CHANGES OF SERUM MAGNESIUM LEVELS IN PATIENTS WITH RHEUMATOID ARTHRITIS STAGE I-II BEFORE TREATMENT

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic disease of unknown etiology, manifested primarily by inflammation of the peripheral joints. The pathogenic mechanisms responsible for the onset and maintenance of the joint inflammation in RA still make it object of investigations. We will discuss some of the aspects of the involvement of magnesium (Mg) in the pathologic processes of RA.

Objectives: To estimate the blood levels of Mg in a group of patients suffering from RA stage I-II before treatment and their correlation with disease activity.

Materials and methods: The study was carried out before therapy, in a group of 41 patients with RA stage I-II ranging in age between 28-65 years. The serum values of Mg were estimated in a group of 24 normal controls of the same age range and presenting no signs of rheumatic disease. The serum Mg levels were measured colorimetrically on a Hitachi 917 autoanalyzer. Data were reported as means±SD. Student's t-test and Fisher's exact test and linear regression models were used. Results are presented as means with 95% confidence limits.

Results: In patients with RA stage I-II, before treatment**,** the decrease of serum Mg levels were significant (ranges from 1.08-1.82 mEq/L, mean value 1.58±0.11 mEq/L vs. normal controls' ranges from 1.42-1.98 mEq/L, mean value 1.69±0.14 mEq/L; p value <0.01). The values of serum Mg found correlated with the severity of the disease. This was mainly due to the extinction of the inflammatory process.

Conclusion: The decrease of serum levels Mg in patients with RA seems interesting since it might have some implications in the alteration of the subjacent bone structure of joint inflammation. This is a trial to assess the Mg

status in RA patients; knowledge that may help better understanding of other markers relevant to the disease or to investigate possible alternative treatment regimens.

Keywords: rheumatoid arthritis before treatment, serum magnesium

Inflammation, irrespective of etiology, is capable of inducing marked systemic alterations in trace metal distribution and metabolism. These trace metal alterations appear to be linked to the production of an acute-phase plasma protein response and to be part of a proposed host-defense/repair system which responds to injury upon activation by factors released from stimulated phagocytes. Magnesium (Mg) is an essential nutrient, meaning that your body needs it for healthy functioning. Mg one of the major cations of the biological systems. It plays an essential role in many cell processes. Mg is required for the proper growth and maintenance of bones and the Mg levels are changed in chronic inflammations [1].

Rheumatoid arthritis is one of the most common forms of arthritis and represents a public health problem, as it affects about 2% of the economically active population. The disease is more common in women than in men and typically begins between the ages of 35 and 60. This problem generates important expenses derived from medical attention and the loss of productivity of the affected patients. RA is a chronic disease that causes inflammation of the joints and surrounding tissues. The late phase of RA is characterized by destruction of the cartilage which leads to deformity. The cause of RA is unknown. Several studies have shown that patients suffering from RA have a shortened life span. This could very possibly be related to their highly elevated level of oxidative stress [2,3].

RA is diagnosed through a combination of joint x-rays and blood tests to screen for the presence of specific markers, specifically the anti-CCP3 IgG (anti-cyclic citrullinated peptide antibody) test and is characterized by chronic inflammation and progressive erosion of synovial cartilage and bone [4,5].

RA is a chronic systemic disease which primarily affects the synovium, resulting in joint damage and bone destruction. If the disease remains untreated it can cause severe bone and systemic complications. Although the etiology of RA remains unknown, there is much evidence suggesting that an infectious agent, in a genetically susceptible individual carrying the "rheumatoid epitope" could be responsible for the initiation of the disease. In RA the immune system is activated and begins attacking innocent tissues, especially cartilage of the joints. The parts assigned to the lymphocyte in RA have suggested to us a study of the lymphocytes participation to the immune inflammatory reactions in this disease. To this end we attempted to study, several metabolic aspects of the lymphocytes and to look for eventual correlation between the metabolic behavior of the lymphocytes in the synovial fluid and that in the peripheral blood in view of a more thorough study of the pathogenic aspects of RA. The subsequent activation of the immune system, especially the monocytes–macrophages, $CD4^+$-T-cells and B-cells, which involve the synovial tissue, are responsible for the expression and chronicity of the disease. It has been suggested that reactive oxygen metabolites and trace elements play some role in the etiology and pathogenesis of RA [6-8].

Recent advances suggest that Mg is an essential cation playing a crucial role in many physiological functions [9]. A better understanding of the pathogenesis of RA will allow an improved therapeutic approach to this difficult and, so far, untreatable disease.

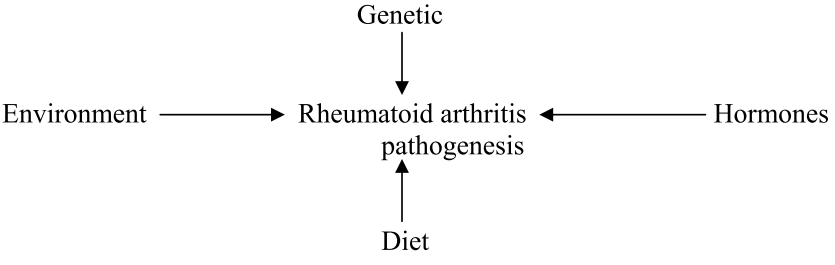

Figure 1. Factors influencing rheumatoid arthritis pathogenesis [3]

Materials and methods

The study was carried out before therapy, in a group of 41 patients with RA stage I-II ranging in age between 28-65 years. Serum values of Mg were estimated in a group of 24 normal controls of the same age range and presenting no sign of rheumatic disease. The serum Mg levels were measured colorimetrically on a Hitachi 917 auto analyzer. Data were reported as means ±SD. Student's t-test and Fisher's exact test and linear regression models were used (significance was assessed at $p<0.05$). Results are presented as means with 95% confidence limits.

Results

We have evaluated serum Mg in 41 patients. The analysis of our results shows that the decrease of serum magnesium levels were ranges from 1.08-1.82 mEq/L, mean value 1.58±0.11 mEq/L in patients with RA stage I-II vs. normal controls' ranges from 1.42-1.98 mEq/L, mean value 1.69±0.14 mEq/L. The statistical significance (p value) was <0.01. Serum Mg levels were studied as a continuous variable using logistic regression analysis. Results are presented as odds ratios with their corresponding 95% confidence intervals (95% CI). To evaluate whether lower Mg reflected a more severe prognosis, we evaluated this association with Spearman correlation coefficients and linear regression models. The most important changes of serum Mg have been observed in the severe forms of disease. The analyses revealed an increased risk of severe prognosis per deviation of 0.11 mEq/L. Patients with the serum Mg levels under 1.40 mEq/L had a more severe prognosis.

Discussion

A decreased level of Mg has been suggested to be reasonable marker of RA. In these analyses we found difference in the association of Mg and severe forms of RA. The sample size of this subgroup is very small, so that definite conclusions cannot be drawn from these analyses. However, the observation that patients with severe prognostic of RA had lower Mg levels compared with non-severe prognosis, most probably reflects the mechanism of Mg action at the cellular level during the pathophysiological process. The linear association between Mg and severe prognosis is in concordance with the available evidence that shows a graded association.

We were interested in understanding if the T-cell-mediated autoimmune responses are considered to play a role in the pathogenesis of RA. Activation of T lymphocytes requires two signals from antigen-presenting cells. The first signal, the binding of the T-cell receptor to its antigen major histocompatibility complex ligand, provides specificity of antigens. The second signal is mediated by co stimulatory molecules, of which a family of proteins called B7 appears to be the most potent. This signal induces T-cell activations clonal expansion and inhibition of T-cell apoptosis [2].

There are two popular theories regarding the pathogenesis of RA. The first suggest that the T cell, through interaction with an - as yet unidentified - antigen, is the primary cell responsible for initiating the disease as well as for driving the chronic inflammatory process. This theory is based upon the known association of RA with class II major histocompatibility antigens, the large number of CD4+ T cells and skewed T cell receptor gene usage in the RA synovium. The second theory suggest that, while T cells may be important in initiating the disease, chronic inflammation is self-perpetuated by macrophages and fibroblasts in a T-cell independent manner [4,5].

From our investigation it results that there are certain changes in the Mg serum levels. It is well documented that decreased Mg leads to severe prognostic. There is, no doubt, a certain relationship between the lymphocytes and Mg. It is well documented that it can interfere with serum Ca decrease levels which and may exaggerate the rheumatoid arthritic symptoms with a concomitant elevation in the P level. This is in good agreement with the morphological modification and changes in the cell proliferation rates observed in several cellular systems where Mg is decreased [6,7].

Calcium preservation may be of value in ameliorating symptoms of bone metabolic disturbances in RA patients instead of using

medications that possibly potentate Ca depletion. Another role it could act as a switch between differentiation and apoptosis as demonstrated during cell line differentiation in vitro. This has been correlated with reduced Mg in response to stress. Apoptosis plays an important role in the regression process of RA. But the cellular mechanism is not clearly identified yet for the action of Mg in the differential control of differentiation and apoptosis [8].

Arthropathy is caused (or aggravated) by Mg deficiency in cartilage. Typical cartilage lesions (e.g., swollen matrix, cleft formation) were found in knee joints of all patients with Mg deficiency.

An understanding of Mg's role in cell physiology and metabolism is not readily forthcoming, largely because of the inherent difficulty in measuring free concentration of the ion [9].

More recently, there has been a renewed interest in the role of Mg in cell function, particularly in rheumatology. With respect to this resurgence in interest in rheumatology, the impetus can be arguably attributed to the ability to readily measure free Mg concentration in the rheumatoid synovial fluid [10,11].

Recent studies have demonstrated the presence of apoptotic synovial cells (Mg-induced) and infiltrating lymphocytes in RA (T cell apoptosis). The presence of these cells suggests that regression of RA may be due to the induction of apoptosis in rheumatoid synovium. Apoptosis serves many functions in the homeostasis of multicellular organisms. Defects in apoptosis may lead to clonal expansion and accumulation of autoreactive lymphocytes, which may result in the rare human autoimmune lymphoproliferative syndrome, a mild autoimmune reaction against cells in the blood. Defects in the clearance of apoptotic cells lead to accumulation of dying cells, which may enter later stages of cell death and release their contents, thereby critically contributing to the etiopathogenesis of the RA [8]. Further studies should be focused on the recognition of molecular mechanism of Mg ions acting in apoptosis. For an efficient therapy of RA, it is necessary to analyze apoptosis and clearance defects and to unravel factors leading to its onset [12].

The results lead to the suggestion that RA, in addition to being an autoimmune disease, is also associated with serum Mg disturbances. We suggest that alterations in Mg concentration may be an injury factor in RA. Mg administration has the potential of being protective under these conditions. Requirements for Mg increase as we grow and age. Supplementation of Mg may also improve haematopoiesis and oxidative stress, because both anemia and oxidative stress were reported to accompany RA [13]. Thus Mg preservation may be a very important treatment trend in RA, instead of using systems that might trigger symptoms through unexpected Mg disturbances. Subsequent studies will probably help us to clarify this problem and the mechanism of metabolic changes in patients with RA [14].

Mg decrease might be a sign of its degenerescence, particularly in the articular cavities probably due to the intense stress on these cells in immune processes. We might therefore speak of an important disturbance of the metabolism of nuclear RNA in the synovial fluid lymphocytes of patients with severe forms of RA. We identified a subgroup of RA patients with significant abnormalities in their Mg concentrations, which was corrected with Mg substitution therapy.

Conclusion

The study of Mg in patients with RA emphasizes changes of serum Mg which prove the participation of Mg in the pathologic processes. These results suggest that magnesium supplementation, or at least high amount of Mg in the diet, may prove to be beneficial for patients with RA.