

Alkaline Mineral Supplementation Decreases Pain in Rheumatoid Arthritis Patients: A Pilot Study

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Abstract: The aim of this pilot study was to investigate the efficacy of an alkaline mineral supplement as a means of suppressing disease activity in rheumatoid arthritis (RA) patients, and to check whether any change occurs in the circulating beta-endorphin concentration. Thirty-seven patients with moderately active RA of at least two years duration, who were receiving stable pharmacological treatment, participated in a 12-week study. All patients were randomly allocated to a supplemented group (30g of an alkaline mineral supplement daily) or to an unsupplemented group. Their usual diet and medication was maintained. Disease activity, pain, and health-associated status were recorded (DAS 28 - Disease Activity Score 28, VAS - visual analogue scale for pain, HAQ - Health Assessment Questionnaire). Plasma immunoreactive endorphin (ir-EP) was measured in the study groups and also in healthy subjects. DAS 28 and VAS decreased in the supplemented group, whereas there was no change in these parameters during the trial in the control group. The functions (HAQ) of the supplemented patients improved. The ir-EP levels increased in both groups but to a higher degree in the supplemented group. During the trial, medication (NSAIDs and steroids) could be reduced in the supplemented group only. Conclusion: This study suggests that an alkaline supplement may improve function and pain in rheumatoid arthritis and may represent an easy and safe addition to the usual treatment of RA patients.

Keywords: Pain, rheumatoid arthritis, acid-base balance, beta-endorphin.

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INTRODUCTION

A large body of epidemiological and experimental studies has demonstrated that nutrition has an important impact on the occurrence and severity of various chronic diseases [1]. The level of disease-associated pain may also be diet-related. For example, patients with rheumatoid arthritis (RA) frequently experience a positive effect of a change in diet on the activity of their disease. The hypothesis of our present study was that patients with RA, consuming an ordinary Western diet as most of the population of the world's developed countries, develop a diet-induced low-grade systemic metabolic acidosis [2]. There is strong evidence that a diet rich in fruit and vegetables acts protectively against a wide variety of human diseases. However, such a diet usually also supplies excess alkalinity, and part of its beneficial effects might be associated with a reduction of the chronic acid load [3]. The chronic inflammatory process in RA patients leads to a local increase in acidity; the pH in synovial fluids from patients with RA is significantly lower than that in patients with osteoarthritis or controls [4]. This change in local acidity might aggravate pain symptoms, especially in connective tissues. Therefore, alkaline supplementation might lead to an improvement of the clinical outcome in RA patients. In patients with chronic low back pain, alkaline supplementa-

tion significantly reduces pain and disability [5]. Our own observations of some RA patients also suggest the positive effect of a complementary treatment with alkalines. We have therefore conducted a pilot study to investigate, in more detail, the effects of an alkaline supplement on pain symptoms in patients with RA. In addition to subjective indicators of pain, disability, and quality of life, the change of the concentration of beta-endorphin (ir-EP) has been determined in the plasma of patients as a more objective parameter of pain problems. Significantly lower ir-EP levels have been reported in RA patients than in controls, and an inverse correlation has been found between the rheumatoid disease activity score and plasma ir-EP concentration [6].

MATERIALS AND METHODS

Patients and Study Design

Prior to commencing the study, approval by the local ethical committee (Scientific Committee of St John's Hospital, Budapest) was obtained, and the ethical principles of the Helsinki Declaration were followed. All patients were informed orally and in writing about the study design and the underlying hypothesis and of the participant's right to withdraw at any time. The study design was a single-center randomized parallel trial over a period of three months.

Patients

Out of 76 outpatient candidates who were screened for the trial and were willing to participate, 37 patients fulfilled

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all the inclusion criteria according to Table 1. These patients were randomly selected into a supplemented group or an unsupplemented control group. Baseline characteristics of patients in both groups are shown in Table 2.

Supplementation

After a 4-week wash-out period (other supplements), patients in the supplemented group started to take, on a twice daily basis, 30 g (2 x 15 g) of a lactose-based alkaline multimineral supplement (Basica Vital[®], Protina Pharmaceuti-

cals, Germany) for a 12-week period in addition to their usual medication. The mineral composition was as follows (mg/daily dose): Ca (400), K (250), Na (250), Mg (100), Fe (5), Cu (1) all as citrates, Zn (5) as gluconate, I (0.1) as potassium iodide, Mo (0.08) as sodium molybdate, Cr (0.06) as chromium chloride, Se (0.03) as sodium selenite. The alkaline mineral supplement was taken twice daily in the form of a powder mixed in one of the following: soup, yoghurt, tea, or cereal. A suitable inert placebo in a similar daily dose was not available, and the use of sugar as a placebo seemed not

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria:	
•	Rheumatoid arthritis based on the 1987 American College of Rheumatology (ACR) criteria
•	Disease duration of at least two years
•	Seropositive for rheumatoid factor
•	Clinically, the disease must have been characterized as stable and under adequate control
•	Current use of non-steroidal anti-inflammatory drugs (NSAID)
•	Disease activity score from 28 joints (DAS28) >2.0 indicating active disease
•	Unchanged corticosteroids for ≥4 weeks, maximum daily oral dose of prednisolone <12.5 mg.
•	No change of daily doses of disease modifying anti-rheumatic drug (DMARD) for ≥3 months
Exclusion Criteria:	
•	Co-morbidity (such as diabetes, gastrointestinal diseases) - except hypertension and osteoporosis.

Table 2. Baseline Characteristics of Patients who Completed the Trial. Data are Presented as Mean (Range) Unless Otherwise Stated

	SD Patients (n=19)	CG Patients (n=17)
Age (years)	61 (32-76)	57 (31-85)
Sex (men/women)*	2/19	2/17
Body Mass Index (kg/m ²)	26.1 (22.3-31.9)	27.6 (17.6-49.5)
Disease Duration (years)	11.8 (2-26)	12.8 (2-22)
Rheumatoid Factor Positive*	19	17
DAS28, Score	5.2 (3.6-6.9) [†]	4.5 (2.8-6.0)
ARA Class I*	0	0
Class II	5	5
Class III	14	11
Class IV	0	1
Current Drugs		
NSAID	19	17
Corticosteroids/mg prednisolone	6/4.6	7/4.2
Co-morbidity		
Hypertension	2/2	4/4
Osteoporosis	1/0	3/3

* Number of patients.

[†] Statistically significant difference between SD and CG, p<0.05.

Abbreviations used in Table 2. : SD - supplementary diet; CG - control group; DAS - disease activity score; ARA -American Rheumatology Association; NSAID - non-steroidal anti-inflammatory drug. The use of other disease modifying drugs was equally distributed over both groups.

to be appropriate. Therefore, a placebo was omitted in this pilot trial. During the trial, patients were not allowed to take any dietary supplements except for the alkaline mineral supplementation in the supplemented group. The individual dose of non-steroidal anti-inflammatory drugs (NSAID) could be adjusted but had to be recorded.

Determinations and Measurements

All patients were evaluated by the same investigator in accordance with a written protocol that included medical history, ACR criteria [7], complete evaluation, articular evaluation, and extra articular evaluation of RA (history of rheumatoid nodules, Reynard's phenomenon, or pulmonary, cardiac, dermal, ocular, and nervous system involvement). Disease activity was assessed by determination of the number of swollen joints, the score of tender and swollen joints, and the duration of morning stiffness (in minutes). A composite disease activity score (DAS 28) [8], a physical function index Health Assessment Questionnaire (HAQ) [9], C-reactive protein (CRP), and rheumatoid factor were measured at baseline and 4, 8, and 12 weeks after starting the trial. DAS28 is a composite disease activity index and also a response index with good discriminatory validity. It includes 28 joint counts for tenderness (tender joint count) and swelling (swollen joint count), the erythrocyte sedimentation rate (ESR), and the patient's global assessment of disease activity on a horizontal visual analog scale (patient global VAS, 0-100mm). As a parameter connected to pain, the level of ir-EP was determined in blood samples of both patient groups and from healthy subjects (6 females, 6 males; mean age: 45 years). Blood samples were collected into K₂-EDTA-containing plastic tubes and then centrifuged, after which plasma aliquots were stored at -20 °C until assayed. Details of the EP radioimmune assay (RIA) including the percental cross-reaction data were as described earlier [10]. In short, synthetic human EP (Sigma) was used both for the standard and ¹²⁵I-labeled tracer, and a second antibody was used to separate the bound and free fractions.

Compliance

Compliance of supplemented patients was monitored by the weekly determination and recording of the pH of the first morning urine with pH paper strips by the patients themselves. Supplementation induced a significant increase in urinary pH by at least one pH unit after one week in all supplemented patients and remained high throughout the supplementation period thus indicating adherence to the supplement.

Statistical Methods

Determined parameters were normally distributed and variations were compared between time 0 and 4, 8, and 12 weeks, respectively, and between the supplemented and unsupplemented groups by using Student's t-test. Frequencies of reduction of medication were compared between groups by means of the Fisher exact test. All reported P values are 2-sided.

RESULTS

A total of 37 patients were enrolled of whom 19 were randomly allocated to the supplemented group and 18 to the unsupplemented control group. In one control patient, an

intra-articular injection with triamcinolone hexacetonide was reported what expectedly influenced the disease activity, and this patient was excluded from the study. Hence, 19 supplemented and 17 control patients completed the trial. At the start of the experiment, the two groups were equal in all respects, except for disease activity score (DAS28). At baseline, the control patients showed a score of 4.5 (range: 2.8-6.0) versus the supplemented group with a score of 5.2 (range: 3.6-6.9); this difference is statistically significant (t-test). At the end of the observation period, the supplemented group, in which members had started with significantly higher disease activity score, showed significantly lower DAS28 compared with control patients (Fig. 1). DAS28 decreased in the supplemented group, whereas there was no significant change in disease activity score during the trial in the control patients. There were also significant differences between supplemented and unsupplemented groups at 4, 8, and 12 weeks. The level of pain (according to the patient's visual analog scale (VAS)) decreased to a considerable extent in the supplemented group (Fig. 2). In the control patients, the pain increased between week 0 and week 4. Be-

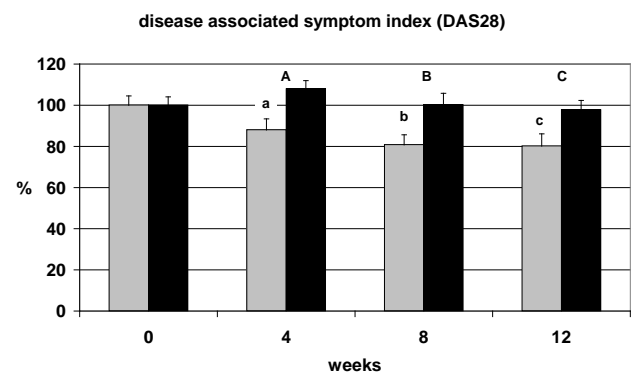


Fig. (1). DAS28 in supplemented (first column) and unsupplemented (second column) RA patients at 0, 4, 8, and 12 weeks. Significant difference in comparisons with time 0 of the respective group; a: $p = 0.049$; b: $p = 0.011$; c: $p = 0.004$. Significant differences between groups; A: $p = 0.006$; B: $p = 0.016$; C: $p = 0.028$; mean \pm SEM.

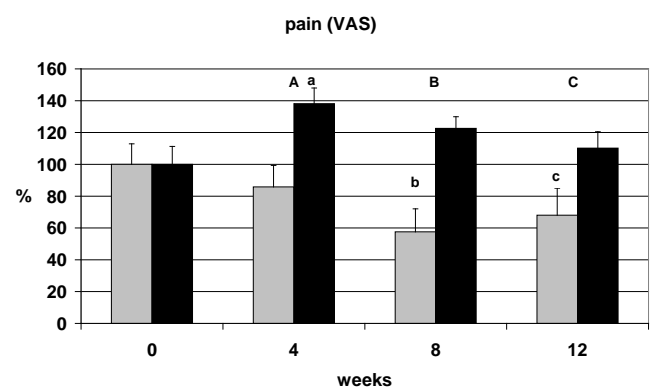


Fig. (2). Pain level according to a visual analog scale in supplemented (first column) and unsupplemented (second column) RA patients at 0, 4, 8, and 12 weeks. Significant difference in comparisons with time 0 of the respective group; a: $p = 0.045$; b: $p = 0.004$; c: $p = 0.048$. Significant differences between groups; A: $p = 0.003$; B: $p = 0.001$; C: $p = 0.037$; mean \pm SEM.

tween groups, significant differences were detected after 4, 8, and 12 weeks. HAQ results showed a significant improvement in supplemented patients by the end of the trial, whereas no change was seen in the control patients (Fig. 3). At the end of the trial, the difference between groups also became significant.

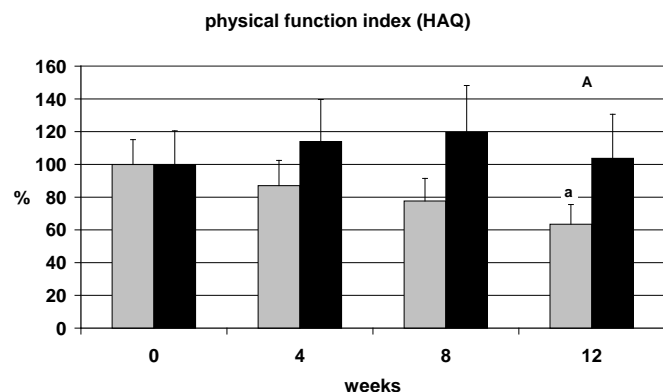


Fig. (3). Physical function index (HAQ) in supplemented (first column) and unsupplemented (second column) RA patients at 0, 4, 8, and 12 weeks. Significant difference in comparisons with time 0 of the respective group; a: $p = 0.009$. Significant differences between groups; A: $p = 0.049$; mean \pm SEM.

ESR, CRP, and the level of rheumatoid factor showed no significant change during the trial in either of the groups (not shown).

In healthy subjects, the plasma ir-EP levels were significantly higher than in RA patients: (plasma ir-EP in fmol/ml, mean \pm SEM) healthy subjects, 12.6 ± 3.9 ($n = 12$); RA patients, 4.1 ± 0.5 ($n = 37$). Plasma ir-EP levels significantly increased in the supplemented and control group; however, the increase in the supplemented group occurred earlier and was higher than in the control patients (Fig. 4); at the end of the supplementation period, there was also a significant difference between both groups.

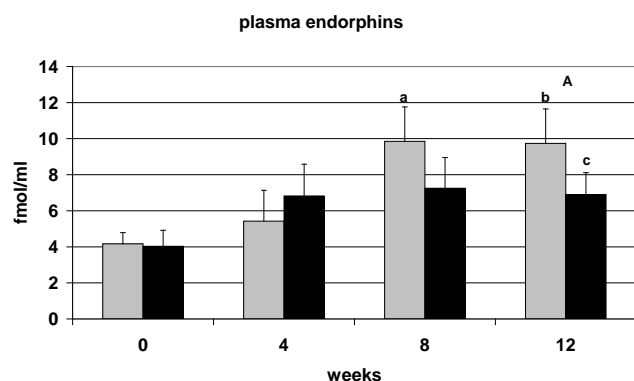


Fig. (4). Plasma endorphin concentration in supplemented (first column) and unsupplemented (second column) RA patients at 0, 4, 8, and 12 weeks. Significant difference in comparison with time 0 of the respective group; a: $p = 0.016$; b: $p = 0.018$; c: $p = 0.045$. Significant differences between groups; A: $p = 0.043$; mean \pm SEM.

At the end of the study, the medication of 6 out of 19 supplemented patients was reduced: in 3 patients, the daily steroid dose was decreased by 2-4 mg, and three other pa-

tients no longer needed to take NSAIDs. In the control group, one patient had to be put on medication because of hypertension during the trial, and one patient's steroid dosage had to be increased, in the other patients medication was unchanged. The reduction in medication in the supplemented compared with the control group was statistically significant according to the Fisher's exact test ($p=0.014$).

DISCUSSION

The cause of RA is still unknown, but it is likely to involve both genetic susceptibility and environmental factors such as diet [11]. The role of nutrition should be clarified with respect to two fundamental aspects: 1) Does it have any effect in the clinical expression of the disease or in susceptibility to RA? 2) Could any diet or nutrient supplementation play a role in the management of RA by alleviating symptoms such as pain, by decreasing the progression of the disease, or by reducing the reliance on or combating the side-effects of NSAIDs? [12].

Case-controlled studies indicate that the lifelong consumption of fish, olive oil, and cooked vegetables may have protective effects on the development or severity of RA [13, 14]. Patients with RA have been reported to consume too much total fat and too little polyunsaturated folic acid (PUFA) and fibre [15]. The so-called Western diet (which is also ingested by most of the population in Hungary) is well known to lead to the development of latent metabolic acidosis [16]. Compensation of this acidosis is possible by increasing the intake of organic mineral salts either from the diet (increased intake of vegetables and fruits) or from supplements. The main alkaline substances in our diet are citrates; a useful supplement therefore should contain a mixture of various citrate salts of sodium, potassium, calcium, and magnesium. The used supplement contains all these salts, together with trace elements and lactose, which increases the bioavailability of minerals. The used dose of the supplement provides a total of 45 mEq base per day. The usual daily surplus of acid in the Western diet is 60 mEq in an elderly population [17], and so a significant reduction in acid load is achieved with the supplementation. There is to date no indication that single constituents of the supplement alone work in improving the symptoms in RA patients.

Supplementation of the usual diet with alkaline minerals improved the DAS28 in this study. Of the contributory factors of DAS, the level of pain changed most remarkably in the supplemented group; however, laboratory parameters indicating the degree of inflammation (ESR, CRP) did not change in either of the groups, indicating that the severity of the disease by itself was not influenced by the supplementation. One might argue that plasma parameters of acid-base status (pH and bicarbonate values) should have been determined in this study; however, these parameters are extremely well buffered, and changes in these parameters are much smaller than the probable pH or buffer changes in the interstitium [18].

The reduced pain sensation can be explained by the significant elevation of plasma ir-EP levels following alkaline supplementation. The exact physiological role of circulating ir-EP is still obscure. What is clear from biochemical studies is that ir-EP binds predominantly to the mu opioid receptors [19] that are present in several peripheral tissues including

immune cells [20, 21] and the synovial membrane [22]. Sporadic experimental data suggest that peripheral ir-EP and its opioid receptor system play a role in the physio-pathology of local inflammatory processes. The above experimental results and the reported negative correlation between RA activity and plasma ir-EP levels [23], together with the general opinion that relative ir-EP deficiency may play a part in the manifestation of autoimmune diseases [24, 25], all suggest a causality between the circulating ir-EP levels and the arthritis-induced pain.

In addition to a pain-reducing direct effect of endorphins, an alternative explanation might be the more alkaline environment in the local surrounding of the joints, as pain receptors are sensitive to small pH changes. Significant changes in pH have been shown to occur in the interstitium without detectable changes in blood pH [18].

The finding that 6 out of 19 patients taking an alkaline supplement could reduce their daily steroid or NSAID dosage also supports the view that a reduction in latent metabolic acidosis has a positive effect on pain sensation. As the chronic need for pain medication is connected to potential side-effects, it is of great importance to find safe adjuvant therapies for these patients, such as supplementation with alkaline minerals, even though the supplementation does not influence the severity of the disease itself.

The limitations of this study include its small sample size and the lack of an active control group. However, the results of this pilot trial should encourage further randomized placebo-controlled studies to investigate the effects of alkali therapy.

CONCLUSIONS

Studies of the effects of dietary habits and nutrient supplementation on RA are, to quote Ollier *et al.* [26], "hampered by the inherent variability in the clinical course of the disease and the wide spectrum of clinical phenotypes." Patients frequently self-prescribe complementary medicines including diet modifications. This leads to considerable difficulties in selecting an appropriate group of patients for study. Improvement in symptoms may be dependent on the severity of the disease and on the underlying inflammatory status. An important finding of this study is the significant decrease in pain and DAS28 level and elevation in plasma ir-EP levels following several weeks of alkaline supplementation. Our study is the first to demonstrate the effect of the metabolic acid-base balance on plasma ir-EP levels. The results of our study suggest that an alkaline supplement may improve function and pain in rheumatoid arthritis and represents an easy and safe addition to the usual treatment of RA patients.

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