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COMBINATION IN USE OF DIFFERENT SERUM BONE MARKERS COULD IMPROVE THE SENSITIVITY OF EACH ASSAY IN DETERMINING BOTH LOW-TURNOVER AND HIGH-TURNOVER BONE[1].

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Back ground:

Neither serum “intact PTH” assay nor “[1-84] assay (Bio- or Whole)” has sufficient sensitivity in determining adynamic bone[1, 2]. On the other hand, serum osteocalcin level, bone formation marker, has sufficient sensitivity in determining adynamic bone but not well enough for hyperparathyroid bone. The combination in use of such different bone metabolic markers could improve the over all sensitivity, while in maintaining each specificity.

Methods: Iliac bone biopsy specimens obtained from 62 haemodialysed patients were analyzed. Serum intact PTH level was measured by “Allegro intact PTH kit (Japan Mediphysics Co., Tokyo, Japan) and serum osteocalcin level was by “Intact osteocalcin assay kit” (Teijin Co. Tokyo, Japan), which detected only an intact molecule of osteocalcin [3].

Results. Bone formation rates (BFR/BS) correlated positively with serum intact osteocalcin concentrations , osteocalcin concentrations assayed by a conventional method , parathyroid hormone (PTH) concentrations , and total alkaline phosphatase concentrations ($r=0.602$, 0.588 , 0.650 , and 0.401 respectively). Based on ROC curve and Youden index analysis, the optimal cut-off value to distinguish adynamic bone disease from a mild lesion was 195 pg/ml of serum PTH concentration (Youden index= 0.233) or 30 ng/ml of serum intact osteocalcin concentration (Youden index= 0.628). The optimal cut-off value to distinguish between hyperparathyroid bone and a mild lesion was 455 pg/ml of serum PTH level (Youden index= 0.63) or 50 ng/ml of serum intact osteocalcin concentration (Youden index= 0.634) (fig. 1, 2)

Since both ROC curve and Youden index suggested that the serum PTH concentration was not a good marker to distinguish adynamic bone from a mild lesion or hyperparathyroid bone, we designed a two-step procedure (fig. 3). The first step was the diagnosis of adynamic bone (cut-off: 65 pg/ml) or hyperparathyroid bone (cut-off: 455 pg/ml) according to serum PTH concentration. In a second step, we assessed serum intact osteocalcin concentration in patients with serum PTH concentrations between 65 and 455 pg/ml. The cut-off values for adynamic and hyperparathyroid bone in this diagnostic approach were 30 and 70 ng/ml respectively. As a result, 49 out of 62 patients were diagnosed properly. The Youden index of this two-step diagnosis was 0.527 and 0.661 for adynamic bone and hyperparathyroid bone respectively. Sensitivity markedly improved to 94.4% and 96.2% for adynamic bone and hyperparathyroid bone respectively, without sacrificing specificity (84.0 and 88.8% respectively).

Conclusion

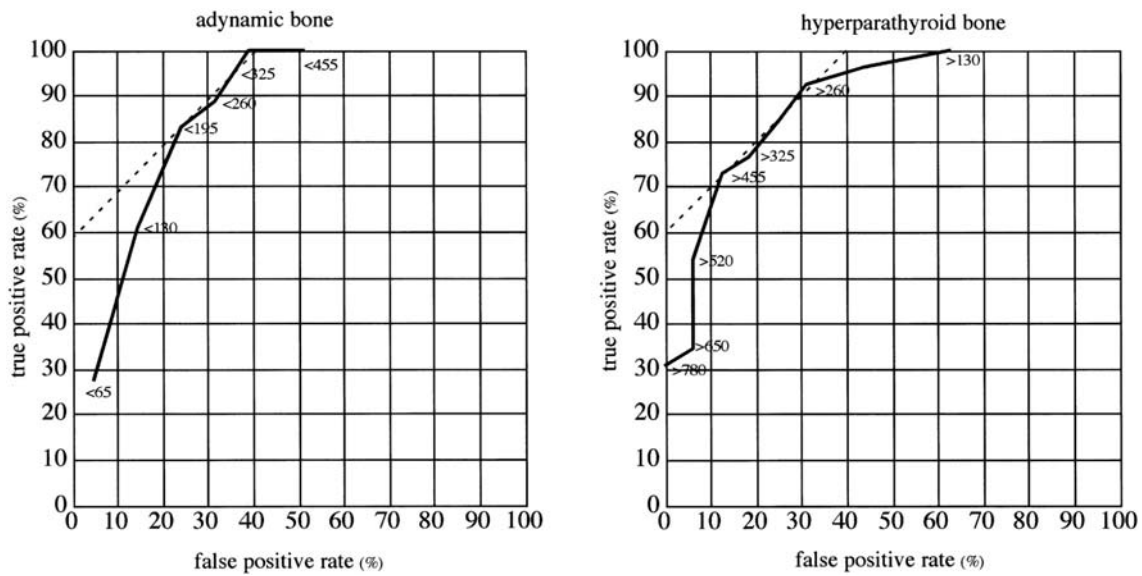


Figure 1. ROC curves for serum PTH concentration in (left) adynamic bone and (right) hyperparathyroid bone. True positive rate represents sensitivity (%) and false positive rate represents [100-specificity] (%) [1].

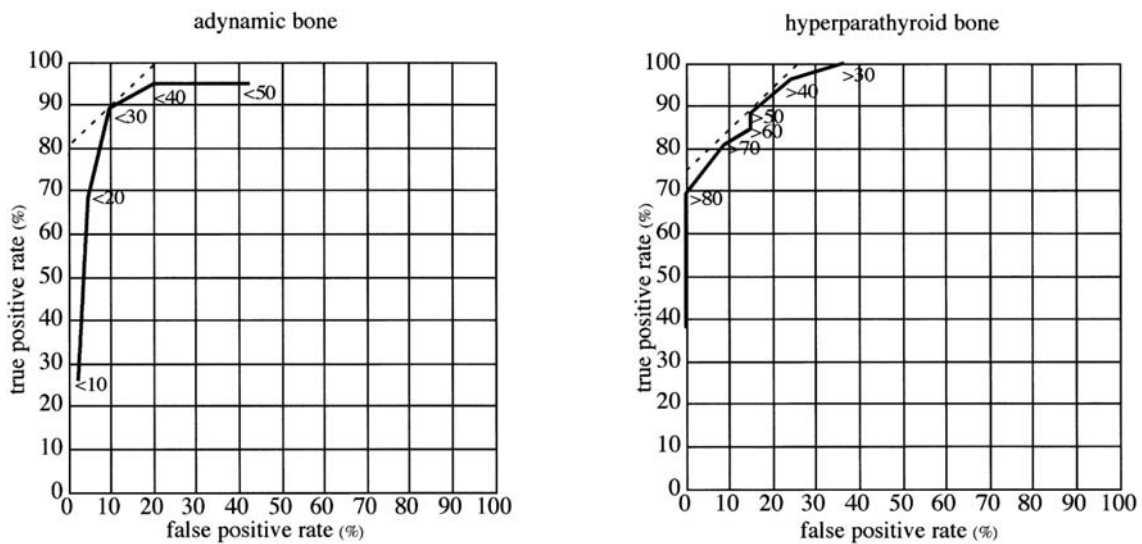


Figure 2. ROC curves for serum intact osteocalcin concentration in (left) adynamic bone and (right) hyperparathyroid bone. True positive rate represents sensitivity (%) and false positive rate represents [100-specificity] (%) [1].

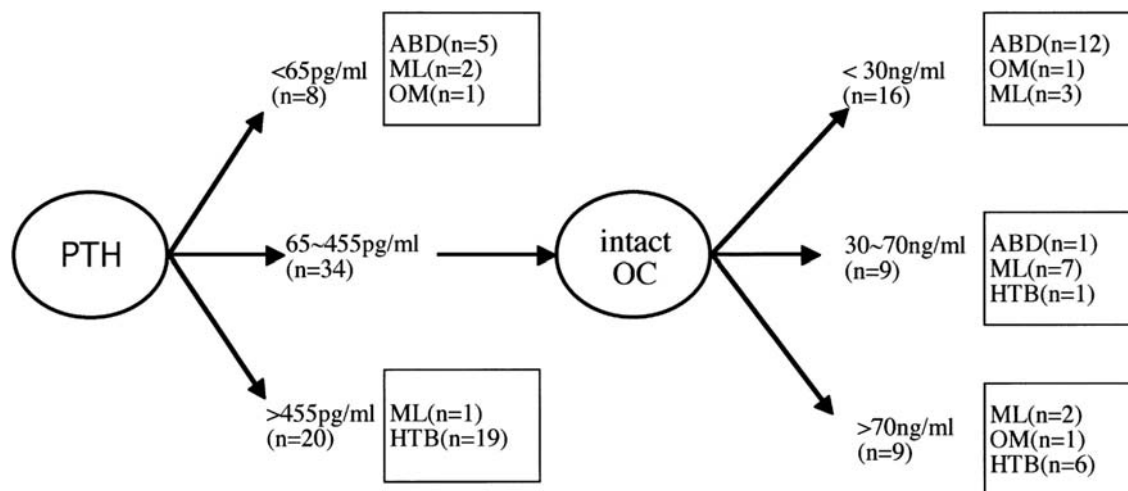


Figure 3. Two-step diagnosis of bone pathology by serum intact PTH and intact osteocalcin measurements[1].

References

1. Morishita T, Nomura M, Hanaoka M, Saruta T, Matsuo T, Tsukamoto Y: A new assay method that detects only intact osteocalcin. Two-step non-invasive diagnosis to predict adynamic bone disease in haemodialysed patients. *Nephrol Dial Transplant* 15:659-667, 2000
2. Lehmann G, Stein G, Huller M, Schemer R, Ramakrishnan K, Goodman WG: Specific measurement of PTH (1-84) in various forms of renal osteodystrophy (ROD) as assessed by bone histomorphometry. *Kidney Int* 68:1206-1214, 2005
3. Hosoda K, Eguchi H, Nakamoto T, Kubota T, Honda H, Jindai S, Hasegawa R, Kiyoki M, Yamaji T, Shiraki M: A sandwich immunoassay for intact human osteocalcin. *Clin Chem* 38:2233-2238, 1992