Renal osteodystrophy and secondary hyperparathyroidism

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Abstract
Secondary hyperparathyroidism with marked parathyroid hyperplasia is the major type of renal osteodystrophy. In addition to classic stimuli for parathyroid hormone (PTH) such as decreased concentrations of ionized calcium and 1,25-dihydroxyvitamin D₃ (1,25(OH)₂ D₃, calcitriol), several mechanisms have been suggested. Those include decreased density of calcitriol and calcium-sensing receptors, as well as the direct action of phosphate. Skeletal resistance to PTH was initially recognized as a blunted calcaemic action of PTH, which has been considered another stimulus for PTH secretion. Once suppression of PTH became possible by newly developed therapeutic modalities, it has been shown that this background abnormality plays an important role in the development of adynamic bone disease in uraemic patients. However, the mechanism of skeletal resistance to PTH has not been fully elucidated yet, but recent papers suggested that osteoprotegerin (OPG) accumulating in uraemic serum might inhibit osteoclastogenesis induced by PTH.

Keywords: chronic renal failure; osteoprotegerin; PTH; RANKL; renal osteodystrophy; vitamin D

Introduction
Various types of bone abnormality are seen in patients with uraemia (Table 1). High turnover bone disease caused by excess PTH is a central feature of renal osteodystrophy seen in chronic dialysis patients [1,2]. This abnormality almost inevitably develops in uraemic patients without appropriate therapeutic modalities.

Major stimuli for PTH secretion in uraemia
Decreased concentrations of ionized calcium and 1,25-dihydroxyvitamin D₃ (1,25(OH)₂ D₃, calcitriol) due to phosphate retention are the most important stimuli for parathyroid hormone (PTH) secretion, which can be corrected in most patients with appropriate therapy. However, it is still difficult to suppress PTH secretion in substantial numbers of patients. Accordingly, several mechanisms for PTH hypersecretion have been suggested (Table 2).

Some of these patients respond to a supraphysiological concentration of calcitriol achieved by calcitriol pulse therapy [3]. These observations suggest that the resistance of parathyroid cells to calcitriol may serve as another stimulus for PTH secretion in chronic renal failure. Reduction of calcitriol receptor density in parathyroid glands is currently considered the main mechanism responsible for the resistance in chronic renal failure [4]. In addition, inhibition of target gene access by uraemic toxins has also been implicated [5]. These abnormalities lead to a progressive disturbance of up-regulation of calcitriol receptor by calcitriol. Decreased density of calcium-sensing receptors in parathyroid glands also has demonstrated [6], a mechanism that still remains to be elucidated.

The role of phosphate in the pathogenesis of secondary hyperparathyroidism (2HPT) through the modulation of serum calcium and calcitriol production has long been recognized as an indirect mechanism. In addition, organ cultures of parathyroid tissue support the direct effect of phosphate to stimulate PTH secretion and synthesis [7]. The underlying mechanisms of this direct action of a phosphate, especially the identification of phosphate sensor, need to be clarified in the future.
Molecular basis of the skeletal resistance to PTH

Calcaemic action of PTH is blunted in uraemic patients, which is referred as increased skeletal resistance to PTH [8]. As this ‘increased skeletal resistance to PTH’ was first recognized in early the

1970s, it has been regarded as one of the major mechanisms for the pathogenesis of 2HPT in chronic renal failure.

Bone histomorphometric studies have revealed that the parameters associated with osteoclastic bone resorption were generally suppressed as compared
with those estimated from values from serum PTH levels in healthy controls [9].

Recently, mechanisms of osteoclastogenesis and osteoclast activation have been elucidated at molecular levels [10]. Three different classes of humoral factors promote osteoclastogenesis, including active vitamin D and its analogues, hormones, and cytokines. Although these humoral factors bind to osteoblasts in an independent manner, they eventually induce the expression of a membrane-bound glycoprotein on the cell surface. This membrane-bound glycoprotein is called receptor activator of NF-κB ligand (RANKL). When RANKL binds to its ligand (RANK) expressed on the surface of osteoclast precursor cells, they start differentiation into mature osteoclasts. RANKL also activates mature osteoclasts. These actions of RANKL on osteoclastic lineage result in increased bone resorption. Disturbance of any of these steps can be responsible for the skeletal resistance to PTH in uraemia.

First, the effects of humoral factors, which promote RANKL expression other than PTH, might be disturbed. As calcitriol is one such factor, this mechanism should at least in part be involved [11]. However, as well known, administration of active vitamin D sterols cannot fully normalize skeletal resistance to PTH in uraemia indicating that the shortage of calcitriol does not play a major role.

Second, PTH activity to induce RANKL might be insufficient. As recently demonstrated, conventional intact PTH assays may detect PTH fragments other than PTH(1–84). Furthermore, a large c-fragment of PTH, which is recognized by ‘intact PTH assay’, but not by ‘whole PTH assay’, competitively inhibits the action of PTH(1–84) [12–14]. Thus, in uraemia, it may be possible that the PTH concentration is overestimated, and that its fragments further suppress the action of PTH. In addition, there may be interference with the pathway from the binding of PTH receptor to RANKL expression in osteoblasts. Although still controversial, it has been suggested that PTH receptor expression in osteoblasts is down-regulated in uraemic patients [15]. The PTH receptor-signalling pathway may also be disturbed in uraemia, a possibility that remains to be elucidated.

Third, steps after induction of RANKL may be disturbed. Osteoprotegerin (OPG) is a decoy receptor for RANKL [16]. Administration of OPG induces transient hypocalcaemia in rats possibly due to the suppression of bone resorption. We have already reported that this OPG accumulates in serum as renal function declines [17]. Furthermore, Sato et al. [18] reported that increased serum OPG levels return to normal 2 weeks after renal transplantation, supporting the important role of the kidney for the clearance of OPG. Thus, it may be possible that accumulated OPG inhibits osteoclastogenesis in uraemic patients, which has been confirmed in part by bone biopsy [19–21]. Modulation of serum OPG levels by medical treatments such as active vitamin D derivatives needs to be clarified for a better understanding of the important role of OPG in skeletal resistance to PTH.

Accumulation of OPG is not a newly developed abnormality, but a background abnormality in dialysis patients. With extremely high PTH levels, the blocking effect of OPG to RANKL may be overcome. Suppression of PTH by recently innovated therapeutic modalities has revealed such an effect of OPG, which is currently recognized as a dynamic bone disease (Figure 1).

If removal of accumulated OPG or the suppression of OPG production by appropriate therapy becomes established, optimal management of bone turnover as well as parathyroid function may be more easy and practical in the near future.

References

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