



REVIEW ARTICLE

Beyond the Joints: Exploring Electrolyte and Renal Complications in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disorder primarily affecting the joints, but its systemic manifestations extend to electrolyte imbalances and renal dysfunction. This review explores the complex interplay between RA, electrolyte disturbances (particularly involving sodium, potassium, calcium, and magnesium), and renal complications. Electrolyte imbalances can exacerbate inflammation and immune dysregulation in RA, either directly or indirectly through renal impairment or pharmacological interventions. Chronic inflammation, hypovolemia, and nephrotoxic effects of medications such as NSAIDs and glucocorticoids contribute to renal dysfunction, including chronic kidney disease (CKD) and, in severe cases, end-stage renal disease (ESRD). While DMARDs and biologics offer therapeutic benefits, they also pose potential risks for renal health. Understanding these interactions is essential for optimizing RA management and minimizing systemic complications.

Introduction

Rheumatoid arthritis (RA) is a chronic and destructive disease of the joints of an autoimmune nature. The primary site of the pathology is the synovium, but RA can also cause systemic extra-articular manifestations. Disease activity has improved over the past decade with the emergence of the biological treatment and continuous updates and progression in disease management with these treatment modalities. Despite optimum treatment, disease activity in RA patients can be affected by other factors like genetics and environmental factors (smoking, infection, co-morbidities, lifestyle, and activity). Electrolyte disturbances can have an impact on several systems, such as cardiovascular, neurological, and musculoskeletal. In this article we review common electrolyte imbalances and their effects on Rheumatoid arthritis patients, either direct effect or indirectly through renal impairment or through anti-rheumatic medications used in the treatment of RA patient.

Rheumatoid arthritis and electrolyte imbalances

Sodium changes in the plasma reflect water and volume depletion/excess. Few studies have demonstrated sodium changes with active inflammation, especially in Rheumatoid arthritis.

Previous studies have reported that sodium and potassium are closely related to the immune system and RA development ^{1,2,3}. A high sodium concentration enhances the differentiation of potentially pathogenic Th17 cells ⁴, promotes pro-inflammatory macrophages ⁵, and reduces the anti-inflammatory responses of T-cells and macrophages ^{6,7}. Sodium may expand CD14+ and CD16+ monocytes and alter the regulatory mechanisms of the innate and adaptive immune systems by causing a functional deficit of macrophages and regulatory T-cells ⁸.

Potassium is mostly intracellular; changes in the distribution of potassium between plasma and intracellular fluid can have a marked effect on the plasma potassium concentration. A study was conducted on hypokalemic patients with rheumatoid arthritis showed an association of high potassium intake with an improvement in disease activity and pain intensity in patients with RA ⁹.

A Japanese study has shown a significant association between salt load index (urinary sodium to potassium ratio) and current disease activity in patients with RA. This result raises the possibility that the urinary Na/K ratio is an independent disease activity marker of RA, and increased Na intake and decreased K intake contribute to RA's pathogenesis and hypertension ¹⁰.

Calcium is essential for bone mineralization and stabilization. An article by E Jäger ¹¹ reviewed the pathophysiological changes of calcium and phosphate in Rheumatoid arthritis. To prevent ectopic calcium deposition in the soft tissue or the vasculature, calcium and phosphate are stabilized by calciprotein particles (CPP) in extracellular fluids. An increase of the CPP concentration in the extracellular fluid beyond a certain threshold results in pro-inflammatory responses in

monocytes and macrophages, inflammasome resulting in the release of interleukin-1 β and interleukin-18. The release of pro-inflammatory cytokines as a result of increased CPPs is enhanced in RA. Bone erosion and subsequent release of calcium and phosphate during the etiopathology of RA can therefore aggravate the joint inflammation in this disease ¹¹.

There are no robust data on the association between RA and Magnesium changes in the plasma. Still, deficiency of Mg in blood causes inward flow of calcium ions, further resulting in increased stimulation of the N-methyl-D-aspartate (NMDA) receptor ^{12,13}. This leads to the release of inflammatory cytokines such as interleukin-6 and tumor necrosis factor ^{14,15,16}. Different studies showed contradicting results on the association between Mg and the risk of RA. A study by Arablou et al. demonstrated that Mg intake was negatively associated with the inflammatory factors of RA, such as Prostaglandin E2 ¹⁷. Another large NHANES study reported a U-shaped relationship between Mg intake and RA in US women ¹⁸.

Renal dysfunction and electrolyte imbalances in rheumatoid arthritis

The kidneys play an important role in maintaining the electrolyte/hydration balance in the body. Renal impairment in RA patients can occur through several mechanisms.

Chronic active inflammation can have an impact on renal function through different processes. Chronic active inflammation in the vascular beds may increase the risk of developing and progressing chronic kidney disease (CKD) due to accelerated atherosclerosis ^{19,20}. Hypovolemia is an important cause of pre-renal acute kidney impairment. Dehydration and anemia secondary to chronic disease like RA can both lead to pre-renal azotemia. Dehydration can also be found in patients due to the side effects of medication. NSAIDs cause renal vasoconstriction and interstitial nephritis, both of which can eventually lead to a chronic nephropathy.

NSAIDs and other anti-rheumatic medications can have a direct effect on renal function, rather than the disease itself, which will be discussed in the following section.

Renal tubular acidosis (RTA) is a non-anion gap acidosis caused by a failure of the renal tubules to maintain acid-base status. Type IV RTA is caused by hyporeninemic hypoaldosteronism, can be a result of treatment with NSAIDs, which is commonly associated with hyperkalemia.

A recent study by Such et al. on Rheumatoid arthritis and the risk of end-stage renal disease ²¹. This study demonstrated that RA is not only associated with the development of CKD, but also associated with the progression of CKD to ESRD, although the precise mechanisms to associate RA and ESRD are not demonstrated. The study showed a relatively higher prevalence of comorbid conditions, such as DM and HTN, which are well-known risk factors of CKD, has been reported among the patients with RA ²². The result from the subgroup analyses in the study suggests that RA is directly associated with the progression of CKD, as the association of RA with the risk of ESRD was significantly

stronger among those without obesity or other comorbidities ²³.

With the current advances in medical management, RA patients rarely develop secondary renal amyloidosis. This can occur in long-standing and poorly controlled RA. Amyloidosis can present with non-specific clinical features, but with renal involvement, patients usually present with proteinuria, which can be nephrotic in range, and progress to renal failure.

Medications and electrolyte imbalances

In terms of RA disease management, electrolytes can be affected by medications related to RA treatment, like Nonsteroidal anti-inflammatory drugs and glucocorticoids (NSAIDs), glucocorticoids (GCs), disease-modifying anti-rheumatic drugs (DMARDs), and biological agents. NSAIDs have Anti-inflammatory properties by inhibition of prostaglandin synthesis and inhibition of cyclooxygenase-2.

Nonsteroidal anti-inflammatory drugs may potentiate the effect of antidiuretic hormone (ADH), leading to water retention ²⁴ by reducing renal synthesis of prostaglandins, which normally antagonize the action of ADH. The serum Na levels of most patients with NSAID-associated hyponatremia usually return to normal within days of withdrawing the responsible drug ²⁵.

Prostaglandins also cause vasodilation of renal arteries, increase sodium loss, and boost renin release. They have a relatively minor impact on the renal system in euvolemic patients with normal renal function. However, in cases of renal insufficiency or hypovolemic states, prostaglandins play a crucial role in maintaining adequate glomerular flow and pressure. NSAIDs exhibit nephrotoxic effects through vasoconstriction, resulting in a decrease in glomerular filtration rate, increased sodium retention and blood volume, papillary necrosis, hyperkalemia, hyponatremia, and interstitial nephritis ²⁶.

Glucocorticoids (GCs) have beneficial anti-inflammatory effects through numerous mechanisms, such as the inhibition of the production of proinflammatory cytokines, adhesion molecules, and COX-2 ²⁷.

GCs act indirectly on Na-K-adenosine triphosphatase (Na-K-ATPase) to transport potassium into cells. In addition, glucocorticoids induce insulin resistance, leading to hyperglycemia and hyperinsulinemia. Glucocorticoid-induced hyperinsulinemia can shift potassium into the cell by increasing the pool of Na-K-ATPase ²⁸. It can also lead to renal excretion of potassium by the mineralocorticoid effect.

DMARDs do not have any direct effect on electrolyte balance in Rheumatic patients. Although this can be noticed with side effects of these medications, which by cause renal impairment.

Methotrexate is a cornerstone medication in RA. With its great potential in RA disease activity, side effects of gastric symptoms like nausea or oral ulcerations can lead to dehydration. Methotrexate is well-known for its effects on liver enzymes and inducing cytopenia; it also can exert nephrotoxic effects when used in high doses. Methotrexate should be avoided in patients with creatinine clearance (CrCl) <50 ml/min, or used with caution with reduced dose in patients with CrCl <80 ml/min ²⁹.

Cyclophosphamide and cyclosporine can both cause renal toxicity, although indirect with cyclophosphamide. Cyclophosphamide will cause hemorrhagic cystitis and increase the risk of bladder malignancy, this can be decreased by using oral instead of IV therapy, keeping in mind the total cumulative dose. Cyclosporine will cause renal toxicity by decreasing renal function; it should be stopped if creatinine increases by 30% above baseline. The effect is usually reversible when discontinuing the medication ³⁰.

Biological agents act directly by blocking certain cytokines in the inflammatory pathway. It will not have a direct effect on electrolyte balance or indirectly affect renal function. Biological agents have been reported as a renal protective treatment ²¹, and a recent study reported that the use of biologic agents lowers the risk of incident CKD ³¹.

Conclusion

Rheumatoid arthritis is a complex autoimmune condition with widespread systemic effects beyond joint involvement. Electrolyte imbalances—particularly involving sodium, potassium, calcium, and magnesium—play a significant role in modulating inflammation and immune responses. Additionally, renal function is intricately linked to RA through mechanisms of chronic inflammation, medication toxicity, and coexisting comorbidities. Medications used to manage RA, including NSAIDs, glucocorticoids, DMARDs, and biologic agents, can contribute to electrolyte disturbances either directly or indirectly through renal impairment. Understanding and managing these interrelated factors are critical for optimizing RA treatment outcomes and minimizing systemic complications, including chronic kidney disease and electrolyte abnormalities.

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