(4) Recent Advances of Therapeutic Approach Toward Renal Osteodystrophy

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Chronic dialysis treatment of end stage renal disease (ESRD) is characterized by a progressive bone disease caused by various mechanisms. In this review, we present a current consideration of the pathophysiology and recent therapeutic approach toward this metabolic abnormalities.

It is well recognized that renal osteodystrophy (ROD) commonly consists of osteitis fibrosa and osteomalacia or combined lesion. The present theory for the etiology of bone abnormalities in ESRD is divided to two main alterations, the one is secondary hyperparathyroidism induced by decreased production of $1\alpha, 25$ dihydroxy vitamin D_3 ($1\alpha, 25[\text{OH}]_2 D_3$) resulting bone resistance to parathyroid hormone (PTH) and decreased intestinal calcium (Ca) absorption, and hyperphosphatemic state leading to hypocalcemia, the other is osteomalacic feature with extensive accumulation of uncalcified osteoid surface probably caused by aluminum (Al) deposition. The source of Al could be orally administered aluminum hydroxide as phosphate binder in order to inhibit intestinal phosphate absorption or Al containing dialysate without use of reverse osmosis.

Therapeutic approach toward ROD should be aimed to prevent or correct those causative factors.

Restriction of phosphate intake and oral use of phosphate binder; It is evident that lowering serum phosphate concentration in ESRD can attribute to prevent the progression of secondary hyperparathyroidism and reduce the extent of progressive decrease of $1\alpha, 25[\text{OH}]_2 D_3$ synthesis.

Use of calcium carbonate as phosphate binder instead of aluminum hydroxide is advantageous over the Al phosphate binder in the toxicity. This complex can inhibit intestinal phosphate absorption as equal as Al phosphate binder. However, it may easily raise serum Ca level above normal range with concomitant use of $1\alpha, 25[\text{OH}]_2 D_3$

or $1\alpha\text{-OH } D_3$.

Continuous ambulatory peritoneal dialysis (CAPD) recently developed as ideal dialytic method of chronic renal failure; CAPD induces relatively sufficient removal of phosphate from extracellular fluid and can maintain its level within the acceptable range without use of phosphate binder. CAPD also could improve dialytic bone disease or prevent loss of bone minerals.

However, it could not always correct the progression of secondary hyperparathyroidism. Furthermore, peritoneal loss of Ca by large amount of drainage volume of effluent and loss of 25 hydroxyvitamin D must be monitored carefully and replenished adequately.

Use of synthetic active vitamin D metabolites; $1\alpha, 25[\text{OH}]_2 D_3$ or $1\alpha\text{ OH } D_3$ are widely used in the treatment and prevention of ROD, in fact, it is possible to elevate serum Ca and reduce serum alkaline phosphatase activity and PTH level. However, those metabolites are less effective in extremely severe hyperparathyroid state indicating as nonsuppressive secondary hyperparathyroidism. Those metabolites also less effective in the Al-related bone disease. In order to prevent a deterioration of bone metabolism early use of those metabolites in accordance with reduction of biosynthesis of $1\alpha, 25[\text{OH}]_2 D$ was studied by some investigators. But its results were still obscure. Therapeutic use of calcitonin; Synthetic eel calcitonin analogue is used clinically expecting to inhibit bone resorption and to sedate bone and joint pain. However, whether this metabolite could improve deranged bone metabolism will require further investigation.

Parathyroidectomy (PTX); PTX is exact means to resolve nonsuppressive secondary hyperparathyroidism refractory to active vitamin D therapy. But it is difficult to discriminate adequacy of carrying this surgery in the case of combined bone

lesion showing characters of osteitis fibrosa and osteomalacia. Unnecessary PTX or even harmful PTX should be avoided strictly.

Use of desferrioxamine (DFO); DFO was originally used to remove iron from tissues by chelation. Application of this agent to Al-related osteomalacia has brought a new therapeutic benefit in past three years. In fact, use of DFO during dialysis decreases bone and joint pain, or muscle weakness. The effect of DFO is clearly demonstrated by measuring serum levels of Al or diminishing Al accumulation in bone tissue with clinical improvement.

Kidney transplantation: Although the prevention of steroid induced bone disease or hypophosphatemic osteomalacia caused by excess loss of phosphate following successful transplantation still remains unresolved, kidney transplantation, at this

time, may offer the only adequate therapy of pathologic disturbances induced by loss of kidney function such as not only excretory but also endocrine function.

In summary, the understanding of pathophysiological mechanisms of dialysis bone disease and clinical use of active vitamin D metabolites have brought remarkable improvement of ROD, nevertheless, there are many cases which do not respond to adequate treatment. This fact means that metabolic abnormalities of ROD is extremely complex.

Thus, further fundamental investigation on bone metabolism, parathyroid endocrinology, vitamin D endocrinology and intestinal transport of minerals will be required in addition of accumulation of clinical observations.

(5) Body Fluid Homeostasis

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1. Introduction

Homeostasis has been an important subject for medical scientists, ever since this term was coined by Cannon in 1932. Sixteen years ago, one of the authors, Kato, made a speech about the same subject at the symposium of this meeting. Since then much advancement occurred in the field of medicine as well as in others. Especially, the recent progress of systems control theory enabled us to develop an entirely new method of describing the homeostatic processes in the body, which will be presented in the present speech, along with other basic aspects of the body fluid physiology in the patients with chronic renal failure.

2. Homeostasis and "Homeostenosis"

In a word, the progression of chronic renal failure can be expressed as the process of decrease in the nephron population in the diseased kidney. Although the remaining nephrons fully work to maintain the homeostasis, the decline in the overall kidney function cannot help leading the body

to the state of "homeostenosis" rather than homeostasis.

Although various biochemical abnormalities are produced by the decompensation thus occurring, the threshold for each of those is variable depending on the degree of development of regulatory systems for that particular clinical parameter. The mode of increase in some substances, such as serum creatinine, which is almost free from regulation, straightly reflects the decline in the kidney function. However, main electrolytes, playing important roles to maintain body fluid homeostasis, more or less show some delay of the appearance of their abnormalities when compared with that of the abnormalities of creatinine.

It seems as if the kidney endeavors to exert its maximal function remaining for maintaining electrolyte balances. Let us assume that the normal GFR of 100 ml/min goes down to 1/10 of it, i.e. 10 ml/min. On the diet containing 15 g/day of NaCl, in order to maintain the in-out balance of