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Expression and significance of cytokines in peripheral blood and bone microenvironment in Kummell's disease, osteoporotic vertebral compression fractures and nonosteoporotic patients

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Abstract

Objective To analyze the expression and determine the significance of cytokines in peripheral blood and vertebral blood in the bone microenvironment of patients with osteoporotic vertebral compression fractures (OVCFs) and Kummell's disease (KD).

Methods From October 2022 to April 2023, 16 patients with osteoporotic vertebral compression fracture (OVCF), 14 patients with Kummell (KD) disease, and 19 patients with lumbar degenerative disease were included in the study. The patients were divided into the OVCF group, KD group and control group. The levels of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) in peripheral blood and vertebral blood in the bone microenvironment were detected by enzyme-linked immunosorbent assay. Receiver operating characteristic (ROC) curve analysis was used to determine the correlation between cytokines and the occurrence of OVCF and KD.

Results The levels of IL-1, IL-6, TGF-β and TNF-α in vertebral blood in the bone microenvironment of the KD group were significantly higher than those in peripheral blood ($p=0.001$, $p<0.001$, $p=0.017$, $p<0.001$). Compared with the control group, the OVCF displayed a marked increase in the expression of IL-1, IL-6, and TNF-α and a significant reduction in the expression of TGF-β ($p<0.001$). In addition, compared with the vertebral blood in the bone microenvironment of the control group, the levels of IL-1, IL-6 and TNF-α in the vertebral blood in the bone microenvironment of the KD group were significantly increased ($p<0.001$). and compared with the vertebral blood in the bone microenvironment of OVCF group, the levels of IL-1, IL-6 and TNF-α in the vertebral blood in the bone microenvironment of the KD group were significantly increased ($p=0.014$, $p=0.020$, $p=0.006$). Moreover, Compared to peripheral blood, the vertebral blood within the bone microenvironment demonstrated increased area under the curve (AUC) values for the associations of IL-1, IL-6, and TNF-α with OVCF and Kummell's disease KD.

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Conclusions The expression levels of IL-1, IL-6 and TNF-α in OVCFs and KD were increased, but that of TGF-β was decreased. The levels of IL-1, IL-6 and TNF-α in the vertebral blood of KD patients were significantly increased, which can promote vertebral osteonecrosis and bone nonunion in KD patients. Alterations in the expression levels of these proinflammatory cytokines maybe demonstrate a significant correlation with the pathogenesis of OVCF and KD.

Keywords Cytokines, Kummell's disease, Bone microenvironment, Osteoimmunology, Osteoporosis, Osteoporotic vertebral compression fractures

Introduction

Osteoporosis is a condition characterized by systemic damage, such as decreased bone mass, weakened strength, and disruption of bone microstructure, which increases the tendency for fragility fractures and mainly affects the aging population [1, 2]. It has been established that patients affected with osteoporosis are prone to osteoporotic vertebral compression fractures (OVCFs) and Kummell's disease (KD). Vertebral compression fracture secondary to osteoporosis can lead to morbidity and even death in older adults. OVCF often results in persistent pain, kyphotic deformity, weight loss, depression, and decreased quality of life [3]. Kummell's disease was first described by Kummell in 1895 [4]. This complicated spinal disease is characterized by back pain, neurological deficits, or kyphotic deformities that can occur after a few weeks or months of asymptomatic period following a minor trauma. The main features include vertebral collapse, intravertebral cleft (IVC) and double-line sign after trauma [5].

The physical stability of the bone is primarily maintained through the relative balance between bone resorption and bone formation. Osteoblasts (OB) contribute to the formation of bone tissue, whereas osteoclasts (OC) can absorb bone tissue. The imbalance of OB and OC activities serves as a key factor in the occurrence and development of osteoporosis. A number of prior studies have indicated that the immune system and the bone system can effectively interact through cytokines, transcription factors, signaling molecules, and membrane receptors. For instance, immune-derived cytokines can potentially regulate the function of osteoblasts, osteoclast progenitors, and mature osteoclasts [6, 7]. The stimulatory inflammatory cytokines that can promote osteoclast generation and bone resorption include IL-1, IL-6, and TNF-α, whereas cytokines that can stimulate bone formation include TGF-β [6–8]. The potential relationship between bone remodeling and cytokines plays a vital role in patients with OVCF or KD. Vertebral bone remodeling can be functionally regulated by 1,25-dihydroxyvitamin D, sex hormones, parathyroid hormone, growth hormone and thyroid hormone in the body. However, vertebral bone remodeling is mainly regulated by a series of different growth factors and cytokines in the local microenvironment. Currently, there are few reports describing the potential relationship between cytokine expression levels and OVCF or KD. Furthermore, to our knowledge, the possible relationship between OVCF or KD and cytokine expression levels in the local vertebral bone microenvironment has not been reported previously.

In this study, we examined the levels and interactions of cytokines expressed in the peripheral blood and vertebral blood in the bone microenvironment of patients with degenerative lumbar diseases, OVCF and KD. We also analyzed the potential clinical application of cytokines in the diagnosis and treatment of OVCF and KD and provided relevant opinions.

Methods

Participant selection

Sixteen inpatients diagnosed with OVCF from October 2022 to April 2023 in our hospital were selected as the observation group OVCF, and 14 inpatients diagnosed with Kummell's disease were selected as the observation group KD for this study (Fig. 1). At the same time, 19 inpatients who were subjected to conventional posterior lumbar open surgery in our hospital were selected as the control group (CG), including five patients with lumbar disc herniation with instability, eight patients with lumbar spinal stenosis and six patients with lumbar spondylolisthesis.The study protocol was approved by the Ethics Committee of authors' affiliated institution. All patients included in this study provided a written informed consent.

The inclusion criteria for osteoporotic vertebral compression fractures were as follows: (1) age $\geq$ 50 years with symptomatic low back pain without any neurological symptoms or signs; (2) computed tomography (CT) or magnetic resonance imaging (MRI) showing fresh vertebral compression fractures (evidenced by vertebral compression or collapse); and (3) bone mineral density (BMD T score ≤ -2.5). The inclusion criteria for Kummell's disease were as follows: (1) age $\geq$ 50 years with symptomatic low back pain, without any neurological symptoms or signs; (2) CT or MRI displaying vertebral collapse with bone necrosis as well as positive signs

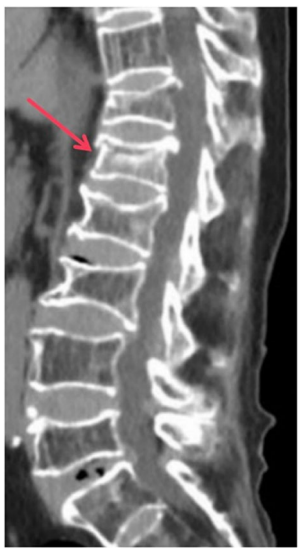

Fig. 1 A 73-year-old female patient was admitted to the hospital with persistent low back pain lasting 20 days. Imaging studies confirmed a diagnosis of Kummell's disease at the L1 vertebra, demonstrating osteonecrosis of the L1 vertebral body

of intravertebral cleft and double-line; and (3) BMD T score ≤ -2.5. The inclusion criteria for the control group were (1) age ≥ 50 years and (2) BMD T score > -2.5.

The exclusion criteria were as follows: (1) patients with malignant tumors, severe coagulation disorders, or hematological diseases; (2) patients with bacterial or viral infections such as pneumonia, influenza, human immunodeficiency virus (HIV), hepatitis B, stroke, or acute myocardial infarction; (3) patients with hepatic and renal insufficiency; (4) patients who had been treated with glucocorticoids or immunosuppressive agents for a long time or those with immune dysfunction; (5) patients with secondary vertebral compression fractures caused by the presence of other diseases such as vertebral tumors or tuberculosis; (6) patients suffering from endocrine diseases (such as Cushing's syndrome, hyperthyroidism, hyperparathyroidism, Paget's disease); and (7) patients who could not tolerate surgery or refused to participate in this study.

All patients were made aware of the study objectives, and informed consent was obtained from them. The study also received ethical approval from the Ethics Committee of the Affiliated Hospital of Southwest Medical University and strictly followed the guidelines of the Declaration of Helsinki (KY2023265).

Bone mineral density measurement

The BMD of the lumbar spine was measured by our hospital's senior radiology staff using a dual-energy X-ray (010–0575, Hologlc, USA) absorptiometry instrument (L1-4). When measuring the BMD, the patient was made to lie supine, and all metal objects were removed from their body. The scanning system was then used to check the BMD of the L1-4 vertebral bodies in sequence, vertically above the patient's body plane. The lowest value of the BMD of the L1-4 vertebral bodies was then recorded.

Blood sampling methods

The blood sampling and processing procedures for all the participants were identical. The peripheral blood and vertebral blood in the bone microenvironment were collected simultaneously on the day of the surgery after admission (fasting for at least 8 h before surgery). Peripheral blood: Approximately two milliliters of peripheral blood was collected by the medical staff in the elbow vein of the upper limb of the patient by using a blood sampling needle and a blood collection vessel without heparin. In the control group, after establishing the screw path and before inserting the pedicle screw, a five centimeters long needle that was connected with a five milliliters empty needle was used by the surgeon to enter the vertebral body along the screw path. Thereafter, approximately two milliliters of vertebral blood was sucked, and a blood collection vessel without heparin was placed immediately. In the OVCF group and KD group, approximately two milliliters vertebral blood was sucked by the surgeon using a five milliliters empty needle connected with the working channel after setting up the working channel during the operation and before balloon opening of the vertebral body. The blood was then quickly inserted into the blood collection vessel without heparin. The collected specimens were centrifuged at 3000 g at 4°C for 10 min. The resulting serum was packed into Eppendorf (EP) tubes and immediately stored at −80°C for future unified testing.

Detection of cytokines

An enzyme-linked immunosorbent assay kit (ELISA, Jianglai Biology, Shanghai, China) was used to detect the concentrations of IL-1, IL-6, TGF-β and TNF-α in the peripheral blood and vertebral blood. All cytokines were tested twice, and the average value of the cytokine concentrations from the two tests was recorded. If the coefficient of variation was > 20%, the sample was retested. The experimental steps strictly followed the manufacturer's instructions.

Statistical analysis

All the data were statistically analyzed using SPSS 24.0 software (SPSS Inc., Chicago, IL, USA). The measurement data are expressed as the mean ± standard deviation. Independent sample t tests were used for intergroup comparisons when the data were normally distributed,

but nonparametric tests were used when the data were not normally distributed. Fisher's exact test was used to estimate the count data. A paired t test was used for the comparison of cytokines in the peripheral blood and vertebral blood. ROC curve analysis was used for the cytokines and whether they were OVCF or KD. $P<0.05$ was considered statistically significant.

Results

Patient baseline characteristics

There was no statistically significant difference observed in age, sex, BMI, ODI index, VAS score, smoking history, alcohol consumption history, history of hypertension, or history of diabetes among the three groups that were analyzed ($P>0.05$). The BMD T scores of the OVCF group and the KD group were significantly lower than that of the control group ($P<0.05$) (Table 1).

Comparison of peripheral blood and vertebral blood cytokines

There was no significant difference noted in the concentrations of IL-1, IL-6, TNF-α and TGF-β in either the peripheral blood or vertebral blood in the control group ($P>0.05$). Interestingly, in the OVCF group, there was also no significant difference in the concentrations of IL-1, TNF-α and TGF-β between the peripheral blood and vertebral blood ($P>0.05$), but the concentration of IL-6 in vertebral blood was significantly higher than that in peripheral blood ($P<0.05$). The concentrations of IL-1, IL-6, TNF-α and TGF-β in the vertebral blood were significantly increased in the KD group ($P<0.05$) (Table 2).

Comparison of the expression of cytokines among the three groups

In both the OVCF and KD groups, the concentrations of IL-1, IL-6 and TNF-α in the peripheral blood and vertebral blood were significantly higher than those in the control group ($P<0.05$), but TGF-β concentrations in the peripheral and vertebral blood were significantly lower than those in the control group ($P<0.05$). There were no significant differences observed in the concentrations of IL-1, IL-6, TNF-α and TGF-β in peripheral blood between the KD group and OVCF group ($P>0.05$). However, compared with the OVCF group, the concentrations

Table 1 General characteristics and comparisons of the three groups

Indicators	GC ($n=19$)	OOVCF ($n=16$)	KD ($n=14$)	*p*
Age (years, x ± s)	42.1	68.8	57.1	0.283
Female (%)	68.79 (4.05)	71.50 (4.54)	70.79 (4.61)	0.174
BMI (kg/m2, x ± s)	22.16 (1.80)	20.69 (1.96)	21.50 (2.71)	0.141
T-score	−0.83 (1.21)	−3.60 (1.00)	−3.62 (1.10)	< 0.001
ODI index	64.32 (5.06)	67.19 (5.72)	66.64 (3.05)	0.184
VAS score	6.11 (0.81)	6.50 (0.73)	6.43 (0.76)	0.278
Smoking history (%)	26.3	25.0	28.6	0.976
Alcohol consumption history (%)	26.3	12.5	28.6	0.503
Hypertension history (%)	21.1	31.3	35.7	0.627
Diabetes history (%)	15.8	18.8	21.4	0.917

Table 2 Comparison of expression levels of cytokines in the peripheral blood and vertebral blood

cytokines	CG Peripheral blood	CG Vertebral blood	*P*	OVCF Peripheral blood	OVCF Vertebral blood	*P*	KD Peripheral blood	KD Vertebral blood	*P*
IL-1 (pg/ml)	147.46 (85.64)	158.71 (76.44)	0.209	349.98 (218.18)	416.59 (246.96)	0.122	341.94 (172.11)	1207.01 (852.60)	0.001
IL-6 (pg/ml)	8.64 (2.78)	7.76 (3.08)	0.125	19.09 (8.54)	25.36 (10.23)	< 0.001	40.86 (20.06)	58.83 (19.44)	< 0.001
TNF-α (pg/ml)	26.07 (10.11)	25.14 (9.44)	0.643	50.93 (14.80)	49.80 (11.79)	0.609	67.76 (16.71)	95.78 (19.48)	< 0.001
TGF-β (ng/ml)	17.26 (6.05)	17.17 (7.34)	0.959	5.84 (4.20)	7.96 (4.56)	0.137	5.96 (3.04)	7.50 (2.93)	0.017

The data in the table represent average values and the data indicated in brackets are standard deviations; O, OVCF; K, KD

of IL-1, IL-6, and TNF-α in the vertebral blood of the KD group were significantly higher ($P<0.05$), but there was no statistically significant difference in the concentrations of TGF-β in vertebral blood of the KD group ($P>0.05$) (Table 3).

ROC curve analysis of OVCF and cytokines

ROC curve analysis of cytokines in the OVCF and control groups is shown in Table 4 and Fig. 2, respectively. The AUC of IL-1 in the peripheral blood for diagnosing OVCF was 0.872 (95% CI = 0.745 ~ 0.998, $P<0.05$). The AUC of IL-6 in the peripheral blood for diagnosing OVCFs was 0.974 (95% CI = 0.920 ~ 1, $P<0.05$). The AUC of TNF-α in the peripheral blood for diagnosing OVCF was 0.928 (95% CI = 0.847 ~ 1, $P<0.05$). The AUC of IL-1 in the vertebral blood for diagnosing OVCF was 0.898 (95% CI = 0.797 ~ 0.999, $P<0.05$). The AUC of IL-6 in the vertebral blood for diagnosing OVCF was 0.987 (95% CI = 0.960 ~ 1, $P<0.05$). The AUC of TNF-α in the vertebral blood in the bone microenvironment for diagnosing OVCF was 0.938 (95% CI = 00.863 ~ 1, $P<0.05$). These results indicated that IL-1, IL-6 and TNF-α in peripheral blood and vertebral blood had certain sensitivity and specificity for the diagnosis of OVCF, but IL-1, IL-6 and TNF-α in vertebral blood were more accurate for the diagnosis of OVCF. IL-1, IL-6 and TNF-α may serve as potential serum markers for the diagnosis of OVCF.

ROC curve analysis of KD and cytokines

The ROC curve analysis results of cytokines between the KD and control groups are shown in Table 5 and Fig. 2. The AUC of IL-1 in the peripheral blood for diagnosing KD was 0.868 (95% CI = 0.749 ~ 0.988, $P<0.05$). The AUC of IL-6 in the peripheral blood for diagnosing KD was 1.0 (95% CI = 1 ~ 1, $P<0.05$). The AUC of TNF-α in the peripheral blood for diagnosing KD was 0.989 (95% CI = 0.964 ~ 1, $P<0.05$). The AUC of IL-1 in the vertebral blood for diagnosing KD was 1.0 (95% CI = 1 ~ 1, $P<0.05$). The AUC of IL-6 in the vertebral blood for diagnosing KD was 1.0 (95% CI = 1 ~ 1, $P<0.05$). The AUC of TNF-α in vertebral blood for diagnosing KD was 1.0 (95% CI = 1 ~ 1, $P<0.05$). These results suggested that IL-1,

Table 3 The expression of cytokines in the three groups was compared and was compared them in pairs

	cytokines	CG	OVCF	KD	P	P (CG VS O)	P (CG VS K)	P (O VS K)
Peripheral blood	IL-1 (pg/ml)	95.51 (166.04)	322.81 (164.41)	288.05 (199.04)	< 0.001	< 0.001	0.001	1.000
	IL-6 (pg/ml)	7.94 (3.38)	15.82 (6.10)	39.99 (21.90)	< 0.001	0.001	< 0.001	0.056
	TNF-α (pg/ml)	24.65 (18.84)	45.47 (26.72)	68.92 (30.01)	< 0.001	0.001	< 0.001	0.199
	TGF-β (ng/ml)	16.42 (8.68)	4.27 (6.00)	5.45 (4.32)	< 0.001	< 0.001	< 0.001	1.000
Vertebral blood	IL-1 (pg/ml)	137.46 (131.78)	369.84 (237.93)	798.48 (903.88)	< 0.001	0.006	< 0.001	0.014
	IL-6 (pg/ml)	6.58 (2.88)	22.79 (13.98)	54.40 (22.91)	< 0.001	0.001	< 0.001	0.020
	TNF-α (pg/ml)	21.99 (12.72)	51.13 (19.87)	91.30 (27.83)	< 0.001	0.005	< 0.001	0.006
	TGF-β (ng/ml)	15.70 (7.58)	6.40 (6.18)	7.72 (4.69)	< 0.001	< 0.001	< 0.001	1.000

The data in table are median, and the data in brackets are interquartile range; O, OVCF; K, KD

Table 4 Results of ROC analysis of cytokines to determine whether OVCF or not

	cytokines	optimal threshold	AUC	sensitivity	specificity	95%CI
Peripheral blood	IL-1	320.608	0.872	0.625	1.0	0.745 ~ 0.998
	IL-6	13.246	0.974	1.0	0.947	0.920 ~ 1
	TNF-α	37.267	0.928	0.875	0.842	0.847 ~ 1
Vertebral blood	IL-1	235.196	0.898	0.813	0.842	0.797 ~ 0.999
	IL-6	13.488	0.987	1.0	0.895	0.960 ~ 1
	TNF-α	30.309	0.938	1.0	0.789	0.863 ~ 1

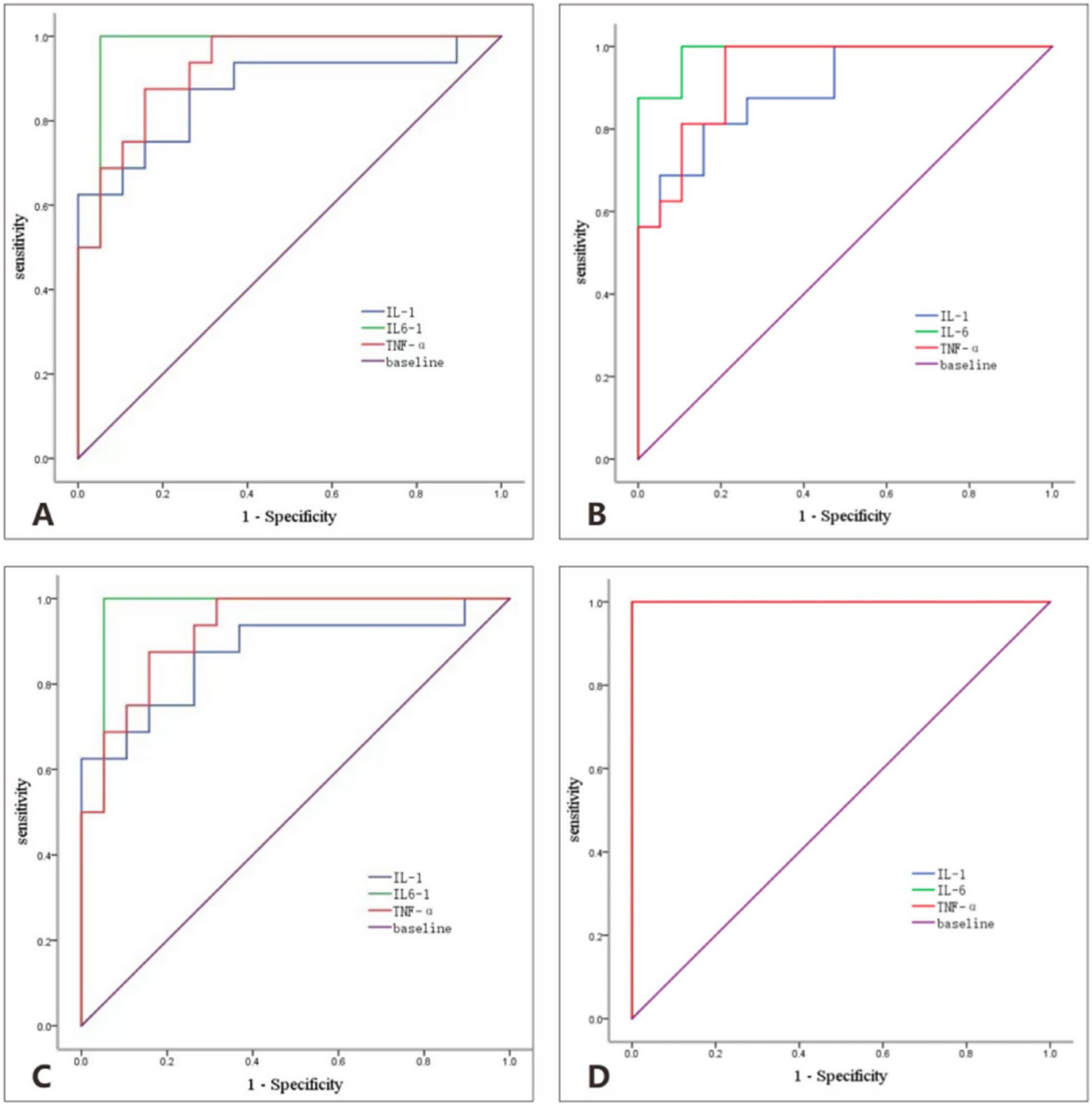

Fig. 2 **A** ROC curve of peripheral blood cytokines in predicting OVCF. **B** ROC curve of vertebral blood cytokines in predicting OVCF. **C** ROC curve of peripheral blood cytokines in predicting KD. **D** ROC curve of vertebral blood cytokines in predicting KD

Table 5 Results of ROC analysis of cytokines to determine whether KD or not

	cytokines	optimal threshold	AUC	sensitivity	specificity	95%CI
Peripheral blood	IL-1	277.845	0.868	0.643	0.947	0.749 ~ 0.988
	IL-6	15.669	1.0	1.0	1.0	1 ~ 1
	TNF-α	38.905	0.989	1.0	0.895	0.964 ~ 1
Vertebral blood	IL-1	590.799	1.0	1.0	1.0	1 ~ 1
	IL-6	35.159	1.0	1.0	1.0	1 ~ 1
	TNF-α	69.547	1.0	1.0	1.0	1 ~ 1

IL-6 and TNF-α in the peripheral blood and vertebral blood exhibited certain sensitivity and specificity for the diagnosis of KD, but IL-1, IL-6 and TNF-α in the vertebral blood could serve as more accurate biomarkers for the diagnosis of KD. IL-1, IL-6 and TNF-α may be potential serum markers for the diagnosis of KD.

Discussion

The term "osteoimmunology" was first coined in 2000, when Aaron and Choi examined the interaction between the immune system and the skeletal system [9]. Osteoimmunology is an interdisciplinary research field that combines aspects of both orthopedics and immunology [10]. A number of prior studies have indicated that the immune system may participate in the pathogenesis of osteoporosis by regulating the activity of osteoblasts and osteoclasts through cytokines [6, 7, 10, 11]. However, few studies have reported the possible relationship between cytokines and the complications associated with osteoporosis, such as OVCF and KD.

We systematically analyzed the expression levels of several cytokines that can promote bone resorption and bone formation in the peripheral and vertebral blood of patients with lumbar degenerative disease, OVCF and Kummell disease. We found that the levels of IL-1, IL-6 and TNF-α in the vertebral blood of the KD group were significantly higher than those in the peripheral blood. These results indicated that the local microenvironment of the diseased vertebral body in KD patients was relatively independent and can be used as an independent compartment that can play a pivotal role in disease progression. This observation could lead to a novel strategy to study KD.

Additionally, we observed that both the OVCF and KD groups had significantly higher levels of IL-1, IL-6, and TNF-α and significantly lower expression levels of TGF-β. There was no difference noted in the levels of IL-1, IL-6 and TNF-α in the peripheral blood between the OVCF group and KD group. However, in the local microenvironment of vertebral bone remodeling, the levels of IL-1, IL-6 and TNF-α in the KD group were found to be significantly higher than those in the OVCF group. As a complex spinal disease, KD is commonly characterized by intravertebral cleft (IVC), osteonecrosis and nonunion in the vertebral body. The specific mechanism underlying the development of KD is still controversial. Bone remodeling is the absorption of old and damaged bone by osteoclasts, which are then replaced by new bone deposited by osteoblasts [12].

IL-1 can mediate osteoclast (OC) generation and inhibit apoptosis through the RANK-RANKL-OPG signaling pathway, leading to increased bone resorption and disruption of the balance between bone resorption and formation [13, 14]. IL-1 can also upregulate the expression of Dickkopf-1 (DKK-1) and sclerostin (Wnt protein antagonist) to inhibit osteoblast (OB) activity and effectively reduce bone formation [15]. Reduction of IL-1 in a mouse model exerted an important effect on the bone microenvironment, resulting in reduced bone resorption, increased trabecular thickness, and bone growth [16]. IL-6, once bound to sIL-6R, can also activate the SHP2/MEK/ERK and SHP2/PI3K/PKB pathways, thereby inhibiting OB bone formation as well as OB mineralization [17]. IL-6 can also downregulate the expression of various genes related to OB, thus leading to decreased bone formation [18]. Elevated IL-6 levels can be used as a potential marker of active osteoclast function [19]. TNF-α can directly bind to TNFRI on preosteoclasts to promote bone resorption by osteoclasts [20]. TNF-α can also promote RANKL secretion, enhance OC activity and bone resorption, and activate the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) signaling pathway to stimulate RANKL-induced OC differentiation [20–22]. TNF-α can also activate the c-Jun N-terminal kinase (JNK) signaling pathway to upregulate the expression of Semaphorin3D, which can also serve as a modulator of osteoclast proliferation as well as OC differentiation [23]. In addition, the combined action of IL-1, IL-6, and TNF-α can substantially enhance OC activity [24].

In this study, IL-1, IL-6, and TNF-α were abundantly expressed in the local bone microenvironment of KD. It has been established that large amounts of IL-1, IL-6, and TNF-α can promote osteoclasts, inhibit osteoblasts, and destroy the balance between bone resorption and bone formation. Whenever there is an imbalance between bone resorption and bone formation, the physiological bone remodeling process can be transformed into a pathological state, thus causing bone tissue destruction and eventually leading to osteopenia or osteolysis [25]. Therefore, we speculate that increased expression levels of IL-1, IL-6, and TNF-α in the bone microenvironment of KD patients could contribute to the occurrence of intravertebral cleft and nonunion of osteonecrosis in the vertebral body. The pathogenesis of KD includes avascular osteonecrosis, microfractures, atrophic nonunion, and nutrition-injured fractures [26]. Overall, the findings of our study provide important new clues to the pathogenesis of KD.

Although peripheral blood is more readily available for clinical studies, peripheral blood cytokine levels may not accurately reflect the expression levels of different cytokines expressed in the vertebral bone microenvironment compared with vertebral blood cytokines. The bone microenvironment of OVCF and KD accurately reflected TNF-α, IL-1, and IL-6 levels in the injured vertebrae. However, TNF-α, IL-1, and IL-6 levels in the bone

microenvironment have been found to be more accurate in predicting OVCF and KD.

There are some limitations associated with our study. Due to the small number of eligible clinical patients, especially KD patients, it may be difficult to represent the overall situation of OVCF and KD patients. In addition, only four representative markers of bone turnover were detected in this study, which could not fully reflect the possible relationship between cytokines and OVCF and KD. Moreover, as it was not possible to compare the cytokine levels in diseased patients with the vertebral blood from healthy middle-aged and elderly people, the control group in this experiment was patients with degenerative lumbar disease.

In the future, the sample size should be increased, the levels of a greater number of cytokines should be detected, and multicenter samples should be collected to increase the reliability and universality of the experiment. Finally, mechanistic experiments should be conducted to verify the potential relationship between cytokines and KD.

Conclusion

In summary, this study revealed that the expression levels of IL-1, IL-6 and TNF-α in OVCFs and KD were significantly increased, whereas the expression level of TGF-β was decreased. The expression levels of IL-1, IL-6 and TNF-α in the vertebral microenvironment of KD were significantly increased, which could effectively promote the occurrence of vertebral osteonecrosis and nonunion in KD. The alterations in expression levels of these proinflammatory cytokines exhibit significant correlations with the occurrence of OVCF and KD, thereby providing novel mechanistic insights for advancing our understanding of these pathological conditions.

Abbreviations

OVCF	Osteoporotic vertebral compression fractures
KD	Kummell's disease
CG	Control group
IL-1	Interleukin-1
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-α
TGF-β	Transforming growth factor-β
IVC	Intravertebral cleft
OB	Osteoblasts
OC	Osteoclasts
BMD	Bone mineral density
VAS	Visual analog scale
ODI	The Oswestry Disability Index
CT	Computer Tomography
MRI	Magnetic Resonance Imaging
ROC	Receiver operating characteristic
AUC	The area under curve
PI3K	Phosphatidylinositol 3 kinase
AKT	Protein kinaseB

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Disclosure
The authors declared that they have no conflicts of interest to this work.

Authors' contributions
S.W. conceived and designed the study and gave final approval to the article. Z.Y.L and Q.X.Y. co-designed the study, analyzed the data, completed the trial and drafted the manuscript.Z.Y.L and Q.X.Y. share the first authorship, due to equal contributions.Y.Z.N. and S.X. collected the data. J.Y.Yand Q.W. drew the images and analyzed the data. All the authors gave permission to publish this article.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
The study also received ethical approval from the Ethics Committee of the Affiliated Hospital of Southwest Medical University and strictly followed the guidelines of the Declaration of Helsinki(KY2023265).This study was retrospectively registered.Registration number:ChiCTR2300075907.Registration date:2023–09-19.

Consent for publication
All authors gave their consent for publication。

Competing interests
The authors declare no competing interests.

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