In the literature, it is clearly reported that the depletion of bone tissue also occurs in young people with a diet particularly rich in meat, and which is therefore "acidotic" [2]. This phenomenon would be verifiable at an early stage by measurement of urinary pH; there would be an imbalance towards an evident acidity, even if this were not pathological. Such an acidity would reflect the attempts of the body to eliminate acidity through urine, using CO_2 produced during inhalation. Following on from this, in the second phase, this effort would be insufficient to eliminate acidity, resulting in a failure to dispose of metabolic acid. The organism, to prevent excessive damage (evolution from osteopenia to osteoporosis), could store excessive acidity in the extracellular matrix, exacerbating pre-existing pathologies, especially musculoskeletal diseases, and possibly causing new disorders. In this situation, paradoxically, the urine should be strongly alkaline.

The citrate hypothesis

The supporters of alkalizing nutraceuticals, consider that citrate administration (that is, potassium, sodium and zinc salts) would have an evident alkalizing effect, resulting in alkalization of acidic urine in the first phase of the process, and in acidification of alkaline urine in the second phase. In both cases, citrate intake would power the bicarbonate buffer system, resulting, in the first case, in a rebalancing of the buffer systems (to restore a normal urinary pH) and in the second case, in the release of stored acid for expulsion with urine that would turn from being alkaline to being slightly acidic.

However, citrate administration could have other more profound consequences, along with pH changes. There are reports in the literature that citrate administration can counteract calcium removal from bones that leads to osteopenia [3], and citrate administration disrupts calcium salt removal from bones by replacing them as a buffer system [4].

From theory to evidence

This theory may be correct, but every theory needs to be proven. To date, the literature shows [5] quite clearly that citrate administration leads to urine alkalization (not for urine classified as being "pathological" but for urine that is merely acidic) (**Fig. 1**). Not only is this the case; use of citrate also reduces arthrosis symptoms and the use of analgesics, thus demonstrating, according to the authors, that a decrease in catabolites removal leads to less pain. However, there is a lack of demonstration that citrate administration in a later and stricter phase of tissue alteration (the phase in which we observe metabolic, non-volatile acid storage) can reduce high urine alkalinity, thus leading to improvement of arthritic pain as well as other diseases related to pH imbalance. Consequently, the purpose of this study was to evaluate the effects of nutraceutical citrates and carbonates in the late stage of the acidosis process, in which we observed clearly alkaline urine.

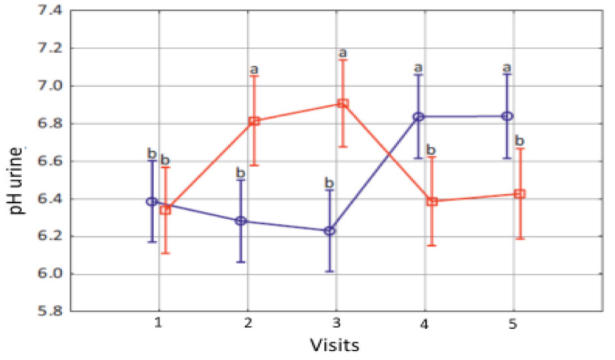


Figure 1 Crossover study of citrate versus placebo administration. Average morning urinary pH at enrolment and subsequent weekly visits. In blue, placebo followed by citrate; in red, citrate followed by placebo. The letters on Figure 1 represent the results where all mean values were compared pairwise to determine possible significant differences. Any mean of the graph can be then compared to any other mean. If the annotation shares one letter (a vs a or b vs b), the corresponding *p* value is >0.05.
If the annotation shares no letter, the corresponding *p* value is <0.05. [Adapted from: van Velden DP *et al*. (2015) Non-allopathic adjuvant management of osteoarthritis by alkalinisation of the diet. Afr J Prim Health Care Fam Med 7(1):780.]

Materials and methods

Study overview

This was a retrospective clinical trial that analyzed the results of 4 weeks of therapy with 2 different food supplements, 1 based on citrate and 1 based on carbonate.
It was conducted on adults of both sexes (>50 years of age) with musculoskeletal disease or tension headache, presenting urinary pH >7.5 for at least 2 successive measurements 15 days apart. Retrospective data studies and analysis were conducted in accordance with good clinical practice rules fixed by the Declaration of Helsinki and in accordance with the European Union Directive 2001/20/EC [6]. Each patient signed consent form and privacy policy documents and approved data analysis and publishing.
Data were collected from 2009 to 2016 in the Italian provinces of Piacenza and Salerno.

Subjects and recruitment criteria

The subjects considered eligible for our retrospective analysis were 467 adults aged between 55 and 90 years of age who presented evident symptomatology of arthrosis, myalgia, headache or chronic migraine, gouty syndrome and chronic cramping pain, receiving analgesic and/or anti-inflammatory and/or antigout and/or muscle-relaxant and/or tranquilizer therapy. Body weight was not considered a limiting factor and so we analyzed normal weight, overweight and obese subjects.
Subjects were excluded from this trial in the following cases: those with secondary dyslipidaemia and/or elevated cardiovascular

risk, with or without a previous history of heart attack and/or stroke; those with liver, kidney or endocrine diseases (except for compensated diabetes); those with oncological diseases; those with severe neurological/ psychiatric illness; those with declared alcohol or narcotic abuse (except for the smoking of cigarettes). Subjects with alkaline urinary pH due to vomiting, urinary tract infections, kidney failure, diuretic therapy, renal tubular acidosis, gastric lavage and respiratory disease caused by hyperventilation were also excluded.

Tested products

Of the 467 subjects enrolled in the study, 422 were treated with Alkaloximed® (hereinafter referred as A). This nutritional supplement was formulated in sachets produced by SIIT (Trezzano sul Naviglio, Milan, Italy), and notified to the Italian Ministry of Health as a food supplement by Pharmextracta spa (Pontenure, Pc, Italy) on April 27 2006, complying with law n°196-2004 (notification number: 22434). It contains: citrates of K, Mg and Zn (4546 mg/ dose), vitamin A (600 µg/ dose), vitamin C (250 mg/dose), vitamin E (18 mg/dose), vitamin B1 (2.1 mg/dose), vitamin B2 (2.4 mg/dose), vitamin B6 (3 mg/dose), vitamin B12 (9 µg/dose) and folic acid (200 µg/ dose). The other 45 subjects used as a control group were treated with Basenpulver Pascoe® (herein after referred as B), produced by NAMED - Lesmo, Mb, Italy (notification number: 907058477), a food supplement in sachets of 4 g/dose containing calcium carbonate, sodium bicarbonate, magnesium carbonate, bisodic phosphate, potassium bicarbonate and zinc sulphate, equal to 613 mg of Ca^{2+}, 377 mg of Na^{+}, 232 mg of Mg^{2+} and 1.5 mg of Zn^{+}.

Protocol

The treatment protocol involved administration of the nutraceutical product twice a day for the first week, separately from the main meals (mid-morning and mid-afternoon) and, for the next 3 weeks, once a day mid-morning or mid-afternoon, according to the preference of the subjects. During the treatment period, patients were advised to limit "acidifying" foods (meat, eggs, cereals and so on) and to choose those that were "alkalizing" (fruit and vegetables) as much as possible. However, no major calorie restrictions were otherwise proposed. The protocol included a first general visit with morning urine analysis. The analysis was then repeated 15 days later (T=0). If pain symptomatology was unchanged and urinary pH remained at decidedly alkaline levels, even if within a range of relative normality (7.5–8.0), the subject began treatment with the nutraceutical preparation. After 4 weeks of therapy (T=4) and concurrently with a new general medical examination, urinary pH was tested again. Due to the difficulty in collecting urine within the prescribed time, some of the data shown as T=4 in **Table 2** refer to a urinary analysis performed within a time frame of 30–32 days from the beginning of treatment.

Clinical evaluations relating to painful symptoms, performed at T=0 and T=4, referred to a visual analogue scale (VAS) according to the Scott and Huskisson model, which considers 0 to be an absence of symptoms and 10 to be the presence of a symptom defined as being "not bearable" [7]. At T=0 and T=4, the use of drugs to control symptoms was also evaluated, expressed as weekly drug doses per subject.

At T=4, data relating to compliance, tolerability and the possible appearance of side effects attributable with relative certainty to treatment were also collected.

Aims

The aims of our evaluation were: the degree of tolerability of the food supplement used for the treatment; the appearance of side effects attributable to the treatments; the trend of urinary pH measurements

after approximately 4 weeks of therapy; the progression of painful symptoms during therapy with alkalizing preparations and the use of drugs to control pain-related symptoms.

Statistical analysis

The Wilcoxon non-parametric test was used to compare outcomes in the same group during different periods. For this purpose, JMP 10 software for Mac OS X was used and statistical significance was considered when $p<0.05$.

Results

As shown in **Table 1**, the 2 groups (considering the large numerical difference between the enrolled subjects, 422 vs 45) demonstrated balanced characteristics (sex and age) and were similarly distributed in terms of the pathology diagnosis.

Four weeks of administration of A, the citrate-based food supplement (**Table 2**), had a clear normalizing effect on urinary pH, with rather alkaline values becoming decidedly more acidic, with a statistically significant variation of approximately 23%.

Otherwise, the administration of B, the carbonate-based product, brought about an insignificant reduction in urinary pH (approximately 4%).

Urinary density values (**Table 2**) indicated that the subjects within both groups had a good urinary concentration capacity and showed no anomalies in tissue hydration.

Indeed, it is known that simply drinking a large volume of water alters urinary pH values, but in this case the urinary density values would also decrease. Administration of A resulted in a statistically significant reduction in pain related to osteoarthritis, myalgia, headache and migraine of 40%, 31%, 32% and 30%, respectively. A decrease in pain was also observed with respect to gouty syndrome and cramps but statistical significance was not achieved (24% and 14%, respectively).

On the other hand, B did not seem to have the ability to cause any significant reduction in pain symptoms. The lower perception of pain reported by subjects treated with A, evident above all at the musculoskeletal and cephalic levels, was confirmed by the reduced use of pain medications (approximately -25%).

This value was obtained by calculating the average doses per subject in the first week of treatment and comparing this to the same parameter measured during the fourth week of treatment (**Table 3**).

Once again, B did not demonstrate any statistically significant advantage regarding the doses of the drugs used. In terms of compliance and tolerability (**Table 4**), A demonstrated good results even if some cases of nausea occurred (7 out of 422 subjects).

B administration was associated with considerably worse compliance and tolerability data, with a high number of nausea and vomiting cases (8 and 3 cases, respectively, out of 45), and this was sometimes aggravated by belching and gastric swelling with reflux sensation.

Table 1 Characteristics of enrolled subjects

Parameter	**A** (N=422)	**B** (N=45)
Sex (F/M)	230/192	25/20
Age (years)	65.9±6.8	67.3±9.5
Diagnosis:		
Arthrosis	307	26
Myalgia	72	12
Headache	15	2
Migraine	10	2
Gout	11	2
Cramps	7	1

Notes: Years are expressed as the mean ± standard deviation.

F = female; **M** = male; **N** = number of subjects

Table 2 Effects of an alkalizing oral therapy based on citrates (A) or carbonates (B)

Parameter*	A (T=0)	A (T=4)	Δ%	*p*	B (T=0)	B (T=4)	Δ%	*p*
Urine:								
Density	1022.4±7.5	1019.2±8.3	-0.32	NS	1018.8±7.8	1010.6±6.9	-0.81	NS
pH	7.85±0.8	6.03±0.6	-23.19	<0.01	7.58±0.6	7.25±0.9	-4.36	NS
VAS for:								
Arthrosis	6.80±2.45	4.10±2.35	-39.71	<0.05	6.35±2.72	6.15±2.56	-3.15	NS
Myalgia	4.65±2.75	3.22±2.20	-30.76	<0.05	5.20±2.34	5.25±2.29	+0.96	NS
Headache	5.46±2.12	3.73±1.84	-31.69	<0.05	5.35±2.55	5.15±2.05	-4.10	NS
Migraine	6.05±2.67	4.21±2.40	-30.41	<0.05	6.75±2.45	6.45±2.60	-4.73	NS
Gout	4.95±1.58	3.83±1.24	-23.63	NS	5.45±2.40	5.29±3.25	-2.94	NS
Cramps	3.55±0.85	3.07±0.67	-13.52	NS	NR	NR	/	/

*****All parameters are expressed as the mean ± standard deviation.
NS = not significant; **NR** = not detected; **VAS** = visual analogue scale

Table 3 Drugs***** (dose/subject/week) used to control symptoms

Parameter	A			B		
	T=0	T=4	*p*	T=0	T=4	*p*
Arthrosis	12.2±2.3	8.3±2.1	<0.05	11.5±3.2	10.7±2.8	NS
Myalgia	9.5±3.6	6.2±2.8	<0.05	10.6±2.7	9.75±3.2	NS
Headache	6.4±2.2	4.0±1.5	<0.05	6.5±3.0	6.0±2.5	NS
Migraine	5.3±1.9	2.8±2.1	<0.05	6.5±2.5	5.5±3.0	NS
Gout	2.5±2.8	1.5±2.5	NS	3.5±3.5	3.0±3.0	NS
Cramps	3.3±2.4	1.9±2.2	NS	NR	NR	/

*****Analgesics, anti-inflammatories, antigout medications, muscle relaxants, tranquilizers (+ any gastro-protectors). Dose/subject/week is expressed as the mean ± standard deviation. This value also includes the use of any gastro-protectors.
NS = not significant; **NR** = not detected

Table 4 Assessment of compliance, tolerability and side effects in the two groups treated

Parameter	**A** (N=422)			**B** (N=45)		
	O	A	NA	O	A	NA
Compliance	402	20	0	27	15	3
Tolerability	321	93	8	21	12	12
Collateral effects:						
Nausea			7			8
Vomiting			0			3
Belching			2			7
Bloating			0			7
Diarrhoea			1			0
Constipation			1			1
Headache			0			0
Insomnia			1			0

Note: N = number of subjects; **O** = excellent; **A** = acceptable; **NA** = not acceptable

Discussion

The results of our study would seem to validate the hypothesis that the administration of citrates in an advanced phase of tissue pH imbalance, as represented by alkaline urine, would lead to an improvement in musculoskeletal symptoms accompanied by urine acidification. The latter phenomenon could be the consequence of the release of stored non-volatile acids from the connective tissue matrix. To better understand the apparent biochemical paradox between results of the literature (citrates administration to alkalinize acid urine) and our results (citrates administration to acidify alkaline urine), we will attempt to analyze in detail the following: blood, tissue and urinary pH; compensatory mechanisms and the role of citrates and carbonates (chemically weak acids) in pH balance processes.

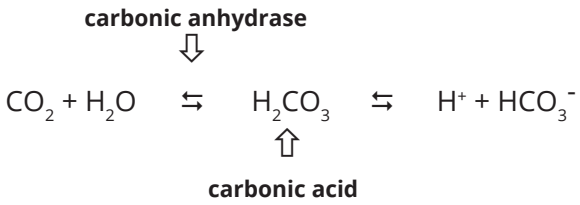
Blood pH

Blood pH, like that of any other fluid, reflects the concentration of hydrogen ions (H^+) dissolved within. Under normal conditions, blood is slightly alkaline, with a pH that varies between 7.35 and 7.45, a very narrow interval.

This is because the enzymatic reactions necessary for the proper functioning of the human organism take place within this precise pH range [8]. The "acid-base balance" is nothing more than the biochemical mechanisms that maintain blood pH within this narrow range. There are numerous factors that can cause changes in blood pH within this range; when, however, the limits are exceeded even by only +/- 0.4 units, the organism can face serious organic compromise that could prove fatal if the situation were not quickly brought back into balance. For this reason, the mechanisms predisposed to the regulation of blood pH are particularly effective. The respiratory and urinary systems together with the solutes of the blood buffer system participate in this control. We will now see how these mechanisms work.

Compensatory mechanisms

When blood acidosis occurs, the body immediately increases ventilation, that is, the frequency and/or depth of breathing; this increases the excretion of CO_2 and causes elevation of blood pH, which then alkalizes. In the opposite case of blood alkalosis, the organism decreases ventilation, which leads to a reduction in emitted CO_2 with subsequent acidification of the blood. This process is triggered by specific chemoreceptors that constantly monitor blood CO_2 and transmit the collected signals to upper ventilation control centers, which in response, increase or decrease the frequency of breathing, and therefore, ventilation. Normally, when the blood CO_2 concentration deviates from the value of 40 mmHg, chemoreceptors detect an anomaly. Obviously, CO_2 is not itself acidic as it does not contain hydrogen atoms but in the blood it combines with water to form carbonic acid, which dissociates into H^+ and HCO_3^- according to the following chemical reaction:



Consequently, when CO_2 concentration increases significantly, the blood environment acidifies:

$$\uparrow CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow \uparrow H^+ + \uparrow HCO_3^-$$

In the periphery of the body, O_2 is consumed and CO_2 is produced as a result of muscular work (or other oxidative reactions).

The CO_2 thus produced is transformed into carbonic acid by the carbonic anhydrase enzyme present in red blood cells and carbonic acid (H_2CO_3) splits into H^+ and HCO_3^- causing an in-

crease in acidity due to an increase in the concentration of H^+. In effect, due to CO_2 elimination with respiration, the equation tends to move to the left (Le Chatelier's principle; each balanced system tends to react to a disturbance imposed on it from the outside, minimizing its effects) with a reduction in H^+, and therefore, acidity [9].

Obviously, in the opposite condition, we will observe the inverse phenomenon:

$$\downarrow CO^2 + H_2O \leftarrow H_2CO_3 \leftarrow \downarrow H^+ + \downarrow HCO_3^-$$

Therefore, the HCO_3^- ion, also known as hydrogen carbonate or bicarbonate ion, acts as a vector to secrete CO_2 but is also used by the system to keep blood pH stable.

The maintenance of a stable blood pH requires a quantity of bicarbonate equal to approximately 24 mEq/l of blood.

There is another very effective buffer system at the kidney level, although this is much slower to activate than the previous system described. Indeed, nephron cells can respond to blood acidosis by secreting larger amounts of H^+, reabsorbing more HCO_3^- and/or promoting the formation of ammonia (NH_3). Ammonia can react with free H^+ ions to form ammonium ion, according to the reaction:

$$NH_3 + H^+ \rightarrow NH_4^+$$

In general, however, the fastest-acting buffer system, although not necessarily the best performing, is that of buffer solutes; in body fluids there are amphoteric substances capable of buffering both acids and bases. These substances are phosphate ions (pKa = 6.8), haemoglobin (pKa = 7.4) and the carbonate system originating in the kidney (pKa = 6.1). Among these three systems, the most efficient is haemoglobin, which is capable of physically extracting H^+, while the most represented is the renal carbonate buffer.

The role of citrates

Citric acid is a key molecule in metabolic processes (for example, the Krebs cycle) that take place within each body cell. As well as being in the human body, citric acid is found in citrus fruits, where it is mainly present in the form of potassium citrate. Lemons contain 5–7% citric acid and oranges approximately 1%, but it is found in moderate concentrations in all types of fruit, especially in kiwis and in strawberries. Citrate has important applications within the pharmaceutical industry; its usefulness is well known, for example, in the prevention of kidney stones due to excess uric acid and cystine [10].

Another application is linked to an alkalizing role in metabolic, gastric and urinary acidosis. After oral administration, citrate (often in the form of a potassium salt) initially plays the role of a gastric antacid. Since citrate is weakly acidic, when it comes into contact with hydrochloric acid present in the stomach (pH = 1.5–3.0) it acts as a base, subtracting H^+ from the hydrochloric acid to form potassium chloride and citric acid. Subsequently, after intestinal absorption, it is partially oxidized to carbonate ion. Carbonate, which is also weakly acidic, easily forms sodium, potassium and calcium carbonates, elements that form part of the compensatory systems responsible for acid-base balance, and therefore, it has a clear buffer action. The citric acid not oxidized to carbonate is excreted in the urine, where it also acts as a chelating agent, reducing the probability of urinary stones [11]. The fact that citrate can be excreted in urine, only apparently contradicts the reasoning that giving citrates in the case of acidic urine would lead to its alkalization. Urinary acidity, a signal of tissue acidosis, is in fact caused by the release of H^+ into the urine from the kidney and is certainly not due to the presence of exogenously administered citrates. The latter operate in the blood and tissues in the form of carbonates, rendering the renal release of H^+ into the urine less necessary.

This phenomenon, and not the renal release of H^+, would be the real responsible of the slighty alkaline urines acidification generated by the administration of citrates.

Could the presence of citrates then at least partially explain the acidifying action shown in the case of alkaline urine (an apparently paradoxical phenomenon with respect to what was observed in the case of acidic urine)?
The answer is yes, to the extent that the symptoms did not change in any way.
No symptom improvement could indicate the lack of alkalizing behaviour of citrates in the connective tissue, which results in no release of stored non-volatile metabolic acids.
In this situation, in the absence of a symptomatic change, urinary acidification could be explained by the presence of citrate in the urine, due to its insufficient transformation into carbonate in the tissues following intestinal absorption.
In this study, however, we observed acidification of the urine accompanied by a significant improvement in musculoskeletal pain and tension-type headache.

Therefore, we hypothesize that pH balance by citrates after transformation to carbonates takes place. The release of metabolic acids from the extracellular matrix is promoted, which stimulates the kidneys to release H^+ into the urine through the Na^+ reabsorption mechanism. In this way, H^+ enters the urine causing its acidification.

The role of micronutrients

The preparation A contained some vitamins whose dosages could have influenced the results and therefore further studies should be carried out to understand their possible role in optimizing the metabolic processes involved. Since in this study there is no control group with different vitamin dosages, there is a difficulty in defining their real contribution and impact on the results of the study both in negative and positive way.

Ineffectiveness of exogenous carbonates

In our study, the carbonate preparation B was less effective than might have been expected. This could be due to a lower intake of the product compared to what was declared, because of its low tolerability, or simply because the dose administered was insufficient to determine the expected effect (**see Table 3**).

The literature clearly demonstrates that carbonates, at the appropriate dosage, are effective alkalizers of acidic urine to the same extent as citrates [12]. In the present study, however, they had less efficacy than citrates.

Alkaline diet

Our results would also seem to demonstrate the importance of a diet rich in micronutrients that contribute to the pH balance. A widely used index to evaluate the "acidifying or alkalizing" characteristics of a food is the so-called potential renal acid load (PRAL).

There are foods with a negative PRAL that are potentially alkalizing, such as vegetables and some types of fruit, and there are foods with a positive PRAL, with an acidifying effect (meat, fish, cereals, chickpeas, lentils, milk derivatives).

Another, even simpler, classification divides foods into those that are acidic but alkalizing, such as citrate-rich vegetables, and those that are acidifying, such as proteins and carbohydrates.

These classifications seem to clearly show the possibility of following an alkaline diet without excessive food sacrifices. Actually, it's not so simple as all cereals have a positive PRAL [13]. This means that only a diet heavily unbalanced towards vegetables and fruit could bring alkalizing benefits.

Such a diet, however, would be very low in energy and far from the Mediterranean diet, which is rich in cereals and derivatives and recognized for its health-promoting potential. Therefore, it appears easier to implement supplementation with exogenous citrates than to follow an "alkalizing diet".

Conclusions

Our study has shown (as has often been reported anecdotally by some advocates of integrated non-allopathic medicine) that the administration of citrates and micronutrients to subjects with potential tissue pH imbalance and concomitant musculoskeletal and/or tension-cephalic pathology has a urinary acidification effect. This leads to an improvement in symptoms so evident as to manifest in a significant reduction in the doses of analgesic drugs used. Based on the data obtained and analysis of the literature, we have also proposed a plausible biochemical explanation for the apparently paradoxical alkalizing activity of citrates and carbonates in subjects with acidic urine. This clinical study presents obvious bias that could have led us to misinterpret the results: the trial is actually a simple retrospective analysis and it has not evaluated clinical outcomes prospectively; the trial was not performed blind or against placebo and, above all, shows a significant numerical imbalance between the two groups examined, which could have minimized the effects obtainable with carbonates.

To remedy these potential sources of error, new studies are currently underway to verify the actions of alkalizing supplements.

Conflict of Interest

The author A. B. is a consultant to the company that produces Alkaloximed. The other authors have no conflicts of interest to declare.

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