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BONE MINERAL LEVELS IN RHEUMATOID ARTHRITIS

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ABSTRACT:

The present case series study of 100 patients of rheumatoid arthritis was conducted over a period of two years at the Department of Orthopedics Liaquat University of Medical & Health Sciences with a view to evaluate the calcium, phosphorus, alkaline phosphatase levels in the patients suffering from rheumatoid arthritis (RA). There were 28 male and 72 females male female ratio was (M: F 4:10.2), age ranging from 17 to 65 years. Rheumatoid factor was positive in 67 and negative in 33 patients. Serum calcium level range was 4.50 to 10.00 mg/dl. Serum phosphorus level range was 2.00 to 7.50 mg/dl. Serum alkaline phosphatase level range was 44.00 to 487.00 u/l.
We conclude that our data suggest that overall bone turnover is increased in RA. Serum calcium is decreased its normal levels and serum phosphorus increased mildly and serum alkaline phosphatase increased moderately.

KEY WORDS: Bone Minerals. R.A

INTRODUCTION

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints. The cause is uncertain. Even though infectious agents such as viruses, bacteria, and fungi have long been suspected, none has been proven as the cause. The etiology of the rheumatoid arthritis, therefore, remains a very active area of research the world over. Some scientists believe that the tendency to develop rheumatoid arthritis may be genetically inherited. It is suspected that certain infections or factors in the environment might trigger the immune system to attack the body's own tissues, resulting in inflammation in various organs of the body such as the lungs or eyes.

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis. Currently, diagnosis of RA may take several weeks, and factors used to predict a poor prognosis are not always reliable. Gene expression in RA may consist of a unique signature. Gene expression analysis has been applied to synovial tissue to define molecularly distinct forms of RA; however, expression analysis of tissue taken from a synovial joint is invasive and clinically impractical[1].

The disease often affects the wrist and small joints of the hand. It also affects other parts of the body besides the joints. In addition, people with rheumatoid arthritis may have fatigue, occasional fevers, and a general sense of not feeling well[2].

Various factors influencing bone turnover and bone loss in rheumatoid arthritis (RA) are illustrated using the example of a postmenopausal woman with a highly active RA. In particular, the relationships between disease activity, vitamin D metabolism, parathyroid hormone (PTH) levels and calcium metabolism are described. High disease activity is associated with low levels of 25-hydroxycholecalciferol, and especially of 1.25-dihydroxycholecalciferol[3].

It has been hypothesized that the stimuli that initiate and perpetuate the severe alterations in bone turnover are based on the inflammatory diseases themselves resulting in multi system damage, a process which specifically induces resorptive factors[4].

Localized bone loss in the form of bone erosions and peri-articular osteopenia constitutes important criteria for the diagnosis of rheumatoid arthritis[5].

In addition, glucocorticoid treatment, which suppresses disease activity, is also known to be as an inducer of osteoporosis[6], affects calcium and bone metabolism and leads to substantial and rapid bone loss. However, some years ago it was clearly demonstrated that generalized osteoporosis can occur in rheumatic patients without glucocorticoid medication[7].

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Besides its effects on bone metabolism, calcium and phosphorus homeostasis, 1,25-dihydroxyvitamin D3 (1,25(OH)(2)D(3), calcitriol) exerts profound effects on the immune system. An overview over the metabolism, molecular and cellular action of 1,25(OH)(2)D(3) with particular regard to its immunomodulatory function. Its success might eventually lead to promising drugs for future therapeutic exploitation of a wide array of immune diseases, such as psoriasis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and others[8].

Biochemical indices of mixed saliva and peripheral blood were studied in 38 healthy subjects and 99 patients with rheumatoid arthritis (RA). Optimal composition of the saliva was abnormal. It lost its buffer function. In RA, permeability of the hematosalivary barrier for cholesterol, calcium, phosphorus, magnesium declines with growing activity of the process with resultant lowering of their content in the saliva, their blood levels being unchanged. Decreased permeability of the hematosalivary barrier results from growing sympathetic influence on the salivary glands reflecting the presence of the autonomic dysfunction in RA. It is pathogenetically related to the process activity[9].

The occurrence of marked decalcification in patients with rhematoid arthritis, and of marginal lipping or osteophyte formation in individuals with degenerative joint disease, suggested that an alteration of calcium and phosphorus metabolism might be a primary feature of these diseases[10].

TABLE 1

SEX

Male	Female	M:F	Total
28	72	4:10.2	100

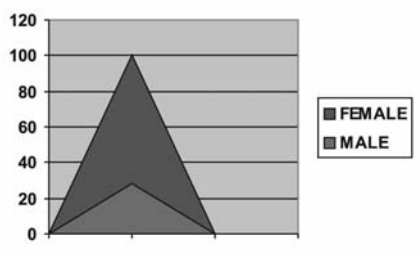


TABLE 2
AGE

Age in years	
Range	48
Minimum	17
Maximum	65
Mean	40
Median	40
Mode	45

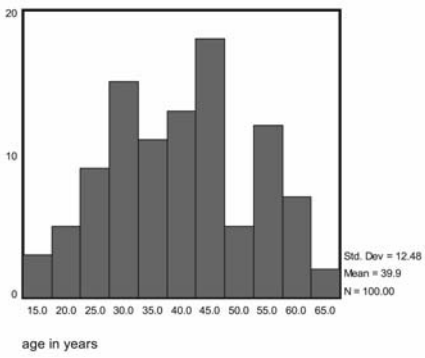
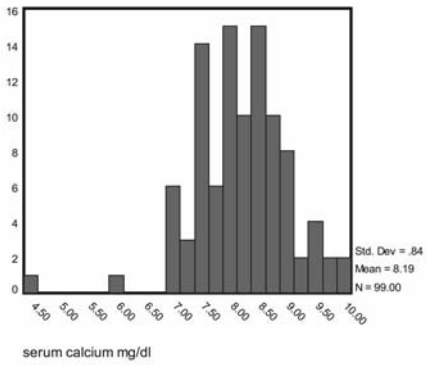
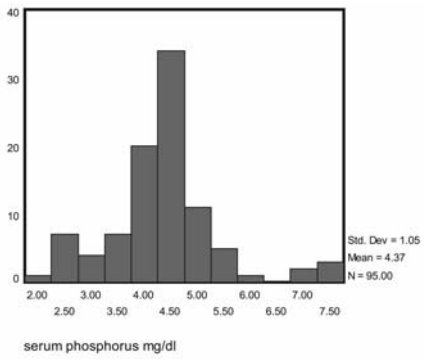


TABLE 3
BONE MINERAL LEVELS

	Serum calcium mg/dl	Serum phosphorus mg/dl	Serum alkaline phosphatase u/l
Range	5.50	5.50	443.00
Minimum	4.50	2.00	44.00
Maximum	10.00	7.50	487.00
Mean	8.19	4.36	156.46
Median	8.20	4.40	133.00
Mode	8.00	4.20	140.00
Standard deviation (SD)	0.83	1.04	79.50
Standard error mean	8.39	0.10	8.16





AIMS & OBJECTIVES

To confirm our hypothesis that in patients with rheumatoid arthritis the bone mineral levels like calcium, phosphorus & alkaline phosphatase in the blood are below normal. If this observation is correct then is it the cause or the effect of the disease?

MATERIALS AND METHODS

This study was conducted at department of Orthopaedic Surgery & Traumatolgy Liaquat University of Medical & Health sciences Jamshoro, from January 2007to December 2008. The duration of the study was two years. The design of the study was interventional**.** Sample size was based on total 100 diagnosed cases of Rheumatoid arthritis. All Patients were collected from out patient department of Orthopaedics of Liaquat University Hospital, Jamshoro & Hyderabad. All patients were diagnosed clinically according to their history & 1987 revised criteria for classification of RA. After diagnosis on clinical background condition regarding disease was explained and registered those all patients who were willing for blood sample to assess the bone mineral levels. At least 3 ml venous blood sample were taken and sent to laboratory in disposable syringe for serum calcium, phophorus, alkaline phosphatase and Rheumatoid factor to confirm the diagnosis. Diagnostic & research laboratory of Liaquat University of Medical & Health sciences was selected. Ultraviolet method serum calcium, Kinetic method serum phosphorus and Rheumatoid factor and IFFC used for alkaline phosphatase levels. Normal ranges according to above mentioned methods were 8.4 -10.8 mg/dl of serum calcium, serum phosphorus was 2.6 – 4.5 mg/dl and alkaline phosphatase was in male 40 129 u/l and in

females 35 – 104 u/l.

The data was collected through detailed proforma completed for each case. It Was entered in statistical program of social sciences (SPSS) into computer with help of biostatistician. Mean median, mode, and range, minimum, maximum, standard deviation and standard error mean were analyzed. Initially all age group data was analyzed then we also analyzed below 35 years and above 35 years age groups.

OBSERVATIONS / RESULTS

One hundred patients were diagnosed clinically as well as positive rheumatoid factor. There were 28 male and 72 females male female ratio was (M:F 4:10.2), females were more affected then males. Most of the patients were from rural areas and poor socioeconomic population. Age ranged from 17 to 65 years, mean age was 39 years, median 40 and mode of age was 45 years. Rheumatoid factor was positive in 67 (67%) and negative in 33 (33%) out of 100 patients. Serum calcium level range was 5.50 mg/dl, minimum was 4.50 mg/dl and maximum was 10.00 mg/dl. Mean was 8.19 mg/dl, median 8.20 mg/dl and mode was 8.00 mg/dl. Standard deviation was 0.83 and standard error mean was 8.39. Serum phosphorus level range was 5.50 mg/dl, minimum was 2.00 mg/dl and maximum was 7.50 mg/dl. Mean phosphorus was 4.36 mg/dl, median 4.40 mg/dl and mode was 4.20 mg/dl. Standard deviation was 1.04 and standard error mean was 0.10. Serum alkaline phosphatase level range was 443.00 u/l, minimum was 44.00 u/l and maximum was 487.00 u/l. Mean was 156.46 u/l, median 133.00 u/l and mode was 140.00 u/l. Standard deviation was 79.50 and standard error mean was 8.16.

Out of 100 patients 40 were age ranged from 17 to 35 years considered as young age group. Mean age was 27 years. There were 11 males 29 females male female ratio was (M: F 2.1:5.4). Rheumatoid factor was positive in 26 (65%) and negative in 14 (35%).

Serum calcium level range was 5.50 mg/dl, minimum was 4.50 mg/dl and maximum was 10.00 mg/dl. Mean was 8.23 mg/dl, median 8.20 mg/dl and mode was 7.80 mg/dl. Standard deviation was 0.98 and standard error mean was 0.89. Serum phosphorus level range was 5.15 mg/dl, minimum was 2.35 mg/dl and maximum was 7.50 mg/dl. Mean phosphorus was 4.59 mg/dl, median 4.50 mg/dl and mode was 4.60 mg/dl. Standard deviation was 1.26 and standard error mean was 0.20. Serum alkaline phosphatase level range was 443.00 u/l, minimum was 44.00 u/l and maximum was 487.00 u/l. Mean was 174.51 u/l, median 145.00 u/l and mode was 145.00 u/l. Standard deviation was 106.57 and standard error mean was 17.52.

Out of 100 patients 60 were age ranged from 36 – 65 years, mean age was 48 years. Bone turn over is usually after 35 years. There were 17 males 43 females male female ratio was (M: F 2.1:5.3). Rheumatoid factor was positive in 41 (68.33%) and negative in 19 (31.66%). Serum calcium level range was 3.90 mg/dl minimum, was 6.00 mg/dl and maximum was 9.90 mg/dl. Mean was 8.16 mg/dl, median 8.20 mg/dl and mode was 7.50 mg/dl. Standard deviation was 0.73 and standard error mean was 9.43. Serum phosphorus level range was 5.20 mg/dl, minimum was 2.00 mg/dl and maximum was 7.20 mg/dl. Mean phosphorus was 4.22 mg/dl, median 4.40 mg/dl and mode was 4.70 mg/dl. Standard deviation was 0.87 and standard error mean was 0.11. Serum alkaline phosphatase level range was 285.00 u/l, minimum was 55.00 u/l and maximum

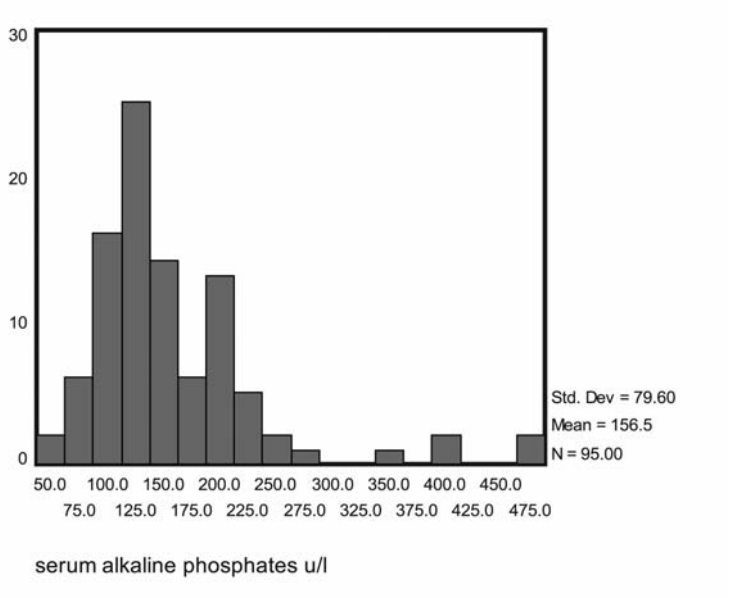


TABLE 4

Age 17 – 35 years (n=40)	Serum calcium mg/dl	Serum phosphorus mg/dl	Serum alkaline phosphatase u/l
Range	5.50	5.15	443.00
Minimum	4.50	2.35	44.00
Maximum	10.00	7.50	487.00
Mean	8.23	4.59	174.51
Median	8.20	4.50	145.00
Mode	7.80	4.60	145.00
Standard deviation (SD)	0.98	1.26	106.57
Standard error mean	0.89	0.20	17.52

TABLE 5

Age 36 – 65 years (n=60)	Serum calcium mg/dl	Serum phosphorus mg/dl	Serum alkaline phosphatase u/l
Range	3.90	5.20	285.00
Minimum	6.00	2.00	55.00
Maximum	9.90	7.20	340.00
Mean	8.16	4.22	144.94
Median	8.20	4.40	129.50
Mode	7.50	4.70	80.00
Standard deviation (SD)	0.73	0.87	54.10
Standard error mean	9.43	0.11	7.10

was 340.00 u/l. Mean was 144.94 u/l, median 129.50 u/l and mode was 80.00 u/l. Standard deviation was 54.10 and standard error mean was 7.10.

DISCUSSION

It is estimated that RA affects about 3% of Americans in the age range of 18-79 years and about 1% of the world's population. RA may begin at any age from infancy to the aged. The mean age of onset is about 45 years, and the female preponderance is about three to one.

In present study, mean age was 39 years, median 40 and mode of age was 45 years. 40 patients' age was below 35 years considered as young age group and mean age was 27 years. Above 35 years were 60 patients and mean age was 48 years.

In 1987 Revised Criteria for Classification of Rheumatoid Arthritis,

1. Morning stiffness, Morning stiffness in and around the joints lasting at least 1 hour.
2. Arthritis of three or more joints. At least three joint areas simultaneously showing soft-tissue swelling or fluid (not bony overgrowth alone) observed by physician. Possible joints include right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand, at least one joint area swollen in a wrist, MCP, or PIP.
4. Symmetric arthritis, simultaneous involvement of the same joint areas on both sides of the body.
5. Rheumatoid nodules, subcutaneous nodules, over bony prominences, or extensor surfaces.
6. Serum rheumatoid factor, demonstration of abnormal amounts of rheumatoid factor by any method that yields <5% positives in normal control subjects.
7. Radiologic changes, radiologic changes typical of RA on posteroanterior views of hand and wrist, which must include erosions or unequivocal bony rarefaction of the involved joints (osteoarthritic changes alone do not qualify).

For classification as RA, at least four of the seven criteria should be satisfied.

The calcium, phosphorus and alkaline phosphatase levels of rheumatoid arthritis has not been adequately studied. Of more significance than the blood levels, in determining the calcium, phosphorus and alkaline phosphatase exchange in the bones, are the direction of flow and rate of metabolism of these substances.

However, detailed analysis, as outlined above, indicates a slight tendency toward an increased rate of calcium metabolism and increased calcium excretion in patients with rheumatoid arthritis[11].

RA itself is associated with osteoporosis that may be localized or generalized[12]. In RA, periarticular osteoporosis has long been recognized one of the earliest radiological signs[13], and it is thought that the release of inflammatory mediators, particularly cytokines, from the different inflammatory cells is the most likely cause[14].

Serum calcium levels were investigated in a cross-sectional study of 394 patients with rheumatoid arthritis, 4490 healthy subjects, and 2609 inpatients at a district general hospital. Patients with rheumatoid arthritis had lower mean calcium levels than the healthy subject (p less than 0.001). Mean serum calcium levels are lower in disease than health; this occurs in RA as well as other diseases[15].

In present study 100 patients were evaluated at tertiary care hospital. Patients with rheumatoid arthritis also had lower mean serum calcium levels (p value is .000). This study also proved that serum phosphorus levels were also increased in rheumatoid arthritis.

In addition, factors that may cause generalized osteoporosis in inflammatory arthritis include circulating pro inflammatory molecules; hormones; altered calcium metabolism; changes in load-bearing of the skeleton; and the effects of antirheumatic and anti-inflammatory drugs[16]

Serum alkaline phosphatase activity, a less specific marker for bone formation, was also increased in RA[17].

In present study serum alkaline phosphatase was also increased the mean difference was 156.46 u/l (P value was .000).

CONCLUSION:

Our data suggest that overall bone turnover is increased in RA. Serum calcium is decreased its normal levels and serum phosphorus increased mildly and serum alkaline phosphatase increased moderately. This study will provide the awareness about variation in bone minerals and their effective therapy to rheumatoid arthritic patients because it's easy and cheap method and also prevent deformities and relieve symptoms of the long time diseased patients.

REFFERENCES

1. Edwards CJ, Feldman JL, Beech J, Shields KM, Stover JA, Trepicchio WL, Larsen G, Foxwell BM, Brennan FM, Feldmann M, Pittman DD. Molecular profile of peripheral blood mononuclear cells from patients with rheumatoid arthritis. Mol Med., 2007 Jan-Feb;13(1-2):40-58.
2. www.arthritis – pain –treatments.com
3. Oelzner P, Buttgereit F, Demary W, Franck H, Kern P, Hein G. The mechanism of bone loss in rheumatoid arthritis. Description based on a case report Z, Rheumatol. 2007, Jul;66(4):337-40.
4. Feldmann M, Brennan FM, Field M, Maini RN. Pathogenesis of rheumatoid arthritis: cellular and cytokine interactions. In: Smolen J, Kalden JR, Maini RN, eds. Recent advances in rheumatoid arthritis. Berlin: Springer Verlag, 1990;850–974.
5. Ramprasath VR, Shanthi P, Sachdanandam P. Curative effect of Semecarpus anacardium Linn. nut milk extract against adjuvant arthritis — with special reference to bone metabolism. Chem Biol Interact, 2006; 160(3):183-92.
6. Reid IR. Glucocorticoid-induced osteoporosis and other forms of secondary osteoporosis. In: Meunier PJ, ed. Osteoporosis: diagnosis and management. London, Martin Dunitz, 1998; PP. 233–50.
7. Allali F, Breban M, Porcher R, Maillefert JF, Dougados M, Roux C. Increase in bone mineral density of patients with spondylarthropathy treated with anti-tumour necrosis factor . Ann Rheum Dis 2003;62:347–9.
8. May E, Asadullah K, Zügel U. Immunoregulation through 1,25-dihydroxyvitamin D3 and its analogs. Curr Drug Targets Inflamm Allergy. 2004, Dec;3(4):377-93.
9. Ulanova EA, Grigor'ev IV, Novikova IA. Hematosalivary mechanisms of regulation in rheumatoid arthritis. Ter Arkh. 2001;73(11):92-4
10. Nachlas, I. W., Studies on the blood calcium and phosphorus in arthritis. J, Bone and Joint Surg., 1927; 9; 37.
11. Marian W. Ropes, Elsie C. Rossmeisl, Calcium and Phosphorus metabolism in rheumatoid arthritis and degenarative joint disease. Medical Clinic of the Massachusetts General Hospital, the Department of Medicine, Harwrd Medical School, and the Massachusetts Department of Public Health, Boston. November 10, 1942.
12. Lange U, Boss B, Teichmann J, Stracke H, Neeck G. Bone mineral density and biochemical markers of bone metabolism in late onset rheumatoid arthritis and polymyalgia rheumatica—a prospective study. Z Rheumatol 2000;59(Suppl. 2):137–41.
13. Star VL, Hochberg MC. Osteoporosis in patients with rheumatic diseases. Rheum Dis Clin N Am 1994;20:561–76.
14. Feldmann M, Brennan FM, Field M, Maini RN. Pathogenesis of rheumatoid arthritis: cellular and cytokine interactions. In: Smolen J, Kalden JR, Maini RN, eds. Recent advances in rheumatoid arthritis. Berlin: Springer Verlag, 1990;850–974.
15. Scott DL, Farr M, Hawkins CF, Wilkinson R, Bold AM, Serum calcium levels in rheumatoid arthritis. Ann Rheum Dis. 1981 40(6):580-3.
16. Oelzner P, Müller A, Deschner F et al. Relationship between disease activity and serum levels of vitamin D metabolites and PTH in rheumatoid arthritis. Calcif Tissue Int 1998;62:193–8.
17. G. Gevers, P. Devos, M. De Roo, Increased levels of osteocalcin (serum bone GLA-Protein) in rheumatoid arthritis. British Society for Rheumatol; 1986.