REVIEW ARTICLE

ROLE OF TRPM6 AND TRPM7 GENE POLYMORPHISMS IN RHEUMATOID ARTHRITIS: A SYSTEMATIC REVIEW

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Rheumatoid arthritis (RA) is a type of the autoimmune disease that adversely effects on the quality of life of the patient, primarily by affecting the joints. Different underlying immune system diseases through a common pathway may proceed to onset of rheumatoid arthritis. Magnesium (Mg) is one of the other essential minerals having significant role in the management of normal immune responses in inflammatory conditions. The exact role of magnesium deficiency (MgD) in pathophysiology of rheumatoid arthritis is still under debate, but several mechanisms are proposed through which, MgD leads to generation of inappropriate immune system functions. Most of the dietary Mg is absorbed in small intestine through paracellular passive mechanism while small amount is transported in blood through Transient Receptor Potential Channel Melastatin member 6 and 7 (TRPM6 and TRPM7). Genetic alterations in TRPM gene results in hypomagnesaemia, which may in turn, increase the risk of onset of pro-inflammatory mediators.

Keywords: Arthritis, magnesium, TRPM6, TRPM7, polymorphism

Pak J Physiol 2022;18(1):63–7

INTRODUCTION

Immune disorders are classified as a set of clinical abnormalities in host's defence system which are manifested by progressive production of pathological immune reactions against body's own antigens.[1] As per studies, the population-based data on determination of global burden of autoimmune diseases reveals that the incidence of these autoimmune diseases varies in different countries ranging from 5–10%, i.e., 9% in England, 6% in other European countries and approximately 7% in United States of America.[2] Among different autoimmune diseases, rheumatoid arthritis (RA) is one of the most common progressive autoimmune disease resulting in organ complications, failures, and disturbed life. The word rheumatoid arthritis came from a Greek word 'Rheumatos' which means 'flowing'. The suffix '-oid' means 'that mimics or resemble' while 'arth' means 'joint' and '-itis" means 'inflammation'.[3] This means that rheumatoid arthritis is a disease that resembles rheumatic fever disease which involves throat infections and further leads to joints inflammation and pain. The characteristics and clinical features of the disease are found in around 2,000–3,000 years old literatures. However, a clearer picture and description of the disease was first demonstrated by Sir Benjamin Collins Brodie, an English Physiologist, in 1819. In 1858, another English Physician Alfred Baring Garrod given the name rheumatoid arthritis to the disease.[4]

The physiological and pathological mechanism underlying disease onset is a complex process that is still being researched. However, several mechanisms and triggers are proposed, which ultimately lead to a common pathway in disease development. Anti-citrulline antibodies and other pro-inflammatory cytokines such as interleukin-1 and interleukin-6 are produced, resulting in chronic joint inflammation.[5] Furthermore, other extra-articular factors such as subcutaneous nodules, interstitial lung disease, pleuritis, endocarditis, and rheumatoid vasculitis may worsen the course of rheumatoid arthritis in the long run.[6] Inflammation of joints involves the activation of both natural and acquired immune systems. The chronic inflammation of joint synovium occurs due to interaction between synoviocytes and immunological cells such as macrophages, natural killer cells, T and B lymphocytes. Similarly, a complex interplay of complement and pro-inflammatory proteins also leads to progression of the disease, i.e., production of Anti-citrullinated peptide antibodies and TNF pathway.[7]

In our body, magnesium is the fourth most common mineral, involved in several biochemical and cellular processes.[8] Although the exact role of magnesium deficiency in inflammatory responses is still unknown, several mechanisms have been proposed. MgD increases thymic cellularity, which increases T-cell function and release of pro-inflammatory chemicals like IL-1, IL-6, TNF-alpha, and histamine, among others.[9,10] Similarly, MgD increases CTL cytotoxicity via an ATP-dependent mechanism.[11]

The recommended daily requirement of magnesium is 360–400 mg/day for an adult person which is completely acquired through exogenous sources, i.e., food.[12] Inside the body, the normal serum Mg levels is maintained through three different mechanisms, i.e., intestinal absorption, Mg storage in

bones and renal excretion. During Mg deficit conditions, Mg from bones is used for constant serum level.[13] About 80–90% of dietary Mg is absorbed in small intestine through paracellular passive mechanism while small amount is transported in blood through Transient Receptor Potential Channel Melastatin member 6 and 7 (TRPM6 and TRPM7).[14]

The main cause of hypomagnesemia related to gastrointestinal absorption is due to acute or chronic diarrhoea rather than vomiting since the concentration of magnesium in lower GI tract secretion is higher than secretion of upper GI tract secretions.[15] Some drugs may also reduce the absorptions of magnesium from GI tract such as proton pump inhibitors such as omeprazole for more than one year. The mechanism behind this malabsorption of magnesium from intestine is the inhibition of TRPM6 and TRPM7 magnesium channels.[16]

Besides these factors, genetic mutations in TRPM6 and TRPM7 genes, i.e., malfunctioning of TRPM6 channels causes hypomagnesemia with secondary hypocalcaemia (HSH) while downregulation of TRPM7 intestinal channel results in increased magnesium influx in colon cells.[17] Research studies have shown that genetic alterations in TRPM gene results in hypomagnesaemia and other related abnormalities which may in turn increases the risk of onset of pro-inflammatory mediators such as IL-1, IL-6, TNF-alpha and histamine.[18,19] The objective of current study was to review the association between TRPM6 and TRPM7 gene polymorphisms and hypomagnesemia leading to onset of rheumatoid arthritis.

METHODOLOGY

This review includes a comprehensive evaluation of the role of TRPM6 and TRPM7 Mg transport channels gene polymorphisms in the dysregulation of serum Mg levels. For achievement of this purpose, online computerized databases were searched manually such as PubMed (*http://www.ncbi.nlm.nih.gov/pubmed*), Cochrane (*https://www.cochranelibrary.com/*) and Amed (*https://www.ebsco.com/products/research-databases/allied-and-complementary-medicine-database-amed*) from January 1990 to December 2020. No language restrictions was imposed. The databases will be searched for terms such as *rheumatoid arthritis, pathogenesis, classification, nutritional elements, and rheumatoid arthritis, TRPM6* and *TRPM7 genetic alterations and serum Mg levels* etc.

The databases were searched for studies and articles in between January 1970 to December 2020. The studies before 1970 were excluded from our review because no study was performed on determination of role of TRPM gene polymorphisms in rheumatoid arthritis disease. Our review included case control, meta-analysis, and related studies while patients on anti-rheumatic treatment, suffering from other inflammatory diseases, case and medical reports were excluded from our review. The titles, abstracts and the content of articles will be selected based on rheumatoid arthritis introduction, name of the author, year of publication, sample size, epidemiology, causes, pathogenesis, factors involved in onset of the disease, immune response, immunomodulation, relationship between minerals and other food components with immune response, association between nutrients and rheumatoid arthritis, blood magnesium level regulation and odds ratio (OR) for risk of onset of rheumatoid arthritis. Data from these filtered studies on association between TRPM6 and TRPM7 gene polymorphisms and onset of rheumatoid arthritis was subjected to statistical analysis using computer-based software.

RESULTS

TRPM6 Gene Polymorphisms and Hypomagnesemia

Online databases as previously mentioned were searched for 'Role of TRPM6 gene polymorphisms and hypomagnesemia' including NCBI, Cochrane and Amed. As per our search, 10 studies were shown in the result in NCBI database, while in Cochrane library, 3 studies were found and in Amed library, 2 studies were found. Four studies were excluded due to article duplication. Out of remaining 11 studies, 5 studies were excluded because those studies were not on estimation of TRPM6 gene polymorphisms and hypomagnesemia. Only 6 studies which were considered for review were following the inclusion criteria as already mentioned, i.e., the studies showed significant results as per our inclusion criteria for studies. Among these studies, 4 articles were research articles while 2 articles were based on meta-analysis.

For 4 research articles[20–23], the calculated odds ratio for TRPM6 gene polymorphism and hypomagnesemia was found to be 1.32 (1.11–146). In these studies, a total number of 724 study samples were analysed in which both male and female subjects were equally distributed. For one meta-analysis of genome wide association study (GWAS) on TRPM6 gene polymorphism and its association with hypomagnesemia[4], the included study samples were more than 100,00 (29,880 RA cases and 73,758 controls) from both Asian and European population, the calculated risk factor (odds ratio) was 8.94 with 95% of confidence interval. According to this analysis, higher levels of serum magnesium level is associated with 8.84 fold increased risk of rheumatoid arthritis.

TRPM7 Gene Polymorphisms and Hypomagnesemia

Online databases as previously mentioned were searched for 'Role of TRPM7 gene polymorphisms and hypomagnesemia' including NCBI, Cochrane and Amed. As per our search, 68 studies were shown in

results in NCBI database, while in Cochrane library and Amed library, no such studies were found. Forty-eight studies were excluded because of the studies were not related to TRPM7 gene polymorphism and its association with rheumatoid arthritis. Twenty articles were screened and out of these, 16 articles were excluded from our review literature because those studies were not on estimation of TRPM7 gene polymorphisms and hypomagnesemia. Finally, only 4 studies which were considered for review were meeting the inclusion criteria, i.e., the studies showed significant results as per our inclusion criteria for studies. Among these studies, 3 were original research articles while one article was based on meta-analysis and was excluded from the study because the review was based upon TRPM7 gene polymorphism and its role in embryonic development. For three research articles[25–27], the calculated odds ratio for TRPM7 gene polymorphism and hypomagnesemia was 1.85 (95% CI: 1.09–3.14).

Association between Hypomagnesemia and Onset of Rheumatoid Arthritis

For meta-analysis of role of decrease serum level of magnesium in onset of rheumatoid arthritis in susceptible patients, we finally performed online databases search as previously mentioned for 'Association between hypomagnesemia and onset of rheumatoid arthritis' including NCBI, Cochrane and Amed. As per our search, 221 studies were shown in the result in NCBI database, while in Cochrane library and Amed library, no such studies were found. The articles were thoroughly screened, and 201 studies were excluded because those studies were not on determination of role of hypomagnesemia in onset of rheumatoid arthritis disease. Twenty articles were then included in our study. However, 11 articles were also excluded from the study because those studies were not related to determination of association between decrease magnesium intake in rheumatoid arthritis disease. Among the remaining 9 studies, 7 studies[28–33] were based on estimation of serum magnesium level in rheumatoid arthritis patients. The odds ratio for decrease magnesium level and onset of rheumatoid arthritis disease in these 7 studies was estimated as 2.8 (95% CI: 1.20–6.58, p=0.021). One study was based on estimation of serum magnesium level in patients suffering from rheumatoid arthritis conducted by Chavan *et al*[29], while the other study was on determination of effects of magnesium intake on radiographic osteoarthritis which was performed by Zeng *et al*[34]. In those two studies, 1,676 newly diagnosed patients were analysed from serum magnesium level. According to the study by Chavan *et al*[29], decrease magnesium level with dyslipidemia and hyperuricemia is a risk factor for rheumatoid arthritis and cardiovascular diseases. In this study, other dietary factors such as calcium, potassium and phosphorus were also studied in patients suffering from rheumatoid arthritis. Along with this, serum bilirubin levels, i.e., both direct and indirect were also increased. The other study by Zeng *et al*[34], the study was not directly related to role of hypomagnesemia in rheumatoid arthritis, rather the case-control study was confined to the findings that increase intake of dietary magnesium is inversely associated with radiographic osteoarthritis and other knee joint problems.

DISCUSSION

Magnesium is one of the important elemental minerals which is required to the body for normal functions including maintenance of intact immune system responses. The exact mechanism involved in the role of magnesium in regulation of inflammatory responses is still unclear, but different indirect mechanisms are proposed through which magnesium plays its role in immunity. Magnesium deficiency is found to be involved in increase thymic cellularity that ultimately increases T-cells functions and release of pro-inflammatory chemicals such as IL-1, IL-6, TNF-α and histamine. Similarly, MgD also increases cytotoxic activity of T-lymphocytes (CTL) through ATP dependent mechanism.[35] According to Libako *et al*[36], due to hypomagnesaemia, there is an increase in intracellular calcium level which causes hyperactivation of phagocytes. Phagocytes are first line of host defence mechanisms against foreign pathogens. The function is achieved through production of cytokines, reactive oxygen species (ROS) and other cytokines which leads to intense inflammatory responses.[36] Similarly, Chavan *et al*[29] also found hypomagnesaemia in RA patients as compared to control subjects which shows that low blood magnesium level is significantly associated with development of RA disease ($p \leq 0.01$).[29] The genetic involvement in the regulation of serum magnesium level cannot be ruled-out.

Genetic influences can be understood by different mechanisms by which different genes can alter the normal physiological functions that regulate the normal body magnesium content. The most important mechanism is the regulation of dietary absorption pattern of magnesium. In intestines, there are two types of magnesium transport channels such as TRPM6 and TRPM7 transport channels that regulates the transfer of dietary magnesium from lumen to systemic circulation. These protein channels are transcripted from TRPM6 and TRPM7 genes. Any genetic alteration in these genes may alter the function of magnesium transport channels, which ultimately results into hypomagnesemia. According to Song *et al*, genetic mutations in TRPM6 gene may result in

diabetes mellitus in susceptible women whose magnesium content is deficient in the diet.[37] Coulter *et al* also found the novel mutations in TRPM6 gene results in decrease serum magnesium level which may be involved in other disorders in the body.[19] Malfunctioning of TRPM6 channels causes hypomagnesemia with secondary hypocalcemia (HSH) while downregulation of TRPM7 intestinal channel results in increased magnesium influx in colon cells.[17]

In our study, 83 studies were included based on determination of association between TRPM6 and TRPM7 gene polymorphisms and hypomagnesemia, but only 9 studies fulfilled our inclusion criteria. As per our review, the odds ratio was found to be 1.32 and 1.85, respectively. This means that the genetic polymorphisms in TRPM6 and TRPM 7 gene are risk factor for development of rheumatoid arthritis in susceptible patients.

In the studies conducted on patients suffering from rheumatoid arthritis, along with magnesium level other parameters like uric acid, hyperlipidaemia, bilirubin level and other minerals were also measured. This reduces the quality of our review literature due to lack of evidence on possible association between hypomagnesemia and onset of rheumatoid arthritis. Similarly, we reviewed the role of decrease serum level of magnesium in onset of rheumatoid arthritis disease in susceptible patients, according to our systemic review, 9 case-control studies were found in which there was decrease serum concentration of magnesium in patients suffering from rheumatoid arthritis and one study was related to inverse association of magnesium intake with osteoarthritis. Both studies were case-control studies in which it was found that the patients suffering from rheumatoid arthritis and osteoarthritis have significant hypomagnesemia ($p<0.01$) and that the magnesium supplementation has a protective role in joint health. However, in these studies, other dietary components were also studied such as calcium, potassium, and phosphorus.

The increase serum level of direct and indirect bilirubin was also found to be elevated in study population. This means that the other dietary factors may act as confounding factor for onset of rheumatoid arthritis. Similarly, the hyperbilirubinemia may also be considered as a factor causing increase joint inflammation.

CONCLUSION

Any genetic alteration in TRPM genes regulating the functions of magnesium transport channels may lead to decreased absorption of dietary magnesium and cause hypomagnesemia which may be a factor for development of rheumatoid arthritis in susceptible patients.

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Received: 8 Jul 2021 **Reviewed:** 19 Dec 2021 **Accepted:** 26 Dec 2021

Contribution of Authors:

SF: Introduction writing
SH: Data extraction
FK: Data extraction
JB: Data extraction
FR: Methodology writing
MA: Discussion writing

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflict of Interest: The authors have no potential conflict of interest to report relevant to this article.

CORRIGENDUM

The name '**Naheed Akram**' may please be corrected, read and cited as '**Naheed Akhtar**' in the article:

ROLE OF PROPHYLACTIC ANTIBIOTICS IN CLEAN SURGERY

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The correct citation of the article will be as follows:

Ziyad Afzal Kayani, Sarmud Latif Awan, Muhammad Arshad Abbasi, Irum Gilani, Naheed Akhtar, Farzana Sabir. Role of prophylactic antibiotics in clean surgery. Pak J Physiol 2019;15(2):38–40.

The authors' affiliations and other details remain the same. The Editorial Team regrets any inconvenience whatsoever caused by this unintentional mistake due to metadata upload on submission.