Prevalence of Vitamin D Deficiency and Secondary Hyperparathyroidism in Nonunion of Traumatic Fractures

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Abstract- Nonunion is common complication of fracture management. Various factors are involved in its occurring. Metabolic and endocrine factors are often overlooked. So that aim of study was to evaluate the level of vitamin D and PTH in patients with unexplained nonunion and fractures due to low energy trauma. In the case control study, 30 patients with tibial nonunion compared with 32 patients with normal bone healing. There were matched according to, surgical treatment, sex, age and body mass index. In order to measure the serum levels of laboratory parameters, vitamin D and parathyroid hormone, blood samples were taken and were sent to a reference laboratory. A high percentage of vitamin D deficiency was observed in tibial unexplained nonunion (60%) versus 30% in normal union. The level of vitamin D in patients with nonunion was significant difference compared with normal union (25.8±20.4 nmol/l versus 49.03±26.9 nmol/l, *P*=0.002). PTH measurement showed that was not meaningful statistical difference between two groups but prevalence of hyperparathyroidism in nonunion was higher than union (33% versus 9.3%). In other laboratory findings were not statistical difference. According to our results, vitamin D deficiency in unexplained tibial nonunion fractures are common. In areas with high prevalence of hypovitaminosis D, that could be one reason of unexplained nonunion.

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Keywords: Bone healing; Nonunion; Vitamin D deficiency

Introduction

Vitamin D is an essential factors in the regulation of calcium, phosphorus balance and bone growth (1). Vitamin D deficiency is considered to be one of the most common medical condition worldwide (2). According to various studied vitamin D deficiency prevalence is 30-50% of both children and adults (3-6).

Fracture nonunion is one of the most complications of orthopedics treatment. A nonunion is defined as a fracture that show no in two plan radiographic sign or clinical evidence of healing over a specialized time period (7). The time of healing were differenced according to bone involved. Causes of nonunion of fracture depend on the injury velocity (motor vehicle accidents or fall from height), soft tissue crushing or injury, bone loss or comminuted fracture (8). Other factors can affected bone healing including treatment methods, infection and preexisting disease. Metabolic and endocrine disease known to retarded bone formation including diabetes mellitus, thyroid disease, parathyroid disease, rickets and osteomalacia, estrogen deficiency, Cushing disease, Paget's disease and malabsorption syndrome (9).

In many recent studies, vitamin D deficiency is the major risk factor for accelerated bone loss and fracture. Insufficient vitamin D level leads to reduced calcium absorption, elevated serum parathyroid hormone and increased rate of bone resorption. Prolonged asymptomatic hypocalcemia stimulated the release of parathyroid hormone (PTH) and if vitamin D is not provided, secondary hyperparathyroidism develops with increased bone turnover and decreases bone mineralization (10,11).

Vitamin D is important mineral related to bone heath. Reduction in bone mass produce osteopenia and osteoporosis which predispose to bone fractures (12). Batra *et al*. demonstrated high prevalence of hypovitaminosis D in the osteopenic patients of both sex (13). Other studied have shown that vitamin D

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insufficiency/deficiency in elderly had significant effects in lower limb fractures in osteoporotic patients and in this patients inadequate vitamin D intake in long time of life can lead to bone demineralization (14-16). The aim of the study was to evaluate the level of vitamin D and PTH in patients with unexplained nonunion and traumatic fractures due to low energy trauma.

Materials and Methods

In case control study, 62 patients with closed tibial fracture in 1/3 middle shaft treated in trauma center between 2006 and 2010 were evaluated. All of traumatic patients (car accidents, motor vehicle accidents or falling etc.) are referred to our hospital. We chose 62 traumatic patients due to pedestrian accident with low energy trauma. They did not have another fracture or problem exception of closed non-comminuted tibial medial shaft fracture. 30 patients with tibial hypotrophic nonunion that there was no acceptable reasons (occurred despite adequate reduction and stability) for nonunion were compared with 32 patients with normal bone healing in 3 to 6 months after same surgical treatment. They were matched according to fracture AO typing and surgical treatment, sex, age and body mass index (BMI). The excluded patients were those with open fracture or comminuted, soft tissue injury, body mass index over than 25 kg/m^2, smokers, consumption of supplements or minerals in 6 months ago, older than 50 year, had metabolic disease or endocrine disease like diabetes and other systemic disease. Written informed consent was obtained from all the patients. An Ethics Committee of Tabriz University of Medical Sciences approved the study.

All patients treated with similar surgical methods, closed reduction and internal fixation with interlocking intramedullary nail. They were following in 6 to 9 months after treatment in first month every 2 weeks then in every month by radiographic and physical examination. Rehabilitation of patients after one weeks of surgical treatment similarly and weight bearing getting started two days after operation. In all patients knee range of motion was performed by physiotherapist after first day of operation. Initial examinations in patients were height (centimeter) through using wall-mounted height testing instrument with the scale of 1.0 cm and weight (kilogram) using a Sega scale. BMI was calculated in accordance with the formula of weight (kilogram) / $height^2$ (meter). The diagnosis of fracture nonunion is based on a combination of clinical and radiographic findings. The clinical hallmark of nonunion in a lower extremity is persistent pain at the fracture site that is aggravated by weight bearing.

Blood samples were taken after 6 month of treatment and sent to the reference laboratory to measure serum levels. Serum 25 (OH) D was measured using Nichols Advantage 25 (OH) D chemiluminescent assay (Nichols Institute, San Clemente, CA). Normal range for serum vitamin D (25 (OH) D) was 23 to 113 nmol/l. PTH was measured using IMMULITE Intact PTH chemiluminescent assay (Diagnostic Products, Los Angeles, CA), PTH over than 54 nmol/l was considered as hyperparathyroidism. Normal range for PTH is 13 to 54 nmol/l. In this study, the patients matched according to duration of exposure to sun light in previous 3 month, sunscreen cream usage, clothing (exposure of hand and face or more than). In order to quantify the level of vitamin D and calcium consumption in the 3 previous month, a food frequency questionnaire which was designed and standard by the Iranian Nutrition Institute was completed.

Statistical analysis

Statistical analyses were done using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). Continuous variables were shown as mean±standard deviation. Normality of the distributions was checked for each variable using the Kolmogorov-Smirnov test. Chi-square statistical tests were used to study qualitative variables, respectively. Nonparametric tests (Mann-Whitney U) were used to study two case and control groups. All statistical analyses were conducted through use of SPSS 16 statistical software. Significance level was set at $P \leq 0.05$.

Results

62 patients, including 22 women and 40 men (between 20 and 50 years) with mean age of 36.3 years completed this study. Mean follow up time was 7.5 month. Prevalence of vitamin D deficiency in nonunion was 18 (60%) patients and in normal union was 8 (30%) patients. Prevalence of hyperparathyroidism was seen in 8 (33%) nonunion and 3 (9.3%) normal union. Figure 1 demonstrates significant difference between vitamin D nonunion and normal union (P=0.002) but according to figure 2 in PTH level were not significant difference however the percents of hyperparathyroidism in nonunion were more than normal union of fracture.

Table 1. Comparison of demographical characteristics and laboratory findings between two groups.

Group	Nonunion N=30	Normal Union N=32	*P*-value
Age (year)	34.5±10.5	37.4±6.2	0.2
Sex (male/female)	18/12	22/10	0.2
Time of hospitalization (day)	7±1	7±2	0.8
Vitamin D (nmol/l)	25.8±20.4	49.05±26.9	0.002
PTH (nmol/l)	40.6±30.7	33.6±16.7	0.4
Calcium (mg/dl)	9.2±0.6	9.1±1.1	0.8
Phosphate (mg/dl)	3.8±0.6	4.0±0.6	0.4
Alkaline phosphatase (mg/dl)	208.7±65.2	226.6±89.2	0.3
BUN (mg/dl)	15.06±4.04	16.2±5.2	0.3
Cr (mg/dl)	0.8±0.2	0.9±0.2	0.4
LDL (mg/dl)	113.8±39.1	135.7±53.4	0.07
HDL (mg/dl)	40.3±9.8	44.1±9.9	0.1
Triglyceride (mg/dl)	208.4±14.8	200.2±10.8	0.8
BMI (kg/m^2)	23.6±2.8	22.4±2.3	0.1
Hemoglobin (g/dl)	10.9±0.2	10.8±0.3	0.1

Demographical characteristics of the patients in two groups and laboratory findings are shown in table 1. Calcium and phosphate level were similar between two groups. We did not observe a significant difference between the groups in complications such as infection that need prolonged prophylactic antibiotics therapy.

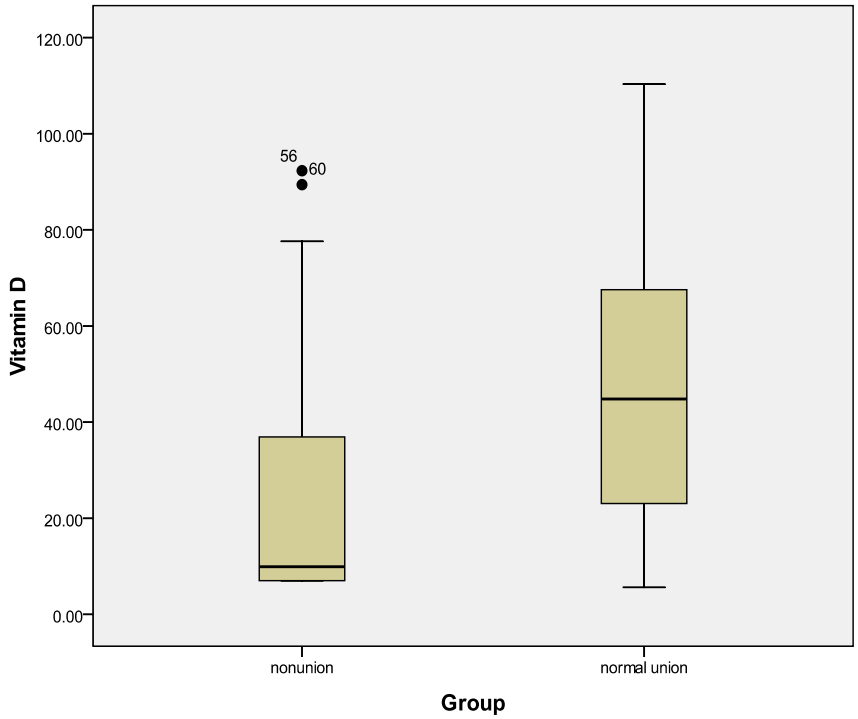

Figure 1. Level of vitamin D in two groups of patients with fracture.

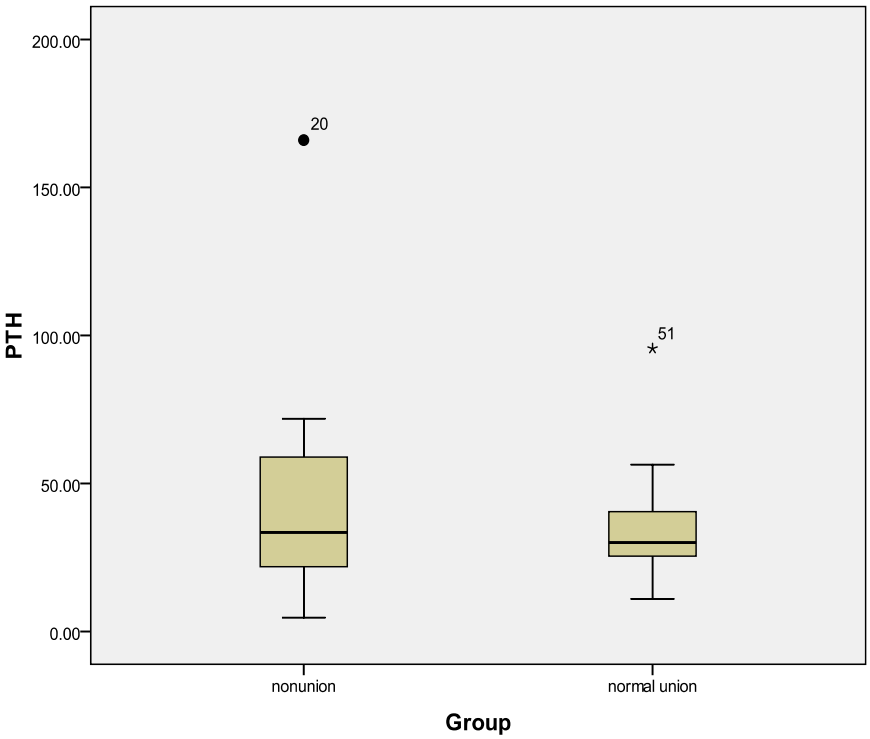

Figure 2. Level of PTH in two groups of patients with fracture.

Discussion

In the lower limb, nonunion can occur in any bone but incidence of nonunion in tibial fracture is higher than others. The overall rate of nonunion has been estimated to be 3% but the rate in tibial fracture have been reported to be near 9% for unselected cases and 73% for displaced, open and comminuted fractures (7,17).

Various factors are involved in nonunion. Mechanical factors in fracture fixation and stability have important role in prevention of nonunion. However, nutritional factors may also affected bone healing after fracture (7,8). According to the Jackson *et al*. meta-analysis, vitamin D3 plays a protective role against falls and fractures (18).

In animal models study by Omeroglu *et al*., vitamin D3 injection intramuscularly in healthy pigs with fracture had a significant effect at the fracture zone healing. Vitamin D3 in this animals accelerated the synthesis and organization of collagen fibers and increased activation of mineralization of the matrix (19). In another experimental study done by Steier *et al.,* the effects of vitamin D2 and fluoride on bone fracture healing were studied. In this study, mineralization rate of fracture was affected by vitamin D2 (20). Papaioannou *et al.* studied patients with acute hip fracture may benefit from a higher daily dose of vitamin D (16).

In our study the prevalence of vitamin D deficiency was 60% in nonunion versus 30% in patients with normal bone healing after fracture. The prevalence of vitamin D has nearly doubled in nonunion of tibial fracture. The level of PTH in patients with nonunion was higher than normal union fracture but was not statistically significant. Serum calcium and phosphate were not difference between two groups. In our study patients with hypovitaminosis D were asymptomatic. Although various factors are involved of nonunion fracture. We tried with exactly matched groups to eliminated confounding factors to get reliable results. In our study, metal implant were similar in all patients. The metal does not seem to affect in the process of bone repair. In an animal study by Rivero *et al*., titanium fiber implants did not make a difference in strength of fixation and increase of bone ingrowth (21).

Birnker *et al.* reported that the most common (68%) metabolic abnormalities in patients with unexplained or patients with history of multiple low energy fracture was vitamin D deficiency (9). This prevalence of vitamin D deficiency was similar to our findings. It seems that vitamin D affected molecular formation and mineralization process. Akalay et al. assessed vitamin D

metabolite level in serum and bone and compared between elective patients and patients after bone fracture. Findings of this study suggested that 24,25 $(OH)_2$ D3 and 1,25 $(OH)_2$ D3 may play a role in susceptibility to bone fracture (22).

Vitamin D is synthesized in the skin under the influence of ultraviolet light or it is obtained from food, especially fatty fish (23). Due to our geographical area and people dressing vitamin D deficiency is common (24). Consumption of food rich in vitamin D is also low (25). Hashemipour *et al.* report in general population in Tehran city (Iran) and Hovsepian *et al*. study in Isfahan city (Iran) showed high prevalence of vitamin D deficiency near to 26.5% among the adult population (24,25). Therefore emphasis to vitamin D deficiency in fracture especially in our region is important and it can be affected results of our treatment. In conclusion, according to our results, vitamin D deficiency in unexplained tibial nonunion fractures are common. In areas with high prevalence of hypovitaminosis D, vitamin D deficiency could be one reason of unexplained nonunion.

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