

Original Article

Expression changes of IL-17 in zoledronic acid combined with PVP technology in the treatment of postmenopausal osteoporotic vertebral compression fracture and its predictive value of relapse

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Abstract

Objective: To investigate the expression of interleukin-17 (IL-17) in zoledronic acid combined with PVP technology for patients with postmenopausal osteoporotic vertebral compression fracture (OVCF) and its predictive value for relapse. **Methods:** 101 OVCF patients treated in our hospital from April 2013 to January 2015 were collected as a research group and treated by zoledronic acid combined with PVP technology. 80 healthy people with physical examination were assigned to the control group. ELISA was used to detect the expression of IL-17 in serum of the two groups. Patients were followed up for 2 years. The expression of IL-17 before treatment was compared between patients with relapse and patients without relapse. The predictive value of IL-17 in relapse was drawn according to ROC curve. **Results:** Before treatment, the expression of IL-17 in the research group increased significantly ($p < 0.05$). After treatment, the expression of IL-17 in the research group decreased significantly ($p < 0.05$). The level of IL-17 in patients with relapse was significantly higher than that in patients without relapse ($p < 0.05$). **Conclusions:** IL-17 is highly expressed in postmenopausal patients with osteoporotic vertebral compression fracture and is expected to be a potential predictor of relapse in postmenopausal patients with OVCF.

Keywords: IL-17, Percutaneous vertebroplasty, Relapse, Zoledronic acid

Introduction

According to the World Health Organization, osteoporosis is considered one of the ten most serious disorders in the world¹. The osteoporotic vertebral compression fracture (OVCF) is the most common type of osteoporotic fracture worldwide². This is a common morbidity among the elderly,

especially postmenopausal women³, with a lifetime risk of vertebral fracture of 8% for women over 50 years old and 27% for men and women over 65 years old⁴. The disease has the characteristics of asymptomatic and gradual deterioration. In the vast majority of cases, the patients usually report that they suddenly fall into a disability state when the fracture occurs for the first time. At this time, the disease is already relatively serious⁵.

Percutaneous vertebroplasty (PVP) is a very effective and widely used surgery to treat OVCF⁶. In addition, fracture surgery pain is an important problem to be addressed. Some studies show that zoledronic acid can be very effective in the treatment of the patients' pain⁷. Therefore, we combine ZOL drugs during PVP surgery to achieve better surgical effects and prognosis⁸. However, some studies have pointed out that the relapse rate of OVCF after PVP is relatively high. During the follow-up period, 21 out of 182 patients treated with

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Table 1. General information.

	Research group (n=101)	Control group (n=80)	χ^2/t	<i>p</i>
Age	65.54±6.85	64.88±6.76	0.647	0.518
Weight (kg)	57.68±5.24	57.36±5.59	0.396	0.693
BMI (kg/m ²)	22.54±3.56	22.68±3.87	0.253	0.801
Fractured vertebral body (n(%))				
T12	32 (31.68)			
L1	36 (35.64)			
L2	33 (32.68)			
Bone mineral density (t)	-3.42±0.23	-0.56±0.28	75.443	<0.001
Time of operation (min)	32.54±5.64			
Bone cement injection (ml)	4.35±0.79			
Intervertebral disc leakage (n(%))				
Yes	7 (6.93)			
No	94 (93.07)			
BGP (ng/mL)	5.24±1.25			
BALP (ng/mL)	18.36±1.75	15.69±1.59	10.610	<0.001

PVP relapsed, with a relapse rate of 11.5%. Therefore, it is of great significance to seek biomarkers that can predict the relapse of OVCF after PVP surgery.

Some studies⁹ have shown that interleukin-17 (IL-17) has harmful effects on bone tissue by stimulating osteoclast formation. We consider whether the patients' condition and fracture relapse can be understood indirectly through the level of IL-17. Therefore, we have investigated the effect of zoledronic acid (ZOL) combined with PVP surgery on the level of IL-17 in OVCF patients and the predictive value of IL-17 on OCVF relapse to provide a reference for clinical practice.

Materials and methods

This study uses prospective analysis to collect 101 OVCF postmenopausal patients, aged 55-70 years, admitted to our hospital as the research group. Another 80 healthy people were enrolled as the control group for this study. There was no significant difference in age, weight, and BMI between the two groups ($p>0.05$). The bone mineral density value was significantly lower in the study group than that in the control group ($p<0.05$). In the study group, there were 32 (31.68%) cases of T12 fracture, 36 (35.64%) cases of L1 fracture, and 33 (32.68%) cases of L2 fracture. The operation time was (32.54±5.64) minutes, and the amount of bone cement injection was (4.35±0.79) mL. There were 7 (6.93%) cases of ml disc leakage (Table 1). Inclusion criteria were as follows: The patients in the research group were diagnosed as fresh fractures, any single vertebral body fracture in T11-L2 vertebral body, direct violent injuries, and pathological fractures. Osteoporosis was diagnosed before treatment, and the patients could tolerate surgery. The clinical indicators in the control group were normal. The clinical data of the two groups were complete, and the 2-year follow-up data were

complete. Exclusion criteria were as follows: Patients with multi-segment fractures, patients with a previous history of thoracolumbar surgery, patients with preoperative evaluation unable to tolerate surgery, and patients with liver, kidney, heart, and lung dysfunction, mental diseases, or abnormal brain judgment. This study informed all patients and their families by letters or telephones with the consent of the medical ethics committee of our hospital and signed informed consent. The inclusion criteria of the control group were: menopausal women with good clinical indicators in a physical examination, willing to attend the research; and those without mental illness.

Intervention methods

Research group: Prone position of the patient was taken, an ECG monitoring system was established, the vital signs of the patient were closely monitored, if the blood pressure was too high, medication was used to control the blood pressure. The surgery was carried out simultaneously by two experienced doctors, with the help of Kirschner wire to locate the "cat's eye" on both sides of pathologic vertebrae of the body surface, and C-arm machine was used for fluoroscopy confirmation. It was conventionally disinfected and draped. 10mL 2% lidocaine and 10mL saline mixture were used for local anesthesia. After anesthesia was satisfied, the manual reduction of pathologic vertebrae was carried out first, two assistants operated countertraction of axilla and both lower extremities, the manual reduction of pathologic vertebrae was carried out by the operator. Then both sides of pedicle of vertebral arch were punctured simultaneously with puncture cone to establish working channel. The whole puncture process was monitored by C-arm machine. When the tips of the puncture cones on both sides reached or approached

Table 2. Analysis of prognostic related indicators.

	Before surgery	One month after surgery	t	p
Loss rate of anterior vertebral height (%)	36.54±5.81	13.65±2.25	36.922	<0.001
ODI score	35.68±4.87	15.24±2.68	36.955	<0.001
VAS score	8.42±2.01	2.33±1.54	24.171	<0.001
Cobb angle	25.65±4.31	12.68±2.64	25.789	<0.001

the midcourt line on the positive X-ray display and reached the first 1/3 of the vertebral body on the lateral X-ray display, the surgery of establishing a working channel was completed, the puncture was stopped, the prepared bone cement was respectively injected into the vertebral body from the working channels on both sides, the C-arm machine monitored the whole bone cement injection process, and if bone cement leakage occurred, the injection operation was immediately stopped. After the bone cement was solidified, the puncture working channel was taken out, and the skin punctured by the surgery did not need to be sutured and was covered with sterile dressing. The injection amount of bone cement was generally 1.5~2.0 mL for unilateral thoracic vertebra and 2.0~2.5 mL for unilateral lumbar vertebra. 4 mg of ZOL for injection (SFDA Approval No. H 20041974, Yangzijiang Pharmaceutical Group Co., Ltd.) was diluted with 100 ml of normal saline, and intravenous infusion was given after surgery for 1 day/time for 10 days. Control group: No surgery was performed and the same amount of normal saline was injected intravenously for 1 day/time for 10 days.

Observation indicators

General data of patients were collected, including age, height, weight, fractured vertebral body, bone mineral density, etc. ELISA was used to detect the expression of IL-17 in serum of the two groups before and one month after treatment. The expression of IL-17 before and one month after treatment were compared. The vertebral body height, The Oswestry Disability Index (ODI), the Visual Analogue Score (VAS), and Cobb angle (the angle of intersection between the vertical line of the upper edge of the rostral vertebral body and the vertical line of the lower edge of the caudal vertebral body) were recorded. Relapse in the follow-up patients within 2 years was recorded. The expression of IL-17 before treatment was compared between patients with relapse and patients without relapse. The predictive value of IL-17 in relapse was drawn according to ROC curve.

Statistical methods

The statistical analysis was performed with SPSS 19.0 (International Business Machines Corporation). The Quantitative data were expressed by (n(%)), and the comparison of the rates between the two groups adopted χ^2 test. The qualitative data were expressed by mean±sd.

Table 3. Analysis of prognosis.

	Prognosis
Joint pain	6 (5.94)
Fatigue	7 (6.93)
Lethargy	5 (4.95)
Anorexia	8 (7.92)
Relapse	13 (12.87)

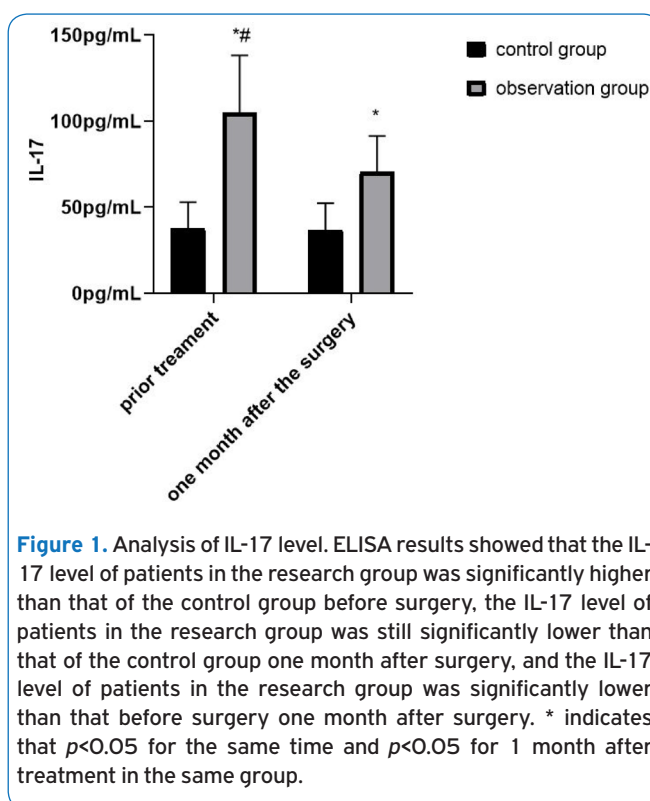


Figure 1. Analysis of IL-17 level. ELISA results showed that the IL-17 level of patients in the research group was significantly higher than that of the control group before surgery, the IL-17 level of patients in the research group was still significantly lower than that of the control group one month after surgery, and the IL-17 level of patients in the research group was significantly lower than that before surgery one month after surgery. * indicates that $p < 0.05$ for the same time and $p < 0.05$ for 1 month after treatment in the same group.

The comparison between the two groups was conducted by independent-samples T-test, ROC curve was used to analyze the predictive value of IL-17 level for OVCF relapse, Kaplan-Meier curve was used to analyze the

2-year recurrence rate of patients in the research group, and $p < 0.05$ was statistically significant.

Results

Analysis of IL-17 level

The expression of IL-17 (104.68 ± 33.59) pg/ml in the research group was significantly higher than that in the control group (37.67 ± 15.32) pg/ml ($p < 0.05$). The level of IL-17 in the research group was still significantly lower than that in the control group (36.88 ± 15.46) pg/ml ($p < 0.05$) one month after surgery. The expression of (78.36 ± 26.85) pg/ml in the research group was significantly lower than that before surgery ($p < 0.05$) (pg/ml) (Figure 1).

Analysis of prognostic related indicators

One month after surgery, the anterior vertebral height loss rate, ODI score, VAS score, and Cobb angle level in the research group were significantly better than those before surgery ($p < 0.05$) (Table 2).

Prognosis analysis

There were 6 (5.94%) cases of joint pain, 7 (6.93%) cases of fatigue, 5 (4.95%) cases of lethargy, and 8 (7.92%) cases of anorexia in the research group during the treatment period. No serious adverse events occurred. The follow-up of the research group for 2 years showed 13 (12.87) cases of relapse (Table 3).

Comparative analysis of IL-17 levels between patients with relapse and patients without relapse

During the follow-up period of 2 years after surgery, there was no significant change in the IL-17 level of patients without relapse. The IL-17 level was taken one year after surgery, and the IL-17 measurement level of patients with relapse was taken from our hospital for follow-up after relapse. The level of IL-17 (70.62 ± 20.84) pg/mL in patients with relapse was significantly higher than that in patients without relapse (40.61 ± 18.67) pg/mL, and the difference was statistically significant ($p < 0.05$) (Figure 2).

Predictive value of IL-17 level for relapse of OVCF

The predictive value of IL-17 level for relapse of OVCF one month after surgery was analyzed. ROC analysis showed that AUC, sensitivity, specificity, and critical level of IL-17 for predicting relapse were 0.854, 89.77%, 69.23%, and 63.02 pg/mL, respectively (Figure 3).

Analysis of risk factors for relapse

The patients were divided into the recurrence group and non-recurrence group according to whether relapse occurred within 2 years after surgery. The results of single-factor analysis of postoperative relapse showed that it was a risk factor for postoperative relapse. Further multifactor

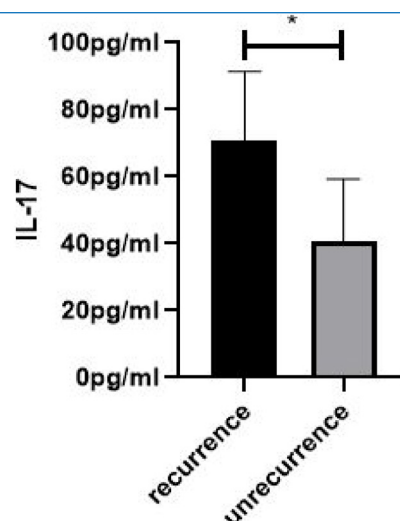


Figure 2. Comparison and analysis of IL-17 levels between patients with relapse and patients without relapse. The level of IL-17 in patients with relapse was higher than that in patients without relapse, and the difference was statistically significant. * indicates that $p < 0.05$.

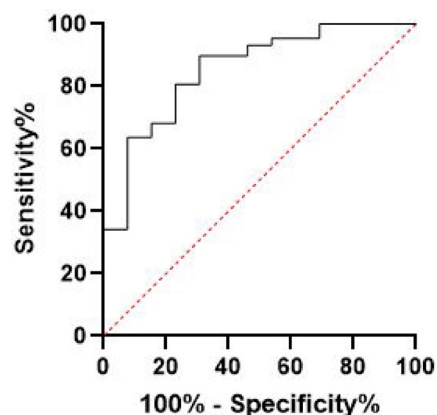


Figure 3. Predictive value of IL-17 level for relapse of OVCF. AUC=0.854.

analysis showed that age, bone mineral density, IL-17 level, and intervertebral disc leakage were independent risk factors for postoperative relapse (Tables 4-6).

Discussion

The prevalence rate of osteoporosis increases with age. OVCF is a common complication of osteoporosis, especially for the elderly. In Europe, the incidence rate of women is 10.7/1000 person/year, while that of men is 5.7/1000 person/year. This has seriously affected the health status

Table 4. Single factor analysis of relapse.

	Relapsed (n=13)	Not relapsed (n=88)	χ^2/t	<i>p</i>
Age (years)			5.139	0.023
<65	2 (15.38)	43 (48.86)		
≥65	11 (84.62)	45 (51.14)		
Weight (kg)	57.14±5.12	57.84±5.84	0.407	0.685
BMI (kg/m ²)	22.85±3.41	22.45±3.69	0.366	0.715
Fractured vertebral body (n(%))				
T12	4 (30.77)	28 (31.82)	0.006	0.940
L1	5 (38.46)	31 (35.23)	0.517	0.820
L2	4 (30.77)	29	0.025	0.875
Bone mineral density (t)	-3.68±0.36	-3.22±0.18	7.234	<0.001
Time of operation (min)	32.84±5.74	32.41±5.36	0.266	0.791
Bone cement injection	4.33±0.52	4.42±0.34	0.816	0.417
Intervertebral disc leakage (n(%))			22.997	<0.001
Yes	5	2		
No	8	86		
IL-17 level (pg/ml) 1 month after surgery	89.62±29.84	72.61±15.67	3.181	0.002
Loss rate of anterior vertebral height (%) after surgery	13.44±2.65	13.62±2.27	0.259	0.796
Cobb angle (°) after surgery	12.54±2.34	12.35±2.36	0.270	0.788

Table 5. Assignment table.

Independent variable	Assignment
Age	<65=0, ≥65=1
Bone mineral density	Continuous variable
IL-17	Continuous variable
Intervertebral disc leakage	Yes =0, No=1
Relapse	Yes=0, No=1

of elderly patients and caused a great burden to society^{10,11}. Some studies^{12,13} show that PVP is a very effective treatment scheme for OVCF, with fast response, effective functional improvement, and better analgesic effect, with fewer complications than conservative treatment, but postoperative relapse is still a problem to be faced. Some studies^{14,15} have pointed out that IL-17 can stimulate local production of osteoclast differentiation factor through inflammatory tissue, increase its expression and secretion, promote osteoclast proliferation and activation, and cause bone destruction. We think that the level of IL-17 may change in patients with relapse due to bone destruction requiring bone cell proliferation. Therefore, we studied the postoperative expression and relapse prediction value of IL-17 in OVCF patients by observing the postoperative level of IL-17 in OVCF patients. In addition, some studies¹⁶ have

pointed out that ZOL can be used to treat or relieve pain. In order to achieve more effective analgesia, better prognosis, and shorter recovery time, we consider the application of ZOL combined with PVP technology for treatment. Therefore, this study explores the expression and relapse value of IL-17 in ZOL combined with PVP technology in the treatment of postmenopausal osteoporotic vertebral compression fracture through prospective analysis so as to provide reference for clinical practice.

In this study, 101 OVCF patients were included as the research group and 80 healthy people as the control group. Patients were treated by ZOL combined with PVP technology, and then the levels of IL-17 in the two groups were compared with those before treatment. Before treatment, the expression of IL-17 in patients in the research group was significantly higher than that in the control group. The expression of IL-17 in patients in the research group was significantly lower after treatment than that before treatment. In addition, we found that BALP and BGP in the study group were higher than those in the control group, and BMD was lower than that in the control group. They all can be used to evaluate the bone structure and metabolism. Therefore, it is speculated that the abnormal expression of IL-17 may also be used to evaluate postmenopausal osteoporotic vertebral compression fractures. Subsequently, we followed up with patients for two years, and 13 patients relapsed. We compared the IL-17 level of patients with relapse and patients without relapse. The level of IL-17 in patients with relapse is significantly higher than that in patients without relapse. Therefore,

Table 6. Multivariate analysis.

	B	S.E.	Wals	df	Sig.	Exp (B)	95%CI	
							Upper limit	Lower limit
Age	0.123	0.058	4.972	1	0.019	1.687	3.167	0.985
Bone mineral density	2.536	0.895	12.454	1	0.023	4.753	7.578	2.547
IL-17	1.652	1.621	6.521	1	0.011	5.362	10.363	1.625
Intervertebral disc leakage	0.057	0.085	4.458	1	0.028	1.524	2.341	1.052

our study believes that the level of IL-17 is expected to be a potential predictor of relapse in postmenopausal OVCF patients. Clinically, there is little research on IL-17 as the prediction index of OVCF, which is the most characteristic part of our research. In addition, we strictly control the inclusion criteria according to the diagnostic criteria, age, and other conditions of OVCF, and strictly abide by the principles of surgery and medication.

A study¹⁷ has pointed out that periostin of postmenopausal women may be a potential biomarker of osteoporosis fracture risk, especially in non-vertebral bone parts, such as limbs, instead of the spine. The study showed that peripheral plasma protein of patients with a non-vertebral fracture is significantly higher than that of patients without fracture, but there is no significant difference in plasma peripheral protein of patients with vertebral fractures. Compared with our research, it measured the predictive value of untreated osteoporotic fracture. Our research points out that the high level of IL-17 is related to its occurrence and high recurrence, and his research points out that the high level of plasma periostin is related to its occurrence, and the research results are consistent. Some studies have pointed out that the interaction between bone and immune system plays an important role in bone internal environment and bone physiological remodeling. Continuous inflammation can stimulate the activity of osteoclasts, leading to bone density decline and eventually lead to fracture. IL-17 plays an important role in promoting¹⁸. After fracture, its location will call polymorphonuclear leukocytes to local tissues, and then the number of polymorphonuclear leukocytes will increase, thus causing systemic inflammatory response syndrome¹⁹. At this time, due to inflammation, lymphocyte secretion increases during the healing process. Osteoblasts and osteoclasts are found to have direct cell-cell contact with lymphocytes. Immune cells have the function of promoting healing in the initial stage and regulating recovery in the later stage. At this time, B lymphocytes will be more than T lymphocytes²⁰. Another related study showed that IL-17 antibody could promote osteoclast transfer and increase the expression of bone lining cells and Wnt10²¹. We suspect that IL-17 plays a continuous destructive role in the continuous process leading to fracture. In the case of acute inflammation after fracture, IL-17 may assist B lymphocytes and T lymphocytes in fracture recovery. In the later stage,

B lymphocytes will be more than T lymphocytes, and its recovery function is greater than the destructive function of IL-17. Patients generally tend to recover, while in the relapse stage, IL-17 will continuously stimulate osteoclasts, thus leading to fracture again. In addition, some studies have pointed out that early PVP surgery is more beneficial to relieve pain and reduce cement leakage and other situations than postponing PVP technology if it adapts to appropriate surgical indications²². Compared with low-viscosity bone cement PVP, high-viscosity bone cement PVP has the same clinical efficacy and fewer complications²³. We consider that early PVP technology of high-viscosity bone cement can be used in relevant research groups in the future to obtain better surgical results. In addition, in the clinical face of osteoporosis and OVCF patients, studies have shown that relevant bone mineral density enhancing drugs and sufficient intake of calcium and vitamin D should be taken, and muscle quality should be improved, weak muscles should be strengthened, and postures should be corrected to achieve better prevention and treatment effects^{24,25}, which also needs to be carried out for a long time after OVCF patients are operated.

In this study, we obtained the high expression of IL-17 in postmenopausal OVCF patients through surgical treatment and 2-year follow-up, and the level of relapsed patients was significantly higher than that of patients without relapse. This is in line with our expected conjecture, but there are still some deficiencies in our study. We discussed the relevant mechanism of IL-17 level and fracture in combination with relevant literature, but our research did not explore the specific relevant mechanism of IL-17 level in OVCF patients, and we consider to explore it in future research. In addition, due to the limited number of patients who meet the relevant inclusion criteria, our study lacks large data samples as a whole, and there will be inevitable errors in the study results. We hope to improve our shortcomings in future research.

Conclusion

IL-17 is highly expressed in postmenopausal OVCF patients and is expected to be a potential predictor of relapse in postmenopausal OVCF patients.

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