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Clinical significance of microRNA-328-3p and bone metabolism biomarkers in gout patients with different musculoskeletal ultrasonography imaging

Qingqing Song[1†], Lifang Xue[1†], Jie Ren[1], Xiaoyu Liu[1], Guilei Li[2], Congcong Liu[2] and Xin Meng[1*]

Abstract

Aims MicroRNA (miRNA) participates in the pathophysiological processes of multiple metabolic diseases, including gout. In gout patients, there is concomitant derangement of bone metabolism. The study aimed to explore the correlation of different ultrasonic manifestations and miR-328-3p levels with bone metabolic markers in gout patients.

Methods A total of 320 gout patients were grouped according to musculoskeletal ultrasound (MSUS) imaging. Serum osteocalcin (BGP), C-terminal telopeptide of type I collagen (CTX-I) and osteopotin (OPN) levels were detected to evaluate bone metabolism. Serum miR-328-3p levels were detected via qRT-PCR. Pearson's correlation analysis was performed to explore the relationships between the variables.

Results Patients with tophi accompanied by bone erosion demonstrated significantly elevated levels of BGP and OPN compared to those with tophi or aggregate of MSU crystals in the absence of bone erosions. Cases with long course of disease exhibited more severe bone destruction. Cases without specific clinical manifestations presented the highest levels of serum miR-328-3p, whereas those with bone erosions demonstrated the lowest values. Significantly negative correlations were also detected for serum miR-328-3p levels with BGP and OPN values in all gout patients.

Conclusion Serum miR-328-3p levels were associated with diverse MSUS manifestations in gout patients. MSUS imaging and miR-328-3p levels are capable of reflecting the joint impairment in gout patients.

Keywords Bone metabolism, miR-328-3p, Gout, Musculoskeletal ultrasound

†Qingqing Song, Lifang Xue the first two authors contributed equally to this work.

*Correspondence:
Xin Meng
mengxin_shengli@163.com
[1]Department of Ultrasonography, Shengli Oilfield Central Hospital, No. 31 jinan road, Dongying 257000, Shandong, China
[2]Clinical Laboratory, Shengli Oilfield Central Hospital, Dongying, China

Introduction

Gout is a metabolic disease precipitated by aberrant uric acid metabolism within the body, leading to the deposition of urate crystals in the joint cavity or the connective tissue of the joint [1]. In China, gout has emerged as the second most prevalent metabolic disease, following diabetes mellitus [2]. The principal clinical manifestations of gout encompass joint swelling, heat pain, and tophi deposition, which seriously impinge upon patients' daily activities and quality of life [3]. Owing to its high sensitivity and specificity, ultrasonography serves as a crucial imaging modality for the diagnosis of gout. Ultrasound is characterized by its simplicity, safety, and relatively low cost, rendering it highly favored by both clinicians and patients [4]. Ultrasonic examination can intuitively reflect the alternations in gout crystals. This property is of great assistance in understanding the progression of patients' conditions and formulating accurate treatment strategies [5]. Recent research findings have indicated that gout patients are concurrently afflicted by derangements in bone metabolism [6]. The deposition of urate within the joint cavities of gout patients can instigate an upregulation in osteoclast activity. The bone metabolism index can sensitively mirror the alterations in bone and joint injury in gouty arthritis [7]. Nevertheless, there exists a paucity of reports regarding the correlation between different ultrasonographic manifestations of gout and bone metabolic markers.

MicroRNA (miRNA) represents a class of small RNA, approximately 18–25 nucleotides in length, which are ubiquitously present in eukaryotes. It exerts a pivotal role in modulating the cell cycle, as well as cellular proliferation and differentiation processes. Accumulating evidence has demonstrated that miRNAs are intricately involved in the regulatory mechanism of a diverse spectrum of musculoskeletal conditions, such as tendon injuries, osteoarthritis, rheumatoid arthritis, and so on [8–12]. Moreover, they hold great potential as biomarkers for the accurate diagnosis and prognosis assessment of diseases [13]. For example, in THP-1 cells, miR-146a upregulation can suppress the release of pro-inflammatory factors induced by monosodium urate (MSU) crystals [14]. Downregulated miR-223-3p and miR-22-3p have been detected in acute gouty arthritis mice, and their upregulation can alleviate gout-induced inflammatory response [15]. miR-328-3p has been reported to be related to bone metabolism [16, 17]. In fracture patients, downregulated miR-328-3p is determined to be correlated with the inactivation of alkaline phosphatase (ALP) [17]. MiR-328-3p has its function in regulating fracture healing through modulating the activity of osteoblasts and engaging in the regulation of bone metabolism [18]. Furthermore, miR-328-3p has been reported to serve as a crucial mediator in the inflammatory response within a variety of human diseases [19, 20]. Considering the significant role of miR-328-3p in bone metabolism and inflammatory disorders, the expression profile of miR-328-3p in gouty arthritis has aroused substantial interest among us.

Therefore, in the present study, a total of 320 gout patients were stratified into groups based on the outcomes of ultrasonography, and serum miR-328-3p levels were assayed. In accordance with the obtained results, the correlations of different ultrasonic manifestations and miR-328-3p levels with bone metabolic markers were evaluated. The aim was to explore the roles of miR-328-3p and musculoskeletal ultrasound (MSUS) in the diagnosis and surveillance of gout.

Materials and methods

Study subjects

A total of 320 gout patients were enrolled under the approval of the Ethnic Committee of Shengli Oilfield Central Hospital, all cases received musculoskeletal ultrasound examination. Based on the outcomes of MSUS, all patients were divided into three groups. Group A ($n = 100$): MSUS imaging manifested no specific manifestation; Group B ($n = 113$): MSUS imaging showed tophi or aggregate of MSU crystals or "double track sign"; Group C ($n = 107$): MSUS imaging manifested bone erosions with or without tophi or aggregate of MSU crystals or "double track sign".

Inclusion criteria: (1) aged from 18 to 70 years old; (2) met the diagnostic criteria for gout [21]; (3) with complete clinical data. Exclusion criteria: (1) had a previous history of other osteoarthritis; (2) with a recent fracture; (3) with secondary gout caused by other causes such as drugs and blood diseases; (4) patients concurrently diagnosed with rheumatoid arthritis; (5) with major organ dysfunctions, such as cardiac, hepatic, and renal insufficiencies.

MSUS

All patients underwent MSUS (Mindray, M58) examination. The probe frequency ranged from 7 ~ 18 MHz, and the examination targeted the metatarsophalangeal joint of the toes, ankle joint, knee joints, wrist joints and other joints commonly affected by gout. For the examination of the knee joint, the patient was placed in supine position. To examine the ankle joints and metatarsophalangeal joints of the toes, the patient was required to assume the supine kneeling position. When examining the wrist and elbow joints, the patient took a seated position and placed the arm naturally straight on the examination bed. The scanning exploration aimed to observe the presence of MSU crystal aggregates, the double-track signs, bone destruction, synovial hyperplasia, joint effusion, etc.

Bone metabolism index detection

5 mL of fasting venous blood was collected from all patients. The serum and plasma were separated and stored at -20℃. Serum osteocalcin (BGP), C-terminal telopeptide of type I collagen, (CTX-I) and osteopotin (OPN) levels were measured using the enzyme-linked immunosorbent assay (ELISA) technique. All the ELISA kits were purchased from Shanghai Enzyme-Linked Biotechnology Co., LTD.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Peripheral blood samples were centrifuged at 4 ℃ for 10 min to isolate serum. Total RNA was extracted from the serum using TRIzol reagent. After measuring the concentration and purity of total RNA by microspectrophotometer, total RNA was reversely transcribed into complementary DNA (cDNA). Then qRT-PCR was performed using cDNA as a template. Relative levels of miR-328-3p were calculated using $2^{-\triangle\triangle Ct}$ method, and U6 was employed as the reference gene.

Statistical analysis

Using SPSS 21.0 software to compare data and calculate the mean value and standard deviation (SD). Chi-square test was employed for group comparison for categorical variables, while ANOVA comparisons by Turkey post hoc test for multiple comparisons of continuous variables. Pearson correlation analysis was used to evaluate the correlation among the indexes. Receiver operating curve (ROC) was used to evaluate the diagnostic efficacy of each index. $P<0.05$ was considered statistically significant.

Results

General data of gout patients with different MSUS images

Based on MSUS images, all gout cases were classified into three groups (Table 1). Among them, 100 patients exhibited no visible MSUS-detected manifestation (group A), 113 cases determined the presence of tophi or aggregate of MSU crystals or "double track sign" (group B), and 107 cases presented with bone erosions, either accompanied or unaccompanied by tophi or aggregate of MSU crystals or "double track sign" (group C). There were no statistically significant differences among the three groups in terms of age, sex, underlying disease and uric acid ($P>0.05$). However, a significant difference was observed for in the disease course, and group C showed the longest disease course, while group A had the shortest ($P<0.001$).

Bone metabolism level of gout cases with different MSUS images

In order to assess the bone metabolism, serum levels of BGP, CTX-I and OPN were measured in different groups. As depicted in Fig. 1, the serum levels of BGP and OPN levels exhibited significant differences among the three groups. Specifically, the patients in group C had the highest levels of both BGP (Fig. 1A) and OPN (Fig. 1C), whereas those in group A had the lowest levels ($P<0.001$). But the serum CTX-I levels showed no significant difference among the three groups (Fig. 1B, $P>0.05$).

Correlation of disease course and uric acid levels with bone metabolism

Furthermore, the correlation of serum BGP and OPN levels with disease course and uric acid was evaluated via Pearson's correlation analysis. The results demonstrated that serum levels of BGP (Fig. 2A-C, $P<0.001$) and OPN (Fig. 2D-F, $P<0.001$) were strongly positively correlated with disease course in all gout patients. However, no significant association was detected with uric acid (Fig. 2G-L, $P>0.05$). The finding indicated that gout patients with a longer disease course exhibited a more severe degree of bone destruction.

Table 1 General data of gout patients with different MSUS images

Items	Groups			*P* value
	A (*n* = 100)	B (*n* = 113)	C (*n* = 107)	
Age, year	46.32±7.90	45.94±7.72	45.97±7.65	0.926
Sex, n (%)				0.915
Male	88 (88.00)	93 (82.30)	95 (88.79)	
Female	12 (12.00)	14 (12.40)	12 (11.21)	
Underlying disease, n (%)				
Diabetes mellitus	55 (55.00)	64 (56.64)	59 (55.14)	0.964
Hypertension	61 (61.00)	58 (51.33)	54 (50.47)	0.242
Disease course, year	2.12±1.00	4.29±2.02	6.98±2.76	< 0.001
Uric acid, mmol/L	486.89±110.49	509.94±109.43	502.26±126.63	0.342

Note: Group A: Musculoskeletal ultrasound (MSUS) imaging manifested no specific manifestation; Group B: Musculoskeletal ultrasound (MSUS) imaging showed gout stone or aggregate of MSU crystals or "double track sign"; Group C: MSUS imaging manifested bone erosions with or without gout stone or aggregate of MSU crystals or "double track sign"

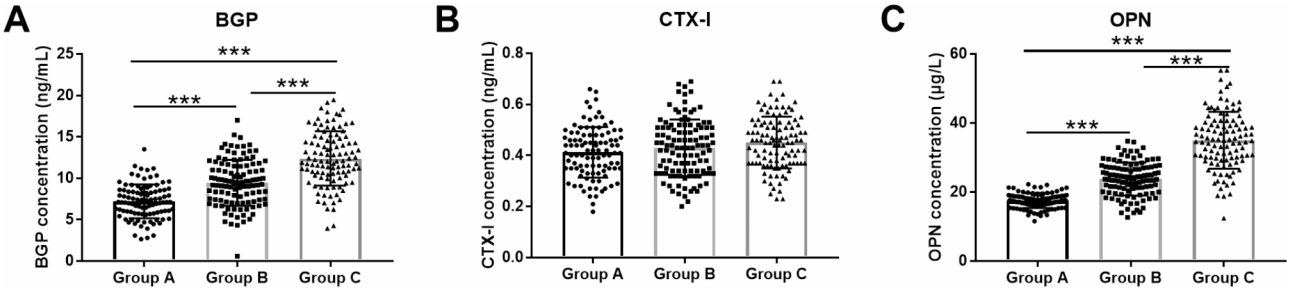

Fig. 1 Bone metabolism level of gout cases with different MSUS images. **A**. BGP levels of gout cases in different groups. **B**. Serum CTX-I concentration of gout cases in different groups. **C**. Serum OPN concentration of gout cases in different groups. *** $P < 0.001$. Comparison was performed between the three groups in pairs using ANOVA by Turkey post hoc test

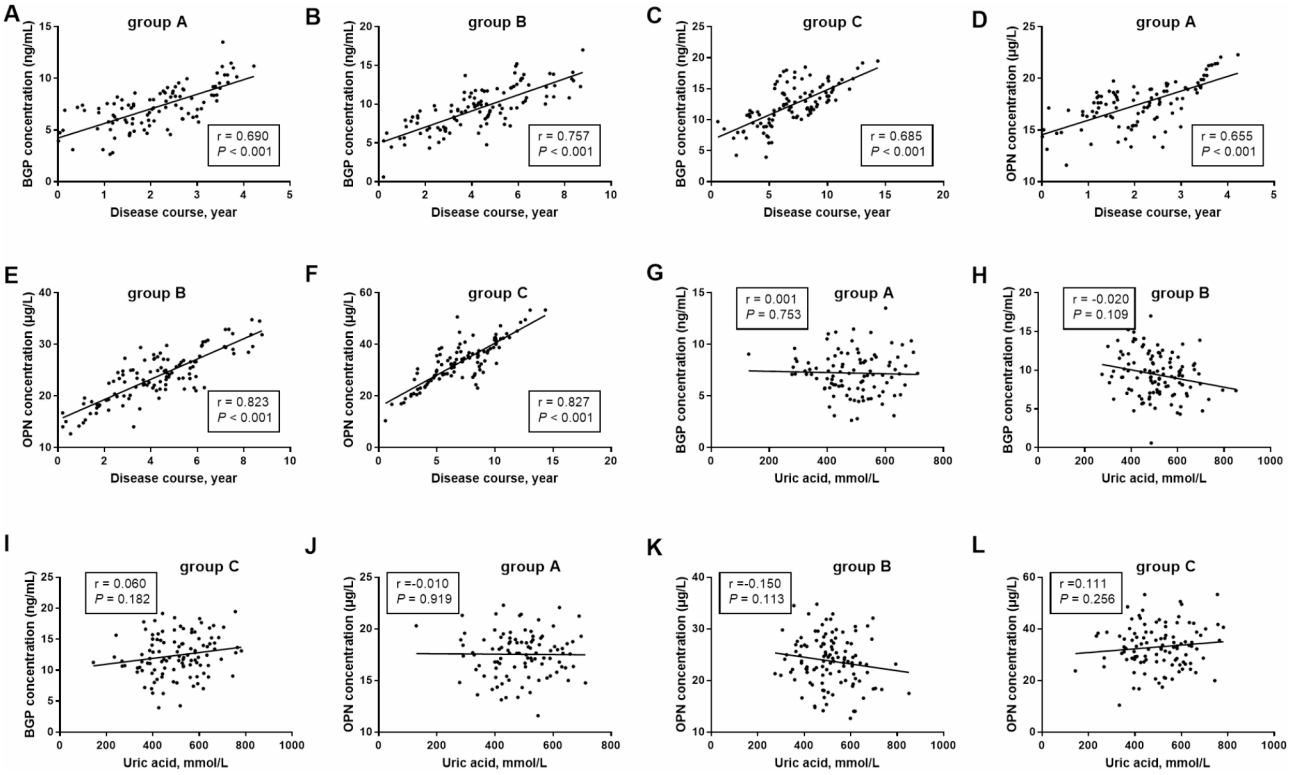

Fig. 2 Correlation of disease course and uric acid levels with bone metabolism. **A-C**. Correlation of serum BGP concentration with disease course of gout patients in different groups. **D-F**. Correlation of serum OPN concentration with disease course of gout patients in different groups. **G-I**. Correlation of serum BGP concentration with uric acid in of gout patients in different groups. **J-L**. Correlation of serum OPN concentration with uric acid of gout patients in different groups

Serum miR-328-3p levels in gout patients with different MSUS images

qRT-PCR results demonstrated the downregulation of serum miR-328-3p levels in group B and C. As illustrated in Fig. 3A, patients in group C had the lowest serum miR-328-3p levels, while those in group A had the highest values, and the difference was significant among the three groups ($P < 0.001$). Then ROC was plotted to assess the discriminatory value for different MSUS images. As depicted in Fig. 3B, the ROC exhibited high efficiency with an area under the ROC (AUC) of 0.838 in differentiating gout cases with MSUS images from those without (sensitivity 0.879, specificity 0.752). Moreover, serum miR-328-3p levels were also capable of differentiating between different MSUS manifestations. As shown in Fig. 3C, serum miR-328-3p can distinguish group B and group C with the AUC of 0.872, the sensitivity and the specificity were 0.773 and 0.770, respectively. It was summarized that serum miR-328-3p levels were correlated with the diverse MSUS manifestations in gout patients.

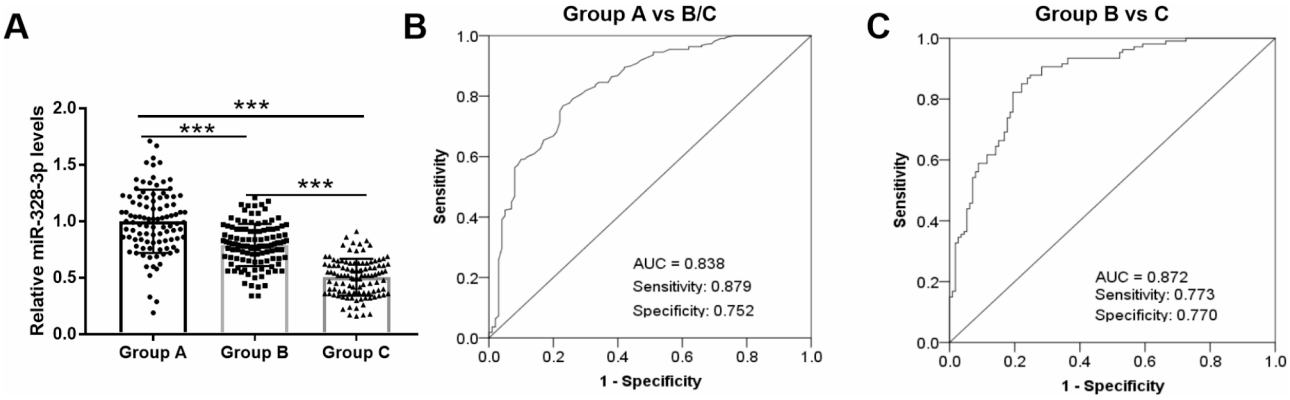

Fig. 3 Serum miR-328-3p levels in gout patients with different MSUS images. **A**. Serum miR-328-3p levels of gout cases in different groups. *** $P < 0.001$. Comparison was performed between the three groups in pairs using ANOVA by Turkey post hoc test. **B**. ROC curve of miR-328-3p in differentiating cases with MSUS manifestations from those without MSUS manifestation. **C**. ROC curve of miR-328-3p in differentiating cases with bone erosions from those just with tophi or aggregate of MSU crystals or "double track sign"

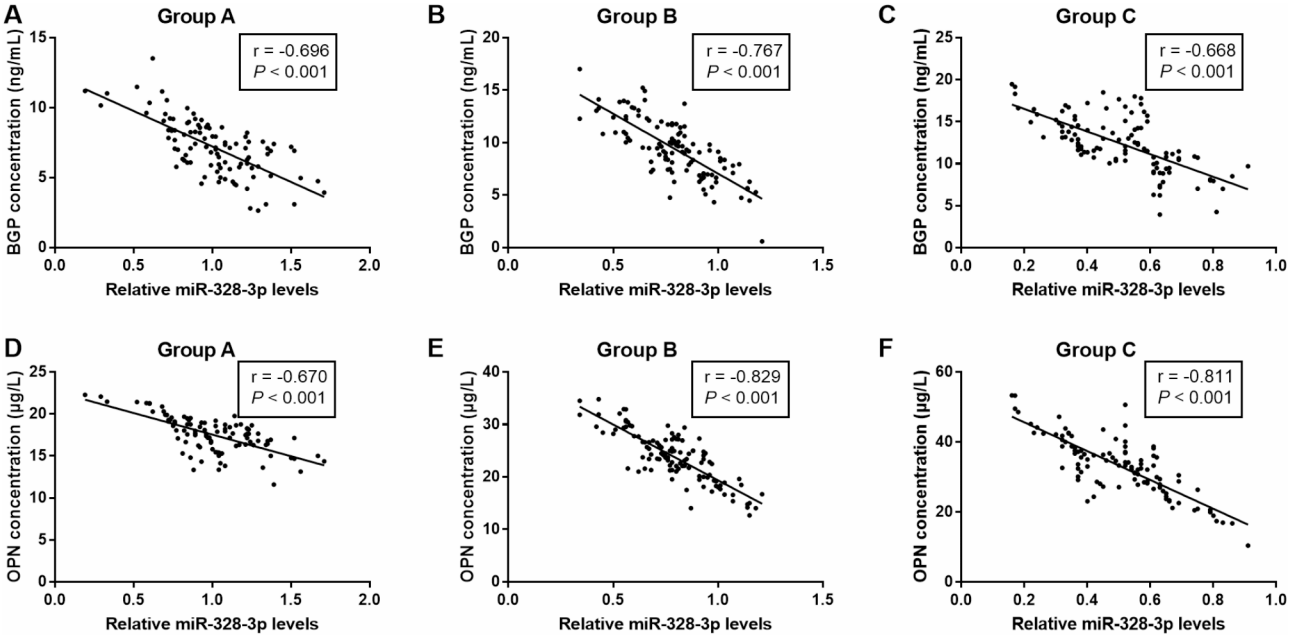

Fig. 4 Correlation of serum miR-328-3p levels with bone metabolism level of gout patients. **A-C**. Correlation of serum miR-328-3p levels with BGP concentration of gout patients in different groups. **D-F**. Correlation of serum miR-328-3p levels with OPN concentration of gout patients in different groups

Correlation of serum miR-328-3p levels with bone metabolism level of gout patients

Pearson's correlation analysis was utilized to assess the correlation of serum miR-328-3p levels with bone metabolism levels in gout patients from different groups. As shown in Fig. 4A-C, in all gout patient groups, serum miR-328-3p levels were negatively correlated with BGP concentration ($P < 0.001$). Similarly, the OPN values and miR-328-3p levels were also negatively correlated in gout patients in different groups (Fig. 4D-F, $P < 0.001$). It was concluded that serum miR-328-3p levels can mirror the degree of gout patients.

Discussion

Gout is an aseptic inflammatory condition precipitated by deranged purine metabolism, resulting in the deposition of urate in soft tissues. It has the potential to induce joint bone destruction, joint dysfunction and other clinical manifestations, exerting a significant impact on patients' daily lives. Ultrasound offers high-resolution imaging of superficial tissues, and in gout patients, four distinct pathological lesions can be identified: tophi, aggregate of MSU crystals, "double track sign", and bone erosions [22]. A total of 320 gout patients were enrolled in this study. These patients were stratified into groups according to the results of MSUS examination. Among them, 220 cases presented with specific manifestations

under MSUS imaging. In particular, 113 cases showed the presence of tophi, aggregate of MSU crystals or "double track sign", and an additional 107 cases exhibited bone erosions, either accompanied or unaccompanied by the aforementioned findings.

During the occurrence and progression of gout, the dynamic imbalance between osteoblasts and osteoclasts leads to bone destruction [23]. Through the measurement of bone metabolism levels, the degree of bone destruction can be indirectly discerned. In the current study, three markers, namely BGP, CTX-I and OPN, were detected to assess the bone metabolism status in gout patients. It is well known that osteoblasts will synthesize and secrete BGP in large quantities during the process of bone formation, which can reflect the functional state of osteoblasts and the rate of bone formation [24]. Studies have shown that the level of BGP is closely related to the severity of arthritis [25]. The level of CTX-1 in blood is directly proportional to the activity of osteoclasts and the degree of bone resorption, which can accurately reflect the osteoclaster-mediated bone resorption [26]. OPN is involved in the adhesion process of osteoblasts, osteoclasts and bone matrix, and can be used as an index to reflect the dynamic balance of bone metabolism [27]. The level of OPN can reflect the severity of arthritis [28]. The results of this study showed that the levels of BGP and OPN were significantly discrepant among patients with different ultrasound manifestations. Specially, the levels of BGP and OPN in patients presenting with tophi and bone erosion were higher than those with tophi or aggregate of MSU crystals but without bone erosions. This indicates that diverse MSUS manifestations in gout patients can reflect the degree of bone damage to a certain extent. Furthermore, in all gout patients, the correlations of serum BGP and OPN levels with the course of the disease and blood urea were evaluated. The results suggested that the longer the disease duration, the more serious the degree of bone destruction in gout patients. However, blood urea levels were unable to reflect the bone damage.

MiRNAs exert a pivotal role in immune regulation and the pathogenesis of diseases [29]. Abundant experimental investigations have demonstrated that miRNAs are closely associated with the occurrence and progression of gout [30]. In a gene polymorphism study relevant to gout, miR-328-3p has been identified as being involved in the development of gout [31]. Based on the current results, serum miR-328-3p levels were determined to be dysregulated in gout patients with diverse MSUS manifestations. It was found that patients without specific manifestations exhibited the highest serum miR-328-3p levels, whereas those with bone erosions had the lowest serum miR-328-3p values. Moreover, significantly negative correlations were also detected for serum miR-328-3p levels with BGP and OPN values in all gout patients. Consistently, miR-328-3p has been extensively reported to be related to bone metabolism [16–18], which corroborates our present findings in gout patients. Collectively, the current findings indicated that serum miR-328-3p levels can serve as an indicator reflecting the degree of bone damage in gout patients. The level of serum miR-328-3p may have already changed before obvious imaging manifestations or clinical symptoms of bone damage occurred in patients with gout. By detecting the level of serum miR-328-3p, it is possible to achieve the early detection of bone damage in gout, which is helpful for doctors to take intervention measures in the early stage of the disease and prevent the further deterioration of the condition.

According to the previous evidence, it was speculated that the downregulation of miR-328-3p observed in patients with bone erosion may be involved in mechanisms such as inflammatory response, differentiation and function of osteoblasts and osteoclasts, and gene epigenetic regulation. In the process of bone erosion, miR −328-3 p abnormal expression may be involved in and inflammation in the body by activating signaling pathways, such as the NF-κB promotes the release of inflammatory cytokines, and compound bone erosion [32]. In addition, down-regulation of miR-328-3p may alter the expression of genes related to osteoblast differentiation, break the balance between bone formation and bone resorption, and promote bone erosion [33]. Down-regulation of miR-328-3p may promote the differentiation of osteoclast precursor cells into osteoclasts, thereby enhancing bone resorption and leading to bone erosion [34]. But the exact mechanism was not explored and verified in the current study. In addition, potential confounding factors influencing miR-328-3p levels, such as medication use or disease severity, are not addressed. Similarly, the relatively small sample size was also a limitation. Therefore, the current findings should be validated in future studies.

In summary, miR-328-3p levels were associated with diverse MSUS manifestations in gout patients. The lowest level of miR-328-3p was found in grout patients presenting with tophus formation and bone erosion. MSUS imaging findings and miR-328-3p levels are capable of reflecting the joint damage of gout patients, and they play an important role in the surveillance of the gout condition. Nevertheless, the sample size in this study was relatively small, and the conclusions require further validation and expansion through larger-scale research.

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Author contributions
QS and LX carried out the research design and conception; JR analyzed and interpreted the data regarding; XL performed the examination of sample; XM contributed essential reagents or tools; QS，LX and XM authors wrote and revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The experimental procedures were all in accordance with the guideline of the Ethics Committee of Shengli Oilfield Central Hospital and has approved by the Ethics Committee of Shengli Oilfield Central Hospital. This study complies with the Declaration of Helsinki. A signed written informed consent was obtained from each patient.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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