Clinical Investigations

\( \beta_2 \)-Microglobulin in Postmenopausal Osteoporosis

H. Rico,¹ E. Ripoll,¹ M. Revilla,¹ P. Relea,² and L. F. Villa

¹Department of Medicine and ²Central Laboratory, Hospital Universitario “Príncipe de Asturias,” Universidad de Alcalá de Henares, 28801 Madrid, Spain

Received January 22, 1993, and in revised form March 8, 1993

Summary: The so-called bone-derived growth factor, or \( \beta_2 \)-microglobulin, has a regulatory function in bone metabolism, stimulating osteoclastic activity. Osteoclastic activity is enhanced in postmenopausal osteoporosis, suggesting that \( \beta_2 \)-microglobulin concentration may also be increased in this disease. \( \beta_2 \)-Microglobulin concentration was found to be raised \((P < 0.001)\) in 30 women with postmenopausal osteoporosis as compared with 30 normal women of similar age; tartrate-resistant acid phosphatase concentration also was raised \((P < 0.001)\), and total body bone mineral content was decreased \((P < 0.001)\). Linear regression analysis revealed a highly negative correlation result between total body bone mineral content and \( \beta_2 \)-microglobulin \((r = 0.577, P < 0.001)\), and a positive correlation result between \( \beta_2 \)-microglobulin and tartrate-resistant acid phosphatase concentration \((r^2 = 0.806, P < 0.001)\). These findings, and the stimulatory effect of \( \beta_2 \)-microglobulin on osteoclastic and osteoblastic activity, suggest that \( \beta_2 \)-microglobulin may play an important role as a local regulatory factor in the pathogenesis of postmenopausal osteoporosis.

Key words: \( \beta_2 \)-microglobulin – Tartrate-resistant acid phosphatase – Bone-derived growth factor – Total body bone mineral content – Postmenopausal osteoporosis

Materials and Methods

The study group consisted of 30 women diagnosed as having postmenopausal osteoporosis based on radiological evidence of more than one vertebral collapse without evidence of previous trauma, after exclusion of the possibility of secondary osteoporosis by biochemical, hematologic, and hormonal studies. None of the women was receiving pharmacological treatment and none was found to have any alteration that might affect calcium metabolism, such as liver disease, diabetes, or renal-function disorders. The patients’ mean ± SD age was 68 ± 5 years. None of them smoked; all drank alcohol only occasionally, and their coffee intake was no more than two cups a day.

The criteria for attributing vertebral collapse to osteoporosis was the loss of more than 25% of the height of the anterior, middle, or posterior part of the body of the affected vertebra. The diagnosis was corroborated by studying the bone mass using dual-energy X-ray total-body bone densitometry with a Norland XR 26 instrument (Norland, Fort Atkinson, WI, USA). Our coefficient of variation (CV) for total-body bone mineral measurements was 1.2% in vivo and 0.6% in vitro. The instrument was calibrated daily by using a reference provided by Norland. The control group consisted of 30 women considered clinically normal, of an age similar to that of the osteoporotic group (69 ± 4 years), in whom radiographic studies of the spinal column using the same criteria as for the women with osteoporosis did not reveal vertebral abnormalities. Analytic studies demonstrated that none of them had alterations that might affect calcium metabolism. Total-body bone mineral content determined by dual-energy X-ray absorptiometry was normal in all of them. As in the group of women with osteoporosis, none of the controls smoked; they consumed alcohol only occasionally; and their coffee intake did not exceed two cups a day. All of the women, controls and osteoporotics, were from the clinic of the Rheumatology Unit of the Hospital Universitario “Príncipe de Asturias,” Universidad de Alcalá de Henares (Madrid, Spain), to which they had been referred for study of possible osteoporosis. The social status of the women in both groups was comparable and none of them worked outside the home or practiced sports. The characteristics of the groups are shown in Table 1.

The biochemical studies made included the usual blood parameters for metabolic bone studies: calcium, phosphorus, total alkaline phosphatase, tartrate-resistant acid phosphatase, creatinine, and total proteins, all measured in serum using a Hitachi automated analyzer (Boehringer, Mannheim, Germany). In the same sample, \( \beta_2 \)-microglobulin concentration was measured using microparticle enzyme immunoassay with a \( \beta_2 \)-microglobulin commercial reagent

Offprint requests to: H. Rico
from Abbott Laboratories (Abbot Park, IL, USA), and an IMX autoanalyzer from the same company. All samples from every woman were analyzed in the same assay to eliminate interassay variation. Assay reproducibility was determined by assaying four samples five times in five different runs at two laboratories. The CVs between runs and between laboratories were determined by components of variance [11], which give a statistical estimate of the variation of replicates of one for multiple assay runs. In every case, CV was less than 6%. Tartrate-resistant acid phosphatase was quantitated in serum in the Hitachi autoanalyzer as the substrate naphthyl phosphate, using a reagent from Boehringer Laboratories (Boehringer, Mannheim, Germany) that reacts specifically with isoenzyme 5b synthesized by the osteoclast [12, 13]; 24-hour urinary calcium excretion was determined by atomic absorption using a Perkin Elmer model 5000 spectrophotometer (Perkin Elmer, Norfolk, CT, USA). The values of the study parameters (mean ± SD) for each group were compared using the Student t test.

Results

Table 1 summarizes the means ± SD of the main parameters studied: significance values are according to the Student t test. In the group of women with osteoporosis there was a significant increase in β2-microglobulin and tartrate-resistant acid phosphatase concentrations (P < 0.001), and a decrease in total body bone mineral content (P < 0.001).

Linear regression study showed a significant correlation (r² = 0.577, P < 0.001) between total body bone mineral content and β2-microglobulin concentration (Fig. 1) and between β2-microglobulin and tartrate-resistant acid phosphatase concentrations (r² = 0.806, P < 0.001) (Fig. 2) in the osteoporotic patients, but not in normal controls (r² = 0.12, P NS for total body bone mineral content and r² = 0.16, P NS for tartrate-resistant acid phosphatase). Tartrate-resistant acid phosphatase concentration also correlated negatively with total body bone mineral content (r² = 0.637, P < 0.001) in the osteoporotic group.

Discussion

Our results indicate that in postmenopausal osteoporosis β2-microglobulin and tartrate-resistant acid phosphatase concentrations are raised, and that these elevations correlate significantly and negatively with total-body bone mineral content. These findings confirm earlier studies showing that tartrate-resistant acid phosphatase concentration correlates significantly and negatively with total-body bone mineral content [14] and with radial and lumbar bone mineral density [15]. Other authors [16] report a correlation between urinary β2-microglobulin concentration and the degree of osteopenia in other disorders. In view of the fact that the tartrate-resistant acid phosphatase determined is synthesized by the osteoclast [12, 13], the strong positive correlation we found between tartrate-resistant acid phosphatase and β2-microglobulin concentrations suggests that both parameters are biological markers of bone resorption and/or remodeling. This concurs with reports by Moe and others [6] that β2-microglobulin stimulates osteoclastic activity. The elevation of β2-microglobulin concentration in Paget’s disease [7] may be due to a similar mechanism. The possible role of β2-microglobulin in the pathogenesis of increased resorption is reinforced by the observed lack of correlation between this parameter and total-body bone mineral content or tartrate-resistant acid phosphatase in our normal controls.

We cannot compare the β2-microglobulin values that we found in postmenopausal osteoporosis with those of other studies because we know of none. However, studies of recent, specific biological markers of bone resorption in postmenopausal osteoporosis report an increase in bone resorption [17, 18], and histomorphometric studies have shown that enhanced bone resorption is accompanied by increased