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Adjunct role of potassium-rich vegetarian diet and a novel potassium food supplement to improve pain in chronic rheumatoid arthritis on supervised standard care: a randomised controlled study

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ABSTRACT

Introduction An earlier food survey showed dietary potassium deficiency in rheumatoid arthritis (RA).

Objective To evaluate an adjunct role of oral potassium to reduce joint pain in RA.

Methods 172 consenting eligible symptomatic patients (median duration 6.5 years) on standard care were randomised into an assessor blind, parallel efficacy, controlled, prospective, multiarm single-centre study (80% power, drug trial design) of 16 weeks duration—arm A (potassium-rich vegetarian diet), arm B (arm A plus novel potassium food supplement) and arm C (control, regular diet). Standard efficacy (American College of Rheumatology recommendation) and safety and diet intake (3-day recall) were assessed at monthly intervals (protocol). Standard soft-ware package (SPSS V.20) was used for statistical analysis; analysis of variance), Mann-Whitney statistic and χ^2 test.; significant $p<0.05$, two sided). Study arms were found matched at baseline. Background RA medication remained stable. Preset target for increased potassium intake (India standards) were mostly achieved and participants remained normokalemic.

Results 155 patients (90.1%) completed the study and several showed improvement (maximum improved measures in arm B). Potassium intervention was safe and well tolerated. Adverse events were mild; none caused patient withdrawal. On comparison, the mean change in pain visual analogue scale (−2.23, 95% CI −2.99 to −1.48) at week 16 (primary efficacy) from baseline was significantly superior in arm B (per protocol analysis). A high daily potassium intake (5–7.5 g, arm B) was significantly associated with low pain (study completion); OR 2.5 (univariate analysis), likelihood ratio 2.9 (logistic regression). Compliance (intervention), diet record and analysis, RA medication and absence of placebo were potential confounders.

Conclusion High oral potassium intake, based on a suitable vegetarian diet and food supplement, reduced joint pain and improved RA. It was a safe adjunct to standard care, Further validation studies are required.

WHAT IS ALREADY KNOWN ON THE TOPIC

⇒ Potassium is a vital micronutrient in health, but little is known about its role in rheumatoid arthritis (RA).
⇒ Patients suffering from symptomatic RA may consume potassium-deficient diet.

WHAT THIS STUDY ADDS

⇒ Increased potassium intake based on a suitable vegetarian diet and a novel food supplement may reduce joint pain and improve RA.
⇒ High oral potassium intake was found safe and well tolerated.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A high potassium intake based on vegetarian diet and food is a useful adjunct to manage difficult symptomatic RA in clinical practice.
⇒ The current recommendations/guidelines on potassium intake should be revised.

Trial registration CTRI/2022/03/040726; Clinical Trial Registry of India.

INTRODUCTION

Rheumatoid arthritis (RA) is a lifelong autoimmune disease characterised by painful polyarthritis and articular deformities, and systemic complications.[1] Patients often suffer from poor quality of life and productivity and reduced longevity.[1] The global burden is enormous and rheumatology care is often inadequate.[2] Standard treatment guidelines focus on drugs and adjuvant therapies such as diet are neglected.[3] In ancient medicinal systems, diet is pivotal in the management of arthritis.[4] An evidence-based therapeutic role of diet in RA seems limited.[5]

We reported low potassium intake in RA.[6] Although an essential micronutrient, its role in RA is not described.[7 8] Weber[9] advocated a strong aetiological link.[9] A population nutrition survey showed low potassium intake and serum potassium in RA subjects.[10] A low body potassium in RA was reported.[11] High potassium chloride (mixed in grape juice) intake for 28 days reduced pain and improved RA.[12]

The current objective was to investigate oral potassium as an adjunct to standard RA treatment. The primary hypothesis was potassium-reduced joint pain in RA. Potassium-rich vegetarian diet and a novel potassium-enriched food supplement were used as active intervention.

METHODS AND PATIENTS

This was a non-commercial investigator- initiated study.[13] The protocol was registered and adhered to the tenets of the 'Helsinki Declaration' (updated) and national guidelines.[14 15] The period of recruitment was from 12 Feb 2014 to 02 July 2014. The last patient last visit was on 12 Dec 2014.

Study design

This was a randomised, single blind (assessor), active control, parallel efficacy, prospective drug trial study of 16 weeks duration. It was carried out in a community-based rheumatology centre (CRD). There were three treatment arms—arm A (potassium-rich vegetarian diet), arm B (arm-A diet plus potassium-enriched food supplement) and arm C (control routine diet). Each randomised participant was examined at baseline and monthly study time points till study completion.

Participants and selection

Volunteer patients from the outpatient clinic of CRD signed an informed consent and were randomised if found eligible on screening.[15] Patients were required to have painful arthritis for at least 8 weeks and supervised standard care for at least 16 weeks prior to enrolment. Patients received a modest allowance for travel and meals. All study procedures and the potassium food supplement (KFS) were provided free of cost to the participants.

Inclusion criteria included (1) adult patient of RA[16] (2) disease duration of at least 6 months (3) maximum pain (joints) ≥4 cm on a visual analogue scale (VAS) in the previous 24 hours (screening). Exclusion criteria included (1) daily prednisolone dose of 10 mg or more anytime during the previous 4 weeks (2) abnormal serum creatinine, blood urea nitrogen assay and serum potassium (≥5.5 mEq/L) assay (3) any medication known to effect body potassium.

Efficacy

The primary efficacy was an improvement in the pain VAS at week 16 (study completion) from baseline. There were several secondary efficacy measures of disease activity and function and safety.[17]

Procedures

Potassium food supplement

The entire process of manufacturing beginning from procurement of standard raw food ingredients (government accredited shops) to the final preparation of standardised mixture was carried out by the study nutritionist (TK, first author) using local resources. The composition, microbial and toxicology results and shelf life are described in online supplemental figure 2. The cost of manufacturing was mostly borne by TK and several related facilities and trained staff were provided free of cost by the CRD. No commercial/manufacturing company was engaged for this purpose. KFS is not available in the market in India or abroad. Several details are described in the patent granted by the Government of India.[18]

One hundred and forty-two gram (one unit) of supplement contained green gram (V radiate, 25 g), cow pea (V unguiculata, 25 g), coriander seed (C sativum, 25 g), cumin seed (C cyminum, 25 g) and 42 g of oral rehydration salt (Indian pharmacopoeia, 3 g potassium chloride, 5.2 g sodium chloride, 5.8 g trisodium citrate, 27 g glucose). The latter contained 2638 mg elemental potassium (green gram 294.6 mg, cow pea 287 mg, coriander seed 247.4 mg, cumin seed 245 mg, oral rehydration salt 1564 mg).

Randomisation/enrolment

Study participants were provided a study information brochure in local language and suitably counselled by TK. A standard computer-generated randomisation schedule (1:1:1) was prepared by SS. Participants were randomised on first come first serve basis.

Diet food record

A validated questionnaire and standard household measures were used in a face-to-face interview with the participants by TK to record retrospectively a 3 successive day diet consumption at all study visits.[6]

Clinical assessment

This was carried out by designated rheumatologists and paramedics in a blinded manner.

A 68/66 joint count was used to assess pain/tenderness and swelling.[17] The pain VAS was a 10 cm-long horizontal scale: 0 for nil pain and 10 for maximum pain. A Likert scale with five categories (asymptomatic to severe) was used to record physician and patient global assessment. A questionnaire-based RA pain score instrument recorded qualitative pain (range 0–144); higher score meant worst pain.[19] The functionality was assessed by a validated modified Stanford health assessment questionnaire (HAQ, range 0–24); higher score indicated more difficulty.[20] Short form 36 (SF 36), with permission from the vendor, assessed physical and mental health (quality of life); higher score meant better health.[21] Improvement and disease activity were assessed by standard indices.[22]

Others

Routine investigations were carried out as per standard of care in RA and to ensure safety of potassium administration. Serum cortisol and spot urinary potassium assay were done.

Study intervention

A potassium-rich vegetarian diet and a novel KFS were active interventions (arm A and arm B). Routine diet was used as active control (arm C) and no placebo was used. All participants in the study were advised to continue their routine schedule of three meals per day. They were not to fast or consume diet other than that advised in the study.

Diet/supplement targetThe potassium-rich diet was to provide at least 3500 mg of elemental potassium daily based on the recommended daily allowance (RDA).[23 24] The addition of KFS in arm B was meant to further increase the daily potassium intake to about 5.5 g.

Diet Brochure

A special diet brochure in the local language was prepared by TK and explained and provided to each participant in arms A and B. A copy is enclosed in online supplemental figure 1. It provided guidance on selection (and quantity) of food items (multiple choice) to prepare a meal for daily consumption by the participant. The meal was essentially a balanced vegetarian diet as per India recommendations.[23 24] Community food habits, cost and availability were duly considered in the brochure. Non-vegetarian food items were discouraged.

Potassium food supplement (arm B)

The dose was three heaped tablespoon (provided) taken two times a day with a glass of water immediately after a meal. This amount corresponded to 1.7–2 g of elemental potassium. Each participant received a 5-week supply of KFS at baseline and every monthly follow-up visit.

Control diet

Participants in arm C continued the ongoing routine diet as per their preference

Compliance

Participants were to strictly follow the allocated diet and any other advise provided in the study. A telephonic remiinder was given every 10–14 days. The unused portion of the KFS was returned and measured at each follow-up visit. The participants were aware that their monthly urinary sample was assayed for potassium

Concurrent medication

Participants continued previous standard RA medication under supervision of a CRD rheumatologist. The medication was to be kept stable but if necessary a change could be made based on clinical judgement. The pain medication was to be used on a need basis for severe/intolerable pain. Other co-morbid disorders were treated by the primary care physician.

Statistical plan and analysis

There was no prior data available to guide sample size. As the primary objective was to evaluate an adjunct role, a modest effect size for pain relief by the therapeutic potassium intervention (arm B) was considered; 10% superior to the control.[25] Based on the sample size tables in the latter publication, and an expected 20% drop out rate, 171 subjects were required (80% power, significant $p<0.05$, two-tailed). There were 57 participants in each study arm.

The daily diet data were analysed by TK in a blinded manner based on standard 'Food Composition Tables' (uncooked and cooked foods).[23 24] The latter was adjusted for the KFS intake in Arm B. The dietary results at week 16 were used for efficacy and compliance.

An intention to treat (ITT, last observation carried forward) and per protocol (completer) analysis was carried out. Standard statistical software package (IBMSPSS V.20, V.2015 and 2018) was used; parametric (one way analysis of variance (ANOVA)), non-parametric (Mann-Whitney statistic, KW signed rank test) and χ^2 test (categorical data) and Bonferroni's correction for repeated measures. Unless stated, all p values in the current report pertain to ANOVA.

Though not intended for the current report, results of some regression models are shown in online supplemental tables 6–8.

OBSERVATIONS AND RESULTS

One hundred and seventy-two patients were randomised and 155 (90.1%) completed the study (per protocol analysis) (figure 1). Seventeen (9.9%) patients were withdrawn prematurely but none was due to an AE.

The study arms were found matched at baseline that included RA disease activity measures. There was some difference in the use of methotrexate and sulfasalazine among the arms (table 1). Overall, the RA was moderately painful and active (table 5). Fifty-one patients (29.6%) recorded comorbid disorders and important being diabetes (10), hypertension (27), ischaemic heart disease (7), chronic acid-peptic disorders (34), haemorrhoids (7) and hypothyroidism (8); number of patients shown in parenthesis. None suffered from clinically apparent extra-articular complications (RA).

Diet

The results of dietary analysis and potassium intake are shown in tables 2 and 3. At baseline, the potassium intake was deficient in each of the study arms; Indian RDA is 3225 mg for women, and 3750 mg for men.[24] However, the potassium intake was substantially increased in the active intervention arms at week 16 with a several fold rise in arm B (median 5648 mg, range 4365–7545 mg); 84% of participants in arm B consumed 5 g or more daily. Several other nutrients were also found increased in the active

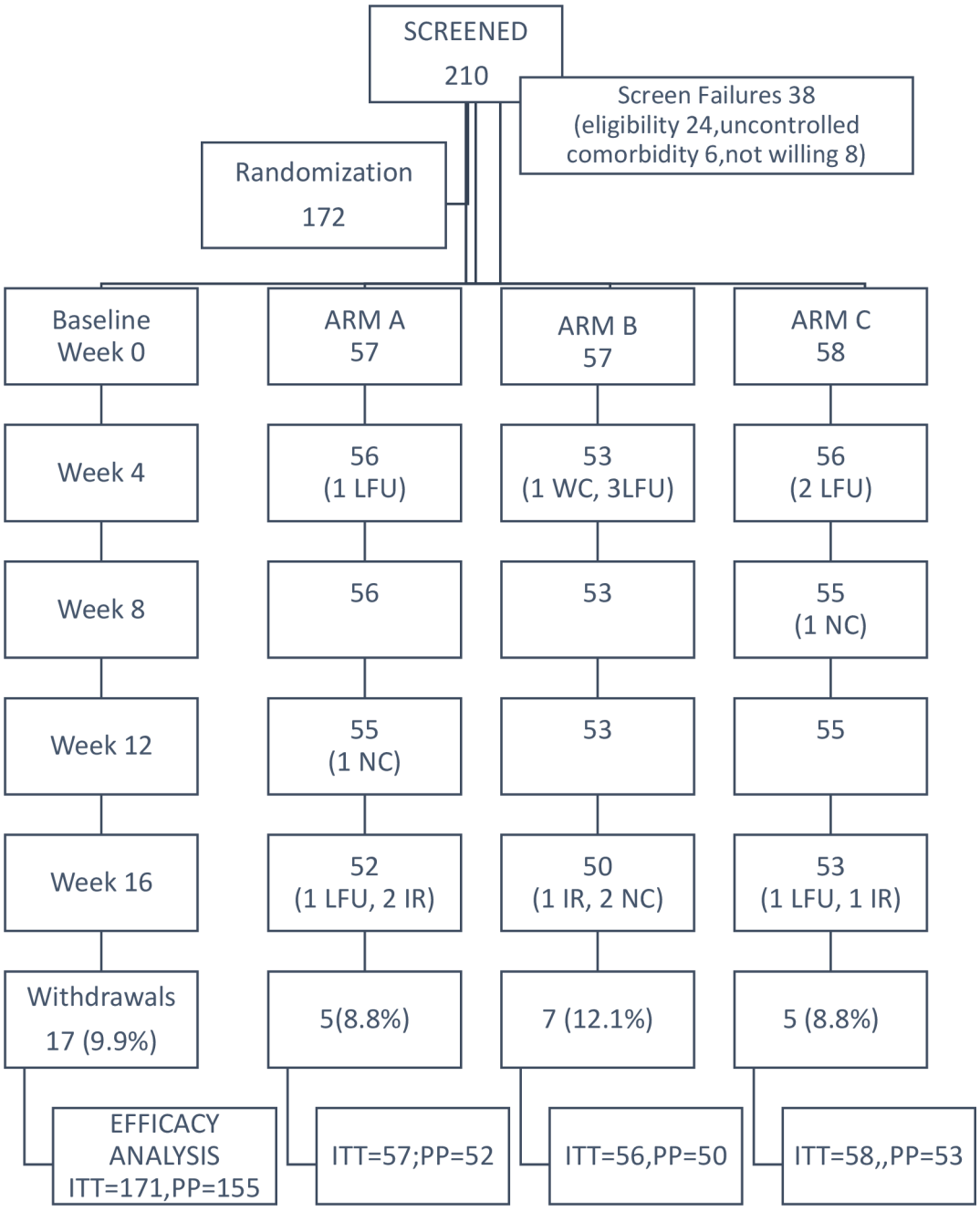

Figure 1 Patient disposition and number withdrawals—a randomised controlled three arm study of potassium intervention in rheumatoid arthritis (arm A, potassium-rich diet; arm B, potassium-rich diet plus potassium food supplement; arm C, routine diet; IR, inadequate treatment response; ITT, intention to treat analysis; LFU, lost to follow- up; NC, not protocol compliant; PP, per protocol analysis; WC: withdrew consent; see text for details).

intervention arms; the measures in arm C seemed stable (table 2).

Less than 5% of participants recorded consumption of eggs, red meat and fish, or other Western style food such as pizza or French Fries.

Safety and tolerability

Adverse events (AE) were reported by 14 patients in arm A (table 4), 16 patients in arm B and 11 patients in arm C (p=0.67, χ^2 statistic). They were mild and mostly related to abdominal complaints. Three patients in arm B required reduction in the daily dose of KFS for relief from mild to moderate abdominal pain/discomfort. Laboratory investigations (routine haematology, metabolic renal and hepatic) remained within normal range. All participants remained normokalemic at all study time points (online supplemental table 1); correspondingly electrocardiography showed normal pattern (table 4).

Efficacy

Primary efficacy: pain (VAS) was reduced at all predetermined study time points (figure 2). The mean change at week 16 from baseline was

Table 1 Baseline demographic and other variables: a randomised controlled potassium diet intervention study in patients suffering from rheumatoid arthritis (RA) and on standard care (A: potassium-rich diet; B: potassium-rich diet plus potassium food supplement; C: routine diet)

Variables	A (n=57)	B (n=57)	C (n=58)	P
Age, mean (years)	50.5 (11.2)	47.3 (12.1)	46.9 (10.5)	0.40*
Women (per cent)	85	91	92	0.70**
Duration (years) RA, mean, median	10.6 (8.1), 8	8.5 (7.4),6	7.4 (5.9), 5	0.08*
Body mass index, mean (Kg/m^2)	24.4 (3.8)	24.3 (4.3)	24.2 (2.9)	0.90*
Pain Score (VAS)>5 cms (per cent)	52.6	54.4	50	0.87**
Erosion hand/joint deformity (per cent)	75.4	50.8	62.1	0.15**
Prior continuous DMARD use duration (month), median (range)	26 (6–240)	18 (6–360)	21(6-216)	0.47*
ESR mm fall first hour, mean	70.6 (2.2)	68.8 (3.7)	67.4 (3.9)	0.84*
C-reactive protein mg/dL, mean	33.3 (39.4)	26.2 (31.1)	25.5 (37.8)	0.45*
RF seropositive (per cent)	76	83	68	0.07**
Serum potassium mEq/L, mean	3.9 (0.5)	3.8 (0.6)	3.9 (0.5)	0.59*
Urine potassium mEq/L, mean	44.4 (25.6)	46.7 (25.8)	42.9 (29.1)	0.88*
DMARD single or combination plus Pred use (per cent)	70.2	61.4	70.6	0.49**
DMARD single agent only (per cent)	19.3	22.8	19	0.89**
Methotrexate use (per cent)	82.4	87.8	60	0.00**
Sulfasalazine use (per cent)	33	19	47	0.01**
Hydroxychloroquine use (per cent)	40	40	47	0.27**
Analgesic use† (per cent)	81	95	90	0.07**
Daily Pred dose mg, mean	5.4 (2.8)	5.3 (2.5)	5.5 (2.3)	0.94*
Weekly methotrexate dose mg, mean	14.8 (4.4)	14.9 (4.4)	13.9 (4.3)	0.56*
Blood Haemoglobin g/dL, mean	11.6 (1.3)	11.6 (1.3)	12.1 (1.3)	0.07*

†Analgesic includes paracetamol and other analgesic use of non-steroidal anti-inflammatory drug/NSAID (diclofenac, naprosyn, etorocoxib, etodolac, nimesulide) more than 4 times a week.
*Analysis of variance.
**χ^2 statistic using count.
*/**significance: p<0.05, two-tailed.
Per cent pertains to proportion of subjects positive.
Mono: single drug; standard deviation shown in parenthesis after mean; see text for details.
DMARD, disease-modifying antirheumatic drug (methotrexate, sulfasalazine, hydroxychloroquine); n, number of patients; Pred, prednisolone.

statistically significantly (p=0.039) as per protocol analysis but not by an intention to treat analysis (p=0.17) (table 5 and online supplemental table 2). The mean change in pain VAS in arm B (95% CI −2.99 to −1.48) was significantly superior to that in arm C (adjusted p=0.02) and arm A (adjusted p=0.04) (table 4).

Secondary efficacy: several variables improved to varying extent although it seemed numerically superior in the majority in arm B (table 4).

RA medication

The background RA medication seemed mostly stable (table 6, online supplemental file 1, table 3). However, there was a conspicuous increase in the number of patients being treated with methotrexate in arm C at week 16 (online supplemental table 3).

Other outcomes

Clinical

At baseline, the mean systolic/diastolic blood pressure (mm Hg) was 131/79 in arm A, 129/80 in arm B and 125/79 in arm C; correspondingly at week 16, it was 117/80, 116/80 and 126/82. The blood pressure was recorded as a routine procedure by the study nurse (sitting position).

Serum cortisol (morning) assay (online supplemental table 1): though not significantly different, the increase was maximum in arm B at week 16

Correlation (online supplemental table 4): potassium intake and pain VAS showed a significant inverse correlation (r=−0.19). Urine potassium assay did not correlate with oral potassium intake or serum potassium.

Table 2 Median (95% CI) of daily energy and nutrient consumption at baseline (week 0) and study completion (week 16) as per protocol analysis: a randomised controlled potassium diet intervention study in patients of rheumatoid arthritis (RA) on standard care (A: potassium-rich diet; B: potassium-rich diet plus potassium food supplement; C: routine diet)

Arm/nutrient	A (n=52)		B (n=50)		C (n=53)		p1	p2
Time points/week	**0**	**16**	**0**	**16**	**0**	**16**		
Energy (Kcal)	2975 (2827, 3123)	3007 (2852, 3161)	2875 (2717, 3033)	3476 (3372, 3580)	2772 (2648, 2897)	2730 (2590, 2870)	0.14	0.00
Protein (gm)	101 (93, 109)	101 (93,111)	96 (88, 103)	126 (111,137)	89 (82, 95)	89 (83, 94)	0.04	0.00
Fat (gm)	72 (69,74)	76 (74,77)	74 (70, 78)	91 (70,133)	76 (74,77)	77 (73,81)	0.35	0.09
Zinc (mg)	13 (12,14)	14 (13,16)	13 (12,14)	18 (16,19)	13 (12,13)	11 (10,20)	0.46	0.11
Calcium (mg)	800 (729,872)	693 (617,769)	696 (638,754)	1196 (1178, 1214)	683 (626,739)	607 (566, 649)	0.01	0.00
Phosphate (mg)	2198 (2058, 2340)	2173 (2012, 2334)	2126 (1990, 2263)	2515 (2216, 3625)	1997 (1871, 2123)	1969 (1857, 2082)	0.08	0.00
Vitamin A (µg)	1181 (1021, 1342)	830 (692, 982)	985 (844, 1128)	1032 (839, 1225)	1040 (836, 1244)	869 (696, 1042)	0.34	0.17
Thiamin (mg)	3 (3,3)	3 (3,3)	3 (3,3)	4 (3,6)	3 (3,3)	3 (3,3)	0.57	0.05
Riboflavin (mg)	2 (1,2)	1 (1,2)	1 (1,2)	2 (1,2)	1 (1,1.1)	2 (1.2)	0.05	0.27
Niacin (mg)	25 (24, 27)	26 (25, 28)	25 (23, 26)	35 (23, 48)	24 (23, 26)	25 (24, 27)	0.65	0.07
Vitamin C (mg)	162 (147,177)	163 (151,177)	152 (139,165)	160 (149,172)	172 (153,192)	169 (156,182)	0.15	0.62
Iron (mg)	34 (32, 37)	33 (32, 36)	31 (29, 34)	41 (36, 44)	23.3 (23, 51)	30 (28, 32)	0.66	0.00
Folic acid (µg)	421 (378, 464)	424.5 (386, 463)	393 (354, 431)	480 (417, 543)	373 (334, 412)	308 (338,397)	0.21	0.00
Sodium (mg)	2668 (2665, 2723)	2653 (2644, 2670)	2649 (2820, 3038)	4501 (4423, 4579)	2654 (2646, 2684)	2647 (2636, 2658)	0.17	0.00
Potassium (mg)	2444 (2445, 2879	2959 (2832, 3282)	2399 (2293, 2729)	6063 (5579, 6097)	2469 (2324, 2858)	2553, (2428, 2920)	0.65	0.00

Measure value rounded to nearest integer and standard deviation to 1 decimal place.
p1: p value, ANOVA, comparing baseline (0 weeks); p2: p value, ANOVA, comparing study completion (16 weeks); Food Composition Tables as recommended by National Institution of Nutrition, Hyderabad (see reference serial 23 in text); significant p<0.05, two-tailed (ANOVA).
ANOVA, analysis of variance; n, number of study participants.

Table 3 Median intake and number (per cent) of patients achieving recommended daily allowance (India) of potassium and increase intake compared with randomisation baseline: a controlled dietary potassium intervention study (n=172) in chronic rheumatoid arthritis [A=potassium-rich diet; B=potassium-rich diet plus potassium food supplement; C=control routine diet]—per protocol analysis

Arm/time point week/daily potassium intake (target)	A		B		C			
	0 (n=57)	16 (n=52)	0 (n=57)	16 (n=50)	0 (n=58)	16 (n=53)	P1	P2
Daily potassium intake—median (range),90th percentile, mg	2902 (937–4697), 3750	2984 (713–4619), 4150	1863.7 (939–4162), 3400	5708.5 (4365–7545), 6560	2697.5 (680–4645), 3900	1749.8 (1039–4579), 3820	0.68	0.00 (0.02)
Minimal RDA (3500 mg) consumption	14 (25%)	24 (46)	12 (21%)	50(100)	19 (33%)	16 (30)	0.31	0.00 (0.23)
Consumption more than baseline	–	38 (73)	–	50 (100)	–	29 (55)	–	0.00 (0.04)
Consumption more than baseline by 20%	–	23 (44)	–	48 (96)	–	15 (28)	–	0.00 (0.10)
Consumption more than baseline by 50%	–	7 (13)	–	47 (94)	–	10 (19)	–	0.00 (0.29)
Consumption more than 1.5 times RDA (5250 mg)	–	0	–	42 (84)	–	0	–	0.00

Target for arm A: 3200 mg daily (modified RDA for men and women); target for arm B: 4800 mg (1.5 times the RDA for women at 3200 mg); 90th percentile is rounded to multiple of 50;,significant p <0.05, two-tailed; P1: comparing baseline-ANOVA (median)/χ^2 (categorical data); P2: comparing study completion week 16—ANOVA (median)/χ^2 (categorical data); parenthesis in P2 shows comparison of arm A and arm C (not adjusted for repeated measure); see text for details.
n, number of study participants; RDA, recommended daily allowance.

Univariate analysis (online supplemental table 6): daily potassium intake of 5 g or more (OR 3.14) was significantly associated with low pain VAS (≤ 4 cm).

Logistic (step forward) regression (online supplemental table 7): a daily potassium intake of 5 g or more (likelihood ratio 2.87) and methotrexate use (likelihood ratio 16.1) were significant predictors of low pain VAS when adjusted for several clinical, medication and diet-related variables.

DISCUSSION

The reduction in joint pain was substantial and significantly superior in patients of chronic symptomatic RA on standard care who consumed high potassium (arm B, potassium-rich vegetarian diet plus a novel potassium-enriched food supplement) as compared with only potassium-rich vegetarian diet (arm A) or a routine diet (arm C) in this randomised, assessor blind, controlled study of 16-week duration. The reduction in pain in arm A and arm B was much more than what was reported as a minimal clinical important difference.[26] Of 155 (90%) patients completed the study. Over 80% patients in arm B consumed 5.2 g or more of elemental potassium daily (range 4365–7545 mg). The AE was generally mild, and none led to a patient withdrawal.

Strengths and implication

The real to life management of RA and the dietary nature, safety and tolerability of the potassium intervention were the core strength. RA is a difficult to treat disorder and the medication is potentially toxic.[1 2] Medicinal use of potassium is fraught with drug toxicity.[8] We used diet and a food supplement to administer potassium in the current study as per recommendations.[27 28] However, the potassium content of food supplements in Europe (500–1000 mg) and USA (<100 mg) seems inadequate to meet the daily requirements and needs to be revised.[28 29] The physiological adjustment to high potassium intake is rapid in the healthy state.[27–29] The baseline potassium intake in the current study was inadequate (table 2) and this has been previously reported both in RA and healthy populations.[6 8 10 28 29] The current potassium intervention was based on preset targets (see methods) and the target for arm B was considered therapeutic by in-house expert consensus. Encouragingly, arm B showed substantial pain reduction. Importantly, all study participants remained normokalemic and further supported our contention of safety with diet based and enriched potassium intake (online supplemental table 1). The clinical benefit of higher potassium intake in painful inflammatory disorders such as RA should be further investigated.

Several unique problems in our setting such as poor socioeconomic status and difficult logistic complicate management of RA.[2 19] Standard conventional disease-modifying anti-rheumatic drugs (DMARD) and steroids are preferred.[1–3] Effective pain management is critical to any successful outcome. Despite standard of care in RA

Table 4 Adverse events (number): a randomised controlled potassium diet intervention study in patients suffering from rheumatoid arthritis (RA) and on standard conventional DMARD with/without steroid treatment [A: potassium-rich diet; B: potassium-rich diet plus potassium food supplement; C: routine diet)

Adverse event	A (N= 57)		B (N =57)		C (N=58)	
	Total episode	Number of patients	Total episode	Number of patients	Total episode	Number of patients
Nausea	5	4	3	3	4	3
Vomiting	3	3	1	1	1	1
Acid-peptic symptoms	3	3	4	4	4	4
Diarrhoea	1	1	2	2	1	1
Constipation	1	1	3	2	2	2
Anorexia	2	2	2	1	2	2
Skin rash	4	4	5	4	2	1
Infections	1	1	3	3	1	1
Vertigo	2	1	0	0	0	0
Oral ulcer	1	1	1	1	0	1
Hair fall	1	1	0	0	2	1
Leucopenia	1	1	0	0	0	0

Infections include upper/lower respiratory tract infections and urinary infections.
DMARD, disease-modifying antirheumatic drug (methotrexate, sulfasalazine, hydroxychloroquine); n, number of patients.

and in particular with modern potent biologic DMARDS, residual pain remains a vexing issue.[1 3 30] On the other hand, despite impressive scientific evidence and universal community concerns, rheumatologists neglect diet in medical practise.[2–4 6 31 32]

Pain is a core issue in RA and a predictor of psychosocial health and disease outcome and is often found to be disproportionate to the clinical assessment.[1 3 17 22 26 30 33 34] Pain VAS is a reliable and valid easy to perform measure.[26] The substantial reduction in pain VAS in arm B was

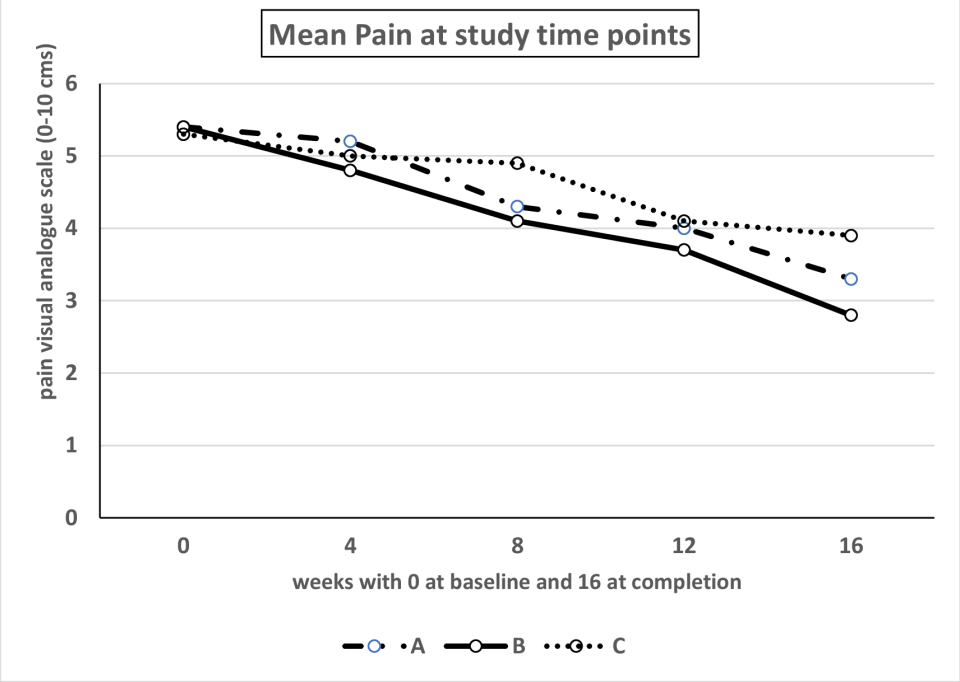

Figure 2 Mean pain visual analogue scale at pre-determine study time points—a randomised controlled three arm study of potassium intervention in rheumatoid arthritis over 16 weeks duration (arm A: potassium-rich diet; arm B: potassium-rich diet plus potassium food supplement; arm C: routine diet; see text for details).

Table 5 Efficacy analysis (per protocol)—showing mean at randomisation baseline and mean change at week 16 along with 95% CI (in parenthesis): a randomised controlled potassium diet intervention study in patients (n=172) of rheumatoid arthritis (RA) on standard care [A: potassium-rich diet; B; potassium-rich diet plus potassium food supplement; C; routine diet)

	A (n=52)		B (n=50)		C (n=53)		P*
Variable (normal range)	**Baseline**	**Mean change**	**Baseline**	**Mean change**	**Baseline**	**Mean change**	
Pain visual analogue score (0–10 mm)	5.45, (5.18, 5.66)	−1.31 (-2.19, −0.43)	5.42 (5.19, 5.65)	−2.23 (−2.99, −1.48)	5.26 (5.01, 5.52)	−1.25 (−2.03, −0.46)	0.03
Swollen joint count (0–66)	2.36, (1.76, 2.99)	−1.76 (−2.49, −1.03)	2.46 (1.84, 3.15)	−0.74 (−2.4, 0.92)	2.5 (1.51, 3.78)	−1.66 (−3.06, −0.25)	0.27
Painful tender joint count (0–68)	11.19 (8.65, 13.74)	−8.63 (−12.17, −5.1)	13.11 (10.21, 16.01)	−8.88 (−12.98, 4.77)	11.96 (8.82, 14.46)	−6.09 (−11.11, −1.07)	0.42
Patient Global Assess (grade 1–5)	2.09 (1.91, 2.22)	−0.55 (−0.91, 0.2)	2.12 (1.89, 2.34)	−0.6 (−0.98, −0.21)	1.96 (1.79, 2.13)	−0.26 (−0.6, 0.07)	0.15
Physician Global Assess (grade 1–5)	1.36 (1.22, 1.49)	−0.42 (−0.58, −0.27)	1.36 (1.19, 1.53)	−0.43 (−0.63, − 0.19)	1.41 (1.25, 1.55)	−0.50 (−0.69, −0.30)	0.84
Health assess Questionnaire (0–24)	5.32 (4.50, 6.14)	−1.94 (−3.22, 0.66)	5.11 (4.18, 6.05)	−2.62 (−4.04, −1.2)	4.60 (3.86, 5.14)	−0.86 (−2.21, 0.48)	0.05
General Health VAS (0–100)	51.03 (47.64, 54.42)	13.61 (5.91, 21.31)	51.78 (47.32, 55.66)	14.82 (5.90, 23.73)	50.39 (48.24, 53.58)	10.92 (3.19, 18.65)	0.61
RA Pain Scale (0–144)	61.96 (53.13, 70.79)	−16.80 (−29.17, 4.44)	56 (47.53, 64.46)	−12.5 (−27.82, 2.82)	63.37 (55.02, 70.43)	−24.09 (−36.83, −11.35)	0.26
Short Form 36—Physical score	42.24 (40.18 43.89)	1.75 (-1.17, 4.69)	41.75 (39.66, 43.31)	3.03 (0.39, 6.45)	43.39 (41.85, 44.70)	0.07 (−2.17, 2.31)	0.15
Short Form 36—Mental score	40.57 (38.01, 42.39)	2.34 (−1.05, 5.74)	41.57 (39.06, 43.05)	1.44 (−1.71, 4.61)	40.49 (38.86, 42.73)	2.81 (−0.55, 6.18)	0.73
ESR (mm fall end 1st hour)	70.48 (72.73, 78.51)	−8.05 (−17.85, 1.7)	68.76 (61.51, 76.56)	−11.66 (−22.30, −1.01)	64.05 (57.67, 72.50)	−8.66 (−17.77, 0.4)	0.76
C reactive protein (mg/dlL)	31.66 (23.17, 44.53)	−18.31 (−33.10, 3.5)	26.89 (17.79, 35.43)	−8.33 (−18.45, −1.8)	23.23 (15.21, 35.98)	−8.57 (−23.77, 6.6)	0.33
Disease Activity Score 28 (ESR)	4.85 (4.67, 5.16)	−1.38 (−1.81,−0.9)	4.97 (4.73, 5.31)	−1.22 (−1.76, −0.68)	4.84 (4.60, 5.07)	−1.05 (−1.62, −0.47)	0.46

*Analysis of variance; significant p<0.05, two-sided; see text for details.
ESR, erythrocyte sedimentation rate; n, number of patients.

Table 6 Mean dose (95% CI) of weekly methotrexate (mg) and oral daily prednisolone (mg) at randomisation baseline and study completion (week 16) and difference in the mean: a randomised controlled potassium intervention diet study (n=172) in rheumatoid arthritis on standard care [A=potassium-rich diet; B=potassium-rich diet plus potassium food supplement; C=control routine diet]

Drug	Baseline	Completion	Mean of the difference at week 16 from baseline
Methotrexate (A), n=47	14.89 (13.62, 16.16)	14.56 (13.10, 15.70)	1.86 (0.07,3.65)
Methotrexate (B), n=50	13.75 (12.5, 14.74	15.95 (15.59, 17.31)	3.44 (1.46,5.42)
Methotrexate (C), n=50	14.02 (13.42, 15.57)	15.07 (13.83, 16.29	5.86 (3.37,8.35)
Prednisolone (A), n=48	5.45 (4.52, 6.38)	3.42 (2.49, 4.35)	−0.88 (−2.36, 0.60)
Prednisolone (B),n=34	5.07 (4.16,5.98)	4.04 (3.17, 4.91)	0.02 (−1.50,1.52)
Prednisolone (C), n=49	5.45 (4.64, 6.26)	4.02 (3.07,4.97)	0.01 (−1.39,1.41)

Baseline comparison, methotrexate, p=0.56.
Completion comparison, methotrexate, p=0.64.
Baseline comparison, prednisolone, p=0.94.
Completion comparison, prednisolone, p=0.58.
Mean of the difference comparison, methotrexate, p=0.02 (pair wise comparison: A–B, p=0.23, B–C, p=0.12, A–C, p=0.009).
Mean of the difference comparison, prednisolone, p=0.46.
Baseline/completion: actual consumption of drug by subjects at baseline and on completion.
Mean of the difference calculation: last observation (dose) was carried forward for subjects withdrawn prematurely and nil (0) dose was considered at baseline for subjects who were begun on the drugs during the study and completed week 16.
Statistical tests: one way ANOVA, significant p.
ANOVA, analysis of variance; n, number of study participants.

consistent with definite improvement in several other measures; significant improvement in function also shown in HAQ (table 5). In our opinion, the latter was likely to be associated with the increased potassium intake.

Diet interventional studies are difficult and often complicated by lack of adequate control.[35] The current study was statistically designed. Chronic RA is a heterogenous disease. However, the study arms were well matched (table 1). The background RA medication remained almost unchanged (table 6, online supplemental file 1). Importantly, the compliance to dietary intervention seemed fair (tables 2 and 3).

The inadvertent lowering of mean systolic blood pressure, although modest, in the active potassium intervention arms (but not in the control arm) was consistent with the beneficial effect of potassium on blood pressure. In retrospect, this also meant that participants were compliant for active diet intervention. Cardiovascular morbidity and premature mortality are major concerns in RA.[36] Several studies have reported the benefit of potassium on blood pressure and other cardiovascular function[8 28 37]

Limitations

Compliance to dietary intervention and protocol, RA medication bias, unblinded nature of intervention and difficulties in recording diet and analysis were of special concern in the current study. Despite varying potassium intake, there were no significant differences in the urinary potassium assay between the arms and this may be due to intense renal compensation (online supplemental table 1).[8 37] Dietary recall can be problematic and 'food composition tables' may underestimate diet analysis.[38]

Participants in the current study were aware of their dietary intervention and this is likely to increase expectation of benefit (placebo effect). We did not use placebo in the current study. The current 16-week study period was considered sufficient to substantially mitigate a placebo effect. Clinical assessments were carried out in a blinded manner.

Erythrocyte sedimentation rate (ESR) and CRP (C reactive protein) are acute phase reactants and were found substantially increased at randomisation baseline (table 1). There was a significant reduction in ESR in group B, which was consistent with pain improvement, but the CRP response was lacklustre (table 5). This is rather unusual and we have no definite explanation. However, in personal experience, the author (AC) has noticed this uncommonly in patients of chronic symptomatic RA with systemic complications and on prolonged therapy with conventional DMARD and low-dose steroids. Such a discordance (ESR-CRP) has been reported in RA, lupus and certain other disorders.[39 40]

The background medication might have introduced some bias that was not recognised. But this seems unlikely in view of a comprehensive analysis of use of DMARD and steroids (table 6, online supplemental file 1, table 3). Interestingly, the overall consumption of analgesics in the current study was modest and there were no significant differences between the arms (online supplemental table 3). However, patients of chronic RA often do not report proper use of analgesics in the experience of the author (AC).

It is also possible that the current benefits of potassium intervention were confounded by the use of balanced

vegetarian diet. Plant-based diets are reported useful in RA.[41] Notably, although several nutrients were found increased in the active intervention arms (table 2), only potassium intake was identified as a significant predictor for low-pain VAS in the regression analysis (online supplemental table 7).

Other studies

Several elegant studies have reported benefit of mediterranean diet (MD) in RA, which was shown to be of modest nature in the cochrane analysis.[42 43] To the best of our knowledge, although predominantly vegetarian the MD was not assessed for potassium and other nutrients.[41]

The benefits of potassium have been mostly reported in conjunction with vegetarian diet, which per se is supposedly anti-inflammatory and in diverse medical disorders such as osteoporosis, hypertension and cardiovascular disorders and dysbiosis.[8 29 44 45] The profound sarcopenia and general debility are common in chronic RA and likely to further contribute to body potassium deficiency and deleterious consequences.[8 46] Modulation of potassium ion channels was reported to control pain and immune-mediated inflammation.[8 47] However, much more research is warranted.

Mechanism of action

The precise mechanism of pain reduction by potassium in the current study is not known. Increased potassium intake (especially therapeutic intervention) has been reported to increase endogenous steroids, which are potent anti-inflammatory (analgesic) agents.[8 9 12] The serum cortisol assay was conspicuously increased in arm B (online supplemental table 1). Other mechanisms may operate and include neurophysiologic effects and potassium ion channels.[47 48]

Vegetables and fruits contain non-chloride forms of potassium, which are reportedly more beneficial for bone strength.[29]

Conclusion

A higher oral potassium intake derived from a suitable diet and a novel food supplement improved joint pains considerably in a substantial number of symptomatic chronic RA patients who were on background standard rheumatology care in this 16-week randomised controlled study. Patients also improved on several other efficacy measures. Oral potassium was a safe adjunct, and higher intake (5–7.5 g/day) was well tolerated. A predominantly vegetarian diet with sufficient potassium intake should be advocated in the management of RA. Pending further validation, some patients with difficult RA may also benefit from a judicious use of potassium-enriched food supplement.

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Ethics approval This study involves human participants and was approved by CRD Ethics Committee Approval 04/02/2014. Participants gave informed consent to participate in the study before taking part.

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SUPPLEMENT FILE 1

Main Text Title- Adjunct Role of Potassium in Painful Rheumatoid Arthritis: A Randomized Controlled Study of Diet and Food Supplement based Intervention in Patients on Supervised Standard Care

SUBJECT: Additional Efficacy Results

Table 1: Median (Standard deviation, 95% confidence intervals) serum cortisol, serum and urine potassium over 16 weeks study period: A randomized controlled potassium-diet study in 172 patients of chronic rheumatoid arthritis on standard treatment[Arm A= potassium rich vegetarian diet, B= potassium rich vegetarian diet plus potassium food supplement, C=control routine diet]-per protocol analysis

Variable	Gp	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	p*	P1	P2
Serum K (mEq/L)	A	3.9 (0.5)	3.8 (0.4)	3.9(0.5)	3.9(0.5))	3.6 (0.5)	0.21	0.59	0.36
	B	3.8(0.5)	3.8(0.4)	3.7 (0.4)	3.9 (0.5)	3.9 (0.4)	0.35		
	C	3.9 (0.5)	3.7 (0.4)	3.7 (0.5)	4 (0.5)	3.8(0.5)	0.99		
Serum Na (mEq/l)	A	140 (6.6)	139 (5.1)	141.5 (5)	142 (6.7)	139 (9.3)	0.52	0.67	0.41
	B	140(5.4)	137 (4.7)	141.5 (9.8)	142 (7.2)	139 (9.1)	0.40		
	C	142 (6.1)	139 (4.3)	139 (6.1)	143 (8.9)	140 (8.1)	0.49		
Urine K (mEq/l)	A	37.6 (25.9)	39 (39.1)	51.5(32.3)	65(42.1)	65.5(34.7)	0.01	0.77	0.50
	B	40 (26.1)	43 (29.6)	48 (34.1)	45 (23.6)	59 (38.5)	0.02		
	C	34.8 (28.9)	45 (39.8)	45 (30.4)	47 (27.8)	55 (36.6)	0.00		
Urine Na (mEq/l)	A	105.5(79.2)	81 (59.2)	95.5 (45.2)	65(93.3)	117 (44.7)	0.51	0.81	0.82
	B	97(63.4)	94.5(84.4)	98.5(70.8)	81(55.3)	116 (53.8)	0.61		

Supplement File 1_Additional Results

	C	99(87.4)	104(66.6)	100(58.5)	101(55.4)	105(43.9)	0.53		
Serum Cortisol (µg/dl) (8-1030 am)	A	5.7 (4.2)	6.8 (3.9)	7.6 (7.1)	8.4 (8.9)	8.2 (7.8)	0.00	0.59	0.55
	B	5.5 (4.8)	6.5 (5.7)	6.9(6.6)	9.4 (9)	8.9(8.5)	0.00		
	C	5.4 (4)	7.6 (7.6)	6.3 (6.6)	8.1 (7.6)	7.1 (7)	0.01		

Note: K: potassium; Na: sodium; Gp: group; Number of patients: 52 Arm A, 50 Arm B & 53 Arm C; Number of Serum samples: 100% serum samples at baseline and completion and 90-94% other visits; Number of Spot Urine Potassium samples: least 48 available at each visit; Urine sample collected for spot urine K assay between 8-11 am; Blood collected for serum cortisol between 8-1030 am; Significant $p<0.05$two-tailedd (ANOVA); No significant differences at $p<0.05$ between groups at study visits using ANOVA ;p*: in-between group change: p1:baseline comparison ; p2: study completion (week 16) comparison; See main text for details

Supplement File 1_Additional Results

Table 2: Correlations (r) between potassium (K) related diet and laboratory variables at baseline and completion and with selected outcomes in patients with symptomatic rheumatoid arthritis (RA) randomized (n=172 patients) to a diet intervention drug trial; data pertains to 155 patient completers.

Variable	Diet K (B)	Diet K (C)	Serum K (B)	Serum K (C)	Urine K (B)	Urine K (C)
Diet K (B)	1	0.038	-0.345**	-0.127	-0.056	0.085
Diet K (C)	0.038	1	-0.129	0.021	0.002	-0.089
Serum K (B)	-0.345**	-0.129	1	0.304**	0.086	-0.09
Serum K (C)	-0.127	0.021	0.304**	1	0.03	-0.94
Urine K (B)	-0.056	0.002	0.086	0.03	1	0.051
Urine K (C)	0.085	-0.089	-0.09	-0.94	0.051	1
Pain VAS (C)	-0.009	-0.193*	-0.081	-0.068	0.114	0.115
Pain MCID (C)	0.114	-0.191*	-0.071	-0.105	0.094	0.088
DAS 28 (C)	0.018	0.006	-0.041	0.029	-0.008	0.079

Note: n:number; B:caseline; C:completion; Diet: daily estimation based on 'Food Composition Table (India); Urine K: spot morning urine assay; Pain VAS: pain visual analogue scale; MCID: minimum clinically important difference; DAS 28: disease activity score based on 28 joints; *:p<0.05; **:p<0.01; See methods above and main test for further explanation

Supplement File 1_Additional Results

Table 3: Efficacy variables of patients suffering from RA on standard of care treatment in intervention and control group (A; K rich diet , B; K rich diet + dietary K suppl C; routine diet): showing mean change (95% confidence interval) over study period (16 weeks) - an Intention to treat analysis.

Variable	A(n=57)		B(n=58)		C(n=57)		P* ANOVA
	Baseline	Mean change	Baseline	Mean change	Baseline	Mean change	
Pain VAS (0-100mm)	5.42	-1.31 (-1.93,-0.7)	5.41	-1.98 (-2.62,-1.34)	5.26	-1.24 (-1.8,-0.67)	0.17
JCSW (range 0-66)	2.37	-1.82 (-2.37,-1.27)	2.49	-0.69 (-1.88,0.48)	2.44	-1.60 (-2.61,-0.6)	0.2
JCPT (range 0-68)	11.19	-9.23 (-11.82,-6.64)	13.11	-8.58 (-12.11,-5.05)	11.64	-5.78 (-9.38-2.19)	0.27
Patient Assess (Grade 1-5)	1.35	-0.42 (-0.58,-0.27)	1.35	-0.41 (-0.63,-0.19)	1.41	-0.5 (-0.69,-0.3)	0.21
HAQ (range 0-24)	5.32	-1.89 (-2.85,-0.93)	5.11	-2.14 (-3.38,-0.91)	4.5	-0.72 (-1.73,0.27)	0.13
General Health (0-100 mm VAS)	51.03	13.44 (8.05,18.83)	51.49	13.41 (6.76,20.06)	50.91	10.30 (4.58,16.02)	0.68
SF36 Physical score	42.03	1.78 (-0.3, 3.87)	41.48	2.83 (0.40, 5.26)	43.28	0.31 (-1.38, 2.01)	0.23
SF36 Mental score	40.20	2.5673 (-0.01,5.15)	41.05	1.30 (-0.94, 3.55)	40.80	2.29 (-0.43, 5.02)	0.76
ESR mm fall 1st hour	70.62	-8.38 (-15.62, -1.13)	69.03	-10.88 (-18.75, -3.02)	65.08	-9.29 (-15.95, -2.63)	0.88
CRP mg/dl	33.85	-22.02 (-35.16, -8.87)	26.61	-8.33 (-15.90, -0.75)	25.6	-11.74 (-23.55, 0.06)	0.2
DAS 28 ESR	4.91	-1.46 (-1.79, -1.14)	5.01	-1.18 (-1.60, -0.77)	4.83	-1.02 (-1.44, -0.60)	0.25
Note: n: number of patients; VAS: visual analogue scale; JCSW: swollen joint count; JCPT: painful joint count; HAQ: health assessment questionnaire (function); SF 36 : Short Form 36 (quality of life); ESR: erythrocyte sedimentation rate; CRP:C-Reactive protein; DAS: disease activity index; Higher value/scores at baseline except for general health and SF 36 indicate worst outcome; Normal ranges are shown in parenthesis after variable; See Text for details							

Supplement File 1_Additional Results

Table 4: Rheumatoid Arthritis Medication (number of patients) at randomization baseline (week 0) and study completion (week 16) in a randomized controlled three arm dietary potassium intervention study (n=172) in chronic Rheumatoid Arthritis [A= potassium rich diet; B=potassium rich diet plus potassium food supplement; C= control routine diet]

Arm/ Drug	A		B		C		p1*	p2*
Time points/week	0 (n=57)	16 (n=52)	0 (n=57)	16 (n=50)	0 (n=58)	16 (n=53)		
DMARD (Single or Combo) + Prednisolone/P (low dose steroid, 5 mg or less daily dose)								
DMARD (Single or combination) plus prednisolone-total	40	35	35	32	41	39	0.49	0.56
Methotrexate(P)	16	13	20	17	12	17	0.2	0.29
HCQS (P)	8	0	2	1	6	2	0.12	0.46
Sulfasalazine (P)	0	2	1	0	6	1	0.04	0.35
Methotrexate + HCQS (P)	3	8	6	8	5	6	0.46	0.84
Methotrexate + Sulfasalazine (P)	8	8	4	4	5	7	0.57	0.42
Sulfasalazine+ HCQS (P)	0	0	0	0	5	1	0.08	0.37
Methotrexate + Sulfasalazine+ HCQS (P)	5	4	2	2	2	5	0.34	0.35
DMARD Combination (no prednisolone)								
DMARD combination-total	11	12	13	12	11	10	0.89	0.41
Methotrexate + Sulfasalazine	5	5	3	3	3	5	0.76	0.98
Methotrexate + HCQS	5	7	9	8	4	5	0.28	0.23
Sulfasalazine+ HCQS	1	0	1	1	4	0	0.99	0.42
DMARD Mono								
HCQS	1	0	3	0	1	0	0.23	0.26
Sulfasalazine	0	0	0	0	2	0	-	-
Methotrexate	5	5	6	6	3	4	0.81	0.81
Total Use of DMARD (Single/Combo with or without Prednisolone)								
Methotrexate	47	50	50	48	34	49	0.00	0.60
Sulfasalazine	19	19	11	10	27	19	0.01	0.14
HCQS	23	19	23	20	27	17	0.27	0.88
Analgesic/NSAID Use								
Analgesic/NSAID	46(81)	40(75)	54(95)	39(75)	52(90)	43(81)	0.07	0.93
Equivalent paracetamol daily use ^ , gm, mean (SD)	1.85 (0.82)	1.37 -0.7	1.8 -0.77	1.41 -0.77	1.9 -0.85	1.46 -0.7	0.83	0.85

Supplement File 1_Additional Results

Note: n: number of study participants; DMARD: disease modifying antirheumatic drug; Analgesic/NSAID^: Daily Analgesic use in varying and/or fixed dose >4 times a week (includes non-steroidal anti-inflammatory drugs/NSAID) ; Daily paracetamol use^^: Combined use of paracetamol and Non-steroidal anti-inflammatory (NSAID) whereby NSAID use was converted into equivalent paracetamol dose by an equation decided a-priori by expert consensus (Each tablet of 50 Diclofenac/100 mg Nimesulide/60 mg Etorocoxib/300 mg etodolac were equated to 1000 mg paracetamol; *p1: baseline comparison of groups; *p2: completion comparison of groups: *: chi-square statistic (Yates correction), degrees of freedom 2, significant $p < 0.05$; See text for details

Supplement File 1_Additional Results

Table 5: Significant Pearson Moment correlation (r) between Diet nutrients and Energy Consumption at Baseline (B) and Study Completion (C) in patients with symptomatic RA randomized (n=172 patients) to a diet intervention drug trial; Data pertains to 155 patient completers.

Diet Variable	**Positive 'r'**	**Negative 'r'**
Potassium (B)	Sodium , Iron (C),	Protein(C),Zinc(C),Calcium (C),Thiamine (C) , Folic A(C)
Energy (B)	Protein (B)*, Zinc (B)*,Calcium (B), Thiamine(B)*, Iron (B), Folic acid (B) **, Sodium (B), Protein (C), Zinc(C), Calcium (C), Thiamine (C)*, Iron (C) *, Folic acid (C)*	
Protein (B)	Energy (B) *, zinc (B)*, calcium(B)*, thiamine (B)*, iron (B), folic acid (B) **, sodium (B), protein (C), zinc(C), calcium (C), thiamine (C)*, iron (C) *	Nil
Fat (B)	Nil	Nil
Calcium (B)	Energy (B), Protein (B)*, Zinc (B), Vitamin A (B), Thiamine (B) *, Iron (B)*, Folic acid (B) *, Sodium (B)*, Protein (C), Thiamine (C) , Iron (C)	Nil
Thiamine (B)	Energy (B) *, Protein (B)*, Zinc (B)*,Calcium (B)*, Iron (B)*, Folic acid (B) *, Sodium (B), Protein (C)*, Zinc (C), Calcium (C), Thiamine (C)*, Iron (C) *, Folic acid (C)*	Nil
Vitamin C (B)	Nil	Calcium (C), Thiamine (C), Iron (C), Folic acid (C)
Iron (B)	Energy (B), Protein (B), Zinc (B), Calcium (B), Vitamin A (B), Thiamine (B) *, Folic acid (B), Sodium (B)	Nil
Folic Acid (B)	Energy (B)*, Protein (B)*, Zinc (B)*, Calcium (B), Vitamin A (B), Thiamine (B)*, Iron (B)*, Sodium (B), Protein (C)*, Zinc (C), Calcium (C) , Thiamine (C)*, Iron (C)	Nil
Vitamin A (B)	Calcium (B)*, Iron (B), Folic acid (B)	Nil
Zinc (B)	Protein (B)*, Thiamine (B)*, Iron (B), Calcium (B), Folic acid (B) *, Sodium (B), Protein (C), Thiamine (C)*, Iron (C), folic acid (C)	Nil
Sodium(C)	Energy (C)*, Protein (C)*, Fat (C), Zinc(C)*, Calcium (C)*, Phosphate(C), Thiamine (C)*, *Iron (C)*, Folic acid (C)*, Vitamin A(C), Potassium (C)	Nil
Potassium (C)	Energy (C), Protein (C)*, Fat (C), Zinc (C)*, Calcium (C), Phosphate(C), Thiamine (C), Iron (C), Folic acid (C), Sodium (C)*	Vit C (B)
Note: n: number ; Diet variables: measured as daily quantity based on standard 'Food Composition Tables (India)'; Abbreviations and acronyms: see above methods; Significance at $p<0.05$ two tailed; * : $p<0.01$; See main text for further details		

Supplement File 1_Additional Results

Table 6: Variables used in Univariate and Logistic Regression Analysis: Definition and Classification of Variables (dummy binary codes- 1 and 2) and Dependent Variables- A Randomized Assessor Blind three Arm Controlled Diet Intervention Study of Symptomatic Rheumatoid Arthritis (RA) (n=172 patients) of 16 Weeks Duration.

Variables for Regression Analysis	**Variable Label**	**Explanatory note / dummy code 1 (equivalent to Yes)**
Potassium /K_Arm	K_Arm	Arm A or B, consumed potassium
K diet arm	K_5_diet arm	Arm A only
Age continuous (years)	Age	continuous data
Age stratified (years)	Age_40l	age less than 40 years
Duration (years)	R_5m	5 years or more
Tobacco	Tobacco	Yes
Menopause	Menopause	Yes
BMI stratified	BMI_25m	25Kg/m^2 and more=overweight and obesity
Joint count pain tender (JCPT)	JCPT_1_7m	7 joints or more painful or tender baseline
Joint count swelling (JCSW)	JCSW_1_2m	2 joints or more swollen baseline
Health Assessment Questionnaire (HAQ)	HAQ_1_6m	6 (total 24) or more disability score baseline, more disability
Physician global assess	PGA_1_3m	3 or more category physician global assess disease severity baseline
Patient assessment disease (PAD)	PAD_!_3m	3 or more category patient global assess disease severity baseline
General Health Assess (GHA)	GHA_1_60l	60mm (VAS) or less score baseline to show more poor health
Early Morning Stiffness (EMS)	EMS_1_30m	30 min or more morning stiff baseline, more severe disease
Rheumatoid Arthritis Pain Score (RAPS)	RAPS_1_60m	60 or more baseline score for more pain
Disease activity score (DAS)	DAS_!_5.1m	DAS28 high on baseline > 5.1 more disease active
Short Form Health Score-physical 36 item (SF36P)	SF36P_1_40l	40 or less score baseline for more physical disability
Short Form Health Score-mental 36 item (SF36M)	SF36M_1_40l	40 or less score baseline for more mental disability
Erythrocyte Sediment Rate (ESR)	ESR_1_50m	50mm fall 1st hour or more measure baseline for more disease severity
Serum Potassium (Sr K)	SrK_1_3.5l	3.5mEq/L or less assay baseline for lesser body potassium
Urine Potassium (K)	UrK_1_40m	40mg or more excretion baseline for more K loss
C-reactive protein (CRP)	CRP_1_12m	12mg/dl or more assay baseline for more disease severity
Rheumatoid Factor (RF) titre	RF_1_120m	120 IU/l or more assay baseline for more seropositive RA
Anti-cyclic citrullinated peptide (CCP) assay	CCP_1	>5 RU/l
Serum Cortisol (Sr Cort)	SrCort_1_7.5 less	Serum cortisol less than 7.5 mg baseline in more painful diseases
Serum Cortisol (Sr Cort)	SrCort_5_7.5 more	Serum cortisol more than 7.5 mg completion in less painful diseases

Supplement File 1_Additional Results

Energy- daily diet consumption	Energy_1_2700m	2700 KCalories or more baseline Kcal consumption
Protein- daily diet consumption	Prot_1_80m	80gm or more protein baseline consumption
Zinc-daily diet consumption	Zn_1_15m	15mg or more zinc baseline consumption
Vitamin C (Vit) daily consumption	VitC_1_130m	130mg or more Vit C baseline consumption
Iron -daily diet consumption	Iron_1_30m	30mg or more Iron baseline consumption
Potassium (K)-daily diet consumption	K_1_2200l	2200 mg or less baseline consumption
Energy- daily diet consumption	Energy_5_2700m	2700 KCaolories or more Kcal consumption on study completion
Protein- daily diet consumption	Prot_5_80m	80gm or more protein consumption on study completion
Zinc-daily diet consumption	Zn_5_15m	15mg or more zinc consumption on study completion
Calcium consumption diet	Cal_5_800m	800 mg or higher calcium consumption study completion
Vitamin C (Vit) daily consumption	VitC_5_130m	130mg or more Vit C consumption on study completion
Iron -daily diet consumption	iron_5_30m	30mg or more Iron consumption on study completion
Sodium (Na)-daily diet consumption	Na_5_4000m	4000mg or more consumption on study completion
K daily diet consumption - completion	K_5_5000m	5000mg or more consumption on study completion
K-daily diet consumption completion	K_5_4000	4000mg or more consumption on study completion
K daily diet consumption - completion	K_5_3000m	3000mg or more consumption RDA on study completion
Methotrexate (MTX) dose mg per week	MTX_1_16m	16mg or more weekly dose baseline for more disease activity
MTX use	MTX_1_yes	use of MTX at baseline
MTX+SZP (sulfasalazine) consumption	MTX_SZP_1_Yes	use of MTX SZP at baseline
Prednisolone (Pred) daily dose mg	Pred_1_6m	6mg or more daily dose of prednisolone at baseline, more active dis
Pred use	Pred_1_Yes	Prednisolone use at baseline
Non-steroidal anti-inflammatory use (NSAID)	NSAID_1_Yes	NSAID use at baseline
Combo use	Combo_1_Yes	Combination use of DMARD at baseline
Combo +Pred use	Combo_P_1_Yes	Combination DMARD plus prednisolone at baseline
MTX use on completion	MTX_5_Yes	MTX use on study completion
MTX dose use on completion	MTX_5_16m	MTX dose 16mg or more on study completion
Pred use on completion	Pred_5_Yes	Pred use on study completion
Pred dose on completion	Pred_5_6m	Pred dose 6mg or more daily on study completion
Combo Use	Combo_5-Yes	Combination DMARD on completion

Supplement File 1_Additional Results

NSAID use on completion	NSAID_5_Yes	NSAID use on completion
Pain on completion	**Pain_5_4l**	**Dependent Variable : pain less than 4 cm on VAS on study completion**
Disease activity score using ESR less than 3.2	**DAS28_5_low**	**Dependent Variable: DAS28 low disease or remission on study completion**
Note: ; n: number; m:more;l:less; K: potassium; Combo: combination; MTX: methotrexate; Pred: prednisolone; SZP: sulfasalazine;		

Supplement File 1_Additional Results

Table 7: Odds Ratio (Association) of Diet Variable and Nutrients with Dependent Variable using Univariate analysis (Z test): A Randomized Assessor Blind three Arm Controlled Diet Intervention Study of Symptomatic Rheumatoid Arthritis (RA) (n=172 patients) of 16 Weeks Duration.

Dependent Variable/ Diet related variable	**Pain change MCID on study completion**		**Pain VAS on study completion less than 4 cm (VAS)**		**DAS28 score on study completion less than 3.2**	
	OR	**'Z'value€**	**OR**	**'Z' value€**	**OR**	**'Z' value€**
K-arm	2.0134*	2.0069	1.5450	1.2749	1.2613	0.6474
K-diet-arm	0.9300	-0.2061	0.9285	-0.2152	1.1229	0.3203
SRK-1_3.5l	0.8467	-0.4363	0.6705	-1.0712	1.3344	0.7539
URK-1_40m	0.5481	-1.8163	0.4711*	-2.3234	1.3900	0.9675
Energy-1_2700m	0.4573*	-2.2719	0.6638	-1.2159	0.5944	-1.4589
Prot-1_80m	0.4805	-1.9691	0.7218	-0.8948	0.4993	-1.8144
Zn-1_15m	1.1794	0.4254	1.0340	0.0882	0.4639	-1.9244
VitC-1_130m	0.7054	-0.9959	0.5611	-1.6852	1.3828	0.8996
Iron-1_30m	1.5119	1.2419	1.2012	0.5628	0.6375	-1.3151
K-1_2200l	1.2631	0.6756	1.2777	0.7245	0.8308	-0.5212
Energy-5_2700m	1.3806	0.8907	0.9775	-0.0640	0.9246	-0.2103
Prot-5_80m	0.7950	-0.6114	1.0017	0.0047	0.5430	-1.5830
Zn-5_15m	1.8395	1.7396	2.0192*	2.0498	0.6301	-1.2815
Calcium__800m	1.6071	1.3102	1.5000	1.1443	0.7070	-0.9308
VitC-5_130m	0.8588	-0.3807	0.7428	-0.7599	1.0715	0.1681
Iron-5_30m	1.6898	1.5761	1.6532	1.5436	0.7166	-0.9732
Na-5_4000m	3.3526*	3.4002	2.5961*	2.7405	0.9427	-0.1611
K-5_5000m	3.8911*	3.5939	2.5909*	2.5737	0.9382	-0.1638
K-5_4000m PP	1.8417	1.7864	1.6561	1.5083	0.9448	-0.1614
K-5_3000m	1.8864	1.8889	1.5277	1.2891	0.9388	-0.1824

Note: n=number; OR: Odds Ratio and testing with population OR=1; €: Estimated after 'log' transformation;; *: Statistically Significant as 'Z' value is either greater than 1.96 or smaller than -1.96 and therefore included in 'Logistic Model'; several variables dummy (binary) coded as per investigator discretion and shown in Table 3; m:more; l:less; MCID: minimum clinically important difference (for pain VAS = 1 cm)

Supplement File 1_Additional Results

Table 8: Logistic regression models (with stepwise forward) in a randomized controlled diet intervention study of symptomatic rheumatoid arthritis (RA) to determine predictors of low pain (4 cm or less on VAS) at study completion (16 weeks): Shows variables (predictors) with significant regression coefficients (Odds ratio)as output in 4 Models

Dependent Variable	**Group Independent Variables and Method**	**R2**	**Predictor (Odds Ratio)**
Pain VAS less than 40 cms on study completion	METHOD=ENTER:age_40less,RA>5 years, tobacco, menopause, BMI_ 25m,JCPT1_7m,JCSW1_2m,HAQ1_6 m,PGA1_3m,P.A.D1_3m, GHA1_60less, EMS1_30m,RAPS1_60m,DAS1_5.1m , SF36P1_40l,SF36M1_40l,ESR1_50m, CRP1_12m,RF1_120m,MTX1_16m, MTX1_yes,MTX_SZP1,yes, PRED1_Yes, Pred1_6m,NSAID1_Yes, Combo1_Yes, ComboP1_Yes,MTX5_16more,MTX5 Yes, RED5_Yes,Pred5_6m, NSAID5_Yes, Combo5_yes,SrCort1, K_Arm ,K5_diet arm,SRK1_40ml,UrineK1_40m, ENERGY1_2700m,Prot1_80m, , ZINC1_15m,VITC1_130m, IRON1_30m, K1_2200l,ENERGY5_2700M,Prot5_8 0m,ZINC5_15m,CALCIUM5_800M, VITC5_130m, IRON5_30m,Na5_4000 m, K5_5000m,K5_4000m, K5_3000m	60.7	Menopause (0.138), HAQ1_6m (0.225), GHA1_60less (0.129), DAS28_1_5more (12.51), RF1_120 more (4.65), MTX1_yes (108.09), Pred5_6more(0.055), K5diet arm (9.58), K5_5000m (20.893)
	METHOD=STEPWISE FORWARD; ALL VARIABLES AS ABOVE IN THE EQUATION; 6 steps to achieve optimum outcome	32.9	RA duration >5years (0.29), HAQ1_6more(0.346**), MTX1_yes (16.096)**, MTX_SZP1_yes (0.078) Pred5_6m (0.327), **K5_5000m (2.876)**
	METHOD=ENTER (Selected variables): age_40less,RA>5 years, menopause JCSW_1_2m P.A.D_1_3m, Pred_5_6m, K_Arm,ENERGY_1_2700more , Na_5_4000more, K_5_5000more	33	MTX1_yes (2.818), UrineK1_40 more, (0.42), RA duration > 5 year (0.341), HAQ1_6more (0.503), Menopause (0.51), GHA1_60less (0.376), ZINC5_15more (1.941)
	METHOD= STEPWISE FORWARD; ALL THE ABOVE SELECTED VARIABLES IN THE EQUATION; 4 steps.	25.3	RA duration>5years (0.295), HAQ1 _6more(0.376), MTX1_yes (2.498), **K5_5000more (3.145)**

Supplement File 1_Additional Results

Note: All models achieved good fit; n: number; R2:percent of the variation explained by the predictors ,as per the method of Nagelkerke; See Table 6 for abbreviations

Supplement File 1_Additional Results

Fig 1: Diet Brochure Provided to Patients for Their Daily Meal Plans to Augment Potassium in the Diet: A Controlled Study of Diet and Food based K intervention in patients suffering from active symptomatic Rheumatoid Arthritis (RA) and Continuing Background Standard RA Medication

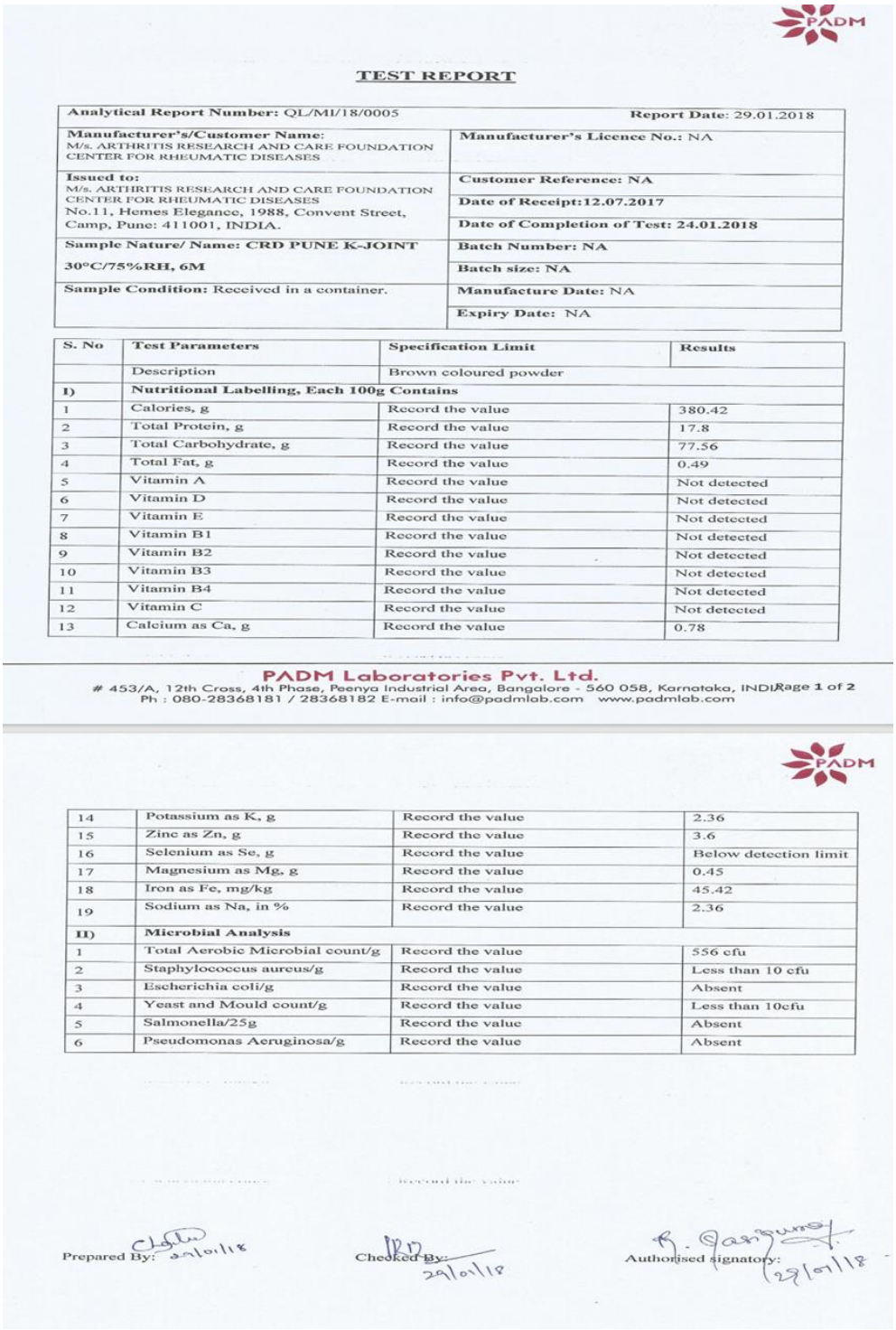
RHEUMATOID ARTHRITIS AND POTASSIUM RICH FOOD  *PATIENT DIET ADVICE BROCHURE* *Center for Rheumatic Disease (CRD),Pune* *Tel: 02026344099* *02026355204*	Diet plays important role in Rheumatoid Arthritis (RA) but there is limited scientific evidence. It is difficult for patients to have properly cooked food with adequate protein, vitamins and essential minerals. Also they should not put on excess body weight which can worsen symptoms of RA. Besides improving general health, diet may helps in reducing the severity and improving the control of arthritis. It is possible that symptom like pain can be managed to some extent to suitable dietary changes. A recent study from Iran in women with RA suggested that K+ supplement to diet reduced pain in joints. We recently carried out a study of patients suffering from RA in the Center for Rheumatic Diseases, Pune; to measure the dietary contents in patients of RA and found that the local diet was not sufficient in K. However this was an early limited study. We now need to understand in a large study to evaluate the role of K+ in diet in patients with RA. This study has been approved by independent Ethical Committee of the institute. We will be providing you advice regarding increase K+ in diet through eating K+ rich foods and some dietary supplement. Please follow the advice described below. Make sure you choose daily cereals or pulses or vegetable or fruits from the items listed below. You are welcome to eat different diet items on different days of week. For example: daily diet may be 3-4 chapatis or Bhakris or 2 katoris dal along with 1 katori vegetable and 1 fruit. You may like to divide the daily requirement between lunch and dinner.

Supplement File 1_Additional Results

Fig 1 (Continued)

Diet advice:	Do's
Cereal: In the form of Chapatti or Bhakri (4 chapati or bhakri in standard size in a day made of Ragi or Wheat flour or Jawar or Bajra) Ragi or wheat Jowar Bajra  Pulses: In the form of gravy (2 katori daily) Mung dal or Chawli or Tur dal  Vegetable: In the form of bhaji (2 katori daily) Shevga or Brinjal or Karela  Fruits: Take 1 Musambi and 1 Banana in the morning and evening  2 Musambi or 2 banana in a day	➢ Drink lots of water, at least 2 liters in a day. ➢ You can consume common and popular vegetable like potato, onion garlic and home made chutney (pudina and green chilies). ➢ Methi seeds are also good source of K+ and you may take them as lado ➢ Methi seeds are also good source of K+ and you may take them as lado ➢ Jaggary may be eaten in any form of like puran poli. Don't ➢ Avoid oily and spicy food. You may use vegetable oil like ground nut or sunflower to cook food. ➢ Avoid tobacco use ➢ Avoid excess salt in diet. Don't add salt in cooked food. ➢ Avoid pickle and chutney or salted snacks like peanut and wafers. ➢ Don't fast or eat special food

Supplement File 1_Additional Results



TEST REPORT

Analytical Report Number: QL/MI/18/0005	**Report Date:** 29.01.2018
Manufacturer's/Customer Name: M/s. ARTHRITIS RESEARCH AND CARE FOUNDATION CENTER FOR RHEUMATIC DISEASES	**Manufacturer's Licence No.:** NA
Issued to: M/s. ARTHRITIS RESEARCH AND CARE FOUNDATION CENTER FOR RHEUMATIC DISEASES No.11, Hemes Elegance, 1988, Convent Street, Camp, Pune: 411001, INDIA.	**Customer Reference:** NA **Date of Receipt:12.07.2017** **Date of Completion of Test: 24.01.2018**
Sample Nature/ Name: CRD PUNE K-JOINT 30°C/75%RH, 6M	**Batch Number:** NA **Batch size:** NA
Sample Condition: Received in a container.	**Manufacture Date:** NA **Expiry Date:** NA

S. No	Test Parameters	Specification Limit	Results
	Description	Brown coloured powder	
I)	**Nutritional Labelling, Each 100g Contains**		
1	Calories, g	Record the value	380.42
2	Total Protein, g	Record the value	17.8
3	Total Carbohydrate, g	Record the value	77.56
4	Total Fat, g	Record the value	0.49
5	Vitamin A	Record the value	Not detected
6	Vitamin D	Record the value	Not detected
7	Vitamin E	Record the value	Not detected
8	Vitamin B1	Record the value	Not detected
9	Vitamin B2	Record the value	Not detected
10	Vitamin B3	Record the value	Not detected
11	Vitamin B4	Record the value	Not detected
12	Vitamin C	Record the value	Not detected
13	Calcium as Ca, g	Record the value	0.78

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14	Potassium as K, g	Record the value	2.36
15	Zinc as Zn, g	Record the value	3.6
16	Selenium as Se, g	Record the value	Below detection limit
17	Magnesium as Mg, g	Record the value	0.45
18	Iron as Fe, mg/kg	Record the value	45.42
19	Sodium as Na, in %	Record the value	2.36
II)	**Microbial Analysis**		
1	Total Aerobic Microbial count/g	Record the value	556 cfu
2	Staphylococcus aureus/g	Record the value	Less than 10 cfu
3	Escherichia coli/g	Record the value	Absent
4	Yeast and Mould count/g	Record the value	Less than 10cfu
5	Salmonella/25g	Record the value	Absent
6	Pseudomonas Aeruginosa/g	Record the value	Absent

Prepared By: 29/01/18 Checked By: 29/01/18 Authorised signatory: 29/01/18