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Correlation of serum osteoprotegerin levels and bone mineral density early after parathyroidectomy in hemodialysis patients

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A B S T R A C T

In patients with renal insufficiency, the variety of metabolic bone diseases occur which caused by vitamin D metabolism and parathyroid disorders. OPG is a member of issue necrosis factor receptor gene family. In dialysis patients the OPG values are higher than the normal range so it could affect the parathyroid hormone metabolism pathway through its inhibitory activities on the osteoclasts. The aim of this study was to investigate the relationship between OPG serum levels and bone mineral density status in dialysis patients after the parathyroidectomy surgery. In Nephrology Section of Internal Medicine Department of Tabriz University Medical Sciences, the cross-sectional descriptive analysis study was conducted on long-term hemodialysis patients with secondary hyperparathyroidism resistant to treatment and the relationship between OPG serum levels and bone mineral density status in dialysis patients after the parathyroidectomy surgery was investigated. There was no significant relationship between OPG level with PTH and age of the patients undergoing parathyroidectomy. In patients, the level of OPG (four months after parathyroidectomy) was significantly lower than its level before the surgery which represented a significant decrease in OPG level (four months after parathyroidectomy) compared to its level before the surgery. ($P<0.001$). Before and after the parathyroidectomy, there was no significant relationship among OPG level of the patients and their PTH level. The patients' BMD increased after parathyroidectomy which indicated the positive effect of this surgery on their bone density.

Introduction

Various types of metabolic bone diseases incidence in patients with RF result from parathyroid and metabolism of vitamin D disorders (1). GFR decrease in these patients causes the accumulation of phosphates disrupting production of

Calcitriol (2) which ultimately cause reduction of ionized calcium, parathyroid gland hyperplasia following continuous stimulation of PTH and finally secondary hyperparathyroidism (3).

Secondary hyperparathyroidism resistant to treatment is a condition in which the amount of PTH remain higher than 1000 in spite of treatment with 16 vials pulses of Calcitriol (4) causing kidney osteodystrophy, calcification out of bone, cardiovascular diseases and that all of these increase death rates in patients undergoing dialysis (4).

OPG is a member of the large family of tissue necrosis factor receptor gene, whic h is more than normal in patients undergoing dialysis. This results in bone regenerate and enhancing new bone formati on (5). Dialysis patients are exposed to the increased osteoclast activity because of higher values of serum OPG and lower amounts of RANKL (6).

PTX is a common therapeutic method for the treatment and control of secondary hyperparathyroidism resistant to treatment that has a significant impact on the improvement of BMD. Although differences among the different types of renal osteodystrophies are not distinguished using the amount of BMD, but it may be used for bone changes measurements in patients on dialysis (7). Doumouchtis et al expressed that hemodialysis patients with lower BMD level have higher levels of osteoprotegerin (8).

Considering lack of enough studies in this field in our country, we decided to assess the effects of change in OPG levels in the reduction of mineral bone density and if their relationship is significant we are able to use this serum marker in the early diagnosis of osteoporosis in this category of patients.

The aim of this study was to investigate the relationship between serum osteointegrin and the status of bone mineral density after carrying out the parathyroidectomy surgery in patients undergoing dialysis.

Methods and Materials

In a descriptive analytical cross-sectional study in Nephrology section in long term hemodialysis patients (over three years) with secondary hyperparathyroidism resistant to treatment, the relationship between serum levels of OPG and BMD was evaluated after parathyroidectomy.

In this study, 20 CRF patients with long term hemodialysis patients (over three years) with secondary hyperparathyroidism resistant to treatment were selected and entered the study that needed total parathyroidectomy according to the KDOQE guide lines.

Some patients have been excluded from the study including who develop recurrent secondary hyperparathyroidism after surgery, recent infections, digestive diseases, malignant diseases, cardiovascular disease, and patients who used mineralocorticoids, immune suppressors and anabolic, and patients who underwent kidney transplantation.

Numbers of 10 hemodialysis patients with iPTH beneath the 300pg/ml were selected as control group and entered the study.

Serum level of OPG and iPTH were determined in patients before surgery and 4 months after surgery.

BMD was performed via radiography through DEXA method in second to fourth lumbar vertebrae and left femoral neck before and 4 months after the total parathyroidectomy.

Result and Discussion

In this study, the relationship between serum OPG and the BMD status was investigated in patients with dialysis after parathyroidectomy surgery and the following results were obtained:

Twenty male patients who under hemodialysis enrolled into the study. The mean age of the patients was 39.80± 8.43 in patients under parathyroidectomy and 43.80±11.84 in control group, respectively (P = 0.396). The mean duration of hemodialysis in patients was 46.30±12.13 month in patients under parathyroidectomy and 50.80±12.96 months in control group (P = 0.434).

The mean level of OPG at before and 4 month after parathyroidectomy was 531.73 ± 256.86 and 480.60 ± 252.86, respectively. The mean level of iPTH at before and 4 month after parathyroidectomy was 1552.40 ± 319.59 and 170.60±127.31, respectively.
OPG level was significantly lower in patients at 4 months after parathyroidectomy than before the surgery indicating significant reduction of OPG level at 4 months after the surgery compared to before (p <001).
Results of assessing bone density of femoral neck and lumbar vertebrae in patients have been shown in Figure I and II.

Today, more attention is paid to OPG (Osteoprotegerin) and its ligand as well as their roles in osteoid metabolism (9-10). It is proved that OPGL plays a vital role in the molecular relationships between dendritic cells and their survival (11-12).

RANK is a receptor for OPG and OPG is a soluble receptor for OPGL, which neutralizes it relationship with RANK and prevents generation of signals. Due to its expression in activated T-cells and its role in the inflammation and loss of bone, more attention is paid to the use of OPGL in autoimmune diseases, especially inflammatory arthritis.

A high level of expression of OPGL is observed in RA (Rheumatoid arthritis) patients experiencing osteoarthritis (13). Due to the use of different measuring methods, some contradictory results have been obtained (14).

On the other hand, other studies show no relationship between OPG and osteoid markers (15). Some researchers have referred to a slightly negative relationship between OPG and calcium concentrations. They have also reported a slightly positive relationship between OPG and PTH (16). Seemingly, OPG concentration is associated with age in human beings. Therefore, it can be said that with an increase in human age, OPG concentration grows. There is also a slight relationship between testosterone and estradiols. Probably in the aforementioned cases, OPG increases but the ratio of OPG/RANKL first decreases and then escalates (16).

In this study, there relationship of OPG with patients' age, calcium levels and PTH was not shown to be significant in patients under parathyroidectomy. Only some studies have confirmed the relationship between OPG and bone density in human and other studies have rejected this assumption (15-17). No clear study has also confirmed the relationship between OPG and osteoporosis (15).

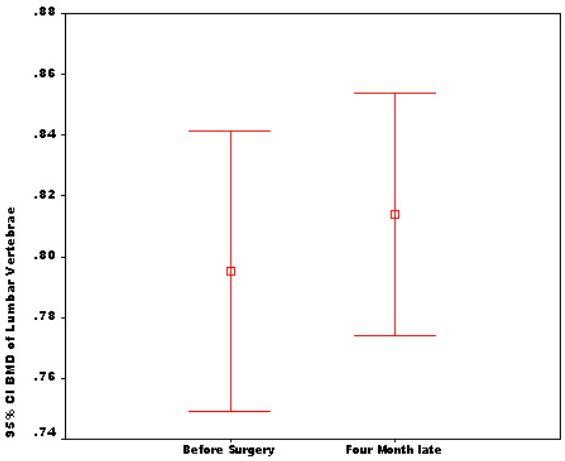

Figure.I Distribution of BMD of Femoral Neck at before and four month late

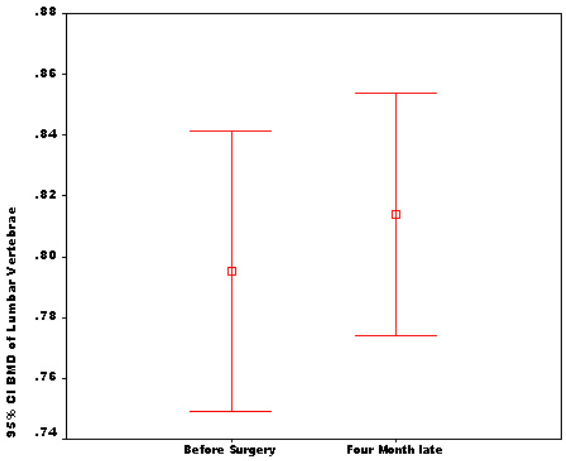

Figure.II Distribution of BMD of Lumbar Vertebrae at before and four month late

In this study, a significant relationship was observed between OPG levels before and after parathyroidectomy and BMD of femoral neck and spine of patients. In general, normal osteoid metabolic activity and durability of osteoid masses depends on the balance between RANKL and OPG. RANKL and OPG signals are complicated and require different factors to work mutually (18).

Lu et al. stated that the level of iPTH reduced following operation in these patients. Moreover, BMD of femoral neck and spine grew. There was also a positive significant relationship between initial iPTH and T-Score of femoral neck (19). Similar to the above study, in the present study the levels of BMD of spine and femoral neck increased significantly following parathyroidectomy. Doumouchtsis et al. stated that OPG and ALP are appropriate experimental criteria for the assessment of osteoid disease in hemodialysis patients (20).

Peters et al. reported no significant difference between levels of ALP, BAP and 25(OH0D before and after parathyroidectomy. Moreover, no significant difference was also observed between OPG levels before and after parathyroidectomy (21). In the present study, the level of OPG four months after parathyroidectomy was significantly lower than the level of OPG before OPG. This decrease reflected a drastic reduction in the level of OPG four months after parathyroidectomy as compared to the before ($P<0.001$). Level of OPG four months after parathyroidectomy was significantly lower than the level of OPG one week after parathyroidectomy. This also indicated a significant decline in the level of OPG, 4 month after parathyroidectomy as compared to one week after it ($P<0.001$). Doumouchtsis et al. stated that there was a significant relationship between levels of iPTH and OPG in patients under hemodialysis (22).

In this study, no significant relationship was observed between the levels of OPG and PTH before and four month after parathyroidectomy. Crisafulli et al. studied the relationship between OPG and BMD of patients under hemodialysis and stated that BMD of spine in patients with high levels of OPG was significantly lower. They also reported an increase in the level of OPG in hemodialysis patients (23).

In a study by Chou et al. in the Nioo0Sung University of Taiwan, the role of parathyroidectomy and kidney transplantation in hemodialysis patients with secondary hyperparathyroidism was studied. The researchers stated that parathyroidectomy and kidney transplantation lead to the improvement of BMD of spine and femoral neck in such patients (24).

Similar to the results of the above study, in the present study the level of OPG in patients with high levels of iPTH was higher than that of patients with low levels of iPTH (25). Furthermore, Avbersek-Luznik et al. stated that the level of OPG in patients with high iPTH levels was higher than that of patients with low levels of iPTH (25).
Chou et al. reported that parathyroidectomy and kidney transplantation in patients with secondary hyperparathyroidism leads to an increase in the BMD of femur, olena, and radius of patients (26).

Conclusion

In patients with parathyroidectomy, a significant decrease was observed in the level of OPG four months after parathyroidectomy as compared to the before. Moreover, no significant relationship was also observed between OPG and PTH levels before and after parathyroidectomy. BMD of patients increased following to the parathyroidectomy. The increase reflected the positive effect of parathyroidectomy on the bone density of such patients

References

1. Nijweide PJ, Burger EH, Feyen JH. (1986) Cells of bone: proliferation, differentiation, and hormonal regulation. Physiological Reviews; 66: 855-886.
2- Fu GK, Lin D, Zhang MY, Bikle DD, Shackleton CH, et al (1997) Cloning of human 25-hydroxyvitamin D-1 alpha-hydroxylase and mutations causing vitamin D-dependent rickets type 1. Mol Endocrinol 11:1961–1970
3- Feinfeld DA, Sherwood LM (1988) Parathyroid hormone and 1,25(OH)2D3 in chronic renal failure. Kidney Int 33:1049–1058
4- Ellis HA, Peart KM: Azotaemic renal osteodystrophy: a quantitative study on iliac bone. J Clin Pathol 1973; 26: 83- 101.
5- Yao Y, Wang G, Wang C, Zhang H, Liu C. (2011) Synergistic enhancement of new bone formation by recombinant human bone morphologic protein-2 and osteoprotegerin in trans0sutural distraction ontogenesis : a pilot study in dogs. J Oral Maxillofac Surg;69: 446-455.
6- Coen G, Ballanti P, Balducci A et al. (2002) Serum osteoprotegerin and renal osteodystrophy. Nephrol Dial Transplant; 17: 233-238.
7- Hampson G, Vaja S, Evans C, Chesters CA, Pettit R, et al (2002) Comparison of the humoral markers of bone turnover and bone mineral density in patients on haemodialysis and continuous ambulatory peritoneal dialysis. Nephron 91:94–102
8- Doumouchtsis KK, Kostakis AI, Doumouchtsis SK, et al. (2008) Associations between osteoprotegerin and femoral neck BMD in hemodialysis patients. J Bone Miner Metab, 26: 66-72.
9- Kong YY, Boyle WJ, Penninger JM(1999). Osteoprotegerin ligand: a common link between osteoclastogenesis, lymph node formation and lymphocyte development. *Immunol Cell Biol*, 77,188-93.
10- Takahashi N, Udagawa N, Suda T(1999). A new member of tumor necrosis factor ligand family, ODF/OPGL/TRANCE/RANKL, regulates osteoclast differentiation and function. *Biochem Biophys Res Commun*,256,449-55.
11- Anderson DM, Maraskovsky E, Billingsley WL(1997). A homologue of the TNF receptor and its ligand enhance T-cell growth and dendritic-cell function. *Nature*,390,175-9.
12- Bachmann MF, Wong BR, Josien R, Steinman RM, Oxenius A, Choi Y(1999).

TRANCE, a tumor necrosis factor family member critical for CD40 ligand-independent T helper cell activation (see comments). *J Exp Med*,189,1025-31.

13- Haynes DR, Barg E, Crotti TN(2003). Osteoprotegerin expression in synovial tissue from patients with rheumatoid arthritis, spondyloarthropathies and osteoarthritis and normal controls. *Rheumatology Oxford*,42,123-34.

14- Seidel C, Hjertner O, Abildgaard N, Heickendorff L, Hjorth M, Westin J(2001). Serum osteoprotegerin levels are reduced in patients with multiple myeloma with lytic bone disease. *Blood*, 98, 2269–71.

15- Browner WB, Li-Yang L, Cummingsa SR(2001). Associations of Serum Osteoprotegerin Levels With Diabetes, Stroke, Bone density, fractures and mortality in Elderly Women. *The J. of Clin. Endocrinology and Metabolism*, 86, 631–637.

16- Szulc P, Hofbauer LC, Heufelder AE, Roth S, Delmas PD(2001). Osteoprotegerin serum levels in men: correlation with age, estrogen, and testosterone status. *J. Clin. Endocrinol. Metab*, 86, 3162–5.

17- Yano K, Shibata O, Mizuno A, Kobayashi F, Higashio K, Morinaga T, et al(2001). Immunological study on circulating murine osteoprotegerin/osteoclastogenesis inhibitory factor (opg/ocif): possible role of opg/ocif in the prevention of osteoporosis in pregnancy. *Biochem. Biophys. Res Commun*, 288,217–24.

18- Trouvin AP, Goëb V(2010). Receptor activator of nuclear factor-κB ligand and osteoprotegerin: Maintaining the balance to prevent bone loss. *Clin Interv Aging*, 5, 345-54.

19- Lu KC, Ma WY, Yu JC, Wu CC, Chu P. Bone turnover markers predict changes in bone mineral density after parathyroidectomy in patients with ren alhyperparathyroidism. Clin Endocrinol (Oxf). 2012 May;76(5):634-42. doi: 10.1111/j.1365-2265.2011.04265.x.

20-Doumouchtsis KK, Kostakis AI, Doumouchtsis SK, Tziamalis MP, Stathakis CP, Diamanti-Kandarakis E, et al. Associations between osteoprotegerin and femoral neck BMD in hemodialysis patients. J Bone Miner Metab. 2008;26(1):66-72. Epub 2008 Jan 10.

21- Peters BS, Moyses RM, Jorgetti V, Martini LA. Effects of parathyroidectomy on bone remodeling markers and vitamin D status in patients with chronic kidney disease-mineral and bone disorder. Int Urol Nephrol. 2007;39(4):1251-6. Epub 2007 Aug 7.

22- Doumouchtsis K, Perrea D, Doumouchtsis S, Tziamalis M, Poulakou M, Vlachos I, Kostakis A. Regulatory effect of parathyroid hormone on sRANKL-osteoprotegerin in hemodialysis patients with renal bone disease. Ther Apher Dial. 2009 Feb;13(1):49-55. doi: 10.1111/j.1744-9987.2009.00653.x.

23- Crisafulli A, Romeo A, Floccari F, Aloisi E, Atteritano M, Cincotta M, Aloisi C, et al. Osteoprotegerin and bone mineral density in hemodiafiltration patients. Ren Fail. 2005;27(5):531-9.

24- Chou FF, Chen JB, Lee CH, Chen SH, Sheen-Chen SM. Parathyroidectomy can improve bone mineral density in patients with symptomatic secondary hyperparathyroidism. Arch Surg. 2001 Sep;136(9):1064-8.

25- Avbersek-Luznik I, Malesic I, Rus I, Marc J. Increased levels of osteoprotegerin in hemodialysis patients. Clin Chem Lab Med. 2002 Oct;40(10):1019-23.

26- Chou FF, Hsieh KC, Chen YT, Lee CT. Parathyroidectomy followed by kidney transplantation can improve bone mineral density in patients with secondary hyperparathyroidism. Transplantation. 2008 Aug 27;86(4):554-7. doi: 10.1097/TP.0b013 e3181814b00.