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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

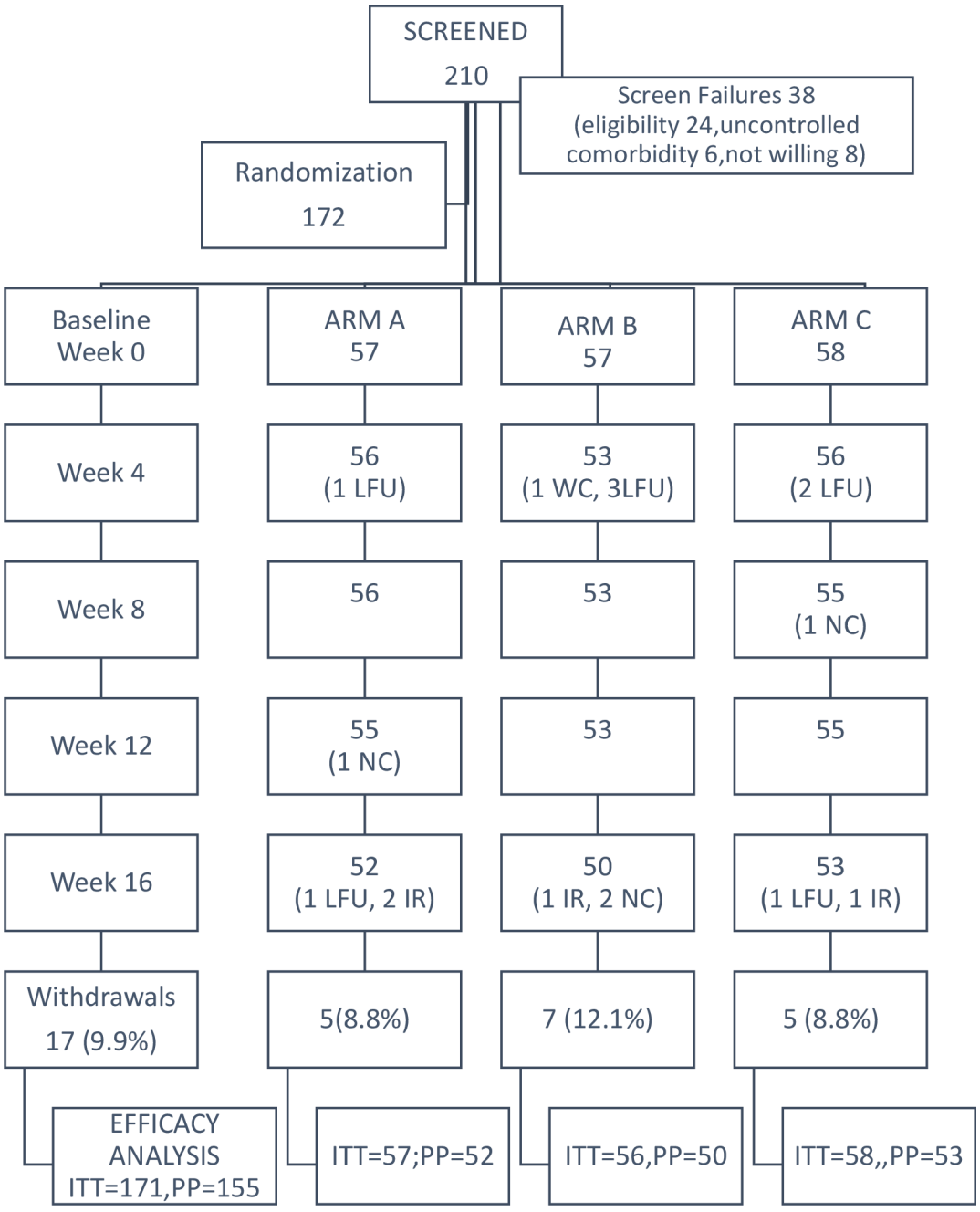

Figure 1 Patient disposition and number withdrawals—a randomised controlled three arm study of potassium intervention in rheumatoid arthritis (arm A, potassium-rich diet; arm B, potassium-rich diet plus potassium food supplement; arm C, routine diet; IR, inadequate treatment response; ITT, intention 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

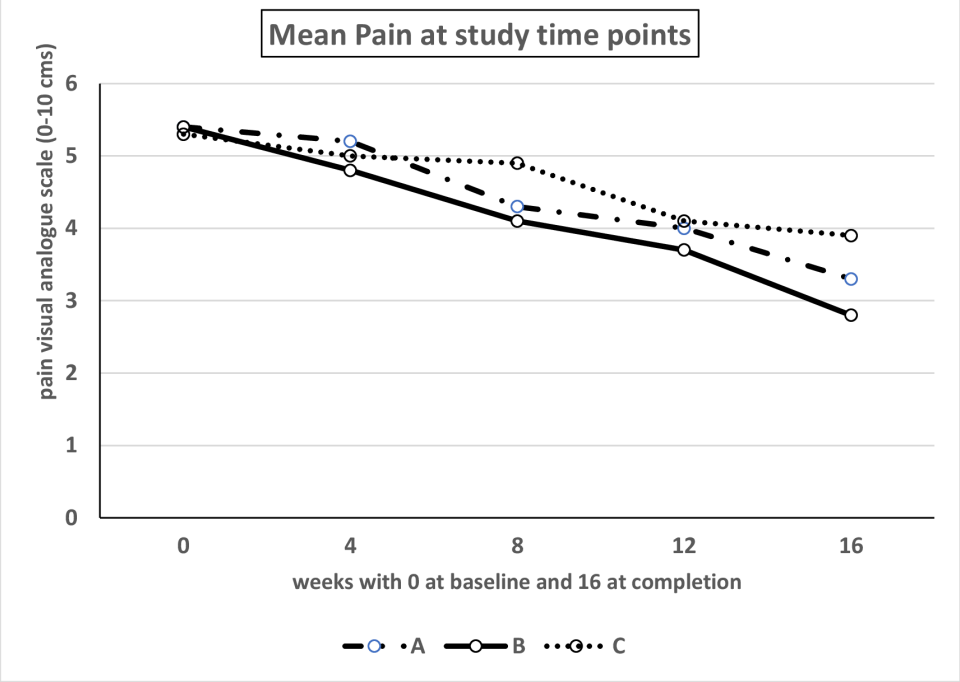

Figure 2 Mean pain visual analogue scale at pre-determine study time points—a randomised controlled three arm study of potassium intervention in rheumatoid arthritis over 16 weeks duration (arm A: potassium-rich diet; arm B: potassium-rich diet plus potassium food supplement; arm C: routine diet; see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

1 O'Dell JamesR. Treatment of rheumatoid arthritis. In: Firestein GS, Budd RC, Gabriel S, et al, eds. *Kelley & firestein's textbook of rheumatology*. Philadelphia: Elsevier Saunders, 2017: 1187–212.
2 Chopra A, Lin H-Y, Navarra SV, *et al*. Rheumatoid arthritis management in the APLAR region: perspectives from an expert panel of rheumatologists, patients and community-oriented program for control of rheumatic diseases. *Int J Rheum Dis* 2021;24:1106–11.
3 Fraenkel L, Bathon JM, England BR, *et al*. American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2021;73:924–39.
4 Chopra A. Ayurvedic medicine and arthritis [Review]. *Rheum Dis Clin North Am* 2000;26:133–44.
5 Nelson J, Sjöblom H, Gjertsson I, *et al*. Do interventions with diet or dietary supplements reduce the disease activity score in rheumatoid arthritis? A systematic review of randomized controlled trials. *Nutrients* 2020;12:2991.
6 Kianifard T, Chopra A. In the absence of specific advice, what do patients eat and avoid? Results from a community based diet

study in patients suffering from rheumatoid arthritis with a focus on potassium. *Clin Nutr ESPEN* 2018;28:214–21.
7 Gumz ML, Rabinowitz L, Wingo CS. An integrated view of potassium homeostasis. *N Engl J Med* 2015;373:1787–8.
8 Kianifard T, Chopra A. A therapeutic role for potassium (K) to reduce pain and complications related to the cardiovascular system and bone in rheumatoid arthritis (RA): a clinical research perspective. *Rheum Res* 2018;3:1–12.
9 Weber CE. Potassium in the aetiology of rheumatoid arthritis and heart infarction. *J Appl Nutr* 1974;26:41–67.
10 Kant AK, Graubard BI, Kumanyika SK. Trends in black-white differentials in dietary intakes of U.S. adults, 1971-2002. *Am J Prev Med* 2007;32:264–72.
11 Nuki G, Boddy K, Kennedy AC, *et al*. Potassium metabolism in patients with rheumatoid arthritis. Effects of treatment with depot tetracosactrin, spironolactone, and oral supplements of potassium chloride. *Ann Rheum Dis* 1975;34:506–14.
12 Rastmanesh R, Abargouei AS, Shadman Z, *et al*. A pilot study of potassium supplementation in the treatment of hypokalaemia patients with rheumatoid arthritis: a randomized, double-blinded, placebo-controlled trial. *J Pain* 2008;9:722–31.
13 Kianifard, Toktam. Effect of potassium supplement on pain in rheumatoid arthritis [PhD dissertation thesis]. Jun 2020. Available: http://hdl.handle.net/10603/262512.
14 National ethical guidelines for biomedical and health research involving human participants. 2017. Available: https://main.icmr.nic.in/sites/default/files /guidelines/ICMR _Ethical_Guidelines_2017.pdf [Accessed 10 Jun 2017].
15 Central drug trial registry of India. Available: http://www.ctri.nic.in/Clinicaltrials/showallp.php?mid1=9077&EncHid=&userName=toktam%20kianifard [Accessed Feb 2022].
16 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
17 Felson DT, Anderson JJ, Boers M, *et al*. American college of rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729–40. 10.1002/art.1780360601 Available: https://onlinelibrary.wiley.com/toc/15290131/36/6
18 Kianifard, Toktam. Composition for relieving symptoms of rheumatoid arthritis. Government of India patent 316682. 2019. Available: https://ipindiaservices.gov.in/publicsearch/ [Accessed 31 Jan 2022].
19 Kianifard T, Kianyfard T, Chopra A. Validation and relevance of rheumatoid arthritis pain scale (RAPS) in Indian (Asian) patients suffering from rheumatoid arthritis. *Clin Rheumatol* 2016;35:63–71.
20 Chopra A, Saluja M. Validation and usefulness of Indian version (CRD Pune) health assessment questionnaire: drug trials, community practice and COPCORD Bhigwan population study. Ind J Rheumatol 2012;7:74–82.
21 Short form 36. Available: https://www.rand.org/health/surveys_tools/mos/36-item-short-form/ scoring.html [Accessed 5 Jan 2017].
22 van Gestel AM, Anderson JJ, van Riel PL, *et al*. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American college of rheumatology European league of associations for rheumatology. *J Rheumatol* 1999;26:705–11.
23 Dietary Guidelines for Indians. A manual. Hyderabad, national Institute of nutrition- Indian council of medical research publication. 2011. Available: http://ninindia.org/DietaryGuidelinesforNINwebsite.pdf [Accessed 12 Jan 2014].
24 Nutritional requirement for Indians. A report of the expert group. Indian council of medical research/ national institute of nutrition Hyderabad; 2020. Available: http://www.nin.res.in/nutrition2020/RDA-short_report.pdf (Accessed
25 Cohen J. Quantitative methods in psychology. A power primer. *Psychol Bull* 1992;112:155–9.
26 Hawker GA, Mian S, Kendzerska T, *et al*. Measures of adult pain. *Arthritis Care Res* 2011;63:S240–52.
27 EFSA, European Food Safety Authority. Opinion of the NDA panel related to the tolerable upper intake level of potassium. 2005. Available: http://www.efsa.europa.eu/en/science/nda/nda_opinions/852.html [Accessed 28 Jul 2022].
28 Assessment of dietary intake of potassium in relation to upper guidance level. Opinion of the panel on nutrition, dietetic products, novel food and allergy of the Norwegian scientific committee for food safety. Oslo, Norway VKM Report; 2017.
29 Institute of Medicine. Dietary reference intakes for water, potassium, sodium, chloride, and sulphate. The National Academies Press, Washington, DC; 2005. Available: https://doi.org/10.17226/10925
30 Ishida M, Kuroiwa Y, Yoshida E, *et al*. Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. *Mod Rheumatol* 2018;28:789–99.
31 Philippou E, Nikiphorou E. Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. *Autoimmun Rev* 2018;17:1074–7.
32 Cutolo M, Nikiphorou E. Don't neglect nutrition in rheumatoid arthritis!. *RMD Open* 2018;4:e000591.
33 Courvoisier DS, Agoritsas T, Glauser J, *et al*. Pain as an important predictor of psychosocial health in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:190–6.
34 McWilliams DF, Walsh DA. Factors predicting pain and early discontinuation of tumour necrosis factor-α-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology biologics register. *BMC Musculoskelet Disord* 2016;17:337.
35 Staudacher HM, Irving PM, Lomer MCE, *et al*. The challenges of control groups, placebos and blinding in clinical trials of dietary interventions. *Proc Nutr Soc* 2017;76:203–12.
36 Charles-Schoeman C. Cardiovascular disease and rheumatoid arthritis: an update. *Curr Rheumatol Rep* 2012;14:455–62.
37 Adrogué HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. *N Engl J Med* 2007;356:1966–78.
38 Park Y, Dodd KW, Kipnis V, *et al*. Comparison of self-automated dietary intakes from the automated self-administered 24 hours recall, 4-day food records and food frequency questionnaires against recovery biomarkers. *Am J Clin Nutr* 2018;107:80–93.
39 Brzustewicz E, Henc I, Daca A, *et al*. Autoantibodies, C-reactive protein, erythrocyte sedimentation rate and serum cytokine profiling in monitoring of early treatment. *Cent Eur J Immunol* 2017;42:259–68.
40 Feldman M, Aziz B, Kang GN, *et al*. C-reactive protein and erythrocyte sedimentation rate discordance: frequency and causes in adults. *Transl Res* 2013;161:37–43.
41 Alwarith J, Kahleova H, Rembert E, *et al*. Nutrition interventions in rheumatoid arthritis: the potential use of plant-based diets [review]. *Front Nutr* 2019;6:141.
42 Hagen KB, Byfuglien MG, Falzon L, *et al*. Dietary interventions for rheumatoid arthritis. *Cochrane Database Syst Rev* 2009:CD006400.
43 Senftleber N, Nielsen S, Andersen J, *et al*. Marine oil supplements for arthritis pain: a systematic review and meta-analysis of randomized trials. *Nutrients* 2017;9:42.
44 Macdonald HM, Black AJ, Aucott L, *et al*. Effect of potassium citrate supplementation or increased fruit and vegetable intake on bone metabolism in healthy postmenopausal women: a randomized controlled trial. *Am J Clin Nutr* 2008;88:465–74.
45 Horta-Baas G, Romero-Figueroa MDS, Montiel-Jarquín AJ, *et al*. Intestinal dysbiosis and rheumatoid arthritis: a link between gut microbiota and the pathogenesis of rheumatoid arthritis. *J Immunol Res* 2017;2017:4835189.
46 Ngeuleu A, Allali F, Medrare L, *et al*. Sarcopenia in rheumatoid arthritis: prevalence, influence of disease activity and associated factors. *Rheumatol Int* 2017;37:1015–20.
47 Bittner S, Bobak N, Feuchtenberger M, *et al*. Expression of K2P5.1 potassium channels on CD4+ T lymphocytes correlates with disease activity in rheumatoid arthritis patients. *Arthritis Res Ther* 2011;13:R21.
48 Tsantoulas C, McMahon SB. Opening paths to novel analgesics: the role of potassium channels in chronic pain. *Trends Neurosci* 2014;37:146–58.