Calcium Metabolism and Parathyroid Function in Rheumatoid Arthritis

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In 40 patients with rheumatoid arthritis with various degrees of bone changes and 8 normal controls, serum calcium, inorganic phosphorus, chloride, alkaline phosphatase and parathyroid hormone were measured to assess the calcium metabolism and parathyroid function. Serum total calcium and serum calcium corrected by serum albumin were both significantly lower in patients with rheumatoid arthritis with advanced bone involvement than in controls, whereas serum inorganic phosphorus tended to be lower in patients with milder bone involvement. Serum Cl tended to be high in rheumatoid arthritis and serum Cl/P ratio was significantly higher than in the controls. Serum alkaline phosphatase was elevated in 5 of 14 cases of rheumatoid arthritis with advanced bone involvement. Serum parathyroid hormone was above the normal range in 12 of 21 cases of rheumatoid arthritis with no apparent bone changes, 2 of 3 cases with mild bone changes, and 9 of 14 cases with advanced bone changes. These findings would suggest parathyroid hyperfunction in rheumatoid arthritis without apparent correlation with the degree of bone involvement.

Key Words: Rheumatoid arthritis, Parathyroid hormone, Radioimmunoassay, Alkaline phosphatase, Calcium, Phosphorus

Rheumatoid arthritis, also known as atrophic arthritis, is characterized by severe atrophic changes or local osteoporosis around the joints. Since the mechanism of development of such pronounced osteoporosis in this disease has not been fully explained, especially in view of the rarity of similar bone changes in other forms of arthritis with a comparative degree of immobilization, an investigation on calcium metabolism and parathyroid function was undertaken in patients with rheumatoid arthritis with bone changes of various degrees.

MATERIALS AND METHODS

Twenty-one patients with definite or classical rheumatoid arthritis according to the ARA criteria without roentgenologically recognizable bone changes, 5 with mild bone changes corresponding to Stage I and 14 with advanced bone changes corresponding to stage IV were studied along with 8 normal control subjects. Serum total calcium was measured by EGTA titration using Calcium Analyzer (Corning), serum inorganic phosphorus by Fiske-SubbaRow method, serum alkaline phosphatase by King-Armstrong method, and serum parathyroid hormone (PTH) by a radio-immunoassay using GP-100 guinea pig antibody against bovine PTH and 125I-labeled highly purified bovine PTH (bPTH 1-84) purchased from Wilson (1) (2). Serum cal-

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Fig. 1. Serum Ca in patients with rheumatoid arthritis with various degrees of bone changes. Serum Ca in mg/dl is shown on the ordinate as open columns and corrected serum Ca (See the text) as shaded columns. C indicates 7 normal control subjects, R4 8 cases of rheumatoid arthritis with advanced bone changes, and R2 8 cases of rheumatoid arthritis with mild bone changes. Mean and SEM.

Calcium was corrected by serum albumin according to the method of Payne (3) by the use of the following formula:

Corrected Serum Ca (mg/dl) =
Serum Ca (mg/dl) - Serum Albumin (g/dl) + 4

None of these patients have been treated with corticosteroid during the last 3 years and have never received high doses exceeding 20 mg prednisolone.

RESULTS

As shown in Fig. 1, serum Ca and corrected Ca were both significantly lower in patients with rheumatoid arthritis with advanced bone changes than in the healthy control subjects (P<0.01), but not in those with milder bone changes. As shown in

Fig. 2. Serum P in rheumatoid arthritis. Serum P in mg/dl is shown on the ordinate and degree of bone involvement on the abscissa as R0 (no bone change), R1 (mild bone change) and R4 (advanced bone change). Mean and standard error. Shaded area shows normal range.

Fig. 3. Serum alkaline phosphatase in rheumatoid arthritis. Serum alkaline phosphatase in King-Armstrong units units is shown on the ordinate, and the degree of bone change on the abscissa, as in Fig 2. Mean and standard error. Shaded area shows normal range.
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Fig. 4. Serum Cl/P in rheumatoid arthritis. Serum Chloride in mEq/L divided by serum P in mg/dl is shown on the ordinate. Serum Cl/P is significantly higher (P < 0.01) in patients with rheumatoid arthritis (R) than in the controls. Mean and standard error.

Fig. 2, serum inorganic phosphorus was significantly higher in patients with advanced bone changes than in those with milder ones, but neither group was significantly different from the controls. Serum alkaline phosphatase was significantly higher in patients with rheumatoid arthritis with advanced bone changes than in those with no bone changes, as shown in Fig. 3. The serum Cl/P ratio was significantly higher in patients with rheumatoid arthritis than in the controls, as seen in Fig. 4.

Serum PTH was elevated in 12 of 20 cases of rheumatoid arthritis with no apparent bone changes, 2 of 3 patients with mild bone changes and 9 of 14 patients with advanced bone changes, shown in Fig. 5.

DISCUSSION

Serum calcium was decreased in patients with rheumatoid arthritis with advanced bone changes regardless of the correction with serum albumin, serum alkaline phosphatase also tended to be high in the group of patients with advanced bone changes, and serum Cl/P was significantly higher in patients with rheumatoid arthritis than in the controls. Serum PTH was elevated in 23 of 37 or more than one-half of patients with rheumatoid arthritis. All these findings point out to a state of parathyroid hyperfunction in patients with rheumatoid arthritis.

Cockel et al (4) reported on hypocalcemia, high serum alkaline phosphatase and
hypoalbuminemia in patients with rheumatoid arthritis and Kennedy et al (5) also accumulated evidence of parathyroid overactivity in rheumatoid arthritis, such as high serum alkaline phosphatase and elevated serum Cl/P ratio along with an increased calcium absorption from the gut. Such apparent parathyroid overactivity in patients with rheumatoid arthritis with associated hypercalcemia indicates secondary hyperparathyroidism. Hypocalcemia might be caused by serum protein abnormalities, low dietary calcium intake or Vitamin D deficiency through increased turnover on account of the overactivity of hepatic microsomal enzyme induced by antirheumatic drugs. Corticosteroid therapy might represent another possible cause of parathyroid hyperfunction. In the present series, however, corticosteroids were not currently used so that the mechanism of parathyroid stimulation should be sought somewhere else.

Though the degree of parathyroid overactivity was not always parallel with the degree of bone involvement thus making it rather difficult to draw a definite conclusion of a direct relationship between these two, the increased parathyroid hormone activity might well represent one of the background factors for the occurrence of bone atrophy probably caused by the increased bone resorption secondary to the immobilization of the joint, in view of the reported preventive effect of thyroparathyroidectomy on the development of immobilization osteoporosis (6).

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