

REVIEW ARTICLE

ROLE OF TOBACCO SMOKING IN CAUSING HYPOMAGNESEMIA AND RHEUMATOID ARTHRITIS

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Rheumatoid arthritis (RA) is a type of immune system disorders that badly affect patient's quality of life. The onset of disease constitutes a complex pathological process, and several mechanisms and triggers are proposed in the development of this disease. Magnesium (Mg) is an important trace element that plays a role in normal functioning of immune system. The deficiency of magnesium is found to be related to abnormal T-cells functions leading to secretion of pro-inflammatory chemicals such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor alpha (TNF- α) and histamine. Similarly, hypomagnesaemia also causes an increase in intracellular calcium level that leads to hyperactivation of phagocytes which are the first line of defence of our immune system. Tobacco smoking is a cause of hypomagnesemia in susceptible patients. The association between tobacco smoking and onset of rheumatoid arthritis is statistically significant in those who are smoking, even for less than 10 years.

Keywords: Rheumatoid arthritis, hypomagnesemia, smoking, risk factor

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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 Rheumatoid arthritis (RA) is one of the most common progressive autoimmune disease resulting in organ complications, failures, and disturbed life. Besides inflammation of joints, rheumatoid arthritis is also associated with other comorbid diseases such as diabetes mellitus and RA-induced psoriasis.² The pathophysiological mechanism behind the onset of disease is a complex process and still under investigation. However, several mechanisms and triggers are proposed which at the end, follows a common pathway in the development of disease. The worldwide prevalence of RA varies, and it is about 1% of total disease burden around the globe. There is no specific age for onset of disease in susceptible patients. The disease can develop in persons of all age groups, but the risk increases with increasing age. In South Asia, the prevalence of disease is not much studied. Only a few cohort studies have been conducted to analyse the frequency of disease in India and Pakistan. The prevalence of rheumatoid arthritis in Pakistan and India is a little higher than that in European and other first world countries. This may be due to dietary patterns and environmental factors that may contribute to the onset of disease. According to a meta-analysis study, the ratio of development of rheumatoid arthritis disease in urban population in Pakistan is 8 per 1,000 people with prevalence of 0.5%. Interestingly, the ratio between male and female in developing the disease is 1:1. In

comparison, the prevalence of rheumatoid arthritis in Indian population was found to be 0.2–1%.³

The relationship between nutrients and normal immune system development is naturally understood phenomenon. Normal and balanced diet promotes the growth and development of and intact immune system. Food rich in vital nutrients such as carbohydrates, proteins, lipids (including essential fatty acids and oils), vitamins and minerals ensures the protection against different diseases including rheumatoid arthritis disease. Magnesium (Mg) is fourth most common micronutrient in our body after sodium (Na), potassium (K), and calcium (Ca). The recommended daily requirement of magnesium is 360–400 mg for an adult person which is completely acquired through exogenous sources, i.e., food.⁴ The normal serum Mg level is maintained through three different mechanisms, i.e., intestinal absorption, Mg storage in bones, and renal excretion. Magnesium is involved in different metabolic and cellular activities. The major function of Mg in our body is to act as cofactor for almost 300 enzymes which are required for metabolism of major biomolecules such as carbohydrates, proteins, and lipids. During Mg deficit conditions, Mg from bones is used for constant serum level.⁵ The exact role of magnesium deficiency (MgD) in inflammatory responses is still under debate, but several mechanisms are proposed through which MgD leads to generation of inappropriate immune system functions.⁶ MgD causes an increase in thymic cellularity that ultimately increases T-cells functions and release of pro-inflammatory chemicals such as IL-1, IL-6, TNF- α and histamine. MgD also increases cytotoxic activity of T-lymphocytes (CTL) through ATP dependent

mechanism.⁷ According to Libako *et al*⁸, MgD causes an increase in intracellular calcium level which causes hyperactivation of phagocytes which are first line of host defence mechanisms against foreign pathogens. Chavan *et al*⁹, 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 ($p<0.01$).

Smoking is a factor which affects most of the normal physiological functions of the body. As per studies, tobacco smoking is related to increased insulin resistance causing diabetes mellitus.⁹ Similarly, smoking has shown the strongest association with onset of rheumatoid arthritis. Different studies around the globe have revealed that smoking increases the risk of development of disease, as well as complicates the course of disease over time.¹⁰ According to the studies, smoking is linked with release of pro-inflammatory chemicals which triggers the abnormal inflammatory responses against common antigens. This may include release of C-reactive proteins (CRP) which are produced in the liver at a high rate because of cytokines release from adipocytes and macrophages.¹¹ As per study, patients who are smokers have high level of serum CRPs than the non-smokers. Besides the production and increase release of CRPs, it is also found that smoking is linked with production of Rheumatoid Arthritis (RA) factor and anti-citrullinated peptide antibody (ACPA). Smoking also enhances the Human Leukocyte antigen (*HLA*) induced disturbance in autoimmune responses in susceptible patients.¹² Tobacco smoking results in production of tetra-chlorodibenzo-P-dioxin (TCDD), a bye-product of burning of organic substances.¹³ The TCDD is a carcinogenic product and is extremely toxic for human body. TCDD results in overproduction of leukotrienes including interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8) which act as a trigger for onset of inflammatory responses in body such as in rheumatoid arthritis.¹⁴ Tobacco smoking causes loss of magnesium and other important minerals from body such as calcium and zinc. Chronic smoking i.e., more than 10 cigarettes per day, causes significant decrease in serum magnesium level as compared to healthy non-smokers.¹⁵ Due to lack of data, the direct link of tobacco smoking and hypomagnesaemia is not known. However, the habit of tobacco smoking is at peak in depressed persons. Chronic stress results in decrease level of serum magnesium through increased renal excretion which produces harmful effects on the body.¹⁶ Tobacco smoking also causes decrease in appetite by causing abnormality in digestive system's ability to absorb bio-elements including magnesium. Based on these facts, it can be assumed that chronic tobacco smoking leads to hypomagnesaemia which can be correlated to other clinical disorders such as rheumatoid arthritis.¹⁷ The aim of the current study is to review the role of smoking

causing hypomagnesaemia associated with onset of rheumatoid arthritis in susceptible patients.

METHODOLOGY

This was a literature review study and included meta-analysis of Mg deficiency in the body which can lead to abnormal immune responses especially in inflammatory diseases. Online databases were searched for 'effect of smoking on serum magnesium level' including the NCBI, Cochrane, and Amed. The search terms included rheumatoid arthritis, smoking and inflammatory diseases, smoking and rheumatoid arthritis, pathogenesis, classification, nutritional elements and rheumatoid arthritis. The databases were searched for articles and studies conducted between Jan 1970 to Dec 2020. Case control, meta-analysis and related studies were included in the review while individual studies such as case reports and medical reports were excluded from our study. Similarly, studies on patients of rheumatoid arthritis taking anti-rheumatic drugs and patients suffering from other comorbid diseases were also excluded from the study. The titles, abstracts and the content of articles were selected or filtered on the basis of introduction to rheumatoid arthritis, author's name, year of publication of the study, sample size, epidemiology, causes, pathogenesis, information on different factors involved in onset of the disease, immunomodulation and immune responses, relationship between minerals and other food components with immunomodulation, association between nutritional components and rheumatoid arthritis, regulation of blood magnesium level and odds ratio (OR) for risk of development of rheumatoid arthritis type of study. Data from these filtered studies on smoking and hypomagnesaemia related to onset of rheumatoid arthritis were subjected to statistical analysis using SPSS-20.

RESULTS

Characteristics of studies on Smoking and Rheumatoid Arthritis

As per our search, 433 studies were shown in the result in NCBI database, while the other two libraries did not show any study on the effect of smoking on serum magnesium level. Of these studies, 9 studies were case-control studies and 5 were cohort studies. The average age of the population obtained from each study was 52 years and among these, 94% were female and 6% were male. In the case-control studies, there were 4,764 cases, and 13,647 control samples. In 5 cohort studies, 9,121 cases were included among 566,044 study population. We classified the duration of smoking into 3 categories, i.e., left smoking after <20 years as 'past smokers', smoking for up to 20 years as 'current smokers', and >20 years as 'ever smokers'.

Subgroup analysis for male population

The summary of odds ratio (OR) for male chronic or ever smokers for onset of rheumatoid arthritis was found as 1.88 (1.55–2.27). Similarly, for current and past smokers, the odds ratio for onset of rheumatoid arthritis was 1.86 (1.48–2.33) and 1.75 (1.32–2.30) respectively. In 7 case control studies^{18–25}, the odds ratio for onset of rheumatoid arthritis in ever, current and past smokers were 1.85 (1.52–2.28), 1.88 (1.48–2.41) and 1.78 (1.33–2.37) respectively. The difference in the smoking status of these subjects was not significant. The tobacco smoking is a risk factor for the development of rheumatoid arthritis in male population who were smokers regardless of the duration of smoking, i.e., ever, current or past smokers.

Subgroup Analysis for Female Population

The Odds ratio for female ever, current, and past smokers for onset of rheumatoid arthritis was found to be 1.26 (1.13–1.43), 1.32 (1.11–1.55) and 1.21 (1.07–1.41), respectively. For the 9 case-control studies^{18–26}, the calculated odds ratio for ever, current, and past smokers for onset of rheumatoid arthritis were 1.26 (1.06–1.55), 1.18 (0.89–1.62) and 1.25 (1.05–1.49) respectively. For these three subgroups of smokers, there was no significant difference between them ($p>0.05$). For the 5 cohort studies^{27–31}, the calculated odds ratio for ever, current and past female cigarette smokers for onset of rheumatoid arthritis was 1.26 (1.06–1.51), 1.36 (1.14–1.66), and 1.21 (0.95–1.48) respectively. In these studies, the difference between the three subgroups was not significant ($p>0.05$). The quality of one cohort study on women smokers²⁷ was inferior than the others because the study was on determination of risk factors for rheumatoid arthritis including oral contraceptives and cigarette smoking. The use of oral contraceptives reduces the risk of rheumatoid arthritis during tobacco smoking. Even then, our results are strong after the exclusion of the study.

Association between hypomagnesemia and RA

For meta-analysis of role of decreased serum level of magnesium in onset of rheumatoid arthritis in susceptible patients, we 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 the 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^{9,32–37} 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.*,⁹ while the other study was on determination of effects of magnesium intake on radiographic osteoarthritis which was performed by Zeng *et al.*³⁸ In those two studies, 1676 newly diagnosed patients were analysed for serum magnesium level. According to the study by Chavan *et al.*,⁹ 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 bilirubin levels were also increased. In other study by Zeng *et al.*,³⁸ 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

This systemic review identified risk factors for the onset of rheumatoid arthritis in susceptible patients. This included the previously discussed environmental risk factors such as tobacco smoking, microbial infections, diet, and environmental pollution. Besides this, genetic factors such as different types of polymorphisms involved in onset of the diseases were also illustrated. The results from this literature review showed some proof of a linear association between lifelong cigarette smoking and RA. Our results also indicated that the risk of onset of rheumatoid arthritis in men is two times more than non-smokers, while the risk of onset of the disease in female is approximately 1.3 times more than the non-smoker women. The association between tobacco smoking and onset of rheumatoid arthritis was statistically significant in those who were smoking for less than 10 years. In patients, who were smoking for more than 20 years, risk of the development of rheumatoid arthritis increased two times as compared to those who were non-smokers. However, the women who were smoking for about 20 years, the risk of development of disease is more than the men. Limited number of articles were included in our study i.e., only 14 studies were included which fulfilled inclusion criteria. Among these 14 studies, 9 studies were based on

original research study while 5 studies were cohort studies, and the publication bias did not affect the results of our review study. The results of our review study are same or in line with the results from previous literature review.³⁹ This shows that tobacco smoking increases the risk of rheumatoid arthritis than in non-smokers, especially in men. This is because that according to experimental study, oestrogen suppresses the onset of rheumatoid arthritis in female mouse model i.e., oestrogen inhibits the release of cytokines produced by T-helper cells. This reduces the risk for development of rheumatoid arthritis.⁴⁰ According to two other studies, it is found that the use of oral contraceptives which decrease the release of oestrogen in female body, enhances the risk factor for development of rheumatoid arthritis in women.^{41–42} Smoking also induces the production of anti-citrullinated peptide antibodies i.e., RF positive patients of rheumatoid arthritis. The exact mechanism is still unknown but Padyukov *et al* showed that smoking and RF shares a common HLA-DRB1 epitope allele which is a significant risk factor for onset of RA positive rheumatoid arthritis.²⁴

The role of decreased serum level of magnesium in onset of rheumatoid arthritis disease in susceptible patients, as per our review, 9 case-control studies were found in which there was decreased 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, other dietary components were also studied such as calcium, potassium and phosphorus. The 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 factors for association of decreased serum magnesium level with onset of rheumatoid arthritis. Similarly, the hyperbilirubinemia may also be considered as a factor causing increase joint inflammation.

CONCLUSION

The risk factor for the development of rheumatoid arthritis is generally equal for both males and females who are smokers than the non-smoker population. Magnesium is involved in regulation of normal immune responses and decrease in serum magnesium level disturbs functions of the normal immune system. Due to lack of evidence, it is very early to conclude that hypomagnesemia is involved in onset of rheumatoid arthritis.

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