Effect of Raloxifene on Parathyroid Hormone in Osteopenic and Osteoporotic Postmenopausal Women With Chronic Kidney Disease Stage 5

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Introduction. This study was aimed to investigate the effects of raloxifene on intact parathyroid hormone (PTH) level and bone mineral density (BMD) for 8 months in women on hemodialysis and women with chronic kidney disease stage 5 not dependent on dialysis to determine its effect on secondary hyperparathyroidism and osteoporosis.

Materials and Methods. Fifty-one women on hemodialysis and 9 with chronic kidney disease stage 5 were randomly assigned to receive oral raloxifene, 60 mg/d, or placebo for 8 months. Baseline blood determinations and BMD were done and repeated after 8 months. Serum levels of total calcium, phosphorus, alkaline phosphatase, and intact PTH were measured.

Results. Serum levels of intact PTH significantly decreased in both groups, and there was no difference between the two groups after 8 months (P = .37). Serum phosphorus levels also decreased by 1.8% in the two groups. After 8 months of treatment, the BMD of the lumbar spine and femural neck decreased by 1.9% in the control group, while an increase in BMD was observed in the raloxifene group,with an average increase in both BMDs of the lumbar spine and the femural neck by 2% (significant in the lumbar spine; P = .01).

Conclusions. Raloxifene has proven to be an effective medication in terms of improving BMD, with no adverse effects. However, it had no effect on controlling hyperparathyroidism in our patients. Long-term studies should be done to investigate the effects of raloxifene in chronic kidney disease and dialysis patients.

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INTRODUCTION

Hypoestrogenemia in climacterium causes high-turnover bone metabolism, relative dominance of bone resorption, and osteopenia.[1] Moreover, high-turnover bone metabolism is commonly observed in patients with chronic kidney disease (CKD).[2] Therefore, postmenopausal women on hemodialysis or CKD postmenopausal women might be at high risk for osteoporosis in addition to CKD-mineral and bone disorders. According to data from the Third National Health and Nutrition Examination Survey (1988 to 1994), a low bone mineral density (BMD) was much more prevalent in those with CKD than in those with normal kidney function; 60% of women with a diagnosis of osteoporosis also were in stage 3, and 23% in stage 4 of CKD.[3]

Unfortunately, despite their very different pathophysiologic states, both osteoporosis and renal osteodystrophy independently increase bone fragility, presenting diagnostic and therapeutic

challenges and collectively increasing the risk of fracture at all stages of CKD.[4] Phosphocalcic metabolism disorders often complicate CKD, appearing very early in the evolution of CKD, when the estimated glomerular filtration rate declines to below 60 mL/min/1.73 m^2, and worsen as kidney function declines. The impairment in the normal physiological mechanisms regulating blood levels of calcium, phosphate, vitamin D, and parathyroid hormone (PTH) has an impact on bone structural integrity. The term of *CKD-mineral and bone disorders* has been chosen by the Kidney Disease Improving Global Outcomes to refer more adequately to the complications of mineral abnormalities.[5] Mahdavi-Mardeh and colleagues studied 2630 hemodialysis patients in Tehran and concluded that strict maintenance of serum calcium and phosphorus levels within the ranges recommended by the Kidney Disease Outcomes Quality Initiative guidelines was difficult to achieve due to multifactorial reasons, the same conclusion as in the previous multicenter studies.[6]

Raloxifene hydrochloride is a selective estrogen receptor modulator that has a lower carcinogenic risk than estrogen and beneficial effects on bone.[7] Raloxifene is commonly used for treatment of postmenopausal osteoporosis in the general population, and use of raloxifene for hemodialysis patients has also been reported.[8] Raloxifene is likely to be an expectant treatment option for osteoporosis in hemodialysis patients, but the effects of the drug in patients with different intact PTH levels have not been examined in detail. In this study, we investigated the effects of raloxifene on intact PTH level and BMD for 8 months in female patients on hemodialysis or with CKD stage 5 not on dialysis to determine its effect on secondary hyperparathyroidism and osteoporosis.

MATERIALS AND METHODS

Participants

From a total of 130 women under treatment in the dialysis units of the University Hospital of Arak and CKD patients reffered to the Nephrology Clinic of this center, we selected 60 women and randomly assigned 25 hemodialysis patients to the placebo group and 26 to the raloxifene group. Of the selected women with CKD stage 5 not on dialysis 4 were assigned to the raloxifene group and 5 to the placebo group. The sample size was calculated based on the results reported by Hernandez and colleagues.[8] Participants were selected according to the following criteria: longer than 1 year of menopause, age greater than 40 years, and evidence of severe osteopenia or osteoporosis according to the World Health Organization criteria (T score below -2.0 standard deviation). The following exclusion criteria were applied: no history of previous hormone replacement therapy, venous occlusive disease, previous history of arteriovenous fistula thrombosis, hepatic disease, and cancer. None of the patients had previous evidance of disease, other than chronic kidney failure, that could affect bone metabolism. The patients who had been recently treated with estrogen, progestrone, tibolone, corticostroids, anticonvulsants, fluoride, bisphosphonates, or calcitonin were also excluded from the study.

Methods

The study protocol was approved by the ethics committee of the Arak University of Medical Sciences. After informed consent was obtained, 30 patients were assigned to the group of oral raloxifene, 60 mg/d, for 8 months, and 30 were assigned to the placebo group by blocking randomly association method. Because of uncontroled intact PTH and CKD-mineral and bone disorders status in most of patients, we adjusted calcium and rocaltrol doses as described in the guidelines (Table 1).[9]

Baseline blood determinations and BMD were done and after 8 months were repeated. Blood analysis was done for serum levels of total calcium, phosphorus, alkaline phosphatase, blood urea nitrogen, and creatinine by standard photometeric methods. Serum intact PTH level was determined by an immunoradiometeric assay (Ibal, Germany).

Bone mineral density of the lumbar spine and femoral neck were performed by dual x-ray absortiometery, with a densitometer (Hologic, WI, USA). The results were shown in milligrams and value of every patient compared to gender-matched young adults by T score. The pricision error of the BMD analysis in our laboratory was 1.2% for anteroposterior spine, and 1.7% for the femoral neck.

The side effects such as deep and superficial thrombophlebitis; arteriovenous fistula, graft, and dialysis catheter thrombosis; dyspepsia; and vasomotor symptoms were assesed monthly through out the study. In monthly evaluation of patients

Table 1. Laboratory Tests Baseline Results in Women on Hemodialysis and Women With Chronic Kidney Disease (CKD) Stage 5

	Raloxifene Group		Placebo Group	
Parameter	**CKD Patients**	**Hemodialysis patients**	**CKD Patients**	**Hemodialysis patients**
Intact parathyroid hormone				
< 150	3 (75.0)	5 (19.2)	5 (100)	4 (16.0)
150 to 300	1 (25.0)	2 (7.8)	0	3 (12.0)
> 300	0	19 (73.0)	0	18 (72.0)
Serum Phosphorus				
< 3.5	0	1 (3.8)	0	1 (4.0)
3.5 to 5.5	4 (100)	5 (19.2)	4 (66.7)	4 (16.0)
> 5.5	0	20 (77.0)	2 (33.3)	20 (80.0)
Serum Calcium				
< 8.4	0	4 (15.4)	0	4 (16.0)
8.4 to 9.5	2 (50.0)	16 (61.5)	4 (16.0)	17 (68.0)
> 9.5	2 (50.0)	6 (23.1)	1 (20.0)	4 (16.0)

we asked about any new fractures.

Differences between groups were examined for statistical significance using the Student *t* test. Data were expressed as mean ± standard deviation. A *P* value less than .05 denoted the presence of a significant difference.

RESULTS

Participants

The mean age of the participants was 62.1 ± 11.8 years in the placebo group and 63.5 ± 11.9 years in the raloxifene group (*P* = .67). Eight patients could not be followed up until the end of study; 6 died because of reasons not related to raloxifene side effect (3 in each group) and 2 patients in the control group discontinued the study for kidney transpalntation and medication withdrawal (because of prolonged hospitalization).

Bone Metabolic Parameters

There were comparable significant decreases in intact PTH in the two groups (*P* = .37; Figure 1), and also phosphorus levels were decreased by 1.8% in the two groups. An increase was shown in the mean of calcium levels in the control group, but there was a significant decrease in serum calcium concentration after 8 months in the raloxifene group. There were no significant differences between the two groups in alkaline phosphatase levels (Table 2).

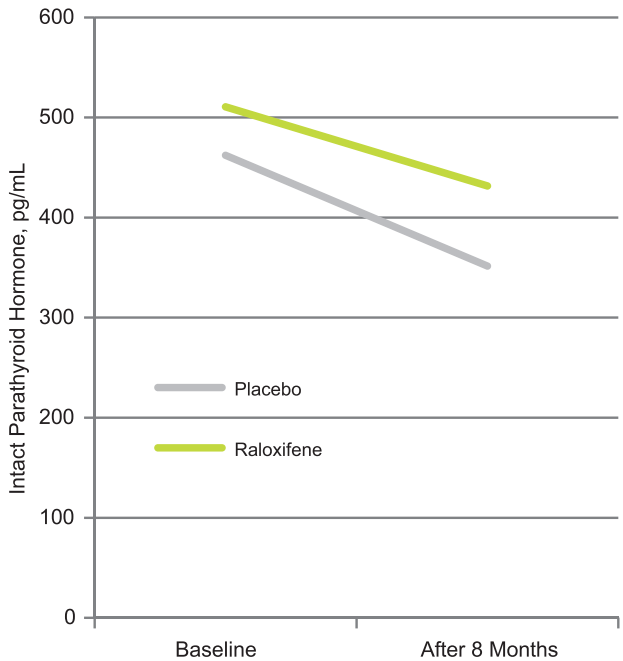

Figure 1. Changes of intact parathyroid hormone values before and 8 months after administration of raloxifene and placebo in women with kidney failure.

Table 2. Serum Values of Bone Metabolism Indicators Before and 8 Months After Administration of Raloxifene and Placebo in Women With Kidney Failure

	Raloxifene Group			Placebo Group		
Serum Parameter	**Baseline**	**After 8 Months**	***P***	**Baseline**	**After 8 Months**	***P***
Intact parathyroid hormone, pg/dL	510.0 ± 375.3	431.5 ± 280.9	.16	462.2 ± 369.6	351.0 ± 359.4	.01
Calcium, mg/dL	9.2 ± 0.7	8.9 ± 0.5	.13	8.9 ± 0.8	9.4 ± 0.7	.03
Phosphorus, mg/dL	6.2 ± 1.8	5.3 ± 1.7	.02	6.6 ± 1.8	5.1 ± 1.0	< .001
Alkaline phosphatase, IU/L	445.9 ± 203.9	650.0 ± 1013.6	.30	483.4 ± 451.3	436.3 ± 358.1	.21

Bone Mineral Density

As shown in Figure 2, after 8 months of treatment, the BMD of the lumbar spine and femural neck decreased by 1.9% in the control group. In contrast, an increase in BMD was observed in the raloxifene group, with an average increase in bone mass of the lumbar spine and femural neck of 2% that was significant in the lumbar spine (P = .007; Table 3).

Bone Fracture

One patient had lumbar spine fracture in the placebo group.

Side Effects of Raloxifene

None of the patients developed side effects, such as deep vein thrombosis, during and following raloxifene therapy.

DISCUSSION

Administration of estrogen has been shown to significantly increase BMD in the lumbar vertebrae after 1 year in postmenopausal dialysis patients.[10] Estrogen has a well-known osteoprotective action and suppresses activation of osteoclasts by PTH.[11] In contrast, the action of PTH on bone resorption is enhanced under the condition of estrogen deficiency. Thus, estrogen appears to influence the action of PTH.[12] Saito and colleagues and Ishani and colleagues showed that reduction of BMD caused by estrogen deficiency was involved in development of bone disease in female hemodialysis and CKD patients, and that raloxifene hydrochloride could improve low BMD in these patients.[13,14]

Severeal studies have reported about vitamin D effects on intact PTH and hyperparathyroidism.

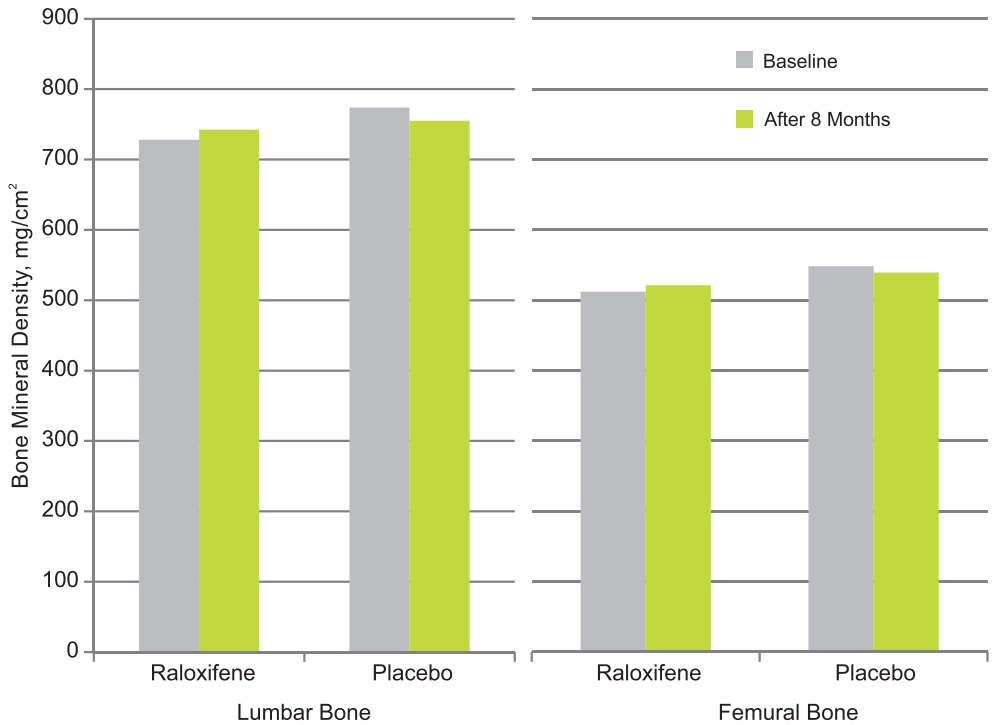

Figure 2. Changes of bone mineral density values of the lumbar spine and femural neck before and 8 months after administration of raloxifene and placebo in women with kidney failure.

Table 3. Tscore and Bone Mineral Density (BMD) of the Lumbar Spine and Femural Neck Before and 8 Months After Administration of Raloxifene and Placebo in Women With Kidney Failure

	Raloxifene Group			Placebo Group		
Serum Parameter	Baseline	After 8 Months	*P*	Baseline	After 8 Months	*P*
T score lumbar spine, SD	-2.9 ± 1.0	-2.8 ± 1.0	.01	-2.4 ± 1.3	-2.5 ± 1.3	.59
T score femural neck, SD	-3.0 ± 0.8	-3.0 ± 0.7	.11	-2.7 ± 1.1	-2.7 ± 1.1	> .99
BMD lumbar spine, mg/cm^2	728.0 ± 108.2	742.4 ± 110.8	.01	773.8 ± 143.7	755.2 ± 160.9	.08
BMD femural neck, mg/cm^2	508.8 ± 91.4	517.9 ± 85.1	.06	544.8 ± 116.4	535.9 ± 113.4	.09

Eleftheriadis and coworkers' study suggested that in hemodialysis patients, 25-hydroxyvitamin D, acting in an autocrine and paracrine way, ameliorates inflammation.[15] Correction of 25-hydroxyvitamin D insufficiency, which is very common in this population, is expected to offer great benefit,[15] but the effect of raloxifene has been examined in a few randomized control trial which evaluated hemodialysis and CKD patients, and most of them included patients with serum intact PTH levels lower than 300 pg/mL. In the present study, we considered patients without any limitation in intact PTH levels.

Hernandez and colleagues' study showed that raloxifene could decreased intact PTH level and bone turneover markers.[8] In another study, the researchers showed that raloxifene did not have any effects on bone turneover markers or intact PTH.[16] Our study demonestrated that raloxifene did not have a positive effect on controling intact PTH ($P = .16$). There were no significant differences between the two groups' bone metabolism after studying the effect of raloxifene and placebo on intact PTH, phosphorus, and alkaline phosphatase. We thought these are due to adjusting calcium and rocaltrol. The prominent decrease in phosphorus (raloxifene group $P = .02$, placebo group $P < .001$) showed the improvig in hemodialysis efficacy. However, we were aware of this, which probably it was better to examine bone turneover markers to evaluate the raloxifene effects, or perhaps the duration of study was not enough to evaluate complete effect of it on bone resorption in this population. A study on 27 Japanese women showed raloxifene treatment was useful for the prevention of BMD deterioration in postmenopausal dialysis patients with controlled PTH levels.[17] In all previous studies on raloxifene treatment, hemodialysis and CKD menopause women demonstrated the improvement in bone loss without any adverse effect, but their duration of treatment and follow-up ranged between 6 months and 3 years.[8,13-18]

As mentioned above, raloxifene has some effects on lipid metabolism and bone mineral density, and a post hoc study showed its renoprotection effect,[19] so overall it is better to evaluate other positive effects of raloxifene on bone metabolism, cardiovascular system, and renal protection. Our data showed the efficacy and safety of raloxifene treatment in postmenopausal women with osteoporosis, we found that the effect of raloxifene on rates of spinal and femoral neck bone loss was significant and in line with some previous reports. These changes were reverse in placebo group.

CONCLUSIONS

Raloxifene has proven to be an effective drug in terms of improving bone mineral density, with no adverse effect. However, it had no effect on controlling hyperparathyroidism in our patients. A long-term study should be done to analysis effects of this medication in CKD and dialysis patients.

CONFLCIT OF INTEREST

None decalred.

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