CHAPTER 5
DISCUSSION
Discussion

This clinical research interventional controlled study was primarily designed to evaluate the role of K+ in reducing pain in RA. In addition, the study used standard measures to record several other possible effectiveness of the intervention to control disease activity and improve quality of life. It was a randomized, single blind (assessor), parallel efficacy, three arm (2 intervention Arms A and B, 1 active control Arm C) study of 16 weeks duration carried out in a community based rheumatology centre. 172 patients suffering from active painful disease were enrolled and continued standard of care drug therapy for RA under supervision of a rheumatologist. 155 patients completed study. Analgesics were permitted as a rescue medication and carefully monitored. The study intervention was essentially based on dietary advise to increase K+ intake. In active Arm A, K+ enriched diet was advised to ensure a daily oral intake of 3.5-4.5 gm K+. Patients in active Arm B received a diet plan similar to Arm A but in addition consumed a food based and augmented (by addition of oral rehydration salt) K+ supplement powder to further increase the daily K+ intake to 7.5-8 gm. Patients in the active control arm C continued routine diet (daily K+ intake 2-3 gm).

The intervention arms were well matched for several baseline demographic and disease activity measures (Table 4.1 and 4.2). The mean pain VAS in the study cohort was 5.34 cms with no differences between the interventions arms (Table 4.1). The mean DAS 28 score in the study cohort was 4.92 with no differences between the intervention arms (Table 4.2). All this indicated that consenting patients on enrolment suffered from moderately severe pain and disease. 17 (10%) patients withdrew from the study with no differences by study groups. The daily mean dietary K+ intake determined at 16 week end point follow up was 2959 mg in Arm A (K+ rich diet), 7081 mg in Arm B (K+ rich diet plus enriched K+ supplement powder) and 2526 mg in Arm C(control). There were no significant imbalances between the groups for methotrexate use (Table 4.15), steroid use (Table 4.15) and analgesic and NSAID consumption (Table 4.14). The patients improved significantly in each of the intervention arms for several clinical and laboratory measures of efficacy including pain VAS (Tables 4.2 & 4.3) both by ITT and PPA.
As pain was the principle therapeutic target, several methods were used to assess pain and analyse the data. However, pain VAS is the gold standard and a core set efficacy measure; patient recorded maximum pain on a horizontal scale marked 0 to 10 cms during the preceding 24 hours.

There was a significant (p= 0.03) reduction in mean pain VAS (Table 4.3) in the B arm as per protocol analysis (completer) and thus the primary alternative hypothesis was accepted that 'oral K reduces pain in RA'. Though the change in mean pain VAS in the B arm was -1.9 cm and superior to -1.3 cm in Arm A and -1.2 cm in Arm C, it was not statistically significant (ANOVA) in the ITT set analysis (Table 2). But in view of a low withdrawal rate (~10%) and the nuances of a diet based intervention, the completer analysis assumes greater significance and merits acceptance. The proportion of patients with at least 50% reduction in pain over the study period was significantly (p<0.05) more in Arm B (Table 4.5, Fig 4.2). Similarly, proportion of patients showing minimal clinically important difference in pain VAS which is a minimum of 10 mm over study period was significantly superior in Arm B (Fig 4.3). The mean percentage improvement in pain at completion over baseline (Table 4.4) was 35% (95% CI 24%, 46%) in Arm B and was superior to Arm A (mean 23%, 95% CI 12%, 35%) and Arm C (mean 20%, 95% CI 9%, 32%). Patients receiving K+ rich diet (Arm A) showed better improvement than patients continuing routine diet (Arm C). In an ITT analysis, patients (a combination group from both Arms A and B) who had been compliant with the K+ diet (empirically based on a minimum mean 3000 mg of K+ in diet daily as determined on completion),

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258 Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011 Nov;63 Suppl 11:S240-52


the mean change (Table 4.10) in pain VAS (-1.87 cms) over study period was superior to Arm C (-1.24 cms); on comparison p=0.06 (Mann-Whitney). Thus, overall, the data supports the primary contention of the current research study that oral diet based K+ intervention reduces pain in patients suffering from RA who were under supervised treatment with standard of care drugs by a rheumatologist.

Both the ACR 20% improvement index (Table 4.8) and DAS 28 EULAR response (Table 4.7) were not statistically different by intervention groups. The ACR 20 response (see section on methodology), Appendix 16, which is a composite index of several core set efficacy measures was overall modest. Interestingly, ACR 70% improvement response (Table 4.8) which is clinically a robust effect was only seen in Arm A (4%) and Arm B (10%) and none in Arm C (p=0.04). The DAS 28 EULAR response (Table 4.7) in each of the arms was moderate in 35-40% patients and good in 28-35% patients in each of the intervention arms. Both these responses are standard responses to evaluate the diseases activity based on several individual measures. RA is a complex disease with several therapeutic targets (see literature review). All patients were on ongoing supervised rheumatology care which often included oral methotrexate (Table 4.15) and low dose oral steroids (Table 4.15) and it is difficult to speculate how much more improvement can be expected by K+ diet intervention. Though the pain (principle inclusion criteria) was moderately severe with a mean of 11-14 painful/tender joints in each of the intervention arms, the number of swollen joints (clinical synovitis) was rather low (about 2) and this probably shows a important effect of ongoing medication. All this is likely to have affected the ACR and DAS 28 response over study period.

However, in addition to relief of pain, there are several other promising clues in the study data to suggest that diet based K+ intervention indeed had some beneficial effect, albeit modest and statistically not significant, on standard inflammatory indices and functionality \(^{259}\) and quality of life \(^{261}\) in the current study. The outcomes (Tables 4.2 & 4.3) of painful/tender joint counts, general health assessment, SF 36 physical score and


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Erythrocyte sedimentation rate were superior in Arm B as compared to other arms; the improvement in Arm B was better than Arm C. The improvement in patient global assessment and HAQ (functional) was almost equal in Arms A and B but superior to Arm C. The improvement change in DAS 28 in Arms A and B exceeded Arm C. However, in contrast, the improvement in RAPS (complex pain questionnaire) and SF 36 mental score was more in Arm C and this inconsistency to the overall results may be more related to the complex nature of these patient centric measures.

In a further ITT analysis of patients (a combination group from both Arms A and B) who were compliant with the K+ diet (empirically based on a minimum mean 3000 mg of K+ in diet daily as determined on completion) and compared to Arm C, the mean change (Table 4T1), was significant (p<0.05) in the K+ diet compliant patients for HAQ, patient global assessment of disease activity and SF 36 physical score; in case of tender/painful joint score it was near significance. The mean pain VAS change in compliant group was -1.86 cms compared to -1.24 cms in the control arm (p=0.1). The overall results with the K+ diet intervention in the compliant group seemed better than that observed in the study cohort.

It may be prudent to conclude that diet based K+ interventions in the current study not only reduced pain but also helped in a better control of disease activity and improved quality of life. Perhaps a longer study period might have been more gratifying. In most of the efficacy measures, including quality of life measures, a conspicuous improvement response was seen within 1-2 months of baseline (Fig 4.7- 4.16).

At least there were two other conspicuous potentially beneficial effects of K+ intervention in this study. Firstly, reduction in systolic blood pressure (BP) was only recorded in Arms A and B (Fig 4.22) It is prudent to add that cardiovascular morbidity and mortality is a major concern in RA and this study observation (systolic blood pressure reduction) is likely to weigh the evidence in favour of therapeutic use of K+ in RA. The beneficial effects of K+ on BP are well known and described earlier (see section 2.10.1, current report). Secondly, though modest, K+ intervention arms showed a superior increase in serum cortisol (morning assay) (Fig 4.21). Dietary K+ intervention may be potent and safer method to increase endogenous steroids and combat
inflammation and modulate the immune responses in RA. Both these spin off benefits of K+ intervention in the current study need to be recognized and further explored. However, in contrast to using K+ salts as drugs, nothing could be more gentle and safe than administering K+ through a planned every day diet as was done in the current study.

A major concern with K+ therapeutic intervention in clinical medicine is adverse events and in particular related to gut and cardiac system. In clinical practise, this is guided by monitoring of acid-peptic symptoms, serum K+ assay and electrocardiograph/pulse (bedside cardiac monitor). RA is not a known indication for therapeutic use of K+. In the current study, after much deliberation with experts and guidance of the ethic committee (CRD), it was decided) that K+ intervention will be predominantly based on diet modification and augmentation. And to evaluate a therapeutic use with higher intake of K+ and simultaneously ensuring patient compliance and safety, it was decided to create a special K+ augmented food based supplement (for Arm B). Patients were well counselled on the precautions to be taken during intervention especially when consuming the supplement powder. There were few instances of acid peptic symptoms and diarrhoea which readily responded to symptomatic treatment. Electrocardiograms were recorded at baseline and completion and did not show any abnormality to suggest a K+ related effect. Laboratory monitoring included blood tests for routine haematological, metabolic, renal and hepatic parameters and remained within normal ranges (Tables 4.21 & 4.22). Serum and urine K+ were carefully monitored and did not exceed normal range (Table 4.18). None of the patients withdrew (Table 4.13) due to drug related adverse events. The frequency of adverse events in the current study was low in each of the intervention arms (Table 4.14). Overall, it was encouraging to note an excellent safety and tolerability profile of diet based K+ intervention in the current study.

In the current study, correlation analysis (Pearson’s ) matrix at baseline (Tables 4.23 & 4.24) showed interesting correlations between several measures of disease activity, demographics, quality of life and K+ related measures. The correlations between standard RA measures were of the same pattern reported in literature ^160^. RAPS, as a measure of pain ^162^ was translated and validated for local Indian use prior to beginning the current interventional study and details are attached as Appendix 3. In the current analysis,
RAPS showed significant (p<0.05) correlation with early morning stiffness (patient), swollen joint count, general health assessment (using VAS), SF 36 physical score, SF 36 mental score, serum C-reactive protein and serum K+. Interestingly, BMI did not correlate with any other measure in this analysis. Also, there was no association between energy consumption (mean calories) and any other measure analysed in the current study.

At baseline, there was no correlation between diet K+ content and pain VAS but at week 16 endpoint follow up (completion), the correlation was -0.22 (p=007) and this lends some credence to one of the primary contention that low diet K+ may be associated with greater extent of pain in RA. Intriguingly, there were no important and consistent correlations (Table 4.24) between diet K+, serum K+, serum sodium-K+ ratio and urinary K+. It was expected that increase in diet K+ will lead to increased serum K+ and/or increased urinary K+ but these assays are likely to be closely related to the timing of oral K+ administration (which was primarily during lunch and dinner in the current study).

K+ is predominately intracellular. After oral intake, there is rapid absorption from upper gut and this threatens to upset the delicate extracellular K+ balance and particularly in plasma. Plasma/serum K+ operates within a narrow normal range and the consequences of both hyper and hypo can be fatal. The upsurge from the gut is quickly managed by rapid shifts between cellular compartment (especially muscles) and/or excretion by renal mechanism. Therefore, it is unlikely that morning serum K+ assay will correlate with dietary K+ (which was predominantly administered during lunch and dinner in the current study) and such was the case (see correlation results). Urinary K+ excretion is the net result of tubular absorption and secretion and is highly variable during the day. This variability is subject to extensive renal and extra renal homeostasis (neuro humoral and circadian rhythm)\textsuperscript{262}.

A 24 hour urinary collection to assay K+ has been recommended which is quite cumbersome especially to the patient. Therefore, a morning urine assay was performed in the current study more out of a compliance (diet) concern rather than any physiological

evaluation. Though, there was some increase in urinary assay for K+ over time in the dietary K+ intervention arms (more so in Arm B with a high K+ intake), the response was somewhat erratic and showed poor correlation with dietary or serum K+ assay. Recently, early morning fasting urine sample was used to estimate 24 hour K+ excretion in a large scale epidemiological study on urinary electrolytes and blood pressure. However, urinary K+ assay may reflect the nutritional status of the diet.

A comprehensive robust multiple variable step forward regression analysis (Appendix 17) was carried out with pain VAS response on study completion as the dependent variable and several independent variables. All patients who exceeded the minimal clinically important difference of change in pain VAS (> 10 mm) over study period from baseline to completion were considered as respondents. In this model, both the K+ intervention arms were combined to create a single variable of diet based K+ intervention. The predictors of response (p<0.05) were K+ intervention, duration of RA illness, serum K+ and diet K+. This signals an important contribution of dietary K+ towards reduction in pain in the current study. Though several studies have addressed psychosocial factors associated with chronic pain, including musculoskeletal there is sparse data in rheumatology literature pertaining to the last two decades to address the predictors of pain in RA.

Prior to the current interventional study, a pilot study (Appendix 2) was carried out to assess the diet in patients of RA and compare with healthy men and women. The focus was to estimate dietary K+. This cross sectional design study demonstrated a significantly low dietary K+ in patients suffering from RA as compared to healthy subjects. The dietary K+ was significantly lesser (P<0.05) in women patients. The RA patients were

263 Mente A, Irvine EJ, Honey RJ, Logan AG. Urinary potassium is a clinically useful test to detect a poor quality diet. J Nutr 2009;139:743-9


predominantly women belonging to perimenopause age group but were somewhat older (p<0.05) than the healthy subjects (control). The study subjects were selected in a community based popular clinic and likely to reflect a more true to life scenario. In addition to K+, other diet estimates were also carried out as per the standard guidelines from NIN/ICMR. Women patients consumed a significantly lower calorie diet with lesser quantity of protein and fat, and several minerals and vitamin B complex (Pilot study, Table 1). On the other hand, except for lesser protein and K+, there were no other significant differences between men in the RA and healthy subject groups (Pilot study, Table 2). When the RDA estimates were considered, the diets of men and women in both the study groups (RA and healthy subjects) appeared healthy except for significantly lower K+ intake. There were some subtle or somewhat borderline deficiencies: riboflavin in case of women patients and riboflavin, zinc and phosphorus in men patients. Low dietary K+ in patients of RA as seen in this report has not been reported earlier to the best of knowledge. However, in view of this finding, it was considered necessary to first ensure a diet adequate in K+ as per standard Indian guidelines and expert consensus in the CRD faculty for the patients in the active K+ intervention arms (Arm A and B) in the current study; extra diet based K+ was added in Arm B to evaluate a probable therapeutic effect.

Some reasons can be postulated for the conspicuous difference between the dietary K+ content of RA patients and healthy subjects in the pilot study (Appendix 2). Is the low K+ content a cause or an effect of RA? It has been described as an important etiological factor but there is very little supportive evidence. RA is a multifaceted disease with several psychosocial consequences and patients tend to neglect and indulge in self denial. Appetite is often poor and often made worse by the several long term medications. But why should there be a selective deficiency of K+ as was shown by the pilot study and later by the baseline diet data (Table 4.19) in the current study? Surprisingly, majority of the study patients were non-vegetarians and possibly highly selective with regards to consumption of vegetables and fruits. The community observes several do’s and don’ts (see above, diet preferences) which are often connected with vegetables, pulses, cereals and fruits. And all these are major sources of K+. 
In an earlier community based survey of 394 patients of chronic arthritis and rheumatism, 36% patients believed that certain foods worsened arthritis (11.2% source foods including tomatoes, citrus fruits; 14.2% too much oily/fried foods; 5% rice; 9.1% some vegetables, milk and milk products; 2.4% non-vegetarian). 4% of all patients believed that their ailment was caused by some dietary indiscretion. Also, in the Indian community though many patients consuming modern drugs, they often follow Ayurvedic advise on diet which can be rather stringent for many dietary items known to be good sources for K+ (such as potatoes, sour foods and night shade vegetables). Patients of RA are known to have food fads caused by several misconceptions and propaganda about diet in the community. Diet related myths and misconceptions or recommendations based on anecdotal evidence have been reported from all over the World and seriously believed by the community. Finally, it is prudent to add, that socioeconomic factors, culture and traditions play an important role in the diet habits of the community and more so in our part of the World and this was beyond the scope of the pilot study.

Maximum care was taken in the current study to create a diet intervention based on local availability and socioeconomics (see brochure attached as Appendix 7). The data on local food consumption in RA patients and healthy men and women was gathered during a pilot study (see Appendix 2) and was pivotal to formulating the current study intervention. The pilot study demonstrated unequivocally a significant (p<0.05) deficiency of K+ in diet of patients of RA and this was much more in women. It is prudent to add, that as per the RDA recommended by Indian guidelines, the diet in RA patients (pilot study, Appendix 2) appeared sufficient with respect to calories, fats, carbohydrates, vitamins and other minerals except for significant lack of K+ and a modest deficiency in proteins. And so it was decided that in the first requirement in the active intervention arm


(A) in the current study was to 'top up the diet in K+ by formulating an appropriate meal plan using adequate vegetables, cereals and pulses. This would enable to determine the clinical effect if any of a K+ adequate diet in the current patients. In view of important emerging data on plausible role of K+ in reducing pain and other diseases activity and improving QOL (including blood pressure effects), as described in literature review and in this section, it was decided to evaluate a possible therapeutic role of higher intake of K+ using dietary means. Thus, another active intervention arm (B) was planned with a much higher K+ intake than the RDA and after much expert consensus and reviewing safety literature on oral K+ the target was set at 7-8 gm K+ daily. The emphasis was on using dietary means to achieve this target. The meal plan of arm A was included in arm B but the patients were asked to consume a specially prepared mixed food powder supplement containing food cereals and pulses highly rich in K+ and mixed with oral rehydration salt (ORS) as per protocol (Appendix 8). The ORS powder was considered because there seemed to be a limit (up to 6 gms or so daily) to how much more K+ could be added through meal plan alone. This was approved by the experts and the ethic committee. It was decided to avoid the medicinal forms of K+ available in the market for several reasons of safety and tolerability.

Dietary surveys are indeed challenging and cumbersome to perform. The investigator must have real to life first-hand information about the knowledge, attitude and practises (KAP) of the local community. And this was achieved through a cross sectional pilot study in the current research. 139 patients of RA and 166 healthy men and women were interviewed in the pilot study (Appendix 2) as per the food frequency questionnaires and study protocol; patients provided a 7 day account of food and beverages consumption- 3 day retrospective recall and completed a 4 day prospective food consumption questionnaire (sent by post). The survey questionnaires were further improved based on the learning. Patients found a seven day recall difficult and so in the main study, they were asked to fill a 3 day recall at baseline in the current intervention but were asked to fill a 5 day daily food consumption questionnaire prior to the next follow up visit (till completion end point). The literature provides support both a single day recall and a
multiple day recall up to 7 days. Studies show under reporting and errors especially with respect to minerals. Nuki et al. showed that the K+ calculated from the diet as per available guidelines was less than that estimated by real time chemical analysis of food consumed by the patients. In the current study, standard Indian guidelines on diet and composition analysis were used.

Valid estimates of nutrient intake are required in order to assess nutritional adequacy of the diet and there are no gold standards. Much is based on empiricism. One of the main errors in dietary assessment is misreporting. A systematic literature search identified that 30% studies under reported diet adequacy and that in 15% studies the energy intake was underestimated when a 24 hour recall was used; the focus was on intake of iron, calcium and vitamin C. The problem of assessing and recommending micronutrient intake in diet in different populations is recognized. There is much reliability on the subject’s recall. The diet survey and analysis in the current study was carried out by a trained proficient dietitian (TK) and a senior rheumatologist (AC) was in charge of the rheumatological supervision and study design. However, considering all factors, there is a possibility that dietary composition estimates in the current study may err to slight extent (<10%). In case of diet K+, as described above by Nuki, the current study observation may be an overestimate.

Several guidelines are in vogue regarding RDA (recommended daily allowance) and dietary intake to promote good health. Needless to add that several factors need to be considered before applying such guidelines. They must cater to the needs to the local

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population. The ought to be sensitive to the culture, traditions and ethnicity and even religious beliefs of the population. Regional geographical and agricultural variations ought to be considered. They should be socioeconomically viable and appealing. Formulation of dietary goals and specific guidelines help in providing required guidance to people in ensuring nutritional adequacy. The dietary guidelines could be directly applied for general population but they should also be used by medical and health personnel, nutritionists and dietitians. It is against this perspective that dietary intervention was planned and carried out in the current study. The recommendations of the Indian guidelines issued by NIN, Hyderabad/ICMR were the overarching principle to decide the nature and content of diet used as intervention (Nutrient Requirements and Recommended Dietary Allowances For Indians. A Report of the Expert Group of the Indian Council of Medical Research 2009. National Institute Of Nutrition, Hyderabad, India). These guidelines provide comprehensive composition and calorie value of a large number of Indian food items, vegetables and fruits, pulses and cereals that are consumed all over India; both cooked and uncooked are described. A web based user friendly standard software application was used to obtain a detail analysis of an item; K+ was not included and thus content was calculated manually.

This study was primarily designed with a hypothesis that oral K+ reduces pain in RA and secondary aims pertained to benefit in reducing disease activity and improving quality of life. And diet was chosen as the media for intervention. To maximize oral intake, K+ was also administered as a mixed food dietary supplement (Appendix 8) in Arm B. As discussed above, significant pain relief and other improvement were observed in Arm B and the result was further endorsed when all patients in the active arm intervention (A+B) were combined and compared to active control Arm C (routine diet). Before attributing all success to K+ in the diet, it is important to consider other dietary factors and contents. Table 4.19 describes the baseline values of diet measures in each of the intervention arms and there were no significant differences. It is prudent to add that significant low diet K+ was no different from the observations and results of the pilot study carried out prior to this intervention study (Appendix 2). Table 4.20 describes the completer values of diet measures and it is obvious that there were several significant differences between the
intervention arms. The intake of energy, proteins, fats, minerals and vitamins (except Vitamins A and C) were much higher in Arm B. Undoubtedly, the increment with K+ was maximal. Several other minerals like copper, magnesium and zinc have been described to benefit RA but the clinical evidence so far has been sparse. Unsaturated fatty acids as in the case of interventional studies with Mediterranean diets were considered important contributors to clinical benefit. It is prudent to add that Mediterranean diets were largely vegetables, fruits, pulses and nuts and nothing else and especially K+ or other minerals were analysed. Another recent RA study showed prolonged clinical benefit of consuming vegan diet without gluten but again no other dietary constituents were analysed. Unlike drugs and single chemical entity, it is difficult to subscribe total success to a single element in a diet. And such was the current case. Therefore, though the current study strongly favours several benefits of oral K+ rich dietary intervention in RA, it is likely this was more of a holistic intervention. The active intervention was essentially a vegetarian diet but much enriched with K+. However, there were several other enriched minerals and vitamins that also might have contributed to the clinical benefits, albeit likely to be a lesser extent, observed in the current study.

Non-pharmacological treatment modalities are often recommended, prescribed and used in addition to drug treatment in patients with RA. Compared to the amount of published literature on drug trials, clinical research in non-pharmacological interventions is woefully inadequate. The evidence of effectiveness varies among the different non-pharmacological modalities, with relatively strong support for exercise and self-management interventions, and modest support for other modalities including comprehensive care interventions. But specific mention of diet is lacking in these reviews. The Cochrane review on diet in RA concludes on a modest note of uncertainty with a plea for more studies. In recent times, there has been a focus on Mediterranean diet which is essentially vegetarian and though makes benefit claims based on unsaturated fatty acids but is bound to be rich in several other minerals like K+ which

have never been assessed. Overall, any dietary intervention is basically holistic in approach and at best can be a useful adjunct to standard of care inclusive of other non-pharmacological interventions such as exercise, physiotherapy and anti-stress management. This is possibly the perspective of the current study though the interventions was critically focussed on the clinical benefits of augmented oral dietary K+ in patients with painful RA.

Compliance to dietary advice and intervention is the most important challenge in diet based interventional studies. There are several psychosocial factors involved which are difficult to circumvent. While it is easier to accept diet based advise rather than a drug, it is more feasible to consume medication rather than follow diet prescription. Other than practicality of the investigative diet, the economics are important at least in the Indian like setting. Patients of RA are already overburdened with disease related expenditure. The results of the pilot study (Appendix 2) were practically utilized in interview with the patients enrolled in the current study to explain the importance of K+ in the diet and whether extra K+ can have an adjunct therapeutic effect (especially pain relief). Based on the pilot study experience, the current study diet questionnaires were modified to make them more consumer friendly. The dietary advise offered to patients in active intervention arms (A and B) was based on the local factors of affordability and access for pulses, cereals, fruits and vegetables, and data on knowledge, attitude and practise (KAP as described in public health) of the community was gathered during the pilot study. Patients were closely questioned at every visit for their adherence to intervention and were further made to fill the diet survey questionnaires. The unused amount of K+ rich mixed food supplement (Appendix 8) used in Arm B was carefully measured by the research investigator before giving a new packet at study follow up visit. Overall, about 20% consumed 3-3.5 gm rather than 4 gm requirement; about 6 patients admitted that they consumed 6-7 tablespoonful (standardized size and provided to the patient) rather than the 9 tablespoon requirement and sometimes the morning dose was missed. Though the patients were cooperative and very eager to fulfil the study obligations of diet, the results in Table 4.19 and Table 4.20 indicate a modest gap between what was desired and what was achieved. Overall, the large majority (76%) of patients satisfied the minimum
requirement of compliance (Table 4.11), compliant data set analysis in ‘methods’ section). Telephone reminders were given to the patient to adhere to the diet and/or supplement advise and report on time. Certain laboratory measures like serum and urinary K+ at every evaluation visit were built into the protocol both for safety and compliance reason. It is prudent to add that as described in this section, there was little if any correlation between diet K+ and serum/urine K+ for reasons connected with the physiology of K+ absorption and homeostasis (described in literature review and this section). Though the duration of the current study was somewhat short and blood pressure was not measured in an ideal standardized manner, it is encouraging to note a drop in systolic BP (Fig 4.21) in K+ intervention arm (statistically not significant). The BP response can be a surrogate marker for compliance as was probably the serum cortisol response described above.

K+ is a dynamic ion with rapid shifts between body compartments. And this is often accelerated during restoration of milieu interior and acid base balance with kidney playing a pivotal role. In clinical practise, the serum/plasma cut offs for hypo/hyper state are well recognized and still need a clinical context for proper interpretation. But the precise cut off for a low and high normal values is contentious and does not seem to bear relationship with clinical phenotype or body K+ status. Some have described the blood serum content to be normal at higher serum values of 4.2-4.8 mEq/l. One point measure may be misleading and it is well known that several inadvertent laboratory related errors can lead to false results. Serum K+ must be assayed within 30 minutes of blood collection as was meticulously done in the current study. Intriguingly, there was no correlation between the several K+ measures in diet, blood and urine in the patients of RA in the current study. In this study, non-fasting spot urine sample was collected rather than the cumbersome 24 hours urine sample that has been recommended. However, several recent elegant large scale epidemiological studies of urinary electrolytes have validated the single early morning fasting urine sample. Total body K+ was not

estimated in the current study as was done by Nuki et al (1975)\textsuperscript{223}. Perhaps, the physiology of K+ in RA is somewhat different and influenced by several factors of disease and medication including steroids.

The pilot study (Appendix 2) demonstrated a low K+ in diet of RA patients which was otherwise reasonably well matched with the RDA recommendation for Indians. Total body K+ may be a better measurement of response to augmented diet K+ as shown by Nuki (1974)\textsuperscript{223}. Also influence of drugs (steroids and NSAID especially) may alter K+ physiology in RA. Though a very low dose (Table 4.15), almost 60% of patients in the current study were taking prednisone for over 6 months at least. Several patients of RA consume a large amount of analgesics, NSAID, DMARD and steroids for prolonged periods and all this is likely to have adverse effect on renal physiology which is critical to K+ homeostasis but such data in RA is sparse.

There is some clinical evidence to support the putative role of K+ in reducing pain and improving disease control and this is comprehensively described in literature review (see sections 2.9.6, 2.10.5, current text). Weber (1974) has maintained for a long time that ‘low body K+’ is an important etiological factor in RA and that it has been neglected by the scientific and clinician community\textsuperscript{273}. Nutrient deficiencies promotive to inflammation are shown to precede development of RA though there is no such data on K+\textsuperscript{274}. Higher intakes of meat and total protein as well as lower intakes of fruit, vegetables, and vitamin C are associated with an increased risk of inflammatory polyarthritis or rheumatoid arthritis\textsuperscript{275}. Vegetables and fruits are excellent sources of K+.

\textsuperscript{273} Weber, C.E. 1974 "Potassium in the Etiology of Rheumatoid Arthritis and Heart Infarction." Journal of Applied Nutrition. 26; 41; Ref to Book, and publication in nature


Nuki (1975) carried out a short duration interventional study using parenteral ACTH in 8 patients of RA on symptomatic therapy to evaluate K+ metabolism (responses included serum and urinary sodium and K+ assays and serum cortisol; subsequently, patients received potassium chloride supplement (rather low dose compared to the current study) or spironolactone. Attempts were also made to standardize and analyse diet intake from a K+ perspective. Low body K+ status was demonstrated and the authors concluded that further studies are required to evaluate its physiological and clinical impact.

Almost, thirty years later, Rastamanesh (2002) completed a short term K+ supplement intervention study in patients of RA with serum hypokalaemia and demonstrated unequivocally significant reduction in pain and disease activity and cortisol increase; no diet manipulations were performed. Some soft evidence also emerged from NHANES survey that RA subjects may be deficient in K+. The current study, with a more comprehensive diet intervention design and consideration of several true to life clinical factors in RA, was a rejoinder to the low K+ status in RA and its possible therapeutic role using K+ enriched diet and dietary based K+ mixed food supplement.

The physiological normal range of serum K+ is narrow and not an accurate marker of total body K+. Thus it may be appropriate to study K+ intervention in patients of active painful RA irrespective of their serum K+ status. In the current study, though significantly low K+ was demonstrated in the diet, none of the patients had any lab defined hypokalemia. Rastamanesh (2008) chose woman patients of RA who were also serum hypokalemic for a small sample size short duration study to demonstrate significant reduction in pain and some disease activity measures following oral K+ supplements administered in grape juice. But this is not likely to be a true to life scenario in RA. The current study was more pragmatic and realistic and the results were more meaningful.

The molecular basis for the current study is really an extrapolation of a large body of experimental and physiological data on K+ in health and disease (literature review). K+ is critical to the normal physiological functioning of membrane sodium-K ATPase pump.

276 Jay N. Arch Intern Med. 2000;160:2429-2436
and K+ ion channels. Downregulation of K+ ion channels and autoantibodies to these channels in chronic pain disorders have been convincingly shown and described in literature review (see sections 2.7.4, 2.8, 2.10, current text). K+ mediates several effects through its ion channel physiology in T cell functions and further reduces oxidant damage. The beneficial vasogenic effects of K+ on blood flow and blood pressure, which have been validated in several studies (see literature review section 2.10.1) may be extrapolated to RA. And this is very important as the evidence piles to suggest that RA is an important cause of premature mortality due to cardiovascular complications. RA is a low cortisol state with excess sympathetic stimulation. Potassium deficiency downregulates, whereas glucocorticoids or potassium overload upregulates Na+, K+-ATPase levels in cell membranes. The close nexus between K+ and serum cortisol and aldosterone (promotes inflammation) is well known and is likely to be beneficial in RA.

It is worthwhile to highlight some of the experimental data to support the vasogenic effects of high potassium diet. K+ enriched diet and increases in serum potassium, even within the physiologic range, cause endothelium-dependent vasodilatation by hyperpolarizing the endothelial cell through stimulation of the sodium pump and opening

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potassium channels. Experimental potassium depletion inhibits endothelium-dependent vasodilatation.

Experimental studies suggest that in addition to its effects on vascular tone, a potassium-rich diet decreases cardiovascular risk by inhibiting arterial thrombosis, atherosclerosis, and medial hypertrophy of the arterial wall. Without alteration in blood pressure, 64 mmol of oral potassium salt improved endothelial function as measured by brachial artery flow-mediated dilation, increased arterial compliance as assessed by carotid-femoral pulse wave velocity, and reduced left ventricular mass and improved its function in a study of 42 adults.

There is much evidence on beneficial role of K+ on bones and may be mostly through indirect means. Low potassium intake has been shown to increase rates of calcium excretion. Potassium salts have been shown to improve calcium balance and reduce bone turnover. But this may be augmented or superseded by other components of fruit and vegetables like Vitamin C and vitamin K. In the Framingham cohort, dietary


283 McCabe RD, Bakarich MA, Srivastava K, Young DB. Potassium inhibits free radical formation. Hypertension 1994;24:77-82


intake measures were associated with better bone mineral density values among surviving members of the original cohort of the Framingham Heart Study (initiated in 1948) in both cross sectional and a 4 year longitudinal study. In 1968 Wachman and Bernstein hypothesized that bone mineral functions as a buffer base and that lifetime buffering of the acid load from the ingestion of mixed diets (similar to consumed in US and Europe) leads to gradual and accumulated bone loss. Two nutrients that may have such buffering effects are potassium and magnesium. A higher dietary acid load (caused by greater consumption of acid-forming Western style foods, such as cereals and meat) believed to result in bone mineral dissolution and greater bone resorption. This results in the release of carbonate, citrate, calcium, sodium, and potassium. Fruit and vegetables also are rich sources of antioxidant vitamins such as vitamin C and -carotene. These could act by reducing oxidative stress, which has been shown to be negatively associated with bone mineral density in adults. Whole diet is more important than isolated nutrients but the evidence linking fruit and vegetables to bone health across the life cycle is not conclusive.

Consensus favours clinical studies to investigate relationship of disease to dietary patterns instead of particular nutrients. There are great difficulties in performing confirmative or manipulative human interventions in diet research. Unlike drugs, dietary


consequences are very gradual. Preventive endpoints call for long wait for disease incidence in compared groups. Sanctity of research can only be assured by catering to entire food intake of study subjects. There is no scope of placebo comparison group. Biomarkers are most useful means to obviate wait for disease incidence. Diet and disease relation has to be examined at the whole person level (e.g. energy balance) as was attempted in the current study (see pilot study Appendix 2, and Tables 4.19 and 4.20).

It has been described above that though the current focus was on diet based K+ intervention, the diet is likely to have contained several other constituents that must have helped patients getting better. Also, this study was not designed to study the clinical implications of inadequate K+ intake or the several other relative or absolute deficiencies found in the diets of RA patients. Diet must be considered in a holistic manner though undoubtedly a large amount of evidence has been put forth in the current study to highlight the clinical benefits of K+ in RA. Adequate potassium in conjunction with adequate magnesium (Mg) is likely to be of greater benefit but was not assessed in the current study. Mg is critical for energy requiring pumps in plasma membranes\textsuperscript{294, 295}.

Departing from the stringent requirements of a placebo controlled double blind study, it was decided to introduce some important pragmatic trial elements in the current study so as to mimic as much as possible the true to life scenario of treating RA in a community setting. The study site was a popular community based rheumatology centre with a daily attendance of 70-100 patients (www.rheumatologyindia.org). This centre is nodal for many community surveys (including COPCORD population surveys) and arthritis camps. The patients were divided almost equally between urban and rural areas and were considered to belong to low-middle socioeconomic status. Patient enrolment, assessments

\textsuperscript{294} Lacapere JJ, Bennett N, Dupont Y, Guillain F: pH and magnesium dependence of ATP binding to sarcoplasmic reticulum ATPase: Evidence that the catalytic ATP-binding site consists of two domains. J Biol Chem 265:348-353, 1990

\textsuperscript{295} Patchornik G, Goldshleger R, Karlish SJ: The complex ATP-Fe(2+) serves as a specific affinity cleavage reagent in ATP-Mg(2+) sites of Na,K-ATPase: Altered ligation of Fe(2+) (Mg(2+)) ions accompanies the E(1)→E(2) conformational change. Proc Natl Acad Sci USA 200;97:11954-59
and monitoring were as per protocol (Appendix 4) and adhered to global standards of
drug trials in RA. GCP guidelines and those of Indian Government regulatory bodies like
ICMR (the current protocol was registered on the CTRI website) were meticulously
followed. The sample size of the current 3 arm interventional study was calculated using
standard formula with a 80% power (Type II error) and a significance at p<0.05; in
absence of any relevant guideline, a difference of 10% between the K+ arm (superior)
and active control )routine diet for pain VAS was assumed based on expert opinion in
CRD. Also, a 20% drop out rate was considered a-priori though the final withdrawal rate
was much less (10-12% in each arm).

Irrespective of whatever may be the cause of low K+ in RA diet, it is imperative to
determine the biological consequences of such a deficiency. A study of low dietary K+
in animal models of RA may be appropriate. It may be important to advocate K+ rich
diets to patients of RA though much more clinical evidence is required. Recently
published guidelines make no mention about the dilemma in patients of RA . It is
prudent to add, that an intervention with oral K+ supplement in patients with active
painful RA may provide interesting clinical insights into its therapeutic role. We intend
to carry out such a controlled diet based experimentation in patients suffering from RA
with pain reduction as the primary target.

The inability to accurately assess dietary intakes makes it impossible to describe
potassium recommendations from observational studies. In this the optimum daily diet
plus supplement based K+ intake was about 7.5-8 gm in most of the patients in Arm B.
The nature and amount of K+ intake was decided a-priori and based on expert opinion
and safety concerns for oral K+. Possibly, this is the maximum dietary based K+ intake
that has ever been evaluated in RA or any other medical disorder. The published
literature reviewed did not provide any reasonable guidance on the amount of K+ that
would be required for any symptomatic benefit in RA. No dosing effect such as
‘increasing pain relief with increasing dietary K+ ‘could be demonstrated in the current
study though there were weak trends and correlations.Future trials may show that
potassium benefits occur at intakes below the current general recommendation of 4700
mg/d. Evidence from trials on blood pressure suggests 3600–3800 mg/d may be
reasonable for heart and bone health\textsuperscript{101, 176, 185, 202}. This is still 1000 mg higher than the generally reported mean consumption of potassium as was observed in the current study also (Table 4.19). Improving the potassium: sodium intake ratio has a stronger advantage to heart health than either dietary constituent in isolation. This may be true for bone health also because these minerals have opposing actions on calcium excretion. Still, public health messages to improve diet quality generally has potential for more far-reaching impacts than encouraging single nutrients in isolation.

But there is very little actual data on how oral loading with K+ using dietary means in RA can be beneficial. But there are several surrogate clues and leads as mentioned above that lend credence to the hypothesis of a putative beneficial role of K+ in RA in the current study. Putting together all the clinical and molecular data on the physiology and pathogenesis of K+ in pain and other disorders like hypertension, stroke, osteoporosis, renal disorders and the unequivocal evidence in the current study that K+ is low in diet in RA it is logical that patients of RA must be advised to consume vegetable and fruit diet which is rich K+. Several other benefits of such diets (see section 2.6.1, current text) have already been shown and in particular Mediterranean diet. K+ supplements, and especially diet based as in the current study, may be required subjects who are otherwise non-vegetarian and/or consume too many processed foods\textsuperscript{296}. Data from 196,373 adults from 52 countries with mainly small and middle income were interviewed (24 hour recall) in the World Health Survey (2002–2003) and results showed that about 78 % of the men and women consumed less than 400 gm of vegetables and fruit daily as recommended by the World Health Organisation\textsuperscript{297}. The current clinical diet intervention study using K+ which is a potentially toxic mineral to treat RA was a unique experiment. Several limitations were recognized and several overcome. To the best of knowledge and

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{296} Kianifard T, Saluja M, Chopra A. Is dietary K+ important in rheumatoid arthritis? preliminary observations. Ann Rheum Dis 2014;73 (Suppl 2): 1169-70
\end{itemize}
\end{footnotesize}
based on literature reviewed, this was a maiden research study of its kind with several novel and innovative features which may provide a platform to develop further the role of current interventions in RA.

It is suffices to say that patients of RA should be advised on suitable diet, preferably vegetarian (as in the current study) and rich in K+. Though this study demonstrated clinical benefits of dietary K+ augmented with a supplement (as in the current study) in patients of RA suffering from painful active disease, it may be considered as a moderately effective adjunct therapy with good safety and tolerability. However, the current study needs further validation in clinical trials of dietary intervention of longer duration. RA continues to be a difficult to treat disorder despite revolutionary advances in drug management. However, though highly effective, this is fraught with drug toxicity and life threatening complications. Long term pain management continues to be a critical problem. Diet based therapeutic intervention has a tremendous socioeconomic appeal to the community and if kept holistic (as in the current study) is bound to provide several clinically relevant benefits including a lesser need of drugs in time as the patient gets better. The current study on diet K+ in RA should be viewed against this perspective.
Limitation and Strength

Limitation:

Several limitations are discussed along with the results under the sections of ‘results’ and ‘discussion. However this provides an overall summary

- Diet analysis depended on survey recall by patients and is subjected to individual variation and comprehension

- Good compliance to a dietary intervention is difficult. It was difficult to assess complete adherence to dietary advice though it seemed to be satisfactory.

- Influence of ethnic, personal habits (use of tobacco) and socioeconomic/affordability and access (to food market) on the study diet and study outcome was not evaluated. It is possible that some patients found it difficult to purchase the required dietary items to prepare the kind of meal advised in the current study

- Single blind design made the patients aware of their intervention and they may have been tempted to share this with other study subjects. There was a concern that patients in Arm B believed that the special diet based K+ mixed food supplement powder was effective for RA and induced an additional placebo effect. Also, these patients might have shared this powder with other members in the family.

- Variation in background medications in standard of care treatment for RA as per the clinical judgment of the rheumatologist in the current study is bound to have been a confounding factor. Almost 60% patients were on stable fixed dose of oral steroids, albeit small and less than 5 mg daily, and this could have interfered with physiological response to oral K+. Also, due to ethic concerns, patients were provided with a full strategy of rescue paracetamol use in case of intolerable pain but might have used it somewhat more indiscriminately to interfere with pain response evaluation at follow up. However, this was preferred to keep the study as close to the real life situation as possible.

- Different doctors / rheumatologist evaluated patients and in absence of any inter observer standardization may have let to measurement errors. It is prudent to add that all patient centric measures were taken by a dedicated trained paramedic and study nurse.

- Blood samples were collected between 9-11 am and may not be truly fasting and this is in special reference to serum cortisol

- Spot urine (morning sample) analysis for K+ was done instead of the ideal 24 hours collection. This may not be able to capture the likely serum and urinary K+ changes induced by the K+ rich lunch and dinner.
Diet K+ and other components estimates were indirect and based standard Indian guidelines and web based software application of the NIN, Hyderabad. The literature is sparse on this subject but one study by Nuki (1975) showed that direct measurement of dietary K+ was less than that recorded from the indirect method based on guidelines by an expert group. Therefore, the current study method may have led to an overestimate of diet K+ and indirectly some dilution of results.

Total body K+ could not estimated. This required isotope study which was both expensive and cumbersome.

The clinical benefits (antioxidant, metabolic and lipid lowering) of other dietary components (fiber, effect of other minerals like copper, zinc) in the current K+ rich vegetarian diet could not be evaluated but is likely to have contributed to the overall health and disease control.

The duration of study was 16 weeks. This duration was considered enough to demonstrate effect on pain relief and disease activity. However, being an adjunct dietary intervention, a longer period might have shown better and consistent clinically beneficial effects.

Strength:

- This was a large sample size study design with 80% power (Type II error) and a significance at p<0.05 (Type I error).
- The study was randomized, single blind (assessor), parallel efficacy study.
- Overall, the study design was pragmatic.
- The intervention was diet based which is of great relevance to patients and medical community.
- The dietary intervention was based on the results of a pilot study survey of diets consumed by RA patients and local healthy people. Care was taken to consider affordability and access when planning K+ rich diet and supplement as intervention.
- Though the focus was on role of K+ in the current diet, dietary analysis included other vital elements like calories consumption and intake of proteins, fats, minerals and vitamins.
- In a pilot study, an Indian translated version of RAPS, a composite pain capture questionnaire, was suitably validated for use prior to its application in the main intervention study.
- The study enrolled patients from a real life scenario of a community based routine rheumatology set up with a standard of care management of RA.
- All consenting enrolled patients continued supervised standard of care treatment for RA.
• Patients in the active control arm continued routine diet.
• The emphasis was on clinical effectiveness and safety.
• Rheumatologists recorded all relevant physician centric measures in particular painful and swollen joint counts.
• A dedicated team of trained paramedics recorded all patient centric measures and were blinded to treatment intervention allocation.
• Besides using standard clinical measures for efficacy in RA, the study used standard dietary data capture questionnaires and several standard quality of life instruments (such as SF 36) to evaluate the effect of K+ in RA.
• A comprehensive laboratory evaluation was carried out to assess safety of the intervention.
• Special assays were set up for urinary electrolytes and serum cortisol.
CONCLUSION

The current randomized controlled study of 16 weeks duration unequivocally demonstrates that oral K+ reduced pain in patients suffering from RA and on treatment with supervised standard of care in a community based rheumatology centre. K+ was administered as enriched K+ vegetarian diet plus food based and mixed (with oral rehydration salt containing potassium chloride) supplement powder. The improvement in several pain measures was statistically significant (p<0.05). Allocation to oral K+ intervention was a significant predictor of response in pain relief.

The augmented diet based K+ intervention also showed clinically modest reduction in disease activity and improved functional and quality of life measures (HAQ, SF 36 physical). There was a trend in reduced systolic BP and higher increment in serum cortisol.

In this study, the safety and tolerability profile of diet based K+ intervention was excellent.

Dietary based K+ augmentation should be considered as a safe and effective adjunct therapy to standard of care drug treatment in patients suffering from RA.

However, several other important results and conclusions are described below.

Other Conclusions:

- Diet K+ was low in RA

- The Indian translated version of RAPS was found to be a feasible and valid pain measuring instrument in RA

- Good safety profile of diet K+ intervention upto 8 gm daily diet K+ intake

- Serum K+ and Urine K+ measures showed inconsistent results vis a vis dietary intake

- The clinical benefits of other dietary components (eg. fiber, minerals) in the diet intervention arms can not be excluded.
Future Direction and Application

The current study has demonstrated sufficient clinical evidence to support a therapeutic role of diet enriched and supplemented K+ in the management of patients suffering from RA on supervised standard of care rheumatology management. In particular, the pain relief, albeit modest and statistically significant, was clinically important. There was enough data to suggest clinical benefits on disease activity and blood pressure.

The study results need to be replicated in more comprehensive controlled clinical interventional studies of longer duration. The focus ought to be diet enriched K+ and food based K+ supplement intervention similar to the current study and sensitive to local conditions. It would be better to control concomitant medication for RA and exclude/reduce to minimum rescue analgesic use after a reasonable initial period. A special emphasis could be on evaluation of cardiovascular and bone health (bone density) measures.

Potassium chloride in a medicinal form may be considered for therapeutic evaluation (pain and disease control) in an exploratory clinical control drug trial in patients of RA as an adjunct therapy.

K+ in dietary form or medicinal form should be administered to animal models of inflammation and RA to comprehensively study its biological effects and mechanism of action.

Dietary advise in RA is probably a neglected subject from a clinician perspective. Larger epidemiological surveys should be planned to study diet in RA. The current study demonstrated K+ deficiency in RA diet and this ought to be studied in different communities. It may be more relevant in communities which predominantly consume non-vegetarian diet including fish. Also, based on the results of current study, clinicians should not hesitate to advise patients on adequate balanced diet preferably vegetarian with ample fruits.