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STUDY OF OXIDATIVE STRESS, SERUM CALCIUM, PHOSPHORUS AND RATIO IN RHEUMATOID ARTHRITIS PATIENTS

Orthopaedics

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disorder, occurs when there are attacks of the immune system on body's tissues especially the joint, causing a painful, swelling, that finally results in bone deformity, increased free radical level in defect joint and reduce the level of the antioxidant system can cause tissue damage. Serum levels of lipid peroxides, calcium, phosphorus and ratio of calcium/phosphorus in RA patients were determined and compared with normal healthy controls. Significant increases in lipid peroxides ($p<0.001$) phosphorus ($p<0.001$) levels were found in patients presenting with RA as compared to controls. Whereas significant decrease in calcium ($P<0.001$) and calcium/phosphorus ratio ($p<0.001$) were found in Rheumatoid arthritis patients as compared to controls. Negative correlation was observed between MDA and Calcium/Phosphorus ratio in patients with rheumatoid arthritis. Our findings suggest that there is a close association between bone loss and oxidative threat in patients presenting with Rheumatoid arthritis. The decrease in serum calcium / phosphorus ratio indicated that, calcium and phosphorus metabolism is altered in RA. Ca and P level can be studied for the preferabletherapeutic management of RA.

KEYWORDS

Calcium,Phosphorus, Rheumatoid Arthritis (RA),Oxidative stress.

INTRODUCTION:

Rheumatoid arthritis is an autoimmune disease that influences the Synovial joint which is characterized by erosive synovitis, that leads to damaging the cartilage and bones as well as systemic complications, including cardiovascular, pulmonary, psychological, and various skeletal problems (1). Autoimmune phenomena and damage of connective tissue within the synovial joint can be resulted from oxidative stress formed within inflamed joint. Radical species that possess oxidative activity, which include reactive nitrogen species (RNS) and reactive oxygen species (ROS), mediate and cause cartilage damage (2).

The calcium role is not clear in RA, however, the relationship between calcium, vitamin D, and parathyroid hormone suggests the possible role of calcium in RA and there is a change in mineral within bone which are calcium, and phosphorus (3). Changes in lipid profile have been observed in different inflammatory disease such as RA (4). RA patients are in increased risks of atherosclerosis and cardiovascular diseases (CVD) than the overall population (5).

This study was aimed to study MDA level as a marker of oxidative stress in patients with RA as well as the changes in Ca, and P level in recently diagnosed RA patients compared to healthy subjects.

MATERIALAND METHODS:

The sample was taken from a group of 60 patients with RA (20 male and 40 female), age (45-70 years). The control was diagnosed if they having any diseases such as diabetes, infectious diseases. RA was diagnosis based on clinical histories such as ESR and rheumatoid factor.

STATISTICALANALYSIS:

Statistical analysis was done by using student t-test to compare between the two groups which performed by GraphPad Prism 6 (GraphPad Software) with the level of significance set at $p<0.05$. The data of this study were given as mean ± standard deviation. Results Sixty patients (20 male and 40 female) were diagnosed with rheumatoid arthritis at SLIMS hospital with 60 healthy people who represent controls.

RESULTS:

In this study patient with RA belonged to the age group of 45-70 years. Among patients of RA 15 patients were males and 25 were females as shown in Table 1.

Table 1 shows comparison of MDA, Calcium and Phosphorus levels in RA with control subjects. Statistically significant increase in levels of lipid peroxide ($P<0.001$) and phosphorus ($P<0.001$) whereas statistically significant decrease in Calcium ($P<0.001$) was found in patients of RA as compared to control subjects. whereas phosphorus level was increased significantly ($P<0.001$) in RA patients as compared to control subjects. On the contrary, calcium/phosphorus ratio was decreased significantly ($P<0.001$) in RA patients as compared to control subjects. On the contrary, lipid peroxide was negatively correlated with calcium/phosphorus ratio ($r=-0.74$).

DISCUSSION:

Bone contains both organic and inorganic material. The organic matter is mainly protein; the inorganic or mineral component is mainly crystalline hydroxyapatite {Ca (PO4)6(OH)2}. Approximately of body's 99% Calcium and 85% Phosphorus are present in bone. The exact reason behind bone erosion and joint deformities is not fully understood. There is continuing interest in the metabolic changes occurring in RA. With these basics this study was undertaken to estimate the serum Calcium /Phosphorus ratio in Ra patients.

Low calcium may be due to prolonged inadequate calcium intake and accelerated osteoporosis. RA patients are vulnerable to steroid induced and disease associated osteoporosis. The high salt intake in our population may exacerbate calcium deficiency. At the proximal tubule, were sodium and calcium absorbs option are linked. Although not specifically studied, many disabled people rely heavily on pre-packed food and meals, much of which is high in sodium.(6) RA is associated with collection of chronic inflammatory cells occurring adjacent to bone with subsequent bone destruction. It is possible that generated oxygen derived free radicals may be important in bone resorption (7). The statistical analysis by unpaired t test shows that the levels of serum calcium were decreased and phosphorus levels were increased statistically, which were highly significant ($p<0.0001$). In RA patients as compared to healthy controls. These results are in accordance with several other studies.(8-12).

Lower calcium level may be due to insufficient calcium intake and quicken osteoporosis, more sodium intake in our food may cause calcium depletion (13). Free radical that produced by ROS that case chronic inflammatory cells nearby bone with subsequent bone destruction (14). Many drugs shave an affected-on calcium metabolism and cause a low level of calcium in RA. It was assuming that high level of phosphorous was related to tissue hypoxia with an elevated in ATP breakdown resulting in the release of inorganic phosphorous from cells. However, hypoxia create by hypertrophy and hyperplasia within synovial joints (15). In patients serum levels of calcium and calcium/phosphorus decreased and further studies on dietary management of calcium and phosphorus are needed.

In the formation of bones, calcium/phosphorus ratio is very important. It is possible that, generation of reactive oxygen species may be particularly important factor for bone,resumption in inflammatory process (16). Hypoxic conditions also disrupt an intracellular ionic environment and alter calcium and phosphorus level (17).

These results are also in accordance with A significantly decreased calcium/phosphorus ratio in RA patients as compared to controls in our study clearly indicates that, there is an altered calcium and phosphorous metabolism in RA. As calcium and phosphorous are important constituent of bone, ultimately bone metabolism is altered in RA, the event observed by many workers (18-19). Negative correlation between calcium/phosphorus ratio and lipid peroxide (r = - 0.74) suggests that the generation of reactive oxygen species in excess may be particularly important in the bone resorption that occurs in association with inflammatory diseases (20).the earlier studies (21). MDA, the product of lipid peroxidation reacts with lysine residues in protein to produce immunogenic molecules, which can exacerbate inflammation. The longer chain polyunsaturated fatty acids are especially potent at increasing lipid peroxidation and causing cell damage by oxidative stress (22). Depolymerization of hyaluronic acid in synovial fluid results into loss of lubricating property of the fluid. It has been reported that, it is very important consequence of exposure of synovial fluid to super oxide (O·2) and hydrogen peroxide (H_2O_2) (23). It is postulated that the elevation of phosphorous was related to tissue hypoxia with an increase in ATP degradation resulting in the release of inorganic phosphorous from cells. Hypertrophy and hyperplasia creates a hypoxic environment in synovial joints. It is corroborated by the reports of low glucose and high lactate levels in rheumatoid synovial fluid (24). Acidosis is another factor that may acts to promote shifts of phosphate from the intracellular to extracellular pool. The rise in serum inorganic phosphate may parallel increase in blood lactate levels suggesting that a state of partial anaerobic metabolism may be contributory factor (25). In RA, hypoxic environment triggers oxygen free radicals generation and alters oxidative metabolism within the cell. It leads to disruption in intracellular ionic environment and altered calcium and phosphorus levels. Some authors suggest that hypocalcemia results due to drugs used in RA, but decreased mean total body calcium levels in RA patients who did not received that corticosteroid drugs strongly suggest that, this is an integral feature of RA (26). Increased oxidative threat in rheumatoid arthritis is evidenced by raised lipid peroxides.

CONCLUSION:

It was observed that Calcium in RA a low level in serum whereas Phosphorous has shown a high level in contrast to control, that can be concluded to be a danger factor for RA cases. These results recommend to increase Ca, P in the dies with a supplement that might be helpful for a patient with RA. Further studying is necessary to estimate various biochemical markers that influences patient with RA.

TABLE 1: Serum levels of total lipid peroxide (MDA), calcium, phosphorus and calcium/phosphorus in control subjects and rheumatoid arthritis patients. (M± SD)

Sr. No	Parameters	No. of Subjects	Control Subjects (60 nos)	Rheumatoid Arthritis patients
1	Serum total lipid peroxide (MDA) µmol/L	60	1.92 ± 0.63	4.62 ± 1.46*
2	Serum Calcium (mg/dl)	60	10.32 ± 1.44	7.86 ± 1.36*
3	Serum inorganic phosphorus (mg/dl)	60	2.89 ± 0.40	4.72 ± 0.90*
4	Calcium/phosphorus ratio	60	3.55 ± 0.45	1.81 ± 0.62*

Values are expressed as mean ± SD; *P < 0.001

TABLE 2 : Pairwise correlation analysis in RA patients

Sr.No	Pairwise correlation of serum parameters	'r' value
1	Negative correlation between lipid peroxide and calcium/phosphorus ratio	- 0.74

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