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Original Research Article

Role of biochemical markers in rheumatoid arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis is the most common chronic, progressive systemic inflammatory arthritis of unknown cause. It affects approximately 1-2% of the population worldwide. It is a form of autoimmune disease principally synovial tissues. As the pathophysiology involves affecting cell mediated immune response, adenosine deaminase may have a role in rheumatoid arthritis. As it involves bones and joints, it is likely that it alters the levels of Serum Calcium, Phosphorus and Magnesium as well as Alkaline Phosphatase which may be helpful in diagnosis or management of the disease.
Aims & Objectives: 1. To evaluate the role of serum adenosine deaminase (ADA) as a marker of cell mediated immunity in Rheumatoid Arthritis. 2. To estimate serum alkaline phosphatase, calcium, phosphorus and magnesium as prognostic markers of Rheumatoid arthritis
Materials and Methods: A cross-sectional, case control study with convenient sampling was undertaken after Institutional Ethical Clearance & informed consent. 30 patients of Rheumatoid Arthritis presenting to the orthopaedic outpatient department of Owaisi Hospital and Research Centre, Hyderabad were taken as cases along with an equal number of age and sex matched controls from January 2021 to June 2021.
ADA levels were estimated by colorimetric assay on ErbaChem 7 semiautoanalyser. Serum Alkaline phosphatase, Calcium, Phosphorus and Magnesium were estimated on Cobas C311 autoanalyzer.
Results: There was a significant increase in levels of Adenosine Deaminase, Alkaline Phosphatase and Serum Phosphorus, while the levels of Calcium and Magnesium were significantly reduced in rheumatoid arthritis
Conclusion: ADA as a marker of cell mediated immunity reflects monocyte / macrophage activity and was increased in our study suggesting immunological and inflammatory process in the pathogenesis of Rheumatoid Arthritis (R.A). It can be used as a non invasive marker of chronic inflammation and may provide additional information about disease prognosis.
Increased levels of Alkaline Phosphatase and Phosphorus associated with low Calcium and Magnesium suggest increased bone resorption in R. A and are useful as markers of disease activity.

1. Introduction

Rheumatoid Arthritis is the most common chronic inflammatory joint disease, affecting 0.5%-1% of the populations in the industrialized world and women more frequently than men (2-3:1).[1,2] It is an autoimmune systemic disorder wherein the body defense mechanism identifies the normal tissue as antigen and evokes a chain of inflammatory reaction resulting in destruction. Though the exact cause is not known chronic infection (bacterial, fungal or viral), environmental factors (polluted atmosphere, smoking) genetic factors and endocrinal factors

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are thought to contribute. It mainly involves the joints, commonly the wrist, hand, knee, ankle and foot.

The disease process starts in the synovium as synovitis with infiltration by inflammatory cells; to begin with monocytes infiltrate the synovium. This is later followed by lymphocytes. As a result the synovium gets thickened. An effusion into the joint develops and as the disease progresses, the cytokines released in the process, e.g. TNF α, interleukin-1 and interleukin-6, histamine, etc destroy the articular cartilage, the bone, the capsule, the ligaments, the tendons and the muscles.[3] The destruction occurs by the formation of a pannus of tissue at the junction of the synovium and the articular cartilage. This pannus erodes the cartilage and the bone and destroys it. Thus arthritis develops.

There is a prominent immunological dysfunction in the joints and many other tissues by accumulation of chronic inflammatory cells including T and B lymphocytes, monocytes and macrophages.

The diagnosis of rheumatoid arthritis has been typically based on the criteria laid down by the American College of Rheumatology (ACR).[4] But the 1987 ACR criteria lacks sensitivity to detect early cases where intervention can be planned to halt the disease at an earlier stage without causing permanent disability. Hence, a plethora of markers have been studied in the quest to find an ideal diagnostic marker.[5–8] Adenosine deaminase (ADA) is an enzyme involved in the metabolism of purine bases, catalyzing the deamination of adenosine, forming inosine in the process.[9] Its main physiological activity is related to lymphocytic proliferation and differentiation. As a marker of cell mediated immunity, its activity is found to be elevated in those diseases in which there is a cell – mediated immune response.[10]

Alkaline Phosphatase (ALP) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating an organic radical and inorganic phosphate. Liver, Bone, and Placenta are primary sources of ALP. Alkaline phosphatase introduced in to clinical practice in 1929, was the first biochemical marker of bone turnover and it is still the best most widely used clinical marker to aid in managing patients with a variety of skeletal disorders. Alkaline phosphatase provides clinically useful evidence of the normal and pathologic process that reflect bone cell activity on the skeleton. Rheumatoid arthritis is characterized by persistent synovial tissue inflammation. Over time, bone erosion, destruction of cartilage, and complete loss of joint integrity can occur. Abnormalities of liver enzymes have also been reported in active rheumatoid disease. Kendall et al.[11] found that alkaline phosphatase was raised in 26% of rheumatoid patients and that it was also higher in more active disease

Calcium is the fifth most common element in the body and the most prevalent cation. The skeleton contains 99% of the body's calcium. It is present predominantly as extracellular crystals of unknown structure with a composition approaching that of hydroxyapatite.[12]

Phosphorus in the form of organic and inorganic phosphate is important and widely distributed element in the human body. Inorganic Phosphate is the fraction measured in serum and plasma by clinical laboratories. The major component of hydroxyapatite of bone is organic phosphate.[12]

For the formation of bone, calcium / phosphorus ratio is very important. RA is associated with localized or generalized osteoporosis. One of the earliest radiological signs of RA is periarticular osteoporosis. It represents an important criterion for the diagnosis of RA.[13]

Magnesium (Mg) is an essential nutrient and fourth most abundant mineral found in the body. Mg levels are altered in chronic inflammation. A decreased level of Mg has been suggested to be reasonable marker of RA.[5]

2. Aims and Objectives

1. To evaluate the role of serum adenosine deaminase (ADA) as a marker of cell mediated immunity in Rheumatoid Arthritis.
2. To estimate serum alkaline phosphatase, calcium, phosphorus and magnesium as prognostic markers of Rheumatoid arthritis

3. Materials and Methods

Patients presenting to the orthopaedic outpatient department of Owaisi Hospital and Research Centre, Hyderabad between January 2021 and June 2021 were studied. The study design was a cross-sectional, case control study with convenient sampling. Institutional Ethical Clearance & informed consent were taken. 30 patients of Rheumatoid Arthritis and an equal number of age and sex matched controls were selected

3.1. Inclusion criteria

Cases of Rheumatoid Arthritis diagnosed clinically and radiologically were included.

3.2. Exclusion criteria

Persons suffering from diabetes mellitus, tuberculosis or any other chronic disease were excluded.

3.3. Methods

ADA levels were estimated by colorimetric assay on ErbaChem7 semiautoanalyser. Serum Alkaline phosphatase, Calcium, Phosphorus and Magnesium were estimated on Cobas C311 autoanalyzer.

3.4. Statistical analysis

Data was analysed using the Student 't' test and p value was determined.

4. Results

1. The age and sex-wise distribution of the two groups was identical.
2. There was a more than two-fold increase of ADA levels among cases as compared to the control groups, which was statistically significant.
3. Levels of Alkaline Phosphatase were also significantly higher among the rheumatoid patients.
4. Serum Calcium levels showed a decreasing trend among the patients of rheumatoid arthritis with a mean value of 7.26 mg/dl which was significantly lower than in controls.
5. Hyperphosphatemia was noticed among the cases which was also statistically significant.
6. As is for calcium, the Magnesium levels were also recorded low among the patients of rheumatoid arthritis, which was also significant.

Table 1:

S.No.	Parameters	Controls Mean ± SD	Cases Mean ± SD	p Value
1.	Adenosine Deaminase U/L	20.59 ±3.01	59.52 ±9.52	<. .001
2	Alkaline Phosphatase U/L	194.53 ±30.71	289.53 ±34.81	<. .001
3	Calcium mg/dl	9.23 ±0.35	7.26 ±0.49	<. .001
4	Phosphorus mg/dl	3.15 ±0.75	5.57 ±0.58	<. .001
5	Magnesium mg/dl	2.12 ±0.23	1.73 ±0.46	<. .001

ADA, ALP, Calcium, Phosphorous & magnesium in cases & controls

5. Discussion

Rheumatoid arthritis is a crippling disease causing permanent disability in the joints affected. Early diagnosis helps in limiting this disability. The search for a gold standard marker for disease identification and progression is still ongoing. Our study showed the possible role of the above biomarkers in disease identification and/or progression. Adenosine Deaminase, Alkaline Phosphatase and Phosphorous levels are increased significantly in rheumatoid arthritis while the Calcium and Magnesium levels decreased significantly among the rheumatoid patients.

Many studies have reported that the increase in ADA is useful as an adjunct to assess inflammation, determine the disease activity and understand some of the patho-physiological aspects of the disease.

ADA which is primarily an extracellular enzyme is a modulator of inflammatory process and can be used as a predictor of inflammation. Though it is increased in other types of arthritis its cost-effectiveness makes it an ideal marker of prognosis.

The bone specific isoform of ALP has been shown to be a sensitive and specific marker of bone metabolism and it is increased in diseases with increased bone turnover. RA is characterized by an imbalance between the bone formation, resorption and chronic inflammation of the synovium leading to the destruction of articular cartilage.[14]

Serum ALP may provide a useful tool for diagnosis prognosis and management of Rheumatoid arthritis. Increase in ALP in rheumatoid arthritis is related to disease activity and is a more sensitive indicator of bone turnover.[15]

The alteration in magnesium level is likely to be due to chronic inflammation & autoimmunity. Some studies have suggested decreased levels of magnesium as a marker of prognosis of RA. Further it has been documented that a decrease in calcium and a simultaneous increase in phosphorous levels is associated with exaggeration of symptoms of RA. The underlying mechanism of above findings though not clearly defined can be taken as markers of degeneration of articular cartilage and of immune process.

Decrease in serum calcium levels maybe due to a defect in the unknown primary malabsorptive process, oxidative stress or osteoporosis leading to disturbance in the intracellular ionic environment associated with effect of drugs used in treatment in RA.

Destruction of synovial cartilage and associated hypoxia may cause degradation of ATP and increase in inorganic phosphorous as seen in patients if RA.

6. Conclusion

ADA as a marker of cell mediated immunity reflects monocyte /macrophage activity and was increased in our study suggesting immunological and inflammatory process in the pathogenesis of Rheumatoid Arthritis (R.A). It can be used as a non invasive marker of chronic inflammation and may provide additional information about disease prognosis.

Increased levels of Alkaline Phosphatase and Phosphorus associated with low Calcium and Magnesium suggest increased bone resorption in R.A and are useful as markers of disease activity.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare no conflict of interest.

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