2. RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder and reported from all over the world. It is an ancient disease and finds descriptions in Charak Samhita, an ancient text of Ayurveda medicinal system. It is a prototypic painful lifelong illness which impacts quality of life and shortens life span; in an Indian series, infections and cardiovascular causes were leading causes of death. Though predominantly an articular disorder, it is a systemic disease with several systemic complications and protean manifestations. Despite striking advances in treatment of chronic diseases, RA continues to be a difficult to treat disorder. Though the ultimate goal of management is to control the disease process and prevent deformities, early and effective treatment of pain and inflammation is the overarching principle. There is a never ending research to find better and safe analgesics and anti-inflammatory drugs. The potential side effects and life

REFERENCES:


2 Chopra A. Epidemiology of Rheumatoid Arthritis. In Ed Mukherjee, Ghosh A. Monograph on Rheumatoid Arthritis Indian College of Physicians (Assoc Physicians India), Kolkata: Marksman Media Services, 2012, pp 1-9


threatening toxicity grips the fear in the patients and community and tremendous concern amongst doctors. Across the World, there is an undying enthusiasm to search and research non pharmacological interventions including diet and nutrition, exercise and physiotherapy for pain management. The current thesis explores the therapeutic role of potassium in relieving pain and inflammation in patients suffering from RA.

2.1 Disease description

RA is a chronic, systemic inflammatory painful polyarticular disorder characterized by affection of small joints of hands and feet. Though both small and large joints and axial joints (spine apophyseal) can be affected, it is predominantly a symmetrical polyarthritis with exclusion of sacro-iliac and distal interphalangeal joints. RA is generally a progressive life long disease but in majority of patients the course is marked by incomplete remissions, flares and relapses. The most dreaded sequel of persistent active disease is articular deformity which can lead to loss of function and reduced quality of life.

2.2 Epidemiology

The incidence of RA is typically two to three times higher in women than men. The disease is generally known to be perimenopause in onset though no age is bar. An
unusually high prevalence of RA in young women was reported by an Indian population survey.  

The prevalence of RA across the World is considered to be 1% of the adult population. However, the WHO ILAR (International League of Associations for Rheumatology) COPCORD (community oriented program for control of rheumatic diseases), launched in 1980s primarily targeted developing countries. COPCORD surveys were completed in over 21 countries in the Asia, South America, Australia and Africa continent. COPCORD was designed as a low cost - low infrastructure local resources based community program. The maiden COPCORD survey in India was completed in village Bhigwan (Pune) in 1996. The details of the program and the prevalence statistics and burden of disease are comprehensively described on the website.

MSK pain and disability has been a primary target and COPCORD surveys has demonstrated MSK pain to be the dominant self reported illness in a community above.

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7 Chopra A. The COPCORD world of musculoskeletal pain and arthritis [editorial]. Rheumatol 2013; 52(11):1925-8


10 http://www.copcord.org
In a recent presentation, COPCORD India surveys covering over 55,000 population in over 13 sites all over India, reported that one-fifth of the population is likely to suffer from MSK pains requiring medical attention and investigation. 12-15% of a rural urban population in the Pune region (India) suffered from some form of painful rheumatic disorder and at least 55-60% suffering from these ailments recorded a significant impact on their life, work and finances. The commonest disorders in the community were soft tissue rheumatism, non specific aches and pains and degenerative arthritis and Inflammatory arthritis, including rheumatoid arthritis, affected less than 10% of the community cases.

In Asia Pacific, the prevalence of RA in COPCORD surveys was much less compared to the conventional 1% prevalence reported in Caucasian population. The prevalence of RA reported was Australia (rural) 0.7%, Pakistan 0.55%, India rural 0.5%, India urban 0.4%, China (Shanghai 1998) 0.47%, Iran (urban) 0.37%, China (Beijing) 0.34%, Iran (rural) 0.32%, China (Shantou) 0.32%, Indonesia (urban) 0.3%, India (urban ACR classification) 0.3%, Vietnam 0.28%, Indonesia (rural) 0.2%, Philippines (rural) 0.2%, China (Shanghai) 0.2%, Philippines (urban) 0.17%, Malaysia 0.15%, and Thailand

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0.12%. However, it is prudent to add that these are highly populated countries and even a small prevalence figure translates into millions of patients suffering from RA\(^\text{13}\).

A very recent Indian report based on pooled all India COPCORD data (urban and rural) and adjusted for age and gender reported a point prevalence of RA to be 0.34\(^\text{12}\).

2.3 Aetiopathogenesis

The cause of RA is not completely understood though several pre-clinical features have been identified\(^\text{14}\). Figure 1 describes the web of causation model applied to RA. It is evident other that host factors, environment and psychosocial factors play an important role in aetiopathogenesis. Half of the risk for RA is believed to be genetic as has been demonstrated by epidemiological studies of twin siblings. There is longstanding evidence that specific HLA class II genotypes are associated with increased risk. The classical risk theory supported by several World wide evidence pertains to the ‘shared epitope’ hypothesis revolving around HLA DR B alleles\(^\text{15}\). It is believed, based on Caucasian studies, that DRB1*0401 and DRB1*0404 alleles\(^\text{16}\) confers a susceptibility and severity

\(^{13}\) Chopra A, Ghorpade R, Sarmukdadum S, Joshi VL, Mathews A, Gauri L et al. 5 million patients and not 0.34% is worrisome: Burden of rheumatoid arthritis in India. Arthritis Rheumatism 2012; 64: V 10 (Suppl):58 (abstract), S23


\(^{15}\) Hameed K\(^1\), Bowman S, Kondeatis E, Vaughan R, Gibson T, The association of HLA-DRB genes and the shared epitope with rheumatoid arthritis in Pakistan, Br J Rheumatol. 1997;36(11):1184-8

risk but this was not entirely borne by studies from India. Several other risk factors pertain to other major histocompatibility complex (MHC) and non-MHC alleles including PADI4, PTPN22 and CTLA4. Over the decades, the ‘infection theory of causality’ has not been abandoned though direct evidence is lacking. RA patients have been described to express several biochemical and endocrine abnormalities of pathological significance such as abnormal protein glycosylation and low spontaneous and stimulated cortisol secretion levels. The interaction between genetic factors and environmental exposures does contribute to the etiology. RA can also have familial predisposition.

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Fig 2.1: Web of causation model applied to rheumatoid arthritis

Environment ———> Genes ———> Personal factors ———> Autoimmunity ———> Rheumatoid Arthritis Disease ———> Disease Activity ———> Fatigue, Pain, Joint swelling ———> Physical, psycho-emotional and Socio-Economic Impairment ———> Progressive disease ———> Disability, Poor Quality of Life, Co-morbidities (Cardio-vascular etc) ———> Reduced Life Expectancy
Several modifiable risk factors have been studied in association with RA including reproductive hormonal exposures, tobacco use, dietary factors, and microbial exposures. Among these risk factors, the strongest and most consistent evidence is for an association between smoking and RA. A history of smoking is associated with a modest to moderate (1.3 to 2.4 times) risk of RA onset and this is strongest amongst patients who are seropositive for citrullinated protein antibodies\(^1^9\).

There is thus scope for identifying environmental predictors that might offer a strategy to prevent the disease. Changes in the female hormonal environment such as in pregnancy, breastfeeding and the use of the oral contraceptive (OC) pill appear to have a role. Of the traditional lifestyle exposures, cigarette smoking has been associated with a consistently increased risk that might also apply to the passive inhalation of smoke. Occupation probably has a minor influence, although exposure to silica dust is of etiological importance. Recent studies have highlighted a role for diet, with suggestions that diets high in caffeine, low in antioxidants and high in red meat may contribute to an increased risk\(^2^0\). Higher intakes of meat and total protein as well as lower intakes of fruit,

\(^{19}\) Silman AJ, Hochberg MC. Epidemiology of the Rheumatic Diseases. 2nd ed. New York: Oxford University Press; 2001

\(^{20}\) Oliver JE1, Silman AJ. Risk factors for the development of rheumatoid arthritis.. Scand J Rheumatol. 2006 May-Jun;35(3):169-74
vegetables, and vitamin C are associated with an increased risk of inflammatory polyarthritis or rheumatoid arthritis\textsuperscript{21,22}.

RA is essentially a synovitis\textsuperscript{23}. The joints are warm, tender, painful on movements and often take a red inflammatory hue. The initial process is intense immune inflammation targeting the synovial membrane. This is followed by gross proliferative changes and angiogenesis. This growing synovium called pannus when not controlled invades bone at juxta-articular site that leads to bone and joint destructive changes with secondary degenerative changes in the cartilage\textsuperscript{24}. RA can produce diffuse inflammation at several extra-articular sites- lungs, heart, eyes, nervous system and skin. It can also produce nodular lesions often seen as cutaneous nodules adjacent to peripheral joints and uncommonly in lungs and other organs.

The diagnosis of RA is essentially clinical based on historical profile of disease onset and symptoms and findings on physical examination. Early morning stiffness lasting for over 30 minutes is invariably complained when the disease is active. X-rays, laboratory testing, and synovial fluid analysis might help support a diagnosis or exclude other


diseases with similar symptoms. 70-80% of patients are seropositive for rheumatoid factor (RF) and anti-cyclic citrullinated proteins (CCP). Radiologically, typical juxta-articular erosions can be identified in early disease and sometimes within 6 months of onset to herald a progressive course and bad prognosis and a need for early aggressive therapeutic intervention.

2.4 Classification Criteria (See Appendix 1)

The earlier 1987 criteria were actually based on hospital cases and were found to have low sensitivity and specificity for diagnosis of early RA. A critical observation in the past two decades has been the need for early diagnosis and recognition of bad prognostic factors so as initiate early carefully monitored aggressive therapy during the so called window of opportunity (to prevent bone and joint damage) to induce low disease activity or remission in RA. It is against this perspective that the new 2010 ACR / EULAR


27 http://www.medicinenet.com/rheumatoid_arthritis/article.htm

Rheumatoid Arthritis Classification Criteria were introduced. These new classification criteria overruled the "old" ACR criteria of 1987 and are adapted for early RA diagnosis. The "new" classification criteria, jointly published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) establish a point value between 0 and 10. In the "new" criteria, clinical, autoimmune serology carries major weight. Destruction of the joints viewed in radiological images was a significant requisite in the 1987 ACR criteria but is no longer is regarded in the recent classification. The new 2010 classification criteria are not intended for the diagnosis in routine clinical care. They were primarily intended to classify disease in epidemiology research and clinical drug trials. They were primarily developed in Caucasian population and are not yet validated for global use and Indian population.

2.5 Management

Rheumatoid arthritis is a long-term life long disease. Early diagnosis of RA and effective treatment with disease-modifying anti-rheumatic drugs (DMARDs) are essential to

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reduce joint destruction and disability\textsuperscript{32,33}. Late diagnosis of RA greatly increases the risk of erosive joint damage.

To ensure normal, productive life, effective management must induce long term sustained remission. The goal of treatment in RA is to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treat pain or al else will fail is a wise adage to remember and needs judicious and rationale use of analgesics and non-steroidal anti-inflammatory drugs (NSAID). DMARD (disease modifying anti-rheumatic drugs) are slow acting drugs but are a cornerstone in all treatment plans and aim to arrest the disease process through immunomodulation and immunosuppression.

Two classes of medications are used to treat RA: fast-acting "first-line drugs" and slow-acting "second-line drugs". The first-line drugs, such as NSAIDs and corticosteroids, are used to reduce pain and inflammation. The slow-acting second-line drugs, such as methotrexate, sulfasalazine, hydroxychloroquin and leflunomide promote disease control, remission and prevent progressive joint destruction. They need careful and intensive supervised monitoring to avoid drug toxicity while achieving maximal efficacy tolerable doses. Methotrexate is the sheet anchor DMARD, both in early and advanced disease, and is used as a monotherapy or in combination with other DMARDs including biologic


agents. Optimal care of patients with RA consists of an integrated approach that includes both pharmacologic and non-pharmacological therapies. Biologic DMARD have revolutionized the management of RA and are very precise target oriented mostly monoclonal antibodies. The current ones target tumor necrosis factor (TNF) (infliximab, etanercept), interleukin (IL) 6 receptor (tocilizumab), B cells (rituximab), T cell coreceptor (abatacept). Biologic DMARD or also called biologic response modifier (BRM) not only control and arrest the disease process more effectively but also treat other complication like osteoporosis, improve quality of life and prolong life. Early therapy with DMARDs has become the standard of care, in that it is capable not only of retarding disease progression more efficiently than later treatment but also, potentially, of inducing more remissions. Many non-pharmacologic treatments are useful for holistic care and include exercise, diet, massage, counseling, stress reduction, physical therapy, and surgery. Active participation of the patient and family in the design and


implementation of the therapeutic program helps boost morale and ensure compliance, as does explaining the rationale for the therapies used. 

Non-pharmacological approaches may contribute to effective analgesia and are often well accepted by patients. Some simple measures which are sometimes recommended (eg, hot or cold packs) have not been well studied. Complementary therapies for pain are often sought out by patients, and require evaluation for their potential role in the palliative care setting. A systematic review shows that educational interventions can have a modest but clinically significant impact on pain, and that this is an underutilized strategy. The role of non-pharmacological approaches to pain management is evolving, and some non-pharmacological and complementary therapies have an increasingly important contribution to make to holistic patient care alongside analgesics. There is evidence to support the use of patient education, cognitive behavioral therapy (CBT), relaxation, and music. Importantly, however, some approaches have not been shown to be of benefit, including TENS, reflexology and acupuncture. For this reason, research on


non-pharmacological approaches to pain management is important. Non-pharmacological treatment modalities are often recommended, prescribed and used in addition to drug treatment in patients with RA. Currently, a considerable number of systematic reviews summarizing the available studies for non-drug care interventions in RA are available. These modalities have traditionally been provided by various health professionals, who are often designated as the ‘multidisciplinary rheumatology team’. 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 joint protection programs, specific orthoses and comprehensive care interventions. Overall, the evidence for effectiveness of massage and electro-physical modalities is absent or weak. In general, few studies in patients with early RA, studies comparing different attributes of non-pharmacological modalities or comprehensive care models and economic evaluations have been performed, so that the optimal timing, intensity, duration and mode of delivery often remain unclear. Informed and sympathetic discussions concerning alternative, controversial, and unproven therapies are also important elements of patient education.

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It is prudent to consider non-pharmacological methods as adjunct to standard care with drugs. At this stage, it may be advisable for the patients to also opt for an adjunct non-drug treatment like educating the patients with counseling alongside the standard of care.

2.6 Diet in RA

Both the patients and community believe that dietary modifications are required in RA. Nutritional status of RA patients appears to be compromised despite adequate intake\(^4\)\(^3\). Although there's no "RA diet" that can treat the condition, some foods may help lower inflammation in the body. And these foods - including fruits and vegetables, whole grains, olive oil, and fish -- may help feel better overall. The best approach to food for people with RA – or anyone else – is a well-balanced diet. Approximately two-thirds of diet should come from fruits, vegetables and whole grains. The other third should include fat-free or low-fat dairy products and lean sources of protein\(^4\)\(^4\). Paying more attention to the foods especially those that reduce inflammation and have lots of antioxidants — may ease rheumatoid arthritis symptoms. In fact, nutritional status of RA patients appears to be compromised despite adequate intake probably due to food fads and misconceptions. Nutritional therapies for RA should include, at the least, an anti-inflammatory diet with a minimum amount of meat, plenty of fish and whole grains, and abundant fruits and vegetables as part of a healthy lifestyle.


2.6.1 Diet Intervention Studies in RA

Several studies have been published on evaluation of different types of diet in alleviating symptoms and reducing diseases activity in RA over the last 5 decades or so. A Cochrane review in 2009 could only include 15 controlled studies (857 patients) studies that met the minimal criteria. Mostly, the studies were short duration and heterogeneous. A single trial with found that fasting, followed by 13 months on a vegetarian diet, may reduce pain (mean difference (MD) on a 0 to 10 scale -1.89, 95% confidence interval (CI) -3.62 to -0.16), but not physical function. Another single trial with that a 12-week Cretan Mediterranean diet may reduce pain (MD on a 0 to 100 scale -14.00, 95% CI -23.6 to -4.37), but not physical function. The authors concluded that effects of dietary manipulation, including vegetarian, Mediterranean, elemental and elimination diets, on rheumatoid arthritis were uncertain.

Efficacy with diet modification has also been noted by several randomized controlled trials (RCT) which for example noted that the vegetarian diet group exhibited considerably better effects across most of clinical variables. A vegetarian diet and a period of fasting was also found to exert a positive effect on pain and indices of disease.

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It is prudent to add that both fasting and a supervised stringent diet, mostly vegetarian, is a pivotal part of management of RA in the Ayurvedic system.\textsuperscript{49}  

A British study looked at the impact of foods from the Mediterranean diet in women with RA.\textsuperscript{50} Patients were randomized into two groups-One group took a cooking class on Mediterranean-style eating and the other group received only written information and made no dietary changes. Women who changed to more of a Mediterranean type diet, consumed more foods rich in antioxidants and other anti-inflammatory substances, including fruits, vegetables, and monounsaturated fats (such as in olive oil used extensively in Mediterranean diet). The latter group over the next 6 months, showed reduction in active disease (less joint pain and morning stiffness) and better overall health compared to the other group. In RA, there is an increase in proinflammatory cytokines. Polyunsaturated fats - especially omega-3 fatty acids help suppress cytokines and other inflammatory chemicals.\textsuperscript{51}


\textsuperscript{50} http://www.bda.uk.com/foodfacts

\textsuperscript{51} http://www.webmd.com/rheumatoid-arthritis/guide/ra-foods
Several studies suggest that the Mediterranean-type diet or its main components may have protective effects on the development or severity of rheumatoid arthritis. Diet perhaps has a more important and diverse role in the RA than is generally known and also includes consideration of food allergies and intolerances. A recent comprehensive review summed up by stating that an integrative approach which includes prudent nutritional practices (based on a Mediterranean-style diet that closely resembles a Paleolithic diet) with multistrain probiotics that synergistically downregulate proinflammatory responses may be a useful long-term management strategy for patients diagnosed with RA.52

The Table below provides a summary of controlled diet studies in RA published in recent times.53,54,55

The diets used in the studies (Table 1) was essentially vegetarian and though not considered nor analyzed is bound to have been rich in several important minerals like K+.

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Table 1: Comparison of selected features of three recent published diet intervention (Mediterranean) studies in RA.

<table>
<thead>
<tr>
<th>Sr No</th>
<th>Diet (Ref)</th>
<th>Sample size/Duration months/Arms</th>
<th>Design</th>
<th>Efficacy end point</th>
<th>Remark (Ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Med (Ref 51)</td>
<td>130/6/2</td>
<td>Convenience allocation; not blind; prior 6 weeks practical demo to active arm (n=65) participants; control (n=55) routine diet; background supervised standard care; limited diet compliance analysis; Baseline: pain VAS 5 cm each arm; DAS 28, active=4.7, control=5</td>
<td>Improved (p&lt;0.05) HAQ, Morning stiff, Patient global, Systolic BP; pain VAS worsened in control (p&lt;0.05)</td>
<td>UK: community based; low socioeconomic class; increased vegetables, fruits, mono-unsaturated fatty acids in active; overall modest benefits</td>
</tr>
<tr>
<td>2</td>
<td>Med (Ref 52)</td>
<td>56/3/2</td>
<td>Randomized; not blind; active (n=29) fed &amp; trained for diet in hospital canteen for 3 weeks and then diet items provided to carry on in home; control (n=27) routine diet; no info on diet compliance; background supervised standard care; Baseline: pain VAS, active=3.2 cm, control=3.1 cm; DAS 28, active=4.4, control=4.3</td>
<td>Improved (p&lt;0.05) pain VAS, HAQ, DAS 28, Swollen joint count, CRP, Patient global; SF 36 no change</td>
<td>Sweden: diet milk and dairy in diet altered for Swedish customs; no diet analysis; active arm lost body weight (p&lt;0.05); modest benefits</td>
</tr>
<tr>
<td>3</td>
<td>Vegan (Ref 53)</td>
<td>66/12/2</td>
<td>Randomized; not blind; active (n=38) on gluten free Vegan diet; Control (n=28) routine vegan diet; Diet advise &amp; practical in week prior; diet compliance by records; baseline match</td>
<td>ACR20 response at 12 months: active=41%, control=4%; reduced IgG &amp; IgA response for anti-gliadin and anti-lactoglobulin antibodies in active arm</td>
<td>Sweden: analysis based on valid compliant completer; high drop out in active and compliance may be an issue; Vegan diet was fruits, nuts, vegetables, root vegetables, rice, millet, corn, sesame (control allowed gluten wheet etc)</td>
</tr>
</tbody>
</table>

Note: Med: Mediterranean diet; n: number of patients; See text for abbreviations

2.7 POTASSIUM

Appropriate intake of certain chemical elements like iron, calcium, sodium and potassium have been demonstrated to be required to maintain optimal health. A balanced diet can
meet all the body’s chemical element requirements. However, supplements can be used when some requirements (e.g., calcium, which is found mainly in dairy products) are not adequately met by the diet, or when chronic or acute deficiencies arise from pathology, injury, medical disorder etc.

Minerals are inorganic elements found in body fluids and tissues. The important macro minerals are sodium, potassium, calcium, phosphorus, magnesium and Sulphur, while zinc, copper, selenium, molybdenum, fluorine, cobalt, chromium and iodine are micro minerals. They are required for several physiological functions including maintenance and integrity of skin, hair, nails, blood and soft tissues. They also govern nerve cell transmission, acid/base and fluid balance, enzyme and hormone activity as well as the blood-clotting processes.

2.7.1 Source and Diet

It is believed that diets were richer in K+ as compared to sodium during the earlier evolution of life on earth. Vegetarian diet is the major sources and contain more potassium than sodium. Cereals, pulses, nuts, oil seeds and fruits are also important sources of K+. Natural diet can provide around 5-10 g (50-150 mmol/day) of potassium chloride. During processing of foods, potassium is washed out and often replaced by sodium. There is no evidence that there is difference between K+ foods with reference to better absorption or utilization; phosphate form is abundant in vegetables and K+ chloride is the medicine form generally available.

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There should be sufficient potassium in the diet to balance sodium intake. As daily losses of potassium are around 30 mmol/day, an intake of 50 mmol is usually sufficient. The ideal desirable sodium : potassium ratio in the diet should be 1:1 (in mmol). In a tropical country like India, the intake must account for loss in sweat (especially sodium) and the fact that vegetarian plant based diets contain lower content of sodium and higher content of K.

There is currently no global consensus on recommended daily allowance for potassium. It is generally believed to be between 3,500 mg to 5,600 mg.57 Diet can provide around 4-7.5 g (50-100 mmol/day) of K+.58 The amount of potassium intake in men is 3750 mg/day and in women is 3225 mg/day. The upper limit of safe range of is considered to be 140 mmol of potassium/day (10 g of KCl).59

At the same time, WHO recommends that the sodium intake be reduced to less than 2000 mg (5 gm sodium chloride) daily.60 Body needs of sodium are not great. Intakes of 1.1-3.3 g of sodium or 2.8-8.3 NaCl per day is considered to be safe and adequate for healthy


adults, by the Food and Nutrition Board of National Academy of Sciences (USA)\(^{61}\). Most dietary sodium is found in the form of sodium chloride, which is 40\% sodium and 60\% chloride.

Data from around the world suggest that the population average potassium consumption in many countries is below 70–80 mmol/day, which was recommended by the 2002 Joint World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) Expert Consultation \(^62\). There is no global consensus. Belgium, Mexico, Spain and the United Kingdom of Great Britain and Northern Ireland recommend daily K+ intake of 90 mmol/day. Bulgaria, Canada, the Republic of Korea and the United States of America recommend a daily intake of 120 mmol of K+. Women consistently have lower levels of potassium intake than men, but both groups commonly consume a level that is below current recommendations. WHO suggests a potassium intake of at least 90 mmol/day (3510 mg/day) for adults (conditional recommendation)\(^63\). The USA dietary guideline\(^64\) lists potassium, calcium, Vitamin D and fiber as a nutrient of concern which are significantly under consumed in the American diet. The major sources of


potassium varied somewhat by age, gender, race/ethnicity, and family income. Indian Diet and Nutrition Guidelines. In 1968, an expert Group constituted by the Indian Council of Medical Research (ICMR) revised nutrient requirement and RDA for Indians in respect of all nutrients except calorie. Revision and update were further made in 1978 and 1988.

As losses of potassium are around 30 mmol/day, an intake of 50 mmol is suggested at the lower end in the Indian guideline. Dietary intake of 140 mmol/day at the upper end is considered to be safe. The ideal desirable sodium : potassium ratio in the diet is 1:1 (in mmol).

The Indian guidelines are comprehensive and updated from time to time. Web based applications are available to study the caloric and composition value of Indian diet and food items. The calorie content and other composition values of food and diet items has been meticulously calculated using modern technology means (colorimeters, photometers, spectrometers) and standard controls by the National Institute of Nutrition, Hyderabad. Dietary K (mostly fruits and vegetables) rather than food supplements

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have been described more safe and easy for consumption. Legumes, bananas and several fruits, milk, potatoes, pulses, cereals are recommended good source of K. Vegetables and fruits are available in abundance in India. Natural fruit juices provide in addition to energy, some vitamins (beta carotenes, vitamin C) and minerals (potassium, calcium). Sodium intake needs to be balanced with potassium intake.

Tender coconut water is stated to contain most of the minerals such as potassium (290 mg%), Sodium (42 mg%), Calcium (44 mg%), magnesium (10 mg%), Phosphorus (9.2 mg%), iron (106 mg%), and copper (26 mg%).

Table 2 shows the RDA for sodium and potassium as recommended by the current NIN/ICMR Indian guidelines.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>SODIUM</th>
<th>POTASSIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADULT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2092</td>
<td>3750</td>
</tr>
<tr>
<td>Female</td>
<td>1902</td>
<td>3226</td>
</tr>
<tr>
<td>INFANT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-6 months</td>
<td>407</td>
<td>628</td>
</tr>
<tr>
<td>CHILDREN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 3 yrs</td>
<td>589</td>
<td>1100</td>
</tr>
<tr>
<td>4 -6 yrs</td>
<td>1005</td>
<td>1550</td>
</tr>
</tbody>
</table>

The exact amount of daily K consumption in Indian diet is unknown but recent Indian guidelines have recommended a daily allowance of 3750 mg for men and 3226 mg for women for oral K+ in diet.
2.7.2 Other Dietary Aspects

The daily requirement value for potassium in disease states may be different from the routine recommendation. When attempting to increase potassium intake to treat disorders, it is desirable to know which foods are high in potassium. It is not sufficient to know the amount of potassium in a given weight of food. What determines how much food we eat is largely determined by the number of calories contained in it. Therefore information on potassium in foods is much more useful if it is expressed as weight of potassium per calorie and comprehensive values for different food items and nutrients have been described by Weber (1974).

Potassium as a mineral is found in varying amounts in almost all foods. Vegetables, especially green leafy varieties, are generally the principle source. High potassium foods from natural food sources like beans, dark leafy greens, potatoes, squash, yogurt, fish, avocados, mushrooms, and bananas, are considered safe and healthy. Dairy products also make important contributions to daily potassium (Weber 1974). Potassium content within the group of fruits and vegetables can vary widely, even between two foods that seem superficially very similar. Lean meat low in fat has fairly consistent amounts of potassium, usually about 2 mg/Cal. It can range from 1 to 3 mg/Cal. Since fats or oils have no or little water to dissolve potassium, and since they are high in calories, they are very low in potassium, approaching zero. Therefore meat with much fat in it will be

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69 http://members.tripod.com/~charles_W/arthritis9.html

lower in potassium per calorie than lean meat. Eggs, like meat are low in potassium. Most of the potassium is concentrated in the white of the egg. Egg whites are comparable to meat in K+ content, and are in fact are higher than most meat items. Vegetables low in starch are the best sources of potassium. They rarely go below 5 mg/Cal., and range up to 20 mg/Cal. or more. The seaweeds are poor sources of potassium. Grains are the low in potassium and will usually contain about 1 mg/Calorie of potassium. Nuts are similar to grain. The bean, peanut and legume seeds are a fairly good source, usually running about 3-4 mg/Calorie.  

Current strategies to increase potassium intakes recommend using foods instead of supplements. Even for patient populations, potassium supplements are not typically recommended, partly due to concern over hyperkalemia. Clinical trials that are sufficiently large and of sufficiently long duration are needed for most of the health benefits attributed to potassium intake to establish causal relationships and dose response to guide public health decisions.

2.7.3 Special High K+ Diets

It is relevant to briefly review some of the popular K+ rich diets described in literature for preventive and therapeutic value.

71 http://members.tripod.com/~charles_W/arthritis8.html

i) DASH (Dietary Approaches to Stop Hypertension) diet. The Dietary Approaches to Stop Hypertension (DASH)-style diet represents a food-based approach to increasing potassium to levels recommended by the Institute of Medicine\(^{73}\). The DASH diet is high in fruits and vegetables and dairy products and is effective at reducing blood pressure\(^{74}\). Potassium content is thought to be the largest explanation of the benefit of this dietary pattern, although the increased level of magnesium, calcium, fiber, and other bioactive constituents may also contribute to lowering blood pressure. In addition to reducing blood pressure, a DASH diet intervention lowered biochemical markers of bone turnover\(^{75}\) and DASH diet scores were associated with reduced risk of kidney stones, partly mediated by increased urinary citrate and volume\(^{76}\). The DASH diet emphasizes vegetables, fruit and low-fat dairy foods — and moderate amounts of whole grains, fish, poultry and nuts. The standard DASH diet provides up to 2,300 mg of sodium daily and the lower sodium DASH diet provides about 1,500 mg of sodium daily. In both versions of DASH, the K\(^+\) content may exceed 3-4 gm daily.


ii) Acid (pH) balance/Vermont Folk Diet: Dr Jarvis (from Vermont, USA) popularized the notion that apple cider vinegar (not white vinegar) and honey could help cure ailments, specifically arthritis and the common cold. Additionally, Apple cider vinegar is purported to reduce blood cholesterol. According to a 1998 study at Innsbruck University Hospital, consuming large amounts of apple cider vinegar may also cause increased blood renin levels (lead to hypertension) and in some cases effected bone density (causing osteoporosis).

(iii) Microbiotic diets: A macrobiotic diet is a dietary regimen which involves eating grains as a staple food, supplemented with other foods such as local vegetables, and avoiding the use of highly processed or refined foods and most animal products. Followers of the traditional macrobiotic approach believe that food and food quality powerfully affect health, well-being, and happiness, and that a traditional, locally based macrobiotic diet has more beneficial effects than others. The modern macrobiotic approach suggests choosing food that is less processed. Other foods recommended include whole grains and whole-grain products such as brown rice and buckwheat pasta (soba), a variety of cooked and raw vegetables, beans and bean products, mild natural seasonings, fish, nuts and seeds, mild (non-stimulating) beverages such as bancha twig tea and fruit. Some proponents of a macrobiotic diet believe that nightshade vegetables (such as brinjal) can cause inflammation in the body and osteoporosis. A macrobiotic diet includes many of the same foods as vegetarian diets, but in macrobiotics some types of fish and other animal foods are included according to individual needs and it is

77 http://www.livestrong.com/article/74823-vinegar-honey-diet
recommended to avoid milk and dairy products. Overall, macrobiotic diet is likely to contain enough K+ \(^{78}\).

(iv) Gerson diet: The Gerson Therapy is a natural treatment that supposedly activates the body's extraordinary ability to heal itself through an organic, plant-based diet, raw juices, coffee enemas and natural supplements. The Gerson diet is plant-based and entirely organic. The diet is naturally high in vitamins, minerals, enzymes, micro-nutrients, and likely to be high in K+ and extremely low in sodium, fats, and proteins.

(v) Vegetarian diet: Large-scale studies have shown that mortality from ischemic heart disease was 30% lower among vegetarian men and 20% lower among vegetarian women than in non-vegetarians.\(^{79}\). Vegetarian diets offer lower levels of saturated fat, cholesterol and animal protein, and higher levels of carbohydrates, fiber, magnesium, potassium, folate, and antioxidants such as vitamins C and E and phytochemicals. Vegetarian diets have been used as a treatment for rheumatoid arthritis, but the evidence

\(^{78}\) http://en.wikipedia.org/wiki/Macrobiotic_diet

is inconclusive whether this is effective. Vegetarian diet is a critical element of Ayurveda and Siddha medicinal systems.

2.7.4 Physiology

It is believed that the primitive man consumed a diet rich in potassium as compared to sodium. Potassium (K+) is the most abundant intracellular cation in the body and maintained at a concentration of about 145 mmol/L in intracellular fluid but at much lower concentrations in the plasma and interstitial fluid (3.8 to 5 mmol/L). Relatively small changes in the concentration of extracellular potassium greatly affect the extracellular: intracellular K+ ratio and thereby affect neural transmission, muscle contraction, and vascular tone. Potassium contributes to intracellular osmolality. Enzymes involved in glycolysis and oxidative phosphorylation are potassium-dependent. It is involved in the maintenance of acid-base balance. K+ is the third most abundant mineral in the body. It is also an electrolyte that regulates electric conductance, blood pressure, water retention, muscle activity, acid-base balance and proper function of every body cell. Intracellular potassium is a result of active K+ uptake by Na+ K+ ATPase cell

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surface pump which operates with a considerable ATP expenditure. Normal K+ homeostasis is regulated by both renal and extra-renal mechanisms. Although several hormones are important, adrenocortical steroids, are important for regulation of electrolytes including potassium. A potassium shift from extracellular to intracellular is caused by increased activity of the Na-K-ATPase pump, which can be directly stimulated by an increase in plasma potassium, insulin, catecholamine, aldosterone and alkalosis.\(^8^4\)

Losses of K+ via the gastrointestinal tract, urinary excretion and sweat, comprises about 800 mg/day (20 mmol), but 1.6 g/day (40 mmol) is needed to avoid low plasma levels and loss of total body K+ in adults. Urinary potassium excretion is considered to reflect dietary potassium intake in health.

Potassium content of the extracellular fluid is about 80 mmol, whereas in the tissue it is around 3500 mmol. Eighty percent of this amount is in the skeletal muscles. The potassium content of bones is negligible (7%). Potassium content decreases with age and adiposity. Total body potassium corresponds closely to lean body mass and to the body nitrogen content. Maintenance of extracellular potassium concentration is complex and is the result of intake, excretion and distribution. Aldosterone and cortisol increase the urinary loss of potassium. Renin and angiotensin have a similar effect. The kidney's ability to conserve potassium is less than that of sodium and serves as the major chronic protective mechanism against toxicity. Even with zero potassium intake, urine continues to excrete potassium and is reduced to a minimum of 5-20 mmol/day. Ninety to ninety-

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five percent is reabsorbed by the proximal renal tubules and loop of Henle and on a normal dietary intake, potassium is secreted by distal tubules.

Potassium is essential for the muscular, cardiovascular, nervous, endocrine, respiratory, digestive, and renal systems. Cell metabolism depends on the maintenance of a high intracellular K+ concentration. Many of the body functions of potassium are due to its ionic character: it generates gradients of concentration, potential, and pressure. Potassium is the predominant osmotically active ion inside the cell. Together with other ions such as sodium and chloride, which are characteristic of the extracellular fluid, potassium determines osmolality and plays a major role in the distribution of fluids inside and outside the cell and hence in the maintenance of cellular volume. In addition, potassium participates in the regulation of the acid–base balance and is involved in cellular growth and division, energy transduction, glycogenesis, protein synthesis, hormone secretion, etc. Consequently, its deficiency causes growth retardation, with a pronounced decrease in circulating levels of growth hormone and somatomedin C and inhibition of protein synthesis.85,86

The physiology of K+ is closely connected to changes in the sodium in body.81, 82 Sodium is the principal cation of extracellular fluid and is involved primarily in the maintenance of osmotic equilibrium and extracellular fluid volume. The body content of the sodium and its concentrations in body fluids are under homeostatic control, kidney

85 Guyton AC, John E Hall, Mario Vaz, Anura Kurpad, Tony Raj. Textbook of Medical Physiology, Elsevier Inc; 2013, 495-498

being the primary organ responsible for maintaining sodium balance through aldosterone action on renal tubular function. When the dietary intake is zero, the level of aldosterone increases and urinary sodium rapidly decreases. Converse is true when sodium intake is high. Man and other mammals have evolved on a no-added salt diet. On land, which may be considered to be a sodium-restricted environment, powerful inbuilt mechanisms such as renal-renin-angiotensin aldosterone and the kinin-prostaglandin systems have evolved a mechanism to maintain blood pressure and renal blood flow on low or minimal sodium intake. Since potassium in the diet is high, animals/man have no such elaborate complicated mechanisms of potassium conservation.

Potassium is rapidly absorbed in the gut by diffusion and is readily distributed in the aqueous compartment throughout the body. Potassium deficiency/excess rarely arises primarily as a result of dietary deficiency/excess. Urinary excretion of potassium is around 40-90 mmol/day and depends on dietary intake. Potassium excretion in urine is increased during catabolic state or whenever tissues break down. Approximately 2.7 mmol potassium is lost for every 1 gram of nitrogen during catabolism or wasting and this ratio remains constant. Potassium is also lost daily through faeces (5-10 mmol). Under normal physiological conditions, only minimal amounts are excreted through the intestine. K+ is also excreted through sweat which at normal rates contains 9.5-60 mmol/L. Potassium is lost in excess in patients treated with diuretics and can lead to depletion if not properly supplemented. Converse is true in cases of renal failure where potassium accumulates. Diarrhea can result in excess loss of potassium in the stools. In severe diarrheas, 90 mmol/24 hr (< 4 g of potassium) can be lost in stools and in infants.
suffering from protein energy malnutrition, potassium deficiency occurs when 10-30% of body potassium is lost. Such a situation can also occur in adults with very acute diarrhea.

During vigorous exercise, potassium is released from muscle cells, leading to an increase in extracellular potassium concentrations which facilitates ongoing muscle contraction and induces vasodilatation, increasing local blood flow. However, liberation of potassium also leads to muscular fatigue. Interrelationships exist between potassium and other nutrients. Potassium and sodium are strongly metabolically interrelated, principally due to sodium potassium (Na-K) ATPase. This enzyme also provides the driving force of the Na-K pump in the cellular membrane for the transport of other solutes, such as amino acids, phosphate, vitamins, and glucose. Potassium depletion, which is more intense if there is a simultaneous excess of sodium, enhances urinary loss of calcium. This interaction may have adverse effects on bone and blood pressure. The net absorption is the difference between fluxes from lumen to blood and from blood to lumen. In the human small intestine, K+ permeability is high and potassium absorption is carried out across the epithelium of duodenum, jejunum, and ileum by passive mechanisms in response to electrochemical gradients and solvent drag. In the proximal small bowel K+ is concentrated through the absorption of water, providing a driving force for the movement of this cation across the intestinal mucosa, preferably through the tight junctions between enterocytes. Duodenum and jejunum absorb this ion even more rapidly than water. Indeed, shortly after a meal, the K+ concentration in jejunum rapidly reaches plasma levels. In the ileum, the trans epithelial electrical potential difference strongly influences its movement. There is no evidence of active potassium absorption in the small intestine, but the existence of an apical membrane H+/K+-ATPase could suggest active
K+ transport. About 90% of daily potassium intake is excreted in the urine and 10% in the stool, although this last percentage can be somewhat higher in cases of diarrhea. When dietary potassium is severely restricted, its fecal loss decreases to approximately 3.5mmol daily. This presumably represents obligatory potassium losses related to K+ digestive secretions (salivary, gastric, biliary, and pancreatic), cell desquamation, and mucus secretion. Potassium concentration in sweat is about 10mmol and this loss is small, provided that the climate and exercise conditions are not extreme.

Both hypokalemia and hyperkalemia, as described clinically (see below) and based on laboratory values (based on normative population data) are considered medical emergencies requiring immediate medical care. Both need a high index of clinical suspicion.

2.7.5 Hypokalemia

Hypokalemia (serum potassium level below 3.5 mmol/L) can result in cardiac arrhythmias, muscle weakness, hypercalciuria, and glucose intolerance. Such disorders, which are correctable by potassium administration, can be induced by diuretics, chloride-depletion associated forms of metabolic alkalosis, and increased aldosterone production. Hypokalemia reduces the capacity of the pancreas to secrete insulin and therefore is a recognized reversible cause of glucose intolerance. There is some limited evidence that hypokalemia can also confer insulin resistance. As moderate potassium deficiency and its adverse side effects can occur without laboratory defined hypokalemia (low
plasma/serum levels), hypokalemia is not a sensitive indicator for use to establish adequacy.

2.7.6 Hyperkalemia

Normal serum potassium levels are generally considered to be between 3.5 and 5.0 mEq/L and levels above 5.0 mEq/L indicate hyperkalemia.

Recent data evaluating the relationship between mortality and levels of potassium in patients with chronic kidney disease who were not on dialysis, found that lower serum potassium levels (i.e., <4.0 mmol/L) were associated with a higher risk of mortality and end-stage renal disease as compared with serum potassium levels between 4.1 and 5.5 mmol/L. Higher levels (> 5.5 mmol/L), on the other hand in this study, were associated with cardiovascular events (or the composite endpoint of cardiovascular events or death). These observations may suggest the need for reevaluation of what constitutes a “normal range” for serum potassium in certain patient populations.

Hyperkalemia develops when there is excessive production (oral intake, tissue breakdown) or ineffective elimination of potassium. Ineffective elimination can be hormonal (in aldosterone deficiency) or due to causes in the renal parenchyma that impair excretion. If the patient has only a moderate elevation in potassium level and no electrocardiographic (ECG) abnormalities, excretion can be increased by using a cation exchange resin or diuretics, and the source of excess potassium (eg, increased intake or

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88 http://en.wikipedia.org/wiki/Hyperkalemia
inhibited excretion) can be corrected\textsuperscript{89}. In patients with severe hyperkalemia, treatment focuses on immediate stabilization of the myocardial cell membrane, rapid shifting of potassium to the intracellular space, and total body potassium elimination. In addition, all sources of exogenous potassium should be immediately discontinued; including intravenous (IV) and oral potassium supplementation, total parenteral nutrition, and any blood product transfusion. Drugs associated with hyperkalemia should also be discontinued\textsuperscript{90,91}.

2.7.7 Potassium administration and toxicity

Therapeutically, both the oral and intravenous forms of potassium are utilized. Overdose of potassium is not as frequently encountered in clinical practice as hyperkalaemia (see above) mostly due to acute or chronic renal disease. Potassium homeostasis is maintained very delicately and is governed by the daily consumption of potassium and the renal excretion mechanisms. Any change in these or related factors can present as hyperkalaemia. However, potassium overdoses leading to serious consequences do occur. Orally, the dose of potassium has to be large enough so that the normal excretory mechanisms for potassium are overcome and clinical toxicity occurs. It takes a much bigger dose of ingested potassium to produce toxicity in a person with normal renal


\textsuperscript{90} http://emedicine.medscape.com/article/240903-treatment

function than in patients with compromised renal function. Potassium toxicity manifests in significant, characteristic, acute cardiovascular changes with ECG abnormalities. Besides cardiovascular effects, neuromuscular manifestations in the form of general muscular weakness and ascending paralysis occur. Gastrointestinal symptoms manifest as nausea, vomiting, paralytic ileus, and local mucosal necrosis which may lead to perforation. It is imperative when treating hyperkalaemia that the whole clinical picture is taken into account rather than the numerical potassium values. Only the extracellular potassium can be measured in the laboratory, yet 98% of the body potassium is intracellular and cannot be measured. In acute overdose situations due to ingestion of potassium salt, the general principles of treatment for overdoses should be followed. Calcium chloride infusion, dextrose and insulin in water, and correction of acidosis with sodium bicarbonate are helpful in controlling the acute, life-threatening cardiac arrhythmias. These modalities do not remove the excess potassium from the body but rapidly correct the life threatening serum levels and push the K+ into the cells. Excess K+ removal from the body is is achieved either by utilising ion-exchange resins or by mechanically removing potassium via haemodialysis. To curtail inadvertent or accidental potassium overdoses, physicians should prescribe any potassium supplements very carefully to their patients and monitor the plasma potassium periodically.

Acute oral administration of potassium to animals causes changes in acid-base balance, respiratory rate and hypernatraemia. Acute oral administration of potassium chloride in

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animals has been reported to cause death by respiratory failure, with gastroenteritis and renal tubular necrosis \(^93,94\).

Controlled studies show that gastrointestinal symptoms (ranging in severity from discomfort to mucosal erosion and ulceration) can occur in healthy subjects taking some forms of K+ supplements, e.g. slow release, wax-matrix formulations, with doses ranging from 24 to 120 mmol/day (0.9 to 4.7 g K) or more, but incidence and severity seem to be more dependent on the formulation than on dose \(^95\).

Dietary K (mostly fruits and vegetables) is considered to be more safe and easy to take. Diet can provide around 4-7.5 g (50-100 mmol/day) of KCL. Safety dose of K+ supplement: K+ in form of pharmaceutical salts has been evaluated for efficacy and safety by various studies. None of the studies has used dietary augmentation by K+ rich foods.

K+ supplement has been used in several human studies and in particular patients suffering from hypertension. Previous clinical study of K+ supplement in patients with


\(^95\) Opinion of the NDA Panel related to the Tolerable Upper Intake Level of Potassium. Eur Food Saf Authority. The EFSA Journal 392:1-6, 2006 (toxicity at lower level also)
RA has evaluated doses up to 6640mg/day for 28 days\(^{96}\) without any significant drug-related toxicity. WHO recommends that up to 4 mmol (156 mg) potassium/kg body weight/day can be given as an oral supplement as KCL with adequate renal function\(^{97}\).

2.7.8 Measurement of K+

K+ is predominantly an intracellular cation but in clinical practice it is the serum K+ (extracellular) level that is standardized for measurement. Serum K+ must be measured within 30 minutes of fresh blood collection to avoid falsely elevated levels due to leak from platelets and RBCs. Platelets release potassium during the clotting process, resulting in higher (0.36 ± 0.18 mmol/L) potassium concentrations in the serum as compared to plasma. Serum potassium is measured by the use of a flame photometer or ion-selective electrode. The procedure is rapid, simple, and reproducible. In interpreting serum potassium, it should be kept in mind that because the intracellular potassium concentration is approximately fortyfold greater than the extracellular concentration, any maneuver that would result in the release of a small amount of intracellular potassium will erroneously raise serum potassium. These include: (1) tight tourniquet; (2) vigorous exercise of the extremity during blood drawing; (3) hemolysis due to vigorous shaking of


the test tube; (4) thrombocytosis (platelet count greater than 600,000); and (5) leukocytosis (WBC greater than 200,000).

The physiological normal range of serum K+ is narrow and not an accurate marker of total body potassium\(^98\). It has been estimated that 60-70% of clinical decisions are based on laboratory results and K+ is among the ten most commonly reported analyses\(^99\). About 4-32% of all laboratory errors occur during the analytical phase of sample testing. But several errors can take place prior to the analysis (32-75%). K+ is usually measured using an Ion-selective electrode. Platelets release K+ during the clotting process, resulting in higher (0.36 ± 0.18 mmol/L) serum K+ concentrations as compared to plasma. It is important to interpret the serum K+ value in a clinical context. In experimental studies, intracellular (in particular blood red blood cells) and total body K+ estimates are also reported.

There are several methods of measurements in clinical and research practice. Urinary electrolytes were measured in several studies on hypertension\(^100\). Urinary K+ is also measured to guide K+ replacement when renal function is normal (see above in section

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on ‘physiology’). The urinary excretion of K+ is not constant throughout the day and ideally 24 hours urinary collection is required for correct measurement. However, in recent times, spot urine analysis of fasting morning sample for K+ has been standardized and used in large scale epidemiology studies. Intracellular K+ has been measured especially in RBCs. K+ is a naturally occurring isotope universally present and in human body has a fixed proportion to the total body potassium, and thus can be measured using radioisotope emission techniques. Of late, sodium-potassium ratio in serum and urine have assumed greater clinical significance in studies pertaining to hypertension and other disorders. K+ in diet is measured through analytical methods (such as atomic absorption spectrometry, photometer) or using standard diet tables (such as the Indian guidelines from NIN, Hyderabad and ICMR) or urinary K+ excretion.

Urinary K+ estimation has been recommended to study the total body K+ balance in clinical disorders characterized by dehydration and hypokalemia but requires normal renal function. Urinary K+ has been an important assay in several epidemiological studies.

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studies of diet K+ intake and hypertension\textsuperscript{104}. Recently, studies have reported that sodium/potassium ratio may be more informative with reference to hypertension\textsuperscript{105}. Dietary K+ measurement generally is guided by standard guidelines on diet and nutrition (described below).

\section*{2.8 K+ Ion Channels}

Complex multicellular organisms require rapid and accurate transmission of information among cells and tissues and tight coordination of distant functions\textsuperscript{106}. Electrical signals and the resulting intracellular ion shifts (sodium, potassium and calcium) control contraction of muscle, secretion of hormones, sensation of the environment, processing of information in the brain, and output from the brain to peripheral tissues. In non-excitable cells, calcium transients signal many key cellular events, including secretion, gene expression, and cell division. In epithelial cells, huge ion fluxes are conducted across tissue boundaries. All of these physiological processes are mediated in part by members of the voltage-gated ion channel protein superfamily. This protein superfamily of more than 140 members is one of the largest groups of signal transduction proteins, and many family members are now the molecular targets for toxins and therapeutic agents. While the role of sodium and calcium ions in the pathophysiology of pain and inflammation has been much elucidated little attention has been paid to the role of K+. The functional elements of the ion channel superfamily of proteins can be divided into three complementary aspects: ion conductance, pore gating, and regulation.

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The human genome contains 40 voltage-gated potassium channels (KV) which are involved in diverse physiological processes ranging from repolarization of neuronal or cardiac action potentials, over regulating calcium signaling and cell volume, to driving cellular proliferation and migration\(^{107}\). With 78 members, potassium channels make up about half of this extended gene superfamily.

### 2.8.1 Classification groups\(^{108}\)

i) Voltage-gated K+ channels (Kv): These are delayed rectifiers, because they are activated slowly to counteract (rectify) depolarization\(^{109}\).

ii) Ca\(^2+\)-activated K+ channels (KCa): They are similar to Kv but have extended intracytoplasmic carboxy terminal which contains regulatory domains.

iii) Two-pore K+ channels (K2P): These differ from other K+ ion channels. They generally lack voltage sensor but are responsible for leak conductance which determines resting membrane potential of all cells\(^{110}\).

iv) Inwardly-rectifying K+ channels (Kir): They lack a well defined voltage sensor domain.

Members of all four major groups of K+ channels are expressed in nociceptive neurons.

#### 2.8.1.1 Kv Channels

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The opening of Kv channels results in an efflux of positive charge, which can serve to repolarize or even hyperpolarize the membrane following depolarization and generation of action potential. Despite the pivotal role of Kv2 role in shaping CNS signaling, its involvement in chronic pain was only recently uncovered. Kv2 subunits are present in small nociceptors\textsuperscript{111} and are also abundantly expressed in myelinated dorsal root ganglion (DRG) neurons. Despite its negligible involvement in DRG excitability, Kv4.2 can strongly modulate pain plasticity and related inflammation in dorsal horn neurons\textsuperscript{112}. Although a few Kv4 activators are available (e.g., NS-5806 and KW-7158), the pacemaking activity of Kv4 channels in cardiac tissue is a major limitation for systemic applications.

The Kv7 (KCNQ or M channels) family is predominantly found in peripheral tissues and appear to be most widely expressed in the nervous system including nociceptors. KV7.1 is also present in cardiac muscle and inadvertent stimulation may cause cardiac arrhythmias as an important side effect. Kv7) are also significantly expressed in nociceptors. The existence of a low-threshold, depolarization activated potassium current was described in 1980 and is referred to as the “M-current” because it was inhibited by the cholinergic agonist muscarine\textsuperscript{113}. The M current is active in the voltage range for action potential initiation and is therefore of particular importance in regulating neuronal firing of nociceptive neurons and excitability of C-type nerve fibres. M channels are most important regulators of resting membrane potential and AP firing threshold (nociceptors). Intraplantar injection of the M channel blocker XE991 into the hind paw of

\begin{itemize}
\item Brown DA, Passmore GM: Neural KCNQ (Kv7) channels. Br J Pharmacol 2009, 156(8):1185-95
\end{itemize}
rats induces moderate pain while peripheral injections of M channel enhancers (or 'openers') such as retigabine and flupirtine produces analgesic effect. Reduced Kv7 function is also involved in inflammatory pain. The general purpose anti-inflammatory diclofenac has also been shown to directly activate Kv7.2/Kv7.3 channels.

2.8.1.2 K2P (background K+ ion channels)

The importance of K2P in pain was highlighted by the discovery of a human K+ channelopathy namely familial migraine with. This fits well with the fact that migraine is associated with secretion of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P by meningeal nociceptors of the trigeminal ganglia, which may lead to sensitization.

2.8.1.3 Other K+ channels

(i) ATP-sensitive K+ channels (KATP) serve as cellular metabolic sensors. This protects neurons under pathological conditions (i.e. ischemia). (ii) Slo1 (name derived from a gene in drosophila species encoding ion channels) is a ubiquitous Ca2+-activated K+ channel also known as BK or Maxi-K channel. The principle function of BK channels in


DRG neurons appears to be shortening of the AP duration, acceleration of repolarization and contribution to fast after-hyperpolarization, effects which limit sensory neuron excitability. (iii) Ca2+-activated K+ channels (KCA): Opening of KCA during neuronal firing hyperpolarizes the membrane and provides feedback inhibition that limits Ca2+ influx and excitability, making them powerful regulators of synaptic transmission at nerve terminals. Big conductance KCA are thought to influence excitability more prominently; illustrative of their significance in pain transduction is the recent finding of a functional coupling with TRPV1 (transient receptor potential cation channel, subfamily V, member 1) in nociceptors. Interestingly, PGE2 and other inflammatory mediators reduce BKCA channel activity in nociceptors and BKCA deletion in these neurons enhances inflammatory pain without affecting acute or neuropathic behaviors. The analgesic effects of ketamine in neuropathic pain and inflammation may also be partly mediated via inhibition of microglia activation following KCA current attenuation.

Finally, KATP opening in the CNS is linked to the antinociception produced by systemic treatment with morphine, NSAIDs, or even gabapentin. Unfortunately, the involvement of KATP in modulation of cardiac rhythmicity, pancreatic insulin secretion, and intestinal function necessitates therapeutic strategies that selectively target the tissues of interest.

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2.9 Pain

Pain is ubiquitous. Musculoskeletal (MSK) pain is the commonest self-reported ailment in the community as shown by urban and rural population surveys in India. Chronic MSK pain is insufficiently addressed by the community and medical fraternity. The hallmark characteristic of RA is chronic MSK and joint pains.

“Pain” represents a final integrative package, the components of which consist of neurophysiological processes as well as contextual, psychological, and sociocultural factors. This is one reason for the discrepancies between preclinical studies (which measure increased tolerance to painful stimuli in animals (anti-nociception), clinical studies (which assess efficacy), and clinical practice, which measures effectiveness.

Pain is fundamental to protection from bodily harm and survival. Though perceived as a simple sensation it is extremely complex in its pathophysiology. Varying in intensity and nature, this complex nature is most evident in chronic disease states and MSK disorders in particular. People differ in their pain tolerance and response. Chronic pain is a disease by itself with several psychosomatic consequences. Pain in all its forms is a therapeutic challenge. Its management is an overarching goal in several diseases like cancer and arthritis. Treat pain or all else will fail. There is no ideal analgesic or universally accepted strategy to combat pain. There are several drugs to choose from in treating pain. Subjects differ in their therapeutic response. Though pain management is central to all medicinal systems, there is an overwhelming preference and use of modern medicines. This is consistent with the almost emergency nature of pain and ‘quick response’ desire in the community. Though highly effective, analgesic drugs have unleashed an epidemic of


123 Chopra A. Community rheumatology in India. A COPCORD driven perspective. Indian J Rheumatol 2009; 4:119-126

iatrogenic drug related toxicity. The misuse, overuse and abuse of analgesic drugs in the community is rampant. Gastrointestinal and the renal system bear the brunt of such toxic effects. All this has led to a never ending search for better analgesics and alternative interventions to modern medicine. Non pharmacologic methods hold a promise but have not been adequately investigated and validated. Though the role of diet and minerals in alleviating pain is a strong community belief it has not been adequately validated.

Despite significant progress, chronic pain remains refractory to treatment and only one-third to two-thirds of patients have reported adequate (>50%) pain relief. Moreover, analgesics and non-steroidal anti-inflammatory agents (NSAIDS; e.g., aspirin) and opioids (e.g., morphine), are associated with adverse dose-limiting side-effects, dependence, and tolerance. The lack of improved treatment reflects our incomplete understanding of the molecular pathophysiology underlying these pain states. Moreover, addiction, tolerance and limited efficacy further hinder successful chronic pain management.

2.9.1 Physiology

The pain experience is much more than just a sensation of pain. Sim and Waterfield (1978) described pain experience as having sensory, affective, evaluative, cognitive and behavioural dimensions with sensory, emotional and physiological outcomes. These components are a result of the complex interaction between the peripheral and central nervous system.

The generation of pain in response to tissue injury involves four basic elements—transduction (conversion of nociceptive stimulus into electrical impulse), transmission, transformation or plasticity and perception. Pain is often simply classified into neuropathic and nociceptive pain. But based on clinical relevance and pathophysiology, it is more practical to view pain as one of the following categories—nociceptive, inflammatory, functional and neuropathic. In clinical practice, an overlap is often seen and this is true of RA. Nociceptive pain can be classified as somatic (for example, muscles, joints) or less often visceral (internal organs). The pain sensation is subserved by the sensory system which can be peripheral and/or central in origin. The peripheral system scheme consists of peripheral nociceptors and free sensory nerve endings.

Nociceptors are polymodal with a diverse range of receptors (including toll like receptors, excitatory amino acids, ion channels, nerve growth factor, opioid) and an outpouring of several mediators (pain and inflammatory) at the site of free nerve endings and synapse (bradykinin, histamine, prostaglandins, cytokines, substance P) with distinct receptors. At the cellular level, transmission of nociceptive signals within the central nervous system is regulated by cellular and intracellular elements that include ion channels (Na⁺, Ca⁺⁺, K⁺), ionotropic and metabotropic receptors (such as glutamatergic, GABA (γ-aminobutyric acid)ergic, serotonergic, adrenergic, neurokinin, and vanilloid receptors), inflammatory cytokines released from activated glial cells (TNF alpha, interleukin 1 beta and interleukin 6), nerve growth factors, intracellular regulators (such as protein kinases (for example, protein kinase C) and transcriptional factors (such as nuclear factor-κB)). And RA is a prototype immune inflammatory disorder with an overwhelming burden of pro-inflammatory cytokines.


Because pain is multidimensional experience, it is not surprising that psychosocial factors such as depression, somatization, poor coping skills, social stressors, and negative job satisfaction can predict the development of chronic pain after an acute episode. And RA is well known to be complicated by several of these factors.

All mechanical events are preceded by electrical events. The first step in generation of most pain signals is electrical excitation of peripheral somatosensory nerves. A complex system of ion channels play a pivotal role in initiation, control and co-ordination of this excitation. The sensory electrical impulse originates with generation of an action potential (AP) at the cell membrane level. The AP is due to changes in the voltage charge of the cell membrane and is predominantly driven by the shift in sodium (Na) and potassium (K) ions. To begin with sodium shifts out and potassium inside the cell in a process called depolarization with energy expended by the ATP and using a sodium-potassium ATPase pump. This is followed by a reversal in the shifts of the ions (called repolarization) and the cell is restored to resting membrane potential. K ions are critical to repolarization state.

Inflammation, nerve injury or degeneration often result in conditions where nociceptive signaling leads to chronic persistent pain. These chronic pain conditions are often characterized by persistent over-excitability of peripheral nociceptors brought about by medium to long-term changes in ion channel activity (i.e. post-translational modifications, changes in trafficking, transcriptional and epigenetic regulation of ion channel gene expression).

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2.9.2 Neuropathic Pain

The estimates of the prevalence of neuropathic pain, though crude, have significantly increased in recent times due to the development of screening questionnaires\textsuperscript{132}. About 15-25% of people with chronic pain are currently thought to have neuropathic pain. Studies show a greater negative impact on quality of life than nociceptive pain and thus neuropathic pain has an important but neglected socioeconomic impact\textsuperscript{133}.

Both peripheral and central mechanisms contribute to the development of chronic pain states and a sustained pathological over excitability of nociceptive afferents (also called “peripheral sensitisation”) is considered to be a trigger. Peripheral sensitization may be due to inflammatory mechanisms, sympathetic sprouting and changes in expression and/or activity of various proteins related to neuronal excitability.

Glial activation and proinflammatory cytokines including interleukin 1β (IL-1β), IL-6, and tumor necrosis factor α (TNF-α) are produced peripherally and centrally in response to nerve injury\textsuperscript{134}. These proinflammatory cytokines play a central role in inflammatory responses after nerve injury through intracellular mediators such as protein kinase C and 3',5'-cAMP. Proinflammatory cytokines also play an important role in sensitization of the CNS and may contribute to allodynia, hyperalgesia and neuroma formation\textsuperscript{135}.


\textsuperscript{133} Smith BH, Torrance N, Bennett MI, Lee AJ. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. Clin J Pain 2007;23:143-9

\textsuperscript{134} Vallejo R, Tilley DM, Vogel L, Benyamin R. The role of glia and the immune system in the development and maintenance of neuropathic pain. Pain Pract 2010;10:167-84

\textsuperscript{135} Leung L, Cahill CM. TNF-alpha and neuropathic pain—a review. J Neuroinflammation 2010;7:27
2.9.3 Inflammatory Pain

RA is primarily an intensely painful inflammatory disorder. Inflammatory pain often has a mix and/or overlap of acute, physiological pain and chronic/neuropathic pain. Inflammation is a complex immune response that occurs in response to tissue damage (i.e. wound or infection), which is aimed at removing the harmful stimuli (e.g. eliminating infectious bacteria) and promoting tissue regeneration. There are several robust and versatile and diverse immunological mechanisms underlying this inflammatory responses. A wide range of chemical factors (released into the extracellular space) recruit immune cells. There is further involvement of afferent sensory fibres innervating the inflamed tissue (the later phenomenon is known as 'neurogenic inflammation'). These factors, often called 'inflammatory mediators', are key triggers of the inflammation 'side effect' – inflammatory pain. The inflammatory mediators are incredibly diverse: prostaglandins, leukotrienes, interleukins (and numerous other cytokines and chemokines), bradykinin, substance P, ATP, growth factors, proteases, protons, nitric oxide (NO), and many others; all of these can be found in the inflamed tissue under various conditions.

Many inflammatory mediators (e.g. bradykinin, histamine, 5-HT) have long been known as endogenous pain-inducing substances or algogens that can directly excite or sensitize the peripheral terminals of nociceptive afferents\textsuperscript{136}. Current research is focussed on the mechanisms of activation or 'sensitization' by inflammatory mediators of various ion channels that can acutely depolarize nociceptors. These include various TRP channels, i.e. TRPV1, TRPV2, TRPV4, TRPA1, TRPM8\textsuperscript{137, 138}, P2X receptors\textsuperscript{139} or tetrodotoxin-


\textsuperscript{137} Ma W, Quirion R. Inflammatory mediators modulating the transient receptor potential vanilloid 1 receptor therapeutic targets to treat inflammatory and neuropathic pain. Expert Opin. Ther. Targets. 2007;11:307–320
resistant voltage-gated Na+ channels Nav1.9 and Nav1.8. However, both acute and long-term hyperexcitability and over-sensitivity of afferent fibres can be also produced by inhibition/downregulation of K+ channel activity. Inflammatory mechanisms whereby this was clearly demonstrated experimentally are sparse but mostly involved M channels.

Several factors can contribute to peripheral sensitization. Inflammatory mediators such as calcitonin gene related peptide and substance P, which are released from nociceptive terminals, increase vascular permeability, leading to localized oedema and the escape of the by-products of injury, such as prostaglandins, bradykinin, growth factors, and cytokines. These substances can sensitize as well as excite nociceptors, resulting in lowered firing thresholds and ectopic discharges.

Similar to neuropathic pain, chronic inflammation is associated with some remodeling and with long-lasting changes in the gene expression within the afferent fibers innervating the inflamed tissue. The data on changes in K+ channel expression profile in chronic inflammation is sparse. The transcript levels of several K2P channels and TASK-2 protein were downregulated in DRG of rat in chronic inflammation model (hind

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139 Cockayne DA, Dunn PM, Zhong Y, Rong W, Hamilton SG, Knight GE, Ruan HZ, Ma B, Yip P, Nunn P, McMahon SB, Burnstock G, Ford AP. P2X2 knockout mice and P2X2/P2X3 double knockout mice reveal a role for the P2X2 receptor subunit in mediating multiple sensory effects of ATP. J. Physiol. 2005;567:621–639


paw injection of complete Freund’s adjuvant, CFA) \(^{142}\). Forty eight hrs incubation of cultured DRG neurons with a cocktail of inflammatory mediators reduced M current density and Kv7.2 expression [an effect that is likely mediated by REST (repressor element 1-silencing transcription factor) as it’s expression was stimulated in the same cultures] \(^{143}\).

2.9.4 K+ Ion Channels and Pain

Chronic pain is associated with abnormal excitability of the somatosensory system. Many ion channels are located at the nociceptor peripheral terminal, affecting neuron excitability after injury and as a result affecting pain sensation. Voltage gated Na+ and Ca2+ channels, TRP, ASIC, ligand gated ion channels, P2X, NMDA, AMPA and Kainate receptors were some of the ion channels have been known to be important etiological factors for more than a decade \(^{144}\). However, in recent times, the role of K+ ion channels has been increasingly recognized as critical determinants of neuronal activity. Opening of these channels facilitates a hyperpolarizing K+ efflux across the plasma membrane that counteracts inward ion conductance and therefore limits neuronal excitability. Accumulating research has highlighted a prominent involvement of K+ channels in nociceptive processing, particularly in determining peripheral hyperexcitability\(^{145}\).


Several preclinical studies demonstrated the role of voltage-gated sodium channels (NaV) in pain. Several adjuvant drugs, such as carbamazepine, act through the blockade of sodium channels. Certain types of calcium channels (N-type, T-type, and L-type), and to a lesser extent potassium channels (hyperpolarization activated cyclic nucleotide gated channels), also play a role in neuropathic pain. These voltage-gated calcium channels are the primary site of action for gabapentinoids, a first-line treatment for neuropathic pain. However, the role of potassium (K+) ion channels has not been sufficiently investigated.

K+ ion channels are essential for controlling neuronal excitability. The resting membrane potential (Em) of dorsal root ganglion (DRG) neuron is in the range of -55 to -65 mV. Increased intracellular Cl- concentration in sensory neurons and inflammation can raise this to around -40 to -30 mV; K+ ion channels are the only ion channels that can drive Em towards -65 mV. Therefore, depolarization of plasma membrane sufficient to trigger AP can be induced by either i) activation of any of the non-K+ channels of the plasma membrane which is the method in majority or ii) inhibition of K+ channels that are open at Em.

K+ channels are the most populous and widely distributed ion channels in neurons. Upon activation, K+ channels facilitate an extremely rapid transmembrane K+ efflux that can influence AP threshold, waveform and frequency. Because K+ channel opening repolarizes (or even hyperpolarizes) the neuronal membrane, this function can limit AP generation and firing rate and

The underlying mechanism in severe chronic pain states is the up regulation or enhancement of depolarizing ion channels. It was shown unequivocally in several experimental studies that non-specific K+ channel inhibition induces spontaneous activity.

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in peripheral fibers and that peripheral hyper-excitability in chronic pain states coincided with down regulation of K+ channel/conductance in sensory nerves. Importantly, down regulation of a K+ channel activity can potentially maintain over excitatory state of the membrane indefinitely. Thus, suppression of K+ conductance may indeed represent a general condition of a ‘painful’ nerve.

Among the mechanisms of neuropathic pain, a general downregulation of the K+ channel pool in injured fibres has been consistently reported. This ‘negative drive’ is likely to represent a general phenomenon. Although this superficially uniform suppression of K+ channels/currents is likely to be caused by several distinct mechanisms, it is one of the major causative factors underlying peripheral sensitization of afferent nociceptive fibers and persistent pain.

A recent study conducted by the Mayo Clinic seem to provide support to the role of K+ ion channel in chronic pain. 159 (50%) of the 319 patients screened showed serum autoantibodies against voltage-gated K+ channels; these patients suffered from chronic pain, which was 5 times more frequent than in patients with any other neurological autoantibodies. Twenty-eight per cent of these patients had chronic pain as a sole symptom. Neuropathology abnormalities found in the cutaneous nociceptive fibres in this study suggested that the pain produced by K+ channel autoantibodies is likely to be due to peripheral origin. This study further demonstrates that when K+ channel activity or abundance in nociceptors was suppressed (whatever the mechanism is), pain was a likely outcome. In agreement with this generalisation, pharmacological augmentation of peripheral K+ channel activity consistently alleviated pain in laboratory tests (see below).

The main hypothesis is that down regulation of K+ channel activity can represent a general mechanism for chronic peripheral nerve over excitability while pharmacological


K+ channel enhancers (or 'openers') may indeed soothe over excitable nerves. As an overview, nociceptors express a robust and versatile K+ channel repertoire (see later) which include voltage-gated K+ channels, background K+ channels (M current) and K+ channels that are operated by various agonists (ATP, sodium, calcium). However, the published literature is silent on the role of oral K+ in modulating K+ ion channels and pain.

2.9.5 Pain Evaluation

Pain is a personal experience. It is indeed a challenge to record pain in a meaningful descriptive and analytical fashion. Translations are cumbersome and pain is subject to the several nuances of the language. Methods to measure pain usually focus on intensity and perception and are critical to the overall management of chronic musculoskeletal pain and disability. Several factors influence the pain experience - personality traits like memory, culture and traditions, age, religion, socioeconomic environment. Pain itself is multifaceted and not easy to measure. Comprehensive measure of pain is difficult.

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150 Anderson KO, Bradley LA, Turner RA, Agudelo CA, Pisko EJ. Pain behavior of rheumatoid arthritis patients enrolled in experimental drug trials Arthritis Care Res 1994;7:64—8
Several instruments are used in patients suffering from arthritis to measure function and quality of life and may also contain questions pertaining to pain- modified Stanford Health Assessment Questionnaire, Multiple Outcome Short Form 36 Physical and Mental scale score, WHO Quality of Life questionnaires. However, few are developed to measure generic pain- McGill Pain Questionnaire, Short-Form McGill Pain Questionnaire, Chronic Pain Grade Scale, Short Form-36 Bodily Pain Scale (SF-36 BPS), RA Pain Score. The most popular method to capture pain intensity is the pain visual analogue scale (VAS) though other similar scales (Numeric Rating Scale, Face Pain scales) are also used. Its popular used is probably due to its oversimplified nature and gross feasibility and socioeconomic appeal in a clinical setting. Pain VAS has been suitably validated in several control drug trial studies. Conceptually, the evaluation of unidimensional pain using VAS in a chronic setting seems to be over simplistic but is the most popular method in global use. Pain needs a comprehensive measure. The details of methodology of pain VAS is described in the 'methods' section of this thesis.

160 Sokka T. Assessment of pain in rheumatic diseases, Clin Exp Rheumatic 2005; 23 (suppl): S77-84
2.9.6 Pain in RA

RA is prototypic severely painful inflammatory disease. It is a lifelong disease and pain is central to the suffering. Pain is multifaceted. The chronic nature of pain is compounded by several psychic factors including anxiety, depression, loss of confidence and self esteem, sleep, fear, feeling of insecurity and apprehension, loneliness and sorrow.

Though the onset of pain is usually due to inflammatory synovitis, complex body mind interactions lead to some kind of a vicious cycle wherein pain begets pain. Inflammatory mechanism dominate (see above). Cytokines (in particular tumor necrosis factor and interleukin 1 beta) are one of the most potent drivers of inflammation. TNF α (tumor necrosis factor) is the cytokine, high up in the hierarchical network cytokine system which is intensely upregulated and leads to stimulation of several other pro-inflammatory cytokines (in particular interleukin 6), migration and proliferation of inflammatory cells (innate and adoptive immunity) to the inflammatory site, angiogenesis and increased blood flow and several other immune inflammatory pathways. These cytokines also contribute to both peripheral and central sensitization (see above) and can also lead to allodynia and hyperalgesia the extent of which has not been investigated in RA.

Several other mechanisms contribute to the intensity and nature of chronic pain in RA. Small nerve endings and fibers are entrapped in inflammatory synovitis to impart a neurogenic or neuropathic component. The mechanical sequel of articular deformities impose physical stresses and misalignment. Several other abnormalities along the pain perception pathway (nociceptor to cortical areas) contribute to chronic pain in RA. Peripheral sensitization, described above, is one such phenomenon. Neuropsychiatric manifestations (see above), both as a sequel and a trigger, complicate pain. The interaction between the anatomically distinct autonomic and somatosensory systems is complex but probably includes the expression of α adrenoceptors on primary afferent sensory fibers, nociceptors, sympathetic sprouting into dorsal root ganglia, and impaired oxygenation and nutrition in response to sympathetically mediated vasoconstriction. And all this may lend features (warmth, redness, tenderness, induration, oedema) of complex regional pain syndrome to articular and extra-articular tissues.
The pain persona in RA is indeed unique and complex. Pain in RA is a complex mixture of inflammation, nociception, neuropathy and functional overlay (affective, emotional and cognitive).

Pain is a core set measure of efficacy in RA, both in clinical practice and drug trial studies. There is no one target for control of pain. Analgesics and non-steroidal anti inflammatory drugs are a cornerstone of treatment but are often combined with several drugs to combat neurogenic element. Effective control of pain encourages adherence to medications and in particular DMARD (disease modifying anti-rheumatic drug). It is prudent to add that effective control of pain is critical to long term compliance to drugs. Pain relief encourages participation in physical therapy and rehabilitation. Diet and nutrition may play a critical role which currently needs to be investigated through control experiments. Though there is some data on the role of diet and in particular Omega 3 fatty acids to reduce inflammation and pain, there is very little data to support a similar role for minerals and trace elements. Copper, zinc and magnesium have been considered in the management of RA. Though K+ has been considered for its role in analgesia and anti-immuno-inflammatory response for over 30 years, there is very little clinical data to support this.

2.9.7 K+ ion channel Based Analgesic and Anti-Inflammatory therapeutics

Typical neuronal firing is characterized by a specific voltage threshold for action potential, and the opening of potassium channels below the threshold (or subthreshold) will lead to the inhibition of initiation and propagation of action potential. Activation

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of a K+ current in most neurons is likely to provide an anti-excitatory effect regardless of the source of over excitability. Therefore pharmacological K+ channel enhancement could be utilized as a strategy to manage pain.

In recent years, research has tried to identify and optimize such enhancers (or openers) and to validate their potential in treatment of pain. The target has been mostly M channels\(^\text{166}\). Channelopathies often underlie pathological pain states and many current and prospective analgesics target ion channels\(^\text{167}\).

The centrally acting retigabine was demonstrated to alleviate mechanical allodynia in inflamed temporomandibular joints induced by complete Freund’s adjuvant (CFA) in rats \(^\text{168}\).

Flupirtine, a close chemical analogue of Retigabine, has been used as a non-opioid analgesic\(^\text{169}\); it actually became first available in Europe in 1984. It is believed to be a M channel (K+) opener activity that underscores its analgesic efficacy. Flupirtine effectively reduces postoperative pain, chronic musculoskeletal pain, migraine and neuralgia\(^\text{169}\).


\(^{169}\) Devulder J. Flupirtine in pain management pharmacological properties and clinical use. CNS Drugs. 2010;24:867–881
As discovered recently, some of the well-known non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and celecoxib also possess strong M channel opener activity, which can be responsible for at least some of their analgesic efficacy.

Overall, KV channels therefore constitute potential drug targets for the treatment of diverse disease processes ranging from cancer over autoimmune diseases to metabolic, neurological and cardiovascular disorders. However, KV channels, in particular Kv11.1 (hERG) with its promiscuous blocker binding pocket and its relevance for cardiac repolarization, also constitute a liability in drug discovery due to drug-induced arrhythmias.

However, the role of dietary K+ augmentation or using K+ rich supplements in a similar strategy is not known as the author could not find any reference in the published literature using Google search engine and pub med.

2.10 Role of K+ in selected clinical disorders

2.10.1 K+ and blood pressure (BP)

There is abundance of literature examining the relationship between K+ and BP and strongly endorsing the benefits of K+ rich diet and supplement in prevention and treatment of hypertension. An Indian cross over randomized controlled cross over trial. Mol. Pharmacol. 2005;67:1053–1066


study also confirmed the beneficial effect of oral K+ on blood pressure\textsuperscript{174}. The role of sodium and salt in blood pressure is well established\textsuperscript{175}.

Fifty-two publications from January 1, 1990, to January 31, 2013, were identified for inclusion into a large systematic study\textsuperscript{176}. Evidence from these studies demonstrates that high salt intake not only increases blood pressure but also plays a role in endothelial dysfunction, cardiovascular structure and function, albuminuria and kidney disease progression, and cardiovascular morbidity and mortality in the general population. Conversely, dietary potassium intake attenuates all these effects and especially reduction in hypertension and stroke rates. Various subpopulations, such as overweight and obese individuals and aging adults, exhibit greater sensitivity to the effects of reduced salt intake and may benefit the most. A diet with modest salt restriction and increased potassium intake is best suited to reduce cardiovascular morbidity and mortality. Low dietary intake of potassium seems to augment the effect of sodium on BP.

\begin{itemize}
\item Haddy FJ, Vanhoutte PM, Feletou M. Role of potassium in regulating blood flow and blood pressure. Am J Physiol Regul Integr Comp Physiol 2006, 290: R546–R552
\item Aaron KJ, Sanders PW. Role of dietary salt and potassium intake in cardiovascular health and disease: a review of the evidence Mayo Clin Proc. 2013,88; 9:987-95
\end{itemize}
The incidence of hypertension was shown to be inversely related to dietary intake of potassium in several epidemiological studies. The lower incidence of hypertension among vegetarians is allegedly due to a diet rich in potassium. Thus increasing dietary potassium is as an essential public health effort. Vegetarian diets are believed to reduce blood pressure because of higher content of fiber and minerals (such as potassium and magnesium) and their lower fat content.

Several investigators have reported antihypertensive activity with oral supplementation with potassium. Dietary supplementation of potassium can lower blood pressure in normal and some hypertensive patients. Again, in contrast to NaCl restriction, the response to potassium supplementation is slow to appear and takes about a week. Such supplementation reduces the need for antihypertensive medication. "Salt-sensitive" hypertension responds particularly well, perhaps, in part, because supplementation with potassium increases the urinary excretion of sodium chloride.

Potassium supplementation can reduce the need for antihypertensive medication. One study showed that with an increased dietary potassium intake in hypertensive subjects, 81% of the subjects needed less than half of the baseline medication and 38% required

\[ \text{180 Svetkey LP, Yarger WE, Feussner JR, De Long E, Klotman PE. Double blind, placebo-controlled trial of potassium chloride in the treatment of mild hypertension. Hypertension 1987;9:444-50} \]
no antihypertensive medication for blood-pressure control, as compared with 29% and 9%, respectively, in the control group at 1 year of follow-up. An increase in dietary potassium can even abolish sodium sensitivity in both normotensive and hypertensive subjects.

dietary intake of >3500 mg/d is recommended for the primary prevention of hypertension.

The potassium: sodium intake ratio has decreased from early to modern times and differs between isolated and modern societies. Potassium intakes have decreased from 150 to 290 mmol/d to 30 to 70 mmol/d (6000–11,600 to 1200–2800 mg/d), whereas sodium increased from 20 to 40 mmol/d to 80 to 250 mmol/d, leading to a shift in the dietary potassium:sodium ratio of >3 to <0.4. Using self-reported dietary intake data, Yang et al., found lower potassium to sodium intake ratios strongly associated with increased all


cause, cardiovascular, and ischemic heart disease (HRs of 1.46, 1.46, and 2.15, respectively).

Though the exact mechanism is not known, several experimental studies have demonstrated an inhibitory effects of serum K+ on vascular smooth muscle proliferation, reduction in macrophage adherence to the vascular wall, arterial thrombosis and free oxygen radicals and reactive oxygen species. Unlike sodium, potassium is vasoactive and causes increased blood flow and vasodilation results from hyperpolarization of the vascular smooth muscle cell subsequent to potassium stimulation by the ion of the electrogenic Na-K pump and/or activating the inwardly rectifying Kir channels (see above). Potassium ions are also released by the endothelial cells in response to neurohumoral mediators and physical forces (such as shear stress) and contribute to the endothelium-dependent relaxations, being a component of endothelium-derived hyperpolarization factor-mediated responses. Potassium is released by endothelial cells. Though the response is believed to be slow and modest, potassium supplements lower blood pressure.

2.10.2 K+ and Stroke

A meta-analysis of 11 prospective studies of potassium intake, stroke, and cardiovascular disease involving 250,000 individuals showed the strongest association with reduction of

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risk of stroke by 21% for every 1.64-g/d (423-mmol/d) increase in potassium intake and a
trend toward a lower risk of cardiovascular disease.\textsuperscript{185}

Much of the ability of dietary potassium to lower the risk of stroke is through its effect on
lowering blood pressure.\textsuperscript{186} However, the effect seems to persist even when baseline blood
pressure was accounted for, suggesting that there may be additional mechanisms for this
benefit.\textsuperscript{187}

2.10.3 K+ and renal disease

Two observational U.S. studies showed that high intakes of potassium are associated with
a reduction in recurrent kidney stones.\textsuperscript{188} Western diets are likely to produce chronic
low grade metabolic acidosis wherein calcium reabsorption in distal tubule is inhibited
leading to calculi. K+ citrate effects urinary pH and reduces formation of calcium oxalate.

\textsuperscript{185} D’Elia L, Barba G, Cappuccio FP, Strazzullo P. Potassium intake, stroke, and cardiovascular

\textsuperscript{186} Kido M, Ando K, Onozato ML, Tojo A, Yoshikawa M, Ogita T, Fujita T. Protective effect of
dietary potassium against vascular injury in salt-sensitive hypertension. Hypertension.
2008;51:225–31

\textsuperscript{187} He FJ, Marciniak M, Carney C, Markandu ND, Anand V, Fraser WD, Dalton RN, Kaski JC,
MacGregor GA. Effects of potassium chloride and potassium bicarbonate on endothelial function,
8.

\textsuperscript{188} Cirillo M, Laurenzi M, Panarelli W, Stamler J. 1994. Urinary sodium to potassium
The incidence of hyperkalemia in patients with chronic renal insufficiency is difficult to assess because of the almost universal use of drugs that influence plasma K+. In one study carried out before angiotensin-converting enzyme (ACE) inhibitors were available and which excluded patients receiving diuretics, plasma K+ was significantly elevated (average value, 4.9 mmol/L) even in patients with only mild-moderate renal dysfunction (serum creatinine 2 to 4 mg/dL) [189]. Hyperkalemia appears to occur more frequently in patients with tubulointerstitial disease or diabetes mellitus[190], [191] but is clearly not confined to these disorders. Patients with renal insufficiency have a diminished ability to acutely excrete a K+ load and, therefore, have more severe and prolonged hyperkalemia when challenged [192], [193]. Because hyperkalemia stimulates aldosterone secretion, one might expect aldosterone levels to be higher in patients with renal insufficiency than in individuals with normal renal function. However, aldosterone measurements have shown


widely varying patterns and its importance as a factor in maintaining K+ balance in renal insufficiency is uncertain. Before reviewing the regulation of K+ excretion in patients with chronic renal insufficiency, it is important to address the issue of whether the hyperkalemia seen in these patients is due to impaired entry of K+ into cells or reflects an increase in intracellular K+ stores. Two general approaches—measurement of total body or striated muscle K+ stores, and assessment of cell membrane Na+, K+-ATPase activity or function were used to address this issue.

2.10.4 K+ and osteoporosis

Life style practices including diet explains 40% of bone mass whereas genetics account for the remaining 60%.

Any bone benefit of dietary potassium is thought to be through its effect on the acid-base balance. However, the role of the skeleton in regulating pH is debatable. Homeostatic mechanisms keep systemic pH tightly controlled at between 7.35 and 7.45. Western diet that is high in meats and cereal grains and low in fruits and vegetables creates a low-

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grade metabolic acidosis. Western diets lead to the production of 75 to 100 mEq acid daily. This systemic state of low grade metabolic acidosis progressively worsens with age as renal function declines. Buffering of this acidic pH by the alkaline calcium salts in the skeleton would lead to bone loss. Accordingly, alkaline potassium salts produced from metabolizing fruits and vegetables or potassium supplements (potassium bicarbonate or citrate, but not potassium chloride) are thought to protect against bone resorption for pH homeostasis. Bone mineral is not in contact with systemic circulation. Direct dissolution of bone mineral due to systemic acidosis is not necessary for bone resorption because extracellular H+ can stimulate osteoclasts directly through interaction with a protein receptor and this is in fact required for the initiation of osteoclast activity. The OGR7 receptor on osteoblasts sense acid levels, which induces intracellular Ca2+ release to mediate receptor activator of nuclear factor kB ligand expression and therefore bone resorption.

Several observational studies show the benefit of vegetables and fruits on bone strength and this is principally considered to be due to K+. K+ intake has been associated with


reduced urinary calcium excretion whether given as citrate or bicarbonate salts. Taken altogether, these studies suggest that organic salts of potassium (such as occurs in fruits and vegetables) in doses sufficient to effectively neutralize NRAE (net renal acid excretion) can improve calcium balance. Flavonoids do not explain the beneficial effects of diet K+ on bone.

Two years of 60 mmol/d (2400 mg/d) potassium as potassium citrate improved BMD and bone microarchitecture in 201 elderly men and women in a controlled drug trial study. Spine BMD was increased (P > 0.001) by 1.7 ± 1.5% over the placebo, which correlated with changes in NRAE, and 1.6% at femoral neck. Tibial trabecular BMD increased (P < 0.001) by 1.3 ± 1.3%. In summary, benefits of potassium on bone were seen typically when given as organic salts at relatively high doses of 60 to 90 mmol/d (2400–3600 mg/d). Organic salts of potassium reduce urinary calcium loss and improve calcium balance at these levels. Perhaps acid-base balance is not the mechanism in healthy kidneys, but as kidney function declined with age, it may be an important mechanism.

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Fruit and vegetable intake may protect against premenopausal bone loss. The benefit of K+ in diet has been shown in studies of elderly men and women including the well known long term follow up of the Framingham Study cohort. The beneficial effect of potassium on BMD and the link with fruit and vegetable intakes was consistent with the theory that a diet rich in alkaline salts protects bone by balancing the acidic metabolites produced from dietary protein (typical of Western diet largely meats and dairy) so that the need for release of alkaline salts from the bone is eliminated.


Two-year of potassium citrate supplementation did not reduce bone turnover or increase BMD in healthy postmenopausal women in a randomized placebo-controlled trial. In this study, 276 postmenopausal women (aged 55–65 y) were randomly assigned to 4 groups: high-dose potassium citrate (55.5 mEq/d), low-dose potassium citrate (18.5 mEq/d), placebo, and 300 g additional fruit and vegetables/d (equivalent of 18.5 mEq alkali). Serum and fasting urine were collected for bone marker assay at baseline and at 3, 6, 12, 18, and 24 months. Bone mineral density (BMD) was measured at baseline and 2 years. Thus it is probable that alkali provision of fruit and vegetable diet does not explain any long-term benefit on bone strength at least in this population group.

2.10.5 K+ and RA

Overall, the data is sparse on the role of K+ in aetiopathogenesis, clinical profile, progression of disease and treatment.

39, 695 people were surveyed in the ‘National Health and Nutrition Survey-III’ (NHANS, 1988-1994) in USA and RA was recorded in 840 individuals. Of these, 691 had their serum tested for potassium. 7.8% had less than 3.6 mEq/l, 34.7% between 3.6 and 4.0, 40.7% between 4.0 and 4.4, and 18.1% above 4.4 mEq/l. These were self reported from different laboratories. It was also suspected that several of these values are


likely to overestimate. In a critical review, Weber (2001) opined that a more likely normal cut off should be above 4.4 mEq/l and that only 18% subjects in this survey cohort of RA were likely to have normal serum potassium. It was proposed that RA patients are likely to have a low body K+ status.

There may also be a subtle impairment in the hypothalamic-pituitary-adrenal (HPA) axis in patients with RA resulting in inadequate cortisol secretion and adrenocorticotropic hormone (ACTH) response to immune-inflammatory process, and impaired electrolyte homeostasis. There is also a disconnect between the HPA and the sympathoadrenal system axis. The glucocorticoids plays an important role in K homeostasis and higher K intake leads to higher cortisol secretion and biosynthesis. Results of a recent clinical intervention trial in Iran showed elevated serum cortisol


followed K supplementation. Patients with RA are also reported to have significantly lower salivary and serum K+, reduced total body K, and lower dietary K intake as compared to healthy subjects. Cellular Na+, K+-ATPase (NKA) activity is impaired in RA and this may benefit through a reduced pro-inflammatory cytokine secretion. Due to altered tissue hydration and proteoglycan loss as a consequence of changes in ionic and osmotic environment of chondrocyte, there may be a lower content of K+ in joint tissues in RA and osteoarthritis.

Charles Weber (1974) has been strongly proposing a causal link between K+ deficiency and RA since several decades but the supporting data is sparse. Weber observed and described a striking similarity between some of the clinical and pathophysiological features in RA and a bout of severe diarrhea to support his hypothesis. In diarrhea, there

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are intense changes in electrolyte balance and several compensatory mechanisms especially endocrinal (and cortisol in particular) and renal come into play. There is hypokalemia along with dehydration and alkalosis. Cortisol conserves potassium by transporting it into cells but serum cortisol levels decline. Potassium deficiency results in reduced cortisol levels which leads to many of the symptoms observed in RA sufferers also. Also, when cortisol levels decline, the copper enzymes are blocked leading to increased copper excretion and reduced action of lysyl oxidase. Low serum cortisol induced by low K+ may predispose people to develop rheumatoid arthritis. Potassium supplementation may help prevent the development of RA as per Weber. Also, copper supplementation has the potential to alleviate symptoms of the condition. Weber further recommends that K+ supplementation is a gentle way to increase cortisol levels. Several other causes of K+ deficiency may be relevant to RA such as psychic stress, aldosterone stimulation, drugs (like diuretics, laxatives and enemas), licorice, grapefruit, intense perspiration, excess vomiting, high or low sodium diet and high consumption of processed foods, grains and fatty foods. Potassium should be automatically prescribed for RA because getting potassium up to normal from the low values in all RA patients is slow even with an unprocessed vegetarian diet. It is not only that K+ is not considered by physicians in regard to RA, most of them do not even believe that a K+ deficiency is likely. This even though many of them prescribe what are actually some form of K+ supplements, but prescribed under euphemistic terms such as salt substitutes.

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220 Weber C. Comment to ‘Genetics of rheumatoid arthritis contributes to biology and drug discovery’. Nature 506, 376 - 381 (7488); Published online: 2014-02-20; doi:10.1038/nature12873
sodium free baking powder, ORT salts (oral rehydration therapy for diarrhea), polarizing solutions, GIK (glucose, insulin, potassium) salts, vegetables, or glucosamine.

Nuki et al (1970) were the first to demonstrate that despite K supplements, inj tetracosactrin (synthetic ACTH) depot caused hypokalemia in RA patients\textsuperscript{221}. Later, the group demonstrated shifts in body K+ when patients of RA were prescribed oral K+ supplements with or without oral spironolactone and with or without depot tetracosactrin (synthetic ACTH) in an interventional study\textsuperscript{222}. 8 patients with definite RA and not responding to symptomatic in patient therapy were enrolled into this 30 day study. Patients were probably not on DMARD and/or oral steroid. Patients were allowed diet with alternative choices, carefully weighed and calculated to contain about 65 mmol potassium and 100-200 mmol sodium daily. Diet consumed was meticulously recorded and any food rejects were made up at the end of each day with food or fruit juice containing equivalent amounts of potassium. Certain items such as coffee, known to be very variable in potassium content, were excluded from the diet and no added salt was permitted; no water intake restriction. Plasma and urine electrolytes and whole body potassium were measured before and after a 2-week administration of depot tetracosactrin (TCS) 0.5 mg on alternate days. TCS was continued for further two weeks.


but with addition of potassium chloride (KCl, 48 mmol/d in 5 patients) supplements or spironolactone (SPR, 200 mg daily in 3 patients). Sample diet was chemically analyzed for K and Na. Total body potassium (TBK) was estimated in each patient before, during and after treatment using the natural occurring radioactive K 40 isotope. In parallel study, six patients of RA (not on steroids or NSAID) received a single intramuscular injection of 0.5 mg TCS and red blood cell (RBC) water and potassium content, plasma electrolyte concentration, and plasma 11-hydroxycorticosteroid (HOCS) levels were measured for 48 hours. At baseline, the measured TBK was significantly less than that predicted from the height, weight, and age formula in patients with RA. TBK did not change during or after treatment. An acute reduction in plasma and red cell potassium, independent of urinary K loss, was shown following TCS and this was accompanied with expected rise in HOCS and late increase in plasma Na. Two weeks post TCS, hypokalemia with a rise in plasma sodium and bicarbonate was seen; increased urinary K loss and volume. This was not accompanied with electrocardiogram changes or a rise in blood pressure. Addition of KCl, did not modify the changes in serum K and Na or TBK observed earlier (prior with TCS). Addition of spironolactone did not increase the serum K and overall pre-treatment changes were sustained. The intracellular (RBC) K+ was reduced in the parallel study following TCS injection and remained so till 48 hours. As the TBK did not change in the main cohort, it is likely that serum K changes (induced by TCS/steroids) was due to cellular shift but this was not entirely supported by the 'rbc' data. Possibly, renal mechanisms (likely renin angiotensin aldosterone) responded to Na and K load and though allowing hypokalemia ensured that TBK remained constant. The investigators also made an observation that despite scrupulous daily diet checks (for K
content), the exact diet K measurement (flame photometry) was considerably less than that computed from dietary tables (95% confidence interval of difference ± 10 mmol). Finally, the significance of low total body K in patients of RA was considered to be uncertain but the authors concluded that further studies are certainly required.

Fourteen biochemical estimations were performed on the serum of 100 consecutive hospital in-patients with RA and 100 control patients matched for age and in a study in UK. Abnormalities of urea, creatinine, uric acid, calcium, albumin, globulin, alkaline phosphatase, and iron were found three (or more) times as frequently in the rheumatoid group. Additionally, the mean values (though within normal range) for sodium, potassium and cholesterol were significantly lower in the RA. These differences were unexplained and not due to corticosteroids. The first proposal of a possible link between low diet K+ and RA and its dietary correction was comprehensively described by De Coti-Marsh. Rastamanesh (2009) proposed a similar relationship between K+ and

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RA based on probable cortisol mediated mechanisms and supported by his clinical trial data.

Rastamanesh (2009) demonstrated an analgesic effect of K+ supplementation in RA in a randomized double blind placebo controlled intervention trial of 28 days carried out in Iran in 36 women patients with active moderate severe painful (VAS> 8 cms ) active seropositive (RF) disease and serum hypokalemia (mean~3 mmol/l). Concurrent stable treatment with corticosteroids and/or DMARD was permitted and all were on a routine diet daily with 3000-mg sodium. 6 gm of K+ salt (chloride) was administered in grape juice daily to 16 patients; in placebo arm 16 subjects consumed only plain grape juice. Incidentally, grape juice also contained natural K+ equivalent to 325mg daily. The total mean potassium daily intake was 1540 mg in placebo and 6495 mg in the active arm. In the potassium group, 43.75% (7/16) of the patients met the criteria of 33% lower pain intensity compared with 6.25% (1/16) in the placebo group (P <.02) at day 28. Also, 31.25% (5/16) of the patients in the intervention group achieved moderate responses, according to the EULAR criteria against 6.25% in the placebo (P < .05); similar significant improvement in DAS 28, painful and swollen joint counts, physician and patient global assess and ESR response. In the active group, mean serum potassium and serum cortisol were significantly raised by 1.51 to 1.75 mmol/L (P<.001) and 81.00 to 115.20 nmol/L (P<.001) respectively at day 28. The K+ supplement was well tolerated; none had side effects. There were negative correlation between change in

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serum K (0.6) and serum cortisol (0.38) with pain VAS in the active; corresponding correlation in placebo was 0.028 and 0.10. Serum K+ and cortisol were positively correlated in the placebo (0.67) and active (0.46) groups after controlling for baseline K+ intake. K+ intake did not significantly correlate with the change in serum K+.

The activity of sodium-K-ATPase is decreased in a magnesium deficiency. The frequency of magnesium depletion in some inflammatory disease states including RA (warrants renewed interest in the relationship between Mg and potassium homeostasis in RA patients. And this may be important from a dietary perspective. It is believed that there should be enough Mg in the diet for optimum K+ absorption and physiological action.

Patients with RA can use K+ supplements if they do not get enough dietary potassium and if they don’t use medications that alter potassium metabolism (angiotensin-converting enzyme inhibitors, β blockers, potassium-sparing diuretics, etc). A supplementation with K+ in patients with RA, when associated with a Na+ restricted diet

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228 Kremer JM, Bigaouette J: Nutrient intake of patients with rheumatoid arthritis is deficient in pyridoxine, zinc, copper, and magnesium. J Rheumatol 23:990-994, 1996

is unlikely to lead to hyperkalemia. A retrospective cohort study defined that, the risk of hyperkalemia did not increase with NSAID use\textsuperscript{230}.

Active rheumatoid arthritis is known to be associated with poor nutritional status, but it has been claimed that the dietary intake of patients with rheumatoid arthritis is not significantly different from that of healthy control subjects\textsuperscript{231}. This apparent discrepancy is explained by the higher energy expenditure in rheumatoid arthritis patients, probably caused by cytokines such as tumor necrosis factor α and interleukin 1-β\textsuperscript{232}. Special attention should be paid to the hazards of malnutrition in rheumatoid arthritis patients and though vegetarian diet may provide enough K+ it may be deficient in calcium and vitamins D and B-12. And thus, extra care is required to ensure a balanced diet in RA.

2.11 K+ ion channels, Immune Cells and RA

Several fundamental functions are attributed to K+ ion channels and voltage gated (Kv) in particular, as described in a section above. In proliferating cells, such as lymphocytes or cancer cells, Kv channels provide the counterbalancing K+ efflux for the Ca+ influx through store-operated inward-rectifier Ca+ channels like CRAC (calcium-release

\textsuperscript{230} A\textsuperscript{jdhe\textsuperscript{y} H. The association between nonsteroidal anti-inflammatory drugs and potassium concentrations pharmacoepidemiological study in Saudi Arabia. Saudi Pharmaceutical J 2012; 20: 69–73


activated Ca+ channel) or transient receptor potential (TRP) channels, which is necessary for cellular activation. In this case, Kv channel blockers inhibit proliferation and 

**suppress cellular activation**.  

The T cell must therefore retain a negative membrane potential through a counterbalancing K+ efflux through Kv1.3 and/or the other T cell K+ channel, the Ca2+-activated channel KCa3.1, in order to be fully activated. Kv1.3 blockers exert their immunosuppressive effect by depolarizing the T cell membrane and thus reducing the driving force for Ca2+ entry through CRAC. 

The Kv1.3 and the KCa3.1 modulate several calcium-dependent cellular processes in immune cells, including T-cell activation and proliferation. Kv1.3 is highly expressed in CCR7– effector memory T (EMT) cells and is emerging as a target for T-cell mediated diseases like multiple sclerosis, rheumatoid arthritis, type-1 diabetes mellitus, allergic contact dermatitis, and psoriasis. KCa3.1 is also expressed in CCR7+ naïve and central memory T cells, as well as in B cells, mast cells, macrophages, dedifferentiated vascular smooth muscle cells, fibroblasts, vascular endothelium, and airway epithelium. The increase in cytosolic calcium concentration following T-cell receptor activation by antigen allows the nuclear factor of activated T cells (NFAT) to translocate to the nucleus. 

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and initiate transcription, ultimately leading to cytokine secretion and T cell proliferation. However, if potassium efflux through Kv1.3 and KCa3.1 is blocked, the T cell membrane depolarizes. Calcium influx through the CRAC (calcium-release activated calcium) channel is consequently reduced and T cell activation prevented. Unlike the calcineurin inhibitors cyclosporine and tacrolimus, Kv1.3 and KCa3.1 blockers are usually viewed as immunomodulators rather than general immunosuppressants because Kv1.3 and KCa3.1 blockers preferentially suppress specific T or B cell subsets.

Kv1.3 blockers may have a potential in the treatment of RA. T cells isolated from the synovial fluid of patients with RA are mainly Kv1.3 high CCR7- TEM cells. In comparison, T cells from osteoarthritis patients are primarily Kv1.3 low CCR7+ naive T cells and TCM cells. In the pristane-induced arthritis model using Dark Agoti rats, 21 days of treatment with ShK-L5-amide significantly decreased the number of affected joints and reduced the severity of radiological and histopathological findings. It was recently reported that Kv1.3 blockers selectively inhibit the Ca2+-signalling, proliferation and in vivo migration of CCR7- effector memory T cells and therefore rather constitute immunomodulators instead of general immunosuppressants. Kv1.3 channels are a therapeutic target for T cell-mediated autoimmune diseases.

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KV1.3 was recently further corroborated as a target for immunosuppression in humans by the finding that clofazimine, which has been clinically used since the 1960s for leprosy, pustular psoriasis, skin graft-versus-host disease and discoid lupus erythematosus, inhibits KV1.3.

CD4+ T helper cells play an important role in the pathogenesis of RA. This is suggested by its association with certain MHC II loci, especially HLA-DRB1, and PTPN22, which is relevant for T cell function. The therapeutic effects of blockade of T cell costimulation by abatacept provides more direct evidence. Activity of CD4+ and CD8+ T lymphocytes critically depend on constitutively expressed K2P5.1, a type of K+ ion channel. The expression of K2P5.1 on CD4+ T cells express is upregulated in autoimmune T cell stimulation disorders like RA.

In an in-vitro study, K2P5.1 expression was measured by RT-PCR in the peripheral blood of 58 patients with RA. Twenty patients in this cohort undergoing therapy change

238 Hegle AP, Marble DD, Wilson GF. A voltage-driven switch for ion-independent signaling by ethera-go-go K+channels. Proc Natl Acad Sci USA 2006;103:2886–2891.15


were followed-up for six months. K2P5.1 expression levels in CD4+ T cells showed a strong correlation to DAS 28 scores. Similar correlations were found for erythrocyte sedimentation rate, C-reactive protein. In addition, K2P5.1 expression levels of synovial fluid-derived T cells were higher compared to peripheral blood T cells. Prospective data in individual patients show a parallel behavior of K2P5.1 expression to disease activity parameters during a longitudinal follow-up for six months. Thus this may be a molecular target for prognosis and treatment in RA.

Cartilage has a high K+ content. Chondrocytes are the resident cells of cartilage which produce, maintain, and degrade the extracellular matrix (ECM). Whilst the cells are non-excitable, they have already been shown to express a rich complement of ion channels. Chondrocyte ion channels are involved in several critical functions including mechanotransduction and apoptosis. Many other functions in chondrocytes, and their precursors, have all been shown to directly involve ion channels. BK is a large conductance calcium activated K channel. Recent studies show rather convincingly that

\cite{Wells2009}

\cite{Mobasheri2012}

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\cite{Wells2009} Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, Aletaha D, van Riel PL: Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on Creactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009, 68:954-960

TRPV4 is activated by stretch and that this results in the opening of a potassium channel and this may also be an important regulator of chondrocyte cell volume.245

2.12 K+, Oxygen related free radicals and RA

A higher extent of reactive oxygen species (ROS) and related oxidant tissue damage is believed to be present in patients with RA.246, 247. An experimental cross-sectional controlled (healthy subjects) study isolated erythrocytes from patients of RA and evaluated lipid peroxidation, antioxidant enzyme activities (CAT, SOD, GSH-Px), level of the -SH groups and GSH and Na-K ATPase (pump). There were no significant differences in CAT and GSH-Px activities. SOD (superoxide dismutase) activity was lower in RA patients indicating a higher accumulation of oxidant radicals. RA erythrocytes showed increased lipid peroxidation. Levels of the GHS and -SH groups are significantly lower in RA patients. Total ATPase and Na-K ATPase activities were decreased in RA patients. Na-K-ATPase is the membrane lipid-protein complex. It contains 30% lipids, most of them are phosphate lipids and cholesterol. ATP is


hydrolyzed by the Na-K ATPase pump to produce energy used to transport ions (dominantly for electric discharge) across the membranes and maintain the cell milieu interior (stable ion content), both of which are fundamental physiological requirements of health.

ROS and several related oxygen derived free radicals inhibit cellular sodium/potassium ATPase activity and inactivate membrane sodium channels, and modify (oxidative) several proteins\(^{249}\). Other known effects include lipid peroxidation, direct inhibition of mitochondrial respiratory chain enzymes and inactivation of glyceraldehyde-3-phosphate dehydrogenase. ROS and oxygen-derived free radicals and nitric oxide (NO) are known mediators of inflammation, pain and/or tissue destruction in inflammatory and painful arthritic disorders. Inducible isoform of nitric oxide synthase (iNOS) also regulates the expression of several pro-inflammatory mediators including cytokines. ROS initiates a wide range of toxic oxidative reactions. They are potential reactants capable of causing DNA single strand breakage, with subsequent activation of the nuclear enzyme poly ADP ribose synthetase (PARS) and this then leads to severe cellular energy depletion and necrotic-type of cell death. Recently, iNOS has demonstrated an inhibitory role in preventing the activation of PARS and associated inflammatory organ damage. Thus, iNOS seems to have a dual and opposite role of adding fuel to the inflammatory fire and

also reducing its sequel of cellular damage and cell death. Experimental evidence supports the inhibitory effects of serum K+ on free radical formation\textsuperscript{250}.

\textbf{2.13 REVIEW OF LITERATURE: SUMMARY STATEMENTS RELEVANT TO CURRENT RESEARCH STUDY}

The current research protocol including research hypothesis, methods and analysis of data and discussion was based on the following literature review derived facts and postulates.

1) RA is a crippling painful autoimmune arthritis with several systemic complications and reduces quality of life and longevity.

2) Millions of patients in India suffer from RA as shown by the COPCORD India surveys.

3) Pain is multicausal and multifaceted and an overarching therapeutic target.

4) Pain in RA though dominantly of inflammatory origin is complicated by several other factors like neuropathic and psychological (cognitive impairment, moods and depression).

5) Measuring pain in clinical practice is a challenge. Visual analogue scale is globally accepted but an oversimplified measure for pain. More comprehensive pain capture instruments are required.

\textsuperscript{250} McCabe RD, Backarich MA, Srivastava K, Young DB. Potassium inhibits free radical formation. Hypertension. 1994;24:77-82
6) Pain relieving medicines are a leading cause of iatrogenic complications which are often life threatening and fatal. There is a need to investigate non-pharmacological methods to treat pain and diet could be an important strategy (current research).

7) There is a crying need to explore non-pharmacological interventions for management of pain and disease control.

8) Though Biologic DMARD agents have revolutionized the treatment of RA and a prolonged remission or good disease control is a realistic goal, it continues to be a difficult to treat disorder.

9) Several non-pharmacological interventions, amongst which exercise, diet and anti-stress measures are of prime importance, are considered to be important adjuncts but neglected in clinical research and practice.

10) Diet is generally believed by the community to be of great relevance and is probably connected with the etiology, progressions and treatment of RA. However, there is sparse evidence in the literature and few well designed community diet intervention studies.

11) There is very little data on the nature of diet consumed by the patients of RA though much is known about the food fads and dietary practices of RA patients. Patients of RA are known to consume diets with poor nutrition and several likely deficiencies.
12) Few elegant true to life controlled diet studies in RA using supervised and/or instruction based interventions with Mediterranean diet or vegan diet have shown significant improvement in symptoms, quality of life measures and disease activity. Though not considered and/or analyzed, these diets were essentially vegetarian and likely to have been rich in several minerals including K+.

13) K+ is an essential mineral to maintain good health and mediates essential physiological functions of nerve transmission (pain in this case) and cellular integrity, osmolality and acid base homeostasis. Muscles and cartilage have a high concentration of K+.

14) Several functions of K+ are mediated through sodium-K+ ATPase pump and K+ ion channels on cell surface. Voltage gated K+ ion channels work in concert with sodium and calcium channels; ion influx and efflux drives several functions including generation of action potential and intracellular signaling. K+ is critical for repolarization of cell membrane.

15) Vegetables and fruits, cereals and pulses and nuts are rich sources of K+.

16) The recommendations and guidelines on Indian diet by the National Institute of Nutrition (NIN), Hyderabad and facilitated by Indian Council of Medical Research are comprehensive and validated over time. The daily requirement of K+ is 3750 mg in man and 3226 mg in woman and should be adequately met with by the diet. NIN also provide a web based application to analyze the Indian diet for calorie and, components including minerals and vitamins.
17) K+ is predominantly an intracellular ion but in clinical practice the assay depends upon extracellular K+ serum/as measured using serum/plasma K+ assay which has a narrow normal safety range. There is little if any data to support a robust association between diet K+ and serum K+ assay. Sodium potassium ration and 24 hours urinary K+ may provide better guidance on total body K+ status.

18) Several elegant studies have demonstrated the downregulation of K+ ion channels and anti-K+ channel autoantibodies in chronic pain disorders. Prolonged opening of the K+ ion channel can reduce or block pain.

19) K+ ion channels are also demonstrated to mediate important T cell functions related to proliferation, stimulation and memory.

20) K+ has also been demonstrated to be anti-oxidant and restrict tissue damage.

21) K+ and serum cortisol are highly connected along with several other hormones to maintain milieu interior of cells; K+ stimulates cortisol secretion.

22) There are no studies to show the effect of supra-physiological K+ oral intake on the K+ and K+ ion channel function in health and disease.

23) K+ is known to be important in prevention and treatment of several medical disorders notably hypertension and stroke.

24) The beneficial role of K+ in control of blood pressure and probably several other related cardiovascular functions is extensively endorsed by a large amount of published literature on well-designed experimental and population studies including diet based interventions.
25) There is some evidence to support the role of K+ in bone health and osteoporosis in particular.

26) There is some data, albeit insufficient, to suggest that K+ status in patients suffering from RA is low and may contribute towards etiology and pathogenesis and the clinical phenotype especially pain and inflammation.

27) A well designed controlled short term small sample size interventional study in patients suffering from RA along with serum hypokalemia used K+ supplement mixed in grape fruit juice and demonstrated a significant relief in pain and reduction in disease activity measures.

28) Diet based K+ interventional studies could not be found in the published literature searched and reviewed for the current research project.