Estrogen Deficiency – Does It Play a Role in Uremic Bone Disease?

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Dear Sir,

Women on dialysis are at risk of complications not only of renal bone disease but also of postmenopausal osteoporosis. The contribution of renal bone disease is greater than that of postmenopausal osteoporosis. Many dialysis patients are oligomenorrheic and estrogen-deficient and are therefore exposed to estrogen withdrawal at an early age. Bone remodeling is controlled by hormonal and local factors in a complex regulatory system and β_2 -microglobulin (β_2 -M) probably interacts via several of these pathways. It has been shown that purified human β_2 -M induces a dose- and time-dependent net calcium efflux from cultured neonatal mouse calvariae [1]. Several cytokines are known to induce bone resorption [2, 3]. It is possible that these cytokines could initiate bone resorption, thus predisposing osteoarticular structures to the deposition of β_2 -M [4]. Many uremic patients on chronic hemodialysis have abnormalities of the hypothalamo-hypophyseal thyroid and gonadal axes. The aim of this study was to evaluate the effect of the abnormalities of these hormones in uremic bone disease.

Thirty female patients with uremia on maintenance hemodialysis and 18 healthy subjects as controls were studied. The mean age in the patient group was 39.4 ± 2.9 and in the control group 45.7 ± 2.4 years. There was no significant difference between the two groups ($p > 0.05$). The average time on dialysis was 4.6 ± 0.6 years and time on menopause was 5.9 ± 1.1 years. All the patients in this study were dialyzed for 4 h 3 times per week. All dialysis patients received aluminum hydroxide and vitamins B and C. None of the patients were diabetic, and only 1 was hypertensive being treated with calcium channel blockers. Serum estradiol (E₂), prolactin (PRL), LH, FSH, β_2 -M, PTH, Ca, P levels and thyroid function tests (TT₃, TT₄, fT₃, fT₄ and TSH) were studied. The relationships between hormonal changes and bone metabolic parameters were investigated. Neither the patients nor the controls received medica-

tions known to affect hormones. All specimens for measuring individual hormones were run in one assay. Commercially available kits were used to measure the hormones.

In the patients, serum E₂, FSH, TT₄, fT₄ and Ca levels were significantly lower, and serum PRL, β_2 -M, PTH and P levels were significantly higher than in the controls ($p < 0.001$; table 1). Serum LH, TT₃, fT₃ and TSH levels were not significantly different between the patient and the control groups ($p > 0.05$). There was a close inverse relationship between decreasing

serum E₂ and increasing serum β₂-M and PTH levels in the patients (p < 0.01). There was no relationship between PRL levels and β₂-M and PTH levels (p > 0.05).

Patients with chronic renal failure on chronic hemodialysis have an abnormal hypothalamohypophyseal axis in the regulation of TSH, PRL, LH and FSH secretion. In addition, a failure in the synthesis and/or release of thyroid hormones is present as

Table 1. Laboratory values of the patient and the control groups

Groups	E ₂ pg/ml	PRL ng/ml	FSH mIU/ml	LH mIU/ml	β ₂ -M ng/ml
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Patient

(n = 30)	35.3 ± 3.8	47.7 ± 7.2	6.5 ± 1.2	14.7 ± 3.4	19,842.5 ± 560.2	790.2 ± 127.7
	9.1 ± 0.3	5.5 ± 0.3	92.1 ± 6.1	6.5 ± 0.3	2.1 ± 0.1	0.9 ± 0.1

Control

(n=18)	178.0 ± 5.8	10.2 ± 0.6	12.5 ± 0.7	120 ± 1.1	1,190.3 ± 88.9	34.9 ± 3.3
	9.6 ± 1.1	3.4 ± 0.1	103.2 ± 2.2	85 ± 0.4	2.8 ± 0.2	8.5 ± 0.4

p value	< 0.001	< 0.001	< 0.001	> 0.05	< 0.001	0.001
	< 0.01	> 0.05	< 0.01	> 0.05		

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well [5]. Estrogen deficiency causes bone loss by stimulating the resorptive activity of mature osteoclast precursors. Estrogen deficiency may lead to an increased secretion of interleukin-1 (IL-1), IL-6, IL-11 and tumor necrosis factor α and β which activate mature osteoclasts indirectly, via a primary effect on osteoblasts, and by stimulating the proliferation and differentiation of osteoclast precursors [6]. Estrogen replacement therapy in women with postmenopausal osteoporosis only stabilizes bone mass and prevents further bone loss without a true anabolic action. This is in contrast to the effect of PTH treatment on osteoporosis, where there is an anabolic effect and an increase in bone mass [6]. The sex steroids, estradiol and the progestins also act directly on the parathyroid gland to increase PTH mRNA at physiologically relevant doses. Cyclic PTH is anabolic to bone, while constant PTH is catabolic. Therefore, estrogen regulates bone strength not only by its direct effect on bone cells but also indirectly by increasing the PTH concentration which would then act on its specific cellular receptor in bone cells. In women with a menstrual cycle this increase of serum PTH would be cyclical and therefore anabolic to bone. This is in contrast to the constantly high serum levels of PTH in renal failure patients with secondary hyperparathyroidism, where the PTH is catabolic, leading to bone resorption [6,7].

In the literature, there is only one report on the effect of hyperprolactinemia on bio-humoral parameters of bone metabolism in women on chronic hemodialysis. And it has been reported that hyperprolactinemia did not significantly contribute to the acceleration of bone metabolic changes [8].

In this study, there was a close relationship between decreasing serum E₂ and increasing serum β₂-M and PTH levels in women on chronic hemodialysis. Hypoestrogenemic women on hemodialysis had high values of bone catabolic parameters. Hypoestrogenemia might contribute to an increase of bone metabolic changes which were already greatly accelerated

due to secondary hyperparathyroidism. Cyclic estrogen therapy might be necessary to treat uremic bone disease. Further controlled studies will clarify this study.

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