Original Article

Changes in alkaline phosphatase, calcium, C-reactive protein, D-dimer, phosphorus and hemoglobin in elderly osteoporotic hip fracture patients

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Background: This study aims to evaluate the association between serum alkaline phosphatase (ALP), calcium (Ca) and phosphorus (P), C-reactive protein (CRP) and D-dimer (D-D), and hemoglobin (Hb) in postoperative and preoperative osteoporotic hip fracture elderly patients.

Methods: A total of 32 operation patients with osteoporotic hip fracture over the age of 65 years old were admitted to the orthopedic unit and prospectively evaluated. All patients were treated according to specific protocols, according to the type of fracture. Fasting blood samples were taken, and serum ALP, Ca and P measurements were respectively performed in six periods: at the time of admission, post-operation, and at postoperative one week, two weeks, one month and three months. Hb, CRP and D-D were also analyzed, and the fracture healing was recorded.

Results: Finally, 32 cases were selected for the present study. The analysis results revealed that the level of serum Ca and ALP slowly increased at two weeks after surgery, and slightly dropped back at three months after the operation. Furthermore, D-D and CRP had a significant effect at pre- and post-operation, and exhibited an obvious downward trend after postoperative one week. The fracture healing and recovery of activities were associated with the Hb levels. The serum levels of ALP, which were adjusted by Ca and P, were associated with Hb and CRP, but not with D-D.

Conclusions: Interestingly, there was an association between CRP and D-D. These findings suggest that early control of inflammation and loss of Ca could play a positive role for the healing of osteoporotic hip fractures.

Keywords: Senile osteoporotic hip fracture; alkaline phosphatase (ALP); calcium (Ca); C-reactive protein (CRP); plasma D-dimer (plasma D-D)

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Introduction

Osteoporosis is a disease characterized by a decrease in bone amount, with consequent increases in skeletal fragility and heightened risk of fractures, and these occur with minimal trauma. More than 90 million patients have an osteoporosis, and there are more than 170 million elderly people in China. It has been reported that over 250,000 people suffer from hip fractures annually in China (1). Osteoporosis fracture has the most serious consequences. Hip fracture as one of the most serious complications of osteoporosis, which has increasingly become a focus of attention. Due to the high mortality, morbidity and disability rates, hip fracture patients have become a major challenge for the healthcare system, as well as for society (2).

At present, as an effective approach to cure hip fractures, an operation is the accepted method, and its effect has been considered to be superior to that of conservative methods (3,4). A timely surgical management that allows early mobilization is the key in reducing the high inherent mortality following these fractures (5). The treatment of osteoporotic hip fracture depends not only on the anti-osteoporosis treatment, but also on the change in internal environment. Bone quality is a very important concept, with respect to osteoporosis hip fractures. It comprehends both bone structure and bone composition, which in turn, includes cells, proteins and mineralization. Calcium (Ca) has an anti-fracture effect based on its key structural role in bone mineralization and metabolic balance (6,7). Serum Ca levels present some changes in different periods of the fracture healing process (8). The fluctuation of serum Ca levels may represent the capability of Ca transportation, reservation, bone metabolism and restoration (9). Studies in older patients have demonstrated the association between chronic anemia and health-related quality of life (10,11). Alkaline phosphatase (ALP) is a marker of bone formation. ALP is widely found in many organs, including liver, kidney and bone. Liver and osteoblasts are the main sources of serum ALP, accounting for about 50% each (12,13). D-dimer (D-D) is a useful marker to monitor prophylaxis in trauma surgery patients (14). Higher Hb levels at hospital discharge correlated with a positive change of overall quality of life in operated frail elderly hip fracture patients (15,16). Serum C-reactive protein (CRP) levels have been reported to be negatively associated with bone mineral density (BMD) in epidemiologic studies (17,18). Thus, CRP is likely to be linked to bone fragility and fracture risk. The effective treatment of osteoporosis and the fracture itself remains as a major issue. In order to achieve solutions to biomechanical and internal environment problems, the material and structural properties of bone that determine its strength and metabolism must be quantified. A number of pharmacological treatments and clinical interventions have been proposed to reduce osteoclastic bone resorption and increase osteoblastic bone formation, in order to improve quality of life, and thereby prevent the progression of fragility. An appropriate treatment of osteoporosis has been reported to reduce fracture risk from 40% to 60% (19). For elderly patients, whose body organs gradually lose function, they are more likely to experience water-electrolyte and acid-base balance disorders, and serious cases can encounter multiple organ failure. Therefore, it is an important reference value for clinical doctors to determine whether perioperative bone metabolism and the internal environment would significantly change in the body. Therefore, it is crucial to predict the intervention points of osteoporotic hip fractures and/or identify the bone biochemical characteristics of fractures, in order to apply evidence-based pharmacological and non-pharmacological treatment options for prevention. The first objective of the present study was to evaluate the association and change rule between serum levels of alkaline phosphatase (ALP) and Ca/phosphorus (P), and CRP and D-D, and hemoglobin (Hb) with the bone healing process, while the second objective was to assess the timing of intervention for the osteoporosis after osteoporotic hip fracture. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-218).

Methods

Patients and methods

The present cohort included 32 geriatric osteoporosis patients (21 females and 11 males), who were admitted to our hospital with hip fractures between January 2015 and May 2016. All patients underwent operative treatment by the same doctor. Osteosynthesis was conducted for the trochan-teric fracture using closed traction reduction, and minimally invasive incision proximal femur rotary intramedullary nailing (Weigao, Dabo, China) fixation.

Blood was taken for laboratory tests at a biochemical service laboratory in six periods: at the time of admission, post-operation, and at postoperative one week, two weeks, one month and three months. The serum samples were

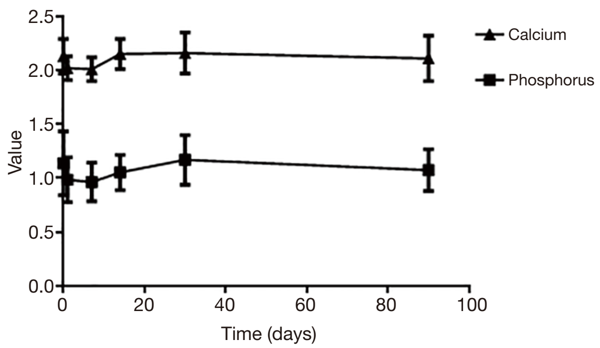

Figure 1 Serum levels of calcium (Ca) and phosphorus (P) according to different stages.

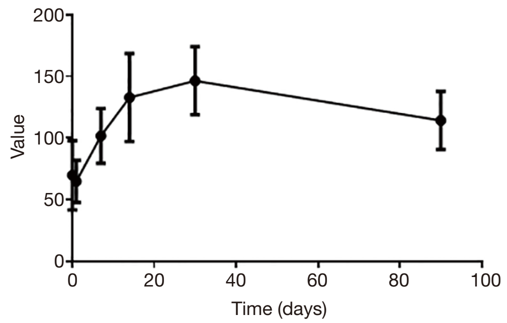

Figure 2 Serum levels of alkaline phosphatase (ALP) according to different stages.

determined for ALP (U/L), Ca (mmol/L), P (mmol/L), D-D (mg/L), CRP (mg/L) and Hb (mg/L), while the routine biochemical parameters were routinely tested in the same laboratory. ALP level was detected by aminoantipyrine phenolic assay (Kim's method) (USA Beckman Coulter Co., Ltd), and Ca, P levels (USA Beckman Coulter Co., Ltd.) were determined by O-cresolphthalein complex ketone assay. CRP values were measured by Scattering turbidimetry (PA990 quick scanning machine, Guangzhou Guolun Technology Co. LTD). D-D were measured by immunoturbidimetry (Sysmex CS5100, Xiesen Meikang Medical Electronics (Shanghai) Co., LTD). Hb were measured by SLS Hb method [Sysmex B2, Xiesen Meikang Medical Electronics (Shanghai) Co., LTD]. All patients were followed-up during their hospital stay and after discharge, and the fracture healing was recorded. The quality of life was assessed by SF-36. The SF-36 assesses health-related quality of life in areas: (I) limitations in physical activities because of health problems; (II) limitations in social activities because of physical or emotional problems; (III) limitations in usual role activities because of physical health problems; (IV) bodily pain; (V) general mental health (psychological distress and well-being); (VI) limitations in usual role activities because of emotional problems; (VII) vitality (energy and fatigue); and (VIII) general health perceptions (20). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of The Third Clinical Medical College of Zhejiang Chinese Medical University (No. 2016ZA105) and informed consent was taken from all the patients.

Statistical analysis

The present data was analyzed by the Statistics Department in our center. The data, which were expressed as mean ± standard deviation (SD), were analyzed using the SPSS 17.0 software (SPSS Inc., Chicago, Illinois, USA), and statistically significant values were set as $P<0.05$ and two-tailed. Mean, standard deviation, median, range and percentage were used for descriptive purposes. The univariate correlation at baseline between Hb and CRP, and between ALP and serum Ca/P were analyzed using Pearson's correlation coefficient and Spearman's rank correlation coefficient, respectively. Analysis of variance (ANOVA) was used to compare serum Ca, P, D-D, Hb, ALP and CRP levels of six different periods. Repeated measures ANOVA was also carried out.

Results

The age at injury of these patients ranged from 65 to 92 years old (mean: 81.68 years old). The mean time from injury to admission was 36.80±38.60 hours, the mean time from admission to surgery was 81.39±55.36 hours, and the mean length of surgery was 1.11±0.27 hours. Furthermore, the mean time from operation to discharge was 23.33±18.73 days. The mean healing time was 3.16±0.7 months. The serum Ca, P, D-D, Hb, ALP, CRP and laboratorial data according to the different stages are listed in *Figures 1-4*. The ANOVA results for the serum Ca and P revealed that there was a significant effect between pre-operation and post-operation (P=0.004, 0.006), between pre-operation and postoperative one week (P=0.002, 0.002) (*Figures 1,5*). The level of serum Ca was slowly increased at two weeks after the surgery, and drop back at three months after the operation. The change in blood Ca level and ALP

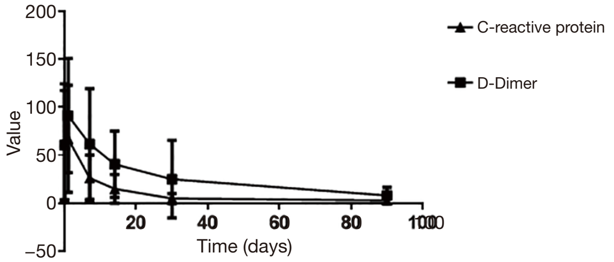

Figure 3 Serum levels of C-reactive protein (CRP) and D-dimer (D-D) according to different stages.

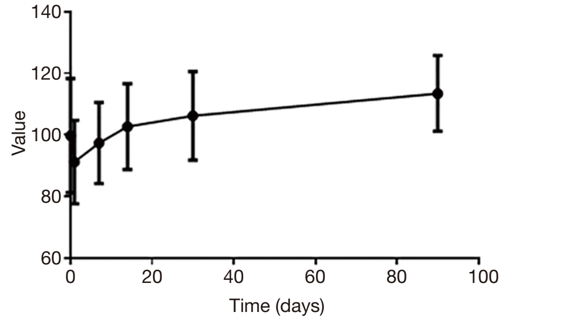

Figure 4 Serum levels of hemoglobin (Hb) according to different stages.

ANOVA							
Ca			Sum of squares	df	Mean square	F	Sig.
Between Groups	(Combined)		0.658	5	0.132	5.587	0.000
	Linear Term	Unweighted	0.081	1	0.081	3.431	0.066
		Weighted	0.072	1	0.072	3.074	0.081
		Deviation	0.586	4	0.146	6.215	0.000
Within Groups			3.864	164	0.024		
Total			4.522	169			

ANOVA							
P			Sum of squares	df	Mean square	F	Sig.
Between Groups	(Combined)		0.956	5	0.191	4.016	0.002
	Linear Term	Unweighted	0.043	1	0.043	0.905	0.343
		Weighted	0.028	1	0.028	0.587	0.445
		Deviation	0.928	4	0.232	4.873	0.001
Within Groups			7.807	164	0.048		
Total			8.763	169			

		Ca	P
Ca	Pearson Correlation	1	0.292**
	Sig. (2-tailed)		0.000
	N	170	170
P	Pearson Correlation	0.292**	1
	Sig. (2-tailed)	0.000	
	N	170	170
**. Correlation is significant at the 0.01 level (2-tailed).			

Figure 5 Serum levels of calcium (Ca) and phosphorus (P) for ANOVA according to different stages.

was consistent, but there was no significant meaning at pre-operation and post-operation (P=0.446) (*Figures 2,6*). The ANOVA results for the D-D and CRP revealed a significant effect between pre-operation and post-operation (P=0.011, 0.015), and the process gradually declined after postoperative one week (*Figures 3,7*). The ANOVA results for Hb revealed a significant effect between pre-operation and post-operation (P=0.02). The level of serum Hb slowly increased after postoperative one week (*Figures 4,8*). In the multiple linear regression analysis with robust standard

ANOVA							
ALP			Sum of squares	df	Mean square	F	Sig.
Between Groups	(Combined)		152791.280	5	30558.256	45.295	0.000
	Linear Term	Unweighted	97261.455	1	97261.455	144.164	0.000
		Weighted	103778.194	1	103778.194	153.824	0.000
		Deviation	49013.086	4	12253.272	18.162	0.000
Within Groups			110643.696	164	674.657		
Total			263434.976	169			

Correlations			
		ALP	Ca
ALP	Pearson Correlation	1	0.195*
	Sig. (2-tailed)		0.011
	N	170	170
Ca	Pearson Correlation	0.195*	1
	Sig. (2-tailed)	0.011	
	N	170	170

*. Correlation is significant at the 0.05 level (2-tailed).

Figure 6 Serum levels of alkaline phosphatase (ALP) and calcium (Ca) for ANOVA according to different stages.

ANOVA							
CRP			Sum of squares	df	Mean square	F	Sig.
Between Groups	(Combined)		117886.697	5	23577.339	16.120	0.000
	Linear Term	Unweighted	98624.304	1	98624.304	67.429	0.000
		Weighted	103079.996	1	103079.996	70.475	0.000
		Deviation	14806.702	4	3701.675	2.531	0.043
Within Groups			231096.694	158	1462.637		
Total			348983.392	163			

ANOVA							
D-dimer			Sum of squares	df	Mean square	F	Sig.
Between Groups	(Combined)		1.209E9	5	2.417E8	10.532	0.000
	Linear Term	Unweighted	9.083E8	1	9.083E8	39.571	0.000
		Weighted	8.718E8	1	8.718E8	37.981	0.000
		Deviation	3.369E8	4	8.422E7	3.669	0.007
Within Groups			3.627E9	158	2.295E7		
Total			4.836E9	163			

		CRP	Ddimer
CRP	Pearson Correlation	1	0.325**
	Sig. (2-tailed)		0.000
	N	164	164
D dimer	Pearson Correlation	0.325**	1
	Sig. (2-tailed)	0.000	
	N	164	164

**. Correlation is significant at the 0.01 level (2-tailed).

Figure 7 Serum levels of C-reactive protein (CRP) and D-dimer (D-D) for ANOVA according to different stages.

error, the serum levels of ALP adjusted by Ca and P were associated with Hb and CRP, but not with D-D. The Paired Samples Statistics results for Hb and SF-36 (physiological function) revealed that Hb level was positively correlated with physiological function (*Figure 9*).

Discussion

The aim of the present study was to evaluate the association between serum levels of ALP with Ca, P, CRP, Hb and D-D after hip fracture. The serum levels of ALP were positively correlated with Ca and P in these patients. Interestingly,

ANOVA							
Hb			Sum of squares	df	Mean square	F	Sig.
Between Groups	(Combined)		7906.686	5	1581.337	7.400	0.000
	Linear Term	Unweighted	5520.275	1	5520.275	25.832	0.000
		Weighted	5151.443	1	5151.443	24.106	0.000
		Deviation	2755.243	4	688.811	3.223	0.014
Within Groups			33765.088	158	213.703		
Total			41671.774	163			

Figure 8 Serum levels of hemoglobin (Hb) for ANOVA according to different stages.

Paired Samples Statistics					
		Mean	N	Std. deviation	Std. Error Mean
Pair 1	Hb	1.0114E2	164	15.98922	1.24855
	Physiological function	50.0793	164	15.06183	1.17613

Paired Samples Correlations				
		N	Correlation	Sig.
Pair 1	Hb & Physiological function	164	0.269	0.000

Paired Samples Test								
Pair 1 Hb-Physiological function	Paired Differences					t	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
	5.10610E1	18.78673	1.46700	48.16421	53.95774	34.806	163	.000

Figure 9 Serum levels of hemoglobin (Hb) and physiological function for Paired Samples Test according to different stages.

there was an association between CRP and D-D. These above mentioned results indicate that promoting bone formation and inhibiting bone absorption, and improving the physical condition should be implemented as early as possible for elderly patients undergoing hip fracture surgery. Osteoporotic hip fracture is a complex fracture that involves many factors (21,22). Osteoporosis fracture is one of the most serious consequences for osteoporosis. Hip fracture and its surgery can significantly increase the serum inflammatory indicators, and excessive inflammatory response may cause the patient's immune exhaustion, resulting in no stress or stress weakness of the body to external antigens (bacteria, etc.), which is not only prone to infection, but also excessive inflammatory response will lead to excessive bone resorption (23,24). Early prevention, timely monitoring, effective anti-osteoporosis and inhibition of excessive inflammatory response during surgical treatment can improve the success rate of fracture treatment and control or reduce the incidence of re-fracture after treatment of osteoporotic fracture. A strategy to secure an adequate and standardized perioperative treatment is important. In particular, there are three clinically relevant indications for utilizing blood biochemical indexes in older osteoporotic hip fracture populations, and monitoring response to therapy: (I) assessment of the physical condition; (II) assessment of the overall secondary fracture risk; (III) the monitoring of the response to therapy.

Elderly patients appear to be less satisfied with life after hip fracture surgery, which produces a substantial negative effect on their quality of life (22). Malnutrition is an important feature of elderly hip fracture patients, and nutritional status has a significant impact on the response of the body skeleton to trauma. Therefore, poor muscle mass and imbalances are important determinants of the decline of organ functions in elderly hip fracture patients. is common after hip fracture surgery (25), while chronic anemia is prevalent in older patients due to their frailty and comorbidities. The elderly are prone to the occurrence of trochanteric fractures, and patients with trochanteric fractures due to the situation a person who loses blood is more likely to become anaemic (26). Studies have demonstrated a positive correlation between Hb levels and quality of life score changes from pre-operation to two months after surgery (10,11,27). Some similar associations between Hb levels and quality of life score changes were also found (28). The loss of blood was associated with medical complications and increased length of hospitalization. In this study, we also found that patients with less Hb loss had a higher quality of life. At the same time, it was found that fracture healing and the recovery of activities were associated with Hb levels in the present study. Therefore, there is vital significance to improve the anemia status as early as possible for osteoporotic hip fracture patients at post-operative recovery.

Osteoporotic fractures healing is a complex physiological process that involves a well-orchestrated series of biological events, including inflammation, intramembranous ossification, chondrogenesis, endochondral ossification, and remodeling (29). Bone turnover is accelerated in the elderly, and is associated with bone loss. Alkaline phosphatase is an indicator of bone formation. Intertrochanteric fracture blood supply abundant, active callus formation stages begin early after fracture. Previous studies have also suggested that bone resorption increases early in the fracture (30), and bone formation increased in later stages (31).

Chronic Ca deficiency in the elderly is a major risk factor for osteoporotic fractures (32). Ca deficiency could lead to an increase in Ca mobilization from bone stores, and also result in the suppression of bone formation (33). P deficiency affects calcification of bone tissue, general weakness, weight loss, bone pain, Osteomalacia and joint rigidity can lead to osteoporosis. There is probably no single cause for accelerated bone resorption in the elderly (34). During these Ca deficiency states, bone formation is suppressed it sure try the best to ensure the supply of Ca in the circulation. Older individuals are likely to be in a chronic and persistent Ca deficiency status. Bone turnover is markedly altered in the elderly when dietary Ca is limited. Clearly, bone resorption is increased by Ca deficiency, but at the same time, bone formation may also be suppressed. The present study revealed that post-operative Ca level is in line with the changes in ALP. These Ca and ALP levels tend to be stable as soon as fracture healing occurs. These findings suggest that Ca supplementation is effective, because it can indirectly block bone resorption. However, it remains unclear what threshold dose of Ca is required to suppress bone resorption. These findings further suggest that the absorption and utilization of Ca should be promoted as early as possible, since this plays a necessary role for the healing of osteoporotic hip fractures. Biochemical indicators of bone metabolism can reflect fracture healing during bone transition state (35).

Serum CRP is an acute phase reactant and marker of general systemic inflammation. Chronic inflammation may lead to increased bone loss and fragility fractures (36). Inflammatory cytokines are associated with increased bone resorption and decreased bone formation (37). Serum CRP levels have been reported to be negatively associated with BMD (12,13,38,39). Similar to these present findings, previous cohort studies have reported the positive association between serum CRP levels and fracture risk (40,41). These present findings indicate that participants with high CRP levels at pre-operation were more likely to develop osteoporosis, even after accounting for fragility fractures and potential confounding factors on fracture healing (37,38). Serum CRP levels have been found to be negatively associated with ALP in the present study. However, the serum levels of CRP were positively correlated with D-D in these patients. Hence, the quality of life score changes. These findings suggest that the early control inflammation plays a positive role, not only to promote bone formation and inhibit bone absorption, but also to improve the state of blood and reduce thrombosis.

In conclusion, the present study demonstrated that the serum levels of ALP were positively associated with Ca and P in these patients. It was also confirmed that CRP is correlated with D-D. Furthermore, Hb levels were associated with the subsequent quality of life score changes at post-operation in osteoporosis hip fracture patients. The number of patients enrolled in this study was small, further research should include additional samples and more subgroups of participant follow-ups, bone turnover biomarkers, intervening measures, longer follow-ups, and so on. Future studies are warranted to quantify the serum levels of bone turnover biomarkers, in order to optimize the bone remodeling process for the timing prediction of osteoporosis hip fractures, and evaluate the timing of intervention for anti-osteoporosis treatment after the occurrence of osteoporotic hip fractures.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-218

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-218

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-218). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional/regional/national ethics/committee/ethics board of The Third Clinical Medical College of Zhejiang Chinese Medical University (No.2016ZA105) and informed consent was taken from all the patients.

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