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Serum levels of bone turnover markers following total joint arthroplasty

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ABSTRACT

Purpose. To evaluate changes in serum levels of bone turnover markers during the first year following a total hip or knee arthroplasty (THA or TKA, respectively).

Methods. 34 women and 13 men (mean age, 68 years) with idiopathic hip or knee osteoarthritis underwent elective THA or TKA. The serum levels of (1) osteoprotegerin, (2) nuclear factor-kappa B ligand (RANKL), (3) osteocalcin, and (4) bone-specific alkaline phosphatase (b-ALP) were determined in each patient on preoperative day 1 and postoperative day 3 and 7, and month 2, 4, 6, 8, 10, and 12.

Results. All 4 markers changed significantly over the 12-month period. At month 12, values of all markers did not return to their preoperative levels uniformly. At month 8, the serum levels of osteoprotegerin, osteocalcin, and b-ALP remained higher than their respective preoperative values. The serum levels of RANKL gradually decreased after month 2, rendering this marker a potential index for fixation.

Conclusions. Bone turnover markers change following arthroplasties. Postoperative month 8 seems to be a milestone in the normal course of these markers.

Key words: *alkaline phosphatase; arthroplasty, replacement; osteoarthritis; osteoblasts; osteocalcin; osteoclasts; osteoprotegerin; RANK ligand; receptor activator of nuclear factor-kappa B*

INTRODUCTION

Despite improvement in prosthetic design, aseptic loosening secondary to loss of the periprosthetic bone or osteolysis remains a major cause of premature failure of total joint arthroplasty (TJA).[1–5] Early detection of periprosthetic osteolysis is difficult.[6] Bone turnover markers have been used to detect osteolysis at an early postoperative stage,[4] and thus provide information regarding osseointegration, bone remodelling, and early aseptic loosening after TJA.[7–10] We evaluated changes in the serum levels of bone turnover markers during the first year

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following a total hip or knee arthroplasty (THA or TKA, respectively).

MATERIALS AND METHODS

This prospective cohort study was approved by our institution's scientific research board. Informed consent was obtained from each patient. Between January 2008 and January 2009, 34 women and 13 men (mean age, 68±4 years) with idiopathic hip or knee osteoarthritis underwent elective THA (16 women and 7 men) or TKA (18 women and 6 men). Patients with any endocrine disorder, secondary arthritis or any disease that could interfere with bone homeostasis were excluded, as were patients receiving medication affecting bone metabolism. No patient had had any fracture or orthopaedic operation in the previous 3 years.

All patients were operated on under spinal anaesthesia by the same group of 3 surgeons. Cobalt-chrome, metal-on-polyethylene prostheses were used for both THA and TKA. For THA, fixation was cementless. For TKA, fixation was cementless in the femur and used polymethylmethacrylate cement in the tibia. A second-generation cephalosporin and an amino glycoside was administered one hour preoperatively and continued for 3 days. Touch-toe weight-bearing walking with the aid of a walker was allowed on day 2. Partial weight-bearing was allowed at week 6 and gradually increased to full weight-bearing at week 12.

Serum levels of (1) osteoprotegerin, (2) nuclear factor-kappa B ligand (RANKL), (3) osteocalcin, and (4) bone-specific alkaline phosphatase (b-ALP) were evaluated in each patient on preoperative day 1 and postoperative day 3 and 7, and month 2, 4, 6, 8, 10, and 12. All samples were evaluated in duplicate in the same assay. Osteoprotegerin was assayed using a commercial ELISA sandwich (intra-assay and inter-assay coefficients of variation [CV] were 5% and 6%, respectively). Soluble, non-complexed human RANKL was detected using an enzyme immunoassay (detection limit, 0.1 pmol/l; intra-assay CV, 4.5–7%; inter-assay CV, 6–8%). Osteocalcin was assessed by radioimmunoassay (range, 0–60 ng/ml [0.172 nmol/l]; sensitivity, 0.30 ng/ml). b-ALP was measured quantitatively using enzyme immunoassay (inter- and intra-assay CV was <10%).

A generalised linear model for repeated measurements was fitted to the data to investigate the effects of time. Time effects were analysed by the F test, and p values of <0.05 were considered significant. A post hoc comparison was made with Bonferroni adjustments.

RESULTS

All 4 markers changed significantly over the 12-month period (p<0.001, Table, Fig.), even after post hoc comparisons with Bonferroni adjustments. The mean serum osteoprotegerin level increased sharply during the immediate postoperative period and then decreased gradually until month 2. The level increased again and reached a second peak at month 8, followed by a gradual decrease. The mean serum RANKL level increased gradually until month 2 and then declined gradually until month 12, with the level becoming lower than the preoperative value. The mean serum osteocalcin level decreased sharply until day 3 and then increased sharply to peak at month 2 and then decreased gradually until month 12. The mean b-ALP level decreased during the immediate postoperative period, then increased gradually to peak at month 8, and then decreased gradually until month 12, with the level becoming greater than the preoperative value.

Changes in the 4 biochemical markers between THA and TKA patients were not significant (Fig.). Nonetheless, the mean serum osteoprotegerin level increased until day 7 in THA patients but until day 3 in TKA patients. The mean RANKL level was higher in TKA than THA patients; the initial increase of RANKL level in TKA patients was not found in THA patients. The mean osteocalcin level peaked at month 2 in TKA patients and month 4 in THA patients.

DISCUSSION

The diagnosis of aseptic loosening in TJA patients is based on clinical symptoms and radiographic evaluation.[7] Despite the importance of early diagnosis, there is no non-invasive method that can efficiently

Table
Generalised linear model for 4 bone turnover markers to evaluate changes over time

Bone turnover marker	F	p Value
Osteoprotegerin	5.899	<0.001
Receptor activitator for nuclear factor-kappa B ligand	5.318	<0.001
Osteocalcin	27.695	<0.001
Bone-specific alkaline phosphatase	56.120	<0.001

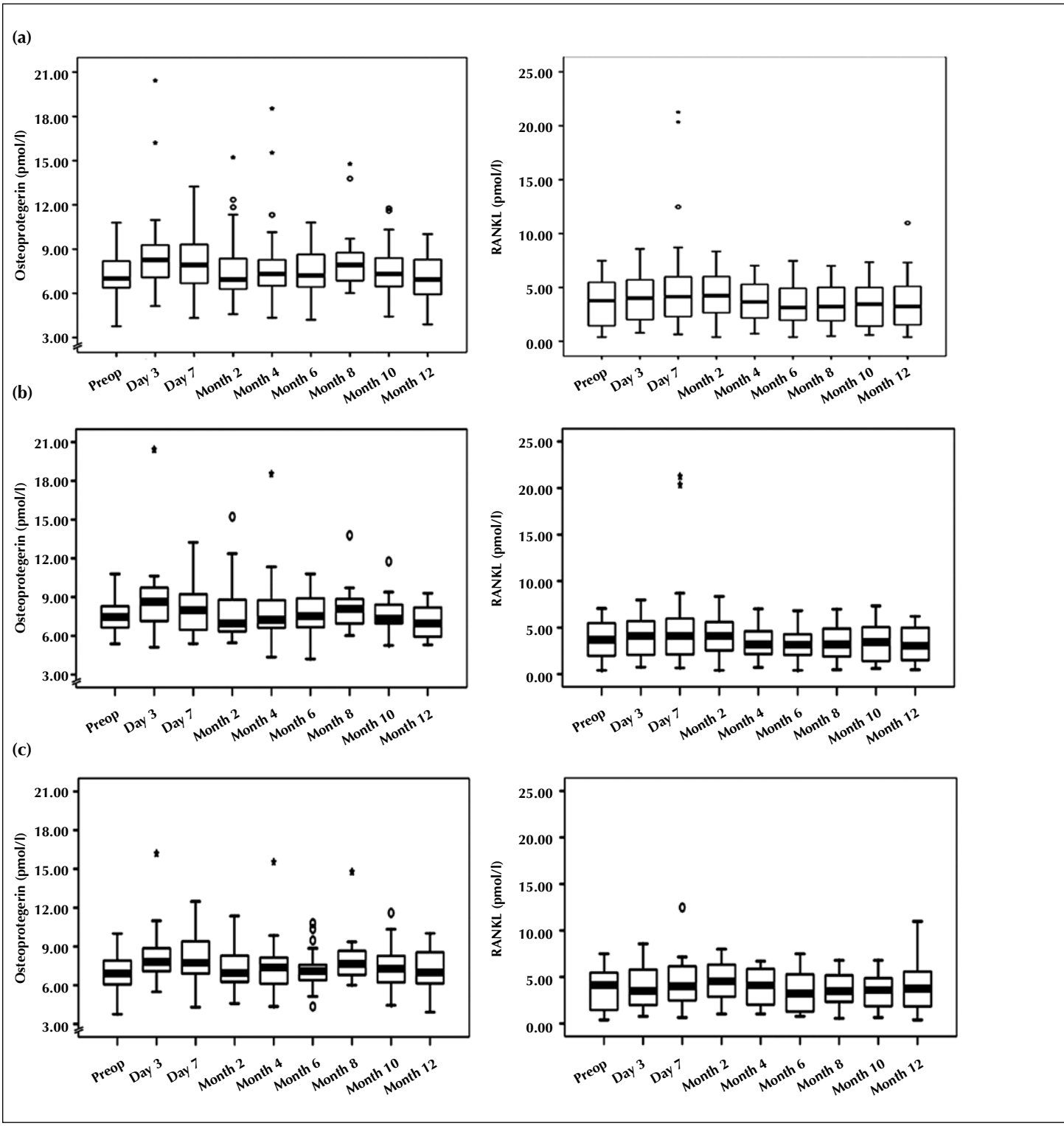
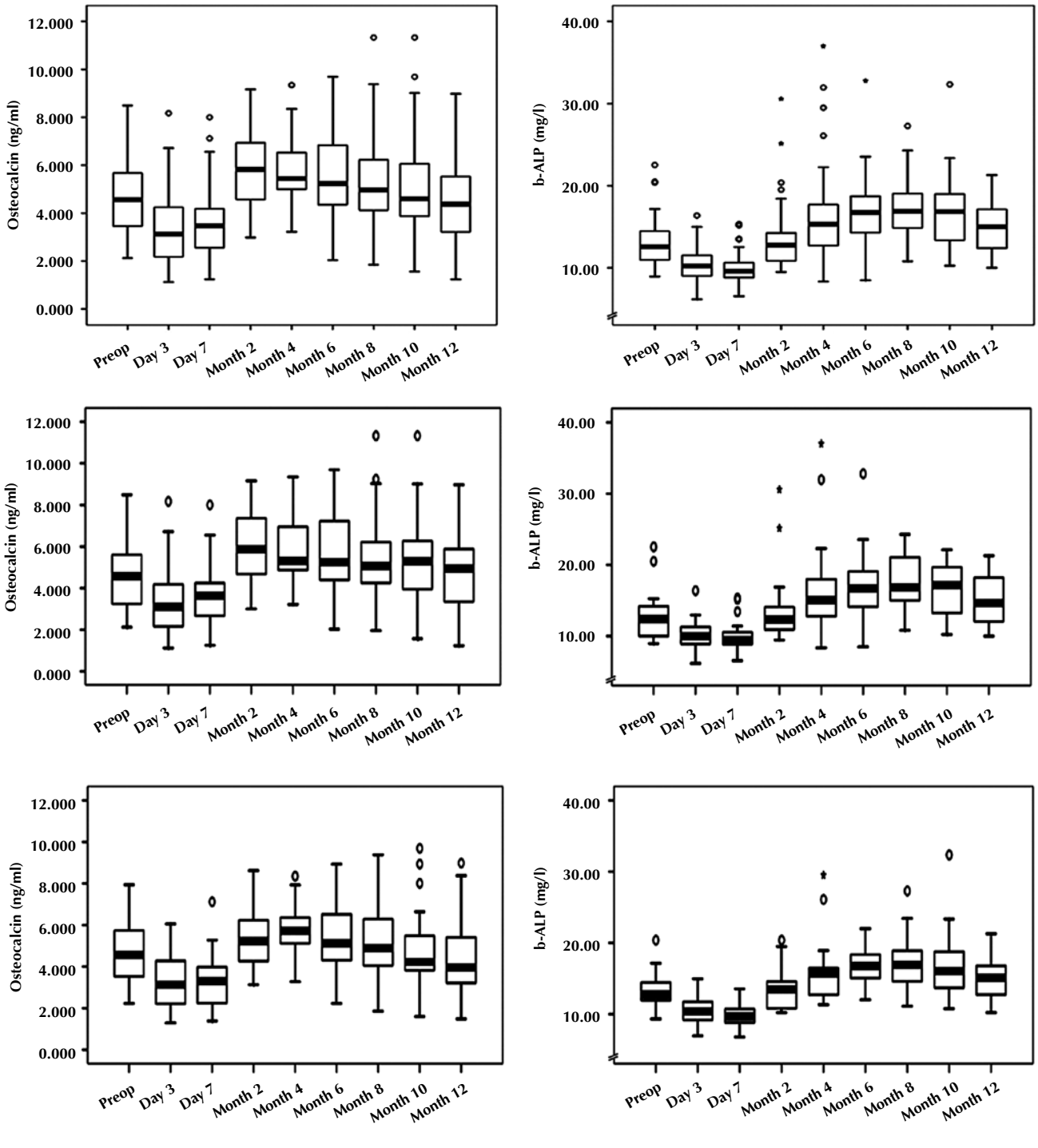


Figure Serum levels of (1) osteoprotegerin, (2) receptor activator for nuclear factor-kappa B ligand (RANKL), (3) osteocalcin, and (4) bone-specific alkaline phosphatase (b-ALP) during the first year after **(a)** total joint arthroplasty, **(b)** total knee arthroplasty, and **(c)** total hip arthroplasty (○ and * denote outlier value extending more than 1.5 and 3 box-lengths from the edge of the box, respectively). The frequency distributions of the markers are presented as box plots. The length of the central box is the variable's interquartile range and contains 50% of the cases. The line across the inside of the box represents the median value. The whiskers protruding from the box go out to the smallest and largest values of the variable.


Osteocalcin (ng/ml)
12.000
10.000
8.000
6.000
4.000
2.000
0.000
b-ALP (mg/l)
40.00
30.00
20.00
10.00
Preop
Day 3
Day 7
Month 2
Month 4
Month 6
Month 8
Month 10
Month 12

detect the early development of aseptic loosening.[1] Bone turnover markers are well recognised in several diseases affecting bone metabolism.[11–14] Nonetheless, their values (if any) remain unknown in TJA patients.[1] Whether the markers can be used to assess implant fixation is not known.

The balance between serum levels of osteoprotegerin and RANKL plays a crucial role in the development of aseptic loosening in THAs.[15] Patients with aseptic loosening of a THA have higher serum osteoprotegerin levels than healthy volunteers or patients with a stable prosthesis.[1] Serum RANKL levels correlate negatively with radiographically detected osteolysis around the femoral stem.[1] Increase in serum osteoprotegerin levels may reflect a compensation mechanism for osteolytic activity occurring in patients with aseptic loosening. In a study evaluating the course of bone formation and resorption during the immediate postoperative period, the markers of bone formation (b-ALP, carboxyterminal propeptide of type I procollagen) were slightly elevated at month 3, whereas urine levels of bone resorption markers returned to normal after 6 months.[8]

In our study, serum levels of osteoprotegerin, osteocalcin, and b-ALP remained elevated at month 8, compared with their respective preoperative values. It is difficult to explain the increase of serum osteoprotegerin levels during the immediate postoperative period. It may be associated with the age-related increase of the serum osteoprotegerin level in elderly patients. This may be a compensatory action against the natural decrease of bone mineral density occurring normally with ageing.[11,12,16] Alternatively, it may be associated with dead bone cells adjacent to the implant due to necrosis or apoptosis.[17] The latter is a strong stimulus for bone resorption that may trigger the compensatory production of bone, leading to increased levels of osteoprotegerin. The temporary immobilisation of patients after TJA might have the same effect, as one week of immobilisation secondary to a hip fracture[18] or a hemiplegic stroke[19] has been reported to increase bone resorption. However, why osteoprotegerin (as opposed to other bone formation markers) responds differently to bone resorption is not clear.

In our study, serum levels of osteoprotegerin showed a double-peak pattern. It is possible that bone remodelling continued for 8 months after TJA, reflecting the attempt of the host bone to reinforce the bone-implant interface.

In our study, the type of operation, implant, or fixation method did not have significant effect on the postoperative levels of the bone formation markers. These findings are consistent with a study reporting no significant differences in levels of bone turnover markers in patients with cemented or non-cemented THA.[8]

The initial increase of the serum levels of RANKL has been reported.[7,8] This may be attributed to the removal of the debris or the heat caused by the cement that leads to bone necrosis in cases of cemented fixation.[8]

The use of bone resorption markers is more appropriate when detecting the early bone loss procedure.[8] The gradual decrease of the serum levels of RANKL after postoperative month 2 renders this marker a potential index for fixation.

The levels of all bone markers did not return to their preoperative values at month 12 uniformly. It therefore seems that 12 months is not enough for assessing the postoperative course of bone turnover markers following a TJA. Follow-up for a longer period is needed to ensure a return to preoperative values. Any fluctuation of these marker levels could be used for early detection of aseptic loosening.

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