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Osteodystrophy in the millennium

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Osteodystrophy in the millennium. Despite three decades of intensive research on the derangements of calcium phosphate metabolism of renal failure, several unresolved issues are still with us at the turn of the millennium: poor control of hyperphosphatemia, relative inefficacy of active vitamin D to prevent progressive parathyroid hyperplasia, and persistence of bone disease despite lowering of parathyroid hormone (PTH) and administration of active vitamin D. Although predictions are problematic, it is not unreasonable to hope that, barring unforeseen side effects, calcimimetics will prove to be valuable for suppressing or even preventing hyperparathyroidism, thus potentially replacing, at least in part, active vitamin D. There is also reason to hope that more effective phosphate binders with fewer side effects will become available and that controlled studies will provide a rationale for the administration of estrogens to dialyzed women. As regards understanding the pathological mechanisms, one can anticipate that the disturbances leading to autonomous growth of parathyroid cells will be elucidated and the signals involved in osteoclast/osteoblast differentiation pathways and osteoclast/osteoblast coupling will be clarified, with obvious impact on patient management.

The literature is replete with warnings against making predictions about the future. Unable to resist the insistence of the organizers, we had to give in and commit ourselves to make predictions, but we find consolation in the consideration that either we are right (in which case future generations will praise us for our clairvoyance) or we are wrong (in which case our predictions will be painlessly and thoroughly forgotten anyway).

This is an interesting time to take one step back and to consider where we might go from here. A number of remarkable developments have recently occurred, both in regard to strategies of patient management and in regard to basic understanding of molecular mechanisms. It is useful first to take stock of what problems persist in 1999 and then speculate about potential future directions.

PHOSPHATE CONTROL

The main problem, perhaps the major problem in the management of divalent ion metabolism, continues to be insufficient control of hyperphosphatemia. As one case in point, even in Japan, where the average weight of the patients is 52 kg and the average duration of hemodialysis $3 \times 4.2 \pm 0.5$ hr [1], predialytic serum phosphate is 1.86 ± 0.54 mM. The average predialytic serum phosphate concentration in 227 patients treated in our center is 1.78 ± 0.52 mM, despite an average use of calcium carbonate of 1.4 ± 1.8 g/day and (with 37% of the patients taking, in addition, low doses of aluminum-containing phosphate binders). Why is it so difficult to normalize serum phosphate? The main issue is the complex kinetics of elimination of phosphate. Phosphate is trapped in deep compartments, and the transfer rate constant for phosphate efflux from the intracellular to the extracellular compartment is low relative to the rate of removal of phosphate during high efficiency dialysis sessions. Most of the phosphate is removed in the first hour of dialysis and despite unchanged dialysance for phosphate, only a relatively small amount of phosphate is subsequently eliminated because serum phosphate concentrations are low. But we also believe that in many instances hyperphosphatemia is simply a surrogate marker for under-dialysis. Against this background, it is of interest that long slow dialysis sessions provide more effective removal of phosphate to the point that one may even have to add phosphate to the dialysate fluid [2]. Apart from the well-known effects of phosphate in the genesis of hyperparathyroidism [3], a high serum phosphate concentration is also a predictor of poor survival on dialysis [4] (abstract; *J Am Soc Nephrol* 9:217A, 1998). This may in part be due to calcification of coronary plaques [5], but in recent experimental studies hyperphosphatemia was also associated with cardiac microcirculatory abnormalities [6].

The problem of phosphate control is compounded by the fact that none of the existing phosphate binders is truly satisfactory. Aluminum-containing phosphate binders are relatively contraindicated because of aluminum toxicity. Calcium-containing phosphate binders predispose to hypercalcemia [7]. This has prompted the development of novel phosphate binding compounds such as polyallylamine hydrochloride (Sevelamer®)—which is effective, but with which it is difficult to consistently

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achieve normophosphatemia [8]—lanthanum carbonate, for which no published information is available, and phosphate binders on the basis of trivalent iron [9, 10], which appear promising and are relatively cheap. Because of the importance of phosphate in triggering hyperparathyroidism [3, 11, 12] and predisposing to cardiovascular events [4, 6], efforts to modify dialysis strategies [2] and to develop new phosphate binders are of prime importance.

RELATIVE INEFFICACY OF ACTIVE VITAMIN D TO CONTROL PARATHYROID GROWTH

There is no doubt that active vitamin D preparations acutely suppress parathyroid hormone (PTH) secretion. Nevertheless, although controlled evidence is not available, it appears that they cannot completely prevent development and progression of parathyroid hyperplasia. In several studies, the duration of dialysis treatment was a potent predictor of parathyroidectomy [13]. According to the EDTA registry [14], up to 10–15% of chronic dialysis patients ultimately require parathyroidectomy. In our center, 16 of 95 patients dialyzed for more than 10 years required parathyroidectomy.

Why is control of parathyroid growth unsatisfactory? There may be several causes. One important point is of course persisting hyperphosphatemia in view of the potent stimulatory effect of phosphate on parathyroid cell proliferation [3, 11, 12]. Another important point is the fact that parathyroid hyperplasia, at least advanced (nodular) hyperplasia, is largely irreversible. It is true that in animal experiments, hyperplastic glands of uremic rats can regress [15], but this may not be an adequate model for what is seen in chronically uremic patients, i.e., nodular parathyroid hyperplasia with monoclonal growth [16], loss of heterozygosity with loss of putative tumor suppressor genes [17] and reduced expression of the vitamin D receptor [18] and calcium receptor [19], respectively. It appears plausible [20], but is currently unproven, that prophylaxis, i.e., normalization of phosphatemia [21] and administration of low doses of active vitamin D [22], may interfere with the development of parathyroid hyperplasia. One must also consider the alternative possibility: that signals other than hyperphosphatemia and diminished active vitamin D are involved in the genesis of parathyroid hyperplasia. In this context, recent observations on the prevention of parathyroid hyperplasia by calcimimetic agents [23] are of considerable interest. At present, the potential role of these agents in the prevention and control of parathyroid hyperplasia cannot be properly assessed.

PERSISTING BONE ABNORMALITIES

In the distant past it had been hoped that once PTH concentrations were kept within the normal range and once active vitamin D was administered, the structure and the dynamics of bone would be normalized. A number of investigators [24, 25] noted that on average bone turnover in dialyzed uremic patients was normal only when the measured immune reaction 1,84 iPTH concentrations were 2- to 3-fold above the normal range. The explanation for this observation is not unambiguous. The assay apparently measures bio-inactive fragments [26], so that in these studies measured 1,84 iPTH concentrations may have been spuriously elevated. On the other hand, in many organs including bone tissue, expression of PTH/PTH-related polypeptide receptor is diminished in renal failure [27, 28], so that it is conceivable that there is an element of hyporesponsiveness to PTH at the receptor level and abnormalities on the postreceptor level are also certainly not excluded. Finally, in many hormonal systems it is not only the concentration of the hormone, but also the temporal pattern of hormone concentrations, that determines end-organ response. Pulsatile secretion of luteinizing hormone (LH)–releasing hormone (RH) provokes LH secretion by the hypophysis, while continuous administration of LH-RH blocks LH release and is used for medical ablation of the hormone. In this context it is of interest that the pattern of pulsatile PTH secretion is strikingly abnormal in uremic patients [29]. Preliminary studies in conjunction with the Department of Pediatrics, Heidelberg, show that the bone cell response to PTH depends on the temporal pattern of exposure to PTH (unpublished data).

It is uncertain whether abnormalities in the calcium regulatory hormones fully explain adynamic bone disease in patients with low PTH. One has certainly also to consider alternative possibilities. Recently we compared subtotally nephrectomized, parathyroidectomized rats that received either solvent or nonhypercalcemic doses of aminoterminal rat PTH and $1,25(OH)_2D_3$ [30]. Bone histology was not restored to normal by administration of the calcium-regulatory hormones. Such unresponsiveness might be explained by the artefactual non-pulsatile mode of administration or by an element of resistance to PTH or $1,25(OH)_2D_3$, as discussed above, but recent insights into the regulation of osteoclast and osteoblast developmental pathways suggest interesting alternative possibilities [31, 32]. In osteoclast and osteoblast differentiation, the calcium regulatory hormones influence only late steps, while colony-stimulating factors (mCSF, gmCSF) or interleukins (IL-6, IL-11) affect early steps. In addition, a circulating molecule of the tumor necrosis factor (TNF) receptor family, osteoprotegerin, is produced in the kidney. It inhibits late stages of osteoclast development, so that one would expect increased osteoclastogenesis if this factor is not present. This was not observed in our study [30]. But circulating substances may also interfere with osteoblast function. As a case in point, Andress [33] documented the presence of a low

molecular weight inhibitor of osteoblast mitogenesis in the plasma of uremic patients. There are further possibilities to consider. In principle, in the genesis of the low bone turnover (adynamic bone disease), either agonists of bone formation could be suppressed or promotors of bone formation be deficient. Known suppressors include IL-11 [34] and IL-4 [35], particularly osteogenic protein-1 or bone morphogenetic protein 7, which is produced by normal renal tubular cells (abstract; *J Am Soc Nephrol* 4:700, 1993) and is presumably reduced or absent in renal failure. Because of the considerable therapeutic potential for the treatment of osteoporosis, many pharmaceutical companies have launched considerable efforts to define these factors. Osteoprotegerin and osteoprotegerin ligand (formerly called TRACE) have been isolated and sequenced. Furthermore, factors essential for osteoblast differentiation, e.g., core-binding factor alpha 1 (CBFA-1) (heterozygous loss of which causes cleidocranial dysplasia in humans) have also been identified [36]. The physiology of these factors in renal failure requires further study, but this whole field potentially opens exciting new perspectives for understanding adynamic bone disease. Even though we have managed to lower PTH and administer active vitamin D, new disturbances are now observed that cannot be fully explained by abnormalities of calcium regulatory hormones.

ESTROGENS AND BONE

Estrogens affect the parathyroid gland as well as bone [37]. Because of the obvious importance in the genesis of postmenopausal osteoporosis, this field has been intensely investigated, but so far this has had disappointingly little impact on the management of female patients on dialysis. Estrogens have remained a Cinderella in the therapeutic repertoire of nephrologists. Only approximately 5% of amenorrheic patients had received estrogens in the modification of diet in renal disease trial. Apart from few preliminary studies [38] that point to preservation or increase of bone mineral content after administration of low dose estrogens to dialyzed amenorrheic women, no information is available. Recently, estrogen analogs—e.g., raloxifen [39]—have become available that selectively affect bone without causing endometrial hyperplasia and endometrial cancer. There is an urgent need to clarify the role of estrogens in the genesis, and their potential in the treatment, of bony abnormalities in uremia.

GENETICS AND BONE DISEASE

Genes, or more precisely genetic polymorphisms, appear to determine both bone mass and susceptibility of the parathyroid to stimulation. Some of the genes that have been implied are the vitamin D receptor, calcium sensing receptor, isocollagens, etc. Currently this field is still murky and the results reported are conflicting [40]. Nevertheless, this field holds great promise and might open new perspectives to better define patients at high risk of secondary hyperparathyroidism or bone loss.

WHAT DO WE EXPECT IN THE NEW MILLENNIUM?

Management of renal bone disease

As far as patient management is concerned, we expect that calcimimetics will become a major tool in the management of the uremic patient, both for the prevention and for the treatment of secondary hyperparathyoidism. The available evidence [41–44] is very encouraging and it is hoped that long-term safety studies do not reveal major extraparathyroidal side effects, a concern because of the nearly ubiquitous expression of the calcium sensor. In this respect, the absence of such effects in a patient treated for 2 years is quite encouraging [45]. It is difficult to predict the relative roles that calcimimetics and active vitamin D will have in the future; these roles will have to be worked out in controlled trials. It is conceivable that active vitamin D may be necessary for maintaining active calcium transport in the intestine or for exerting specific effects on the numerous target tissues which express vitamin D receptors, for instance muscle, vasculature, immune cells, etc.

Secondly, we expect that we shall see more effective phosphate binders with fewer side effects.

Finally, we presume that clinical nephrologists will recognize that estrogens are potent agonists on bone and will use these compounds more liberally.

Pathophysiological mechanisms

Clinical common sense helps to predict what is plausible and what is not with respect to management of renal bone disease. When one comes to basic research, however, one is on more uncertain ground. Presumably, the fundamental challenge will be to clarify why control of parathyroid growth is disturbed, i.e., to explain the occurrence of monoclonal growth, loss of heterozygosity with hypothetical loss of tumor suppressor genes, and dedifferentiation of parathyroid cells, so that vitamin D receptor and calcium sensor molecules are no longer expressed normally. Recent studies showed alterations of genomic DNA in blood cells of dialyzed patients. One could therefore speculate that it is in the parathyroid gland as well as in the remnant kidney (in other words tissues actively proliferating in uremia, but normally exhibiting low cell turnover) that such genomic lesions lead more readily to abnormal growth, i.e., monoclonal parathyroid nodules and renal cell carcinoma, respectively. It is still puzzling why one mostly sees autonomous, but not malignant growth, in the parathyroids of uremic patients.

There are also glaring deficits in our understanding of the signals of the osteoclast/osteoblast differentiation pathways and similar defects in understanding how the balance between bone resorption and formation is maintained, i.e., the coupling between the two processes. Knowledge of these mechanisms is crucial for the understanding of adynamic bone disease and bone loss, respectively. Because of the enormous potential market that treatment of osteoporosis offers, these issues are currently hotly investigated by the pharmaceutical industry, as evidenced by the recent cloning of osteoprotegerin and the osteoprotegerin ligand in pharmaceutical laboratories.

The above listing may to some extent reflect personal preferences and there is undoubtedly room for many other considerations. We are skeptical whether one area, namely vitamin D analogs, holds great potential. Although these compounds are conceptually quite attractive, one sorely misses clinical head-on comparisons of efficacy and safety with calcitriol or 1-alpha.

While it is dangerous to make predictions, the above insights hopefully are closer to the truth than the famous statement of Kaiser Wilhelm, who predicted in 1914: "Herrlichen Zeiten gehen wir entgegen" ("I shall lead you to the days of glory").

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