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Potential role of serum chemerin values in osteoid osteoma: A prospective cross-sectional study

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ABSTRACT

Aim: Chemerin is a novel adipokine that is being investigated as a diagnostic tool or therapeutic target in many diseases. In this prospective cross-sectional study, we aim to investigate the potential utility of serum chemerin levels as an adjunctive diagnostic tool for osteoid osteoma.

Methods: This study consists of 20 patients diagnosed with osteoid osteoma (Group 1) and 20 healthy patients (Group 2). Age, gender, tumor localization, surgery types and chemerin values of all patients were recorded and evaluated.

Results: A total of 40 patients, 20 from group 1 and 20 from group 2, were included in our study. Group 1 had a median age of 17.5 (IQR: 15.25-19.75) years, and Group 2 had a median age of 19 (IQR: 17.25-20) years (p=0.172). In terms of gender, 60% (n=12) of Group 1 and 55% (n=11) of Group 2 were male (p=0.749). Tumor nidus size varied among the participants with a median measurement of 8 (IQR: 5.25 to 8.75) mm. The median chemerin level in Group 1 was 0.94 (IQR: 0.68-1.29), while in Group 2, it was 1.89 (IQR: 1.08-3.72). The difference was statistically significant (p<0.001). The cut-off value was determined to be 1.5, with a sensitivity of 100% and a specificity of 62%.

Conclusions: The results of our research indicate that patients with osteoid osteoma have lower levels of chemerin than healthy individuals. This suggests that chemerin may have potential as a biomarker for diagnosis. Additionally, our analysis using ROC showed that chemerin has good diagnostic capabilities.

Keywords: Chemerin, osteoid osteoma, bone tumors, diagnosis, biomarker.

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1. Introduction

Osteoid osteoma is a benign bone tumor commonly seen in children and young adults, notorious for causing severe nocturnal pain. Despite its small size, this tumor significantly impacts patients' quality of life, often necessitating intervention. Diagnosing osteoid osteoma can be challenging due to its small size and nonspecific symptoms [1-3]. Hence, the exploration of biomarkers that can facilitate early and accurate diagnosis is of paramount importance. One such promising biomarker is chemerin [4].

Chemerin is a chemoattractant protein initially recognized for its role in inflammation and adipocyte differentiation. Recent research, however, has unveiled its potential significance in bone metabolism [4]. Chemerin has been found to regulate osteoblast differentiation and bone formation, thereby implicating it in

various bone disorders [5]. Given its roles in bone biology and inflammation, both critical aspects of osteoid osteoma, chemerin presents a compelling candidate for investigation in the context of this bone tumor.

In this prospective cross-sectional study, we aim to investigate the potential utility of serum chemerin levels as an adjunctive diagnostic tool for osteoid osteoma.

2. Materials and methods

This research was conducted on patients who were admitted to the Orthopedics and Traumatology Clinic of our hospital between November 15, 2023 and April 15, 2024 and were diagnosed with osteoid osteoma. The diagnosis of osteoid osteoma was confirmed based on radiological imaging, anamnesis, and clinical findings that were in agreement with osteoid osteoma. The study comprised 20 patients (Group 1), while the control group included 20 healthy individuals (Group 2).

For the patient group, characteristics such as age, gender, tumor size, tumor localization, treatment applied to the tumor, follow-up period, and recurrence were recorded. The data were collected from the hospital's information management system, ensuring all patient identifiers were removed to maintain data confidentiality. Both patient and control groups were compared regarding variables such as age, gender, and serum chemerin levels.

Patients who had previously received treatment for osteoid osteoma, those presenting with a recurrence of the disease, those whose pathology results were not consistent with osteoid osteoma, and those with metastatic bone diseases were excluded from the study. In addition, patients with endocrine diseases (such as Cushing's disease and acromegaly), inflammatory rheumatism (including rheumatoid arthritis and spondyloarthropathy), smokers, heavy alcohol users (consuming more than 20g of ethanol per week), and those using steroids or estrogens were also excluded. Patients with a chronic illness or an acute inflammatory disease that could affect serum chemerin levels at the time of presentation were left out of the study. Furthermore, as this is a prospective study, patients who wished to withdraw from the study were also excluded.

2.1. Collection and preservation of serum specimens: Patients were kept fasting for 8 hours prior to the collection of blood samples. Following this fasting period, 5 cc of blood was drawn from a peripheral vein. The collected blood samples were immediately transferred to sterile biochemistry tubes. These tubes were then centrifuged at a speed of 5000 rpm for 5 minutes to separate the serum from the other blood components. After centrifugation, the serum was carefully separated and immediately transferred to Eppendorf tubes. To ensure the preservation of the samples, the Eppendorf tubes were stored at -80 degrees Celsius until the day of analysis.

2.2. ELISA assay of chemerin in serum: The serum levels of chemerin were measured using the Enzyme-Linked Immunosorbent Assay (ELISA) technique. On the day of the analysis, the serum samples were thawed to reach room temperature before initiating the testing procedure. The assay for serum chemerin was performed using the Enzyme-Linked Immunosorbent Assay (Human Chemerin ELISA) method. The assay was performed according to the manufacturer's protocol provided with the commercially available chemerin assay kit (Chemerin; Elabscience Biotechnology, USA. Catalog No: E-EL-H0698). The measurements were carried out using BioTek ELx50 Microplate Washer and BioTek ELx800 Microplate Reader (BioTek Instruments, Inc. USA) instruments.

The microplate washer was used to wash the microplate wells, eliminating unbound substances, while the microplate reader was used to quantify the absorbance, which is proportional to the concentration of chemerin in the samples. The data obtained from the ELISA readings were used to calculate the chemerin levels in each of the serum samples. The assay procedures were performed maintaining high standards of precision and accuracy to ensure the reliability of the results.

2.3. Diagnostic criteria for osteoid osteoma: Though there is no absolute consensus for the diagnosis, the most commonly utilized criteria include: The patient experiences intermittent, localized pain that intensifies during the night and is relieved by aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) **(**Table 1**)**. The appearance of an osteoid osteoma on a plain radiograph, which is classically a small, round, radiolucent nidus, accompanied by surrounding sclerosis. This appearance supports the diagnosis of osteoid osteoma **(**Figure 1**)**.

Table 1: Patients' presenting complaints.

Complaints	**N**	**%**
Pain	19	95
Swelling	6	30
Synovitis findings	1	5

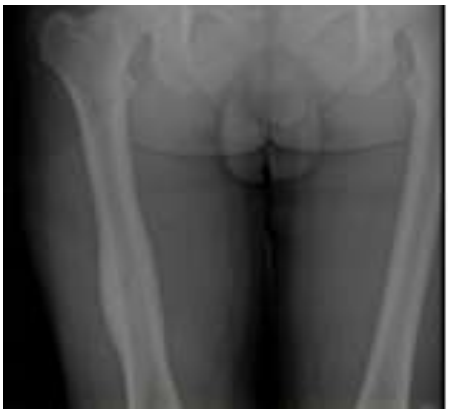

Figure 1. Anteroposterior plane radiograph of the osteoid osteoma located in the femur.

A characteristic finding in a CT scan is a nidus in the shape of a target **(**Figure 2**)**.

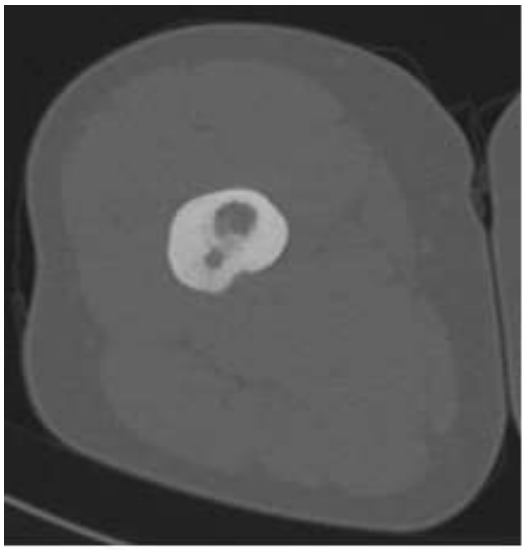

Figure 2: An axial tomography section showing the nidus of osteoid osteoma located in the femur.

The experimental protocol was approved by the Dicle University Local Ethics Committee (Decision No: 11.10.2023/273).

2.4. Statistical analysis: An extensive statistical analysis was conducted on the patient data, which involved assessing descriptive statistics (mean±std. deviation [SD] or median [IQR]), frequencies, and other attributes across all categories. Student's T-test Shapiro-Wilk and Kolmogorov-Smirnov tests were studied for the distribution of continuous variables. The Receiver Operating Characteristic (ROC) analysis was employed to evaluate cut-off analysis. Spearmen correlation test was used for the corelation between the chemerin levels and tumor size. All statistical analyses were performed using SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). P-values were two-sided, and a p-value of $\leq$ 0.05 was considered as statistically significant.

3. Results

The study consisted of two groups, each with 20 participants. In our study population, pain

was the most prevalent complaint, reported by 95% of participants (n=19). This was followed by swelling, with 30% of participants (n=6) reporting this symptom. Synovitis findings were notably less common, reported by only one participant, representing 5% of the total group **(**Table 1**)**.

Our study population was characterized by a median age of 19 (IQR:16.25-20) years. The cohort was predominantly male, with 58% (n=23) of the participants identifying as such. Tumor nidus size varied among the participants with a median measurement of 8 (IQR: 5.25 to 8.75) mm. In examining the distribution of tumor localization, the majority were found in the femur, accounting for 40% (n=8) of cases. This was followed by the tibia at 30% (n=6), the humerus at 15% (n=3), the hand at 10% (n=2), and the calcaneus at 5% (n=1). A range of treatment methods were employed. Most notably, curettage was the predominant treatment option, utilized in 55% (n=11) of cases. Radiofrequency ablation was also a commonly used treatment, administered to 35% (n=7) of patients. Conservative treatment was less commonly utilized, representing only 10% (n=2) of the cases. The median follow-up period extended to 18.5 (IQR: 17.08-19) months. Within this period, a recurrence rate of 10% (n=2) was observed among our study participants **(**Table 2**)**.

Group 1 had a median age of 17.5 (IQR: 15.25-19.75) years, and Group 2 had a median age of 19 (IQR: 17.25-20) years. The difference in age between the two groups was not statistically significant (p=0.172). In terms of gender, 60% (n=12) of Group 1 and 55% (n=11) of Group 2 were male (p=0.749). However, there was a significant difference in chemerin levels between the two groups. The median chemerin level in Group 1 was 0.94 (IQR: 0.68-1.29), while in Group 2, it was 1.89 (IQR: 1.08-3.72). The difference was statistically significant (*p*<0.001) **(**Table 3**)**.

Table 2. General findings of the individuals.

Parameters	**N (%)**
Age*	19(16.25-20)
Gender (Male)	23(58%)
Tumor nidus size (mm)*	8(5.25-8.75)
Tumor localization	
Femur	8(40%)
Tibia	6(30%)
Humerus	3(15%)
Hand	2(10%)
Calcaneus	1(5%)
Treatment	
Curettage	11(55%)
Radiofrequency	7(35%)
Conservative	2(10%)
Follow-up*	18.5(17.08-19)
Recurrence	2(10%)

** median (IQR)*

Table 3. Comparison of characteristics between groups.

Parameters	**Group 1 (n=20)**	**Group 2 (n=20)**	***p*-value**
Age*	17.5 (15.2-19.7)	19 (17.2-20)	*0.172*
Gender (male)#	12 (60%)	11 (55%)	*0.749*
Chemerin levels*	0.94 (0.68-1.2)	1.89 (1.08-3.7)	***<0.001***

The cut-off value was determined to be 1.5, with a sensitivity of 100% and a specificity of 62% **(**Figure 3**)**.

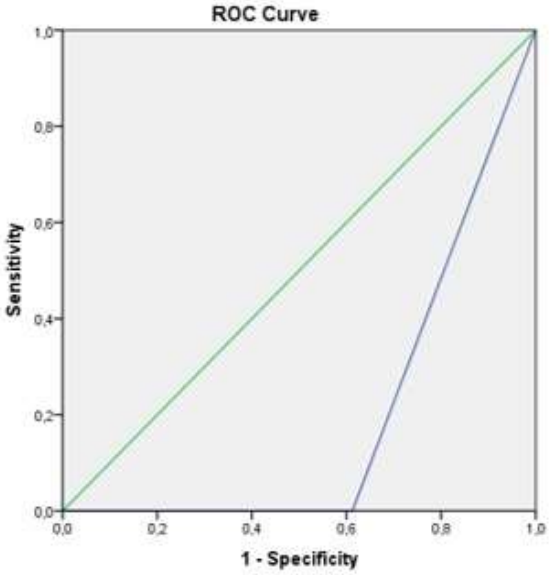

Figure 3: ROC Analysis graphic

4. Discussion

Osteoid osteoma is the third most common benign tumor of bone and is predominantly seen in young, male patients [6]. Its pathogenesis has not yet been fully elucidated. Diagnosis is sometimes delayed, especially in atypical localized lesions. Numerous disorders can mimic OO, and vice versa, which frequently results in a prolonged diagnostic and therapy process and related problems [7]. Park et al found that 28.6% of osteoid osteoma cases had normal radiography despite very typical clinical presentations [8]. In a case series consisting of osteoid osteomas in the hand bones, the mean time from the first complaint to diagnosis was reported as 20.5 months [9].

Chemerin is an adipokine discovered in recent years. It has been shown that the cervical spine plays various roles in the pathogenesis of inflammatory and metabolic diseases in many organs (such as the adipose tissue, cardiovascular system, reproductive system, skeleton and joints) [10]. A study investigating the role of chemerin in hematopoietic stem cell (HSC) osteoclastogenesis has shown that blocking chemerin stops osteoclastogenesis differentiation [11]. Periprosthetic osteolysis is the most important long-term complication of total joint replacement, and ultra-high molecular weight polyethylene (UHMWPE) particles are responsible for it. In a study by Zhao et al. it was shown that blocking the chemerin/ChemR23 signal reduced the osteoclastogenic effect of UHMWPE particles on bone cells and increased their osteogenic effect [12]. In a study by Ma et al. it was found that the level of chemerin in synovial fluid and synovial membrane was significantly higher in patients with knee osteoarthritis compared to the control group. At the end of the study, the authors found that chemoresin may be a valuable biomarker for determining the severity of knee osteoarthritis [13]. In a study by He et al. the serum chemerin level was found to be significantly higher in patients with osteoporosis compared to the control group. In both groups, a negative correlation was found between chemerin and bone mineral density (BMD) [14].

We included a total of 40 patients in our study, with 20 from each of the two groups. The median chemerin level was 0.94 (IQR: 0.68-1.29) in Group 1 and 1.89 (IQR: 1.08-3.72) in Group 2. We found that the chemerin level in the osteoid osteoma group was significantly lower than in the control group ($p<0.001$), and there was no correlation between nidus size and chemerin ($p>0.05$). Our study suggests that chemerin could be a useful biomarker for osteoid osteoma. The ROC analysis showed an AUC of 0.80, indicating good diagnostic ability with high sensitivity (100%) at a cut-off value of 1.5 ng/ml. However, the specificity was relatively low (62%), meaning that chemerin

may not be specific to osteoid osteoma and could indicate other conditions as well. More research is necessary to validate these findings and explore the exact role of chemerin in the pathogenesis of osteoid osteoma.

This study has several notable strengths that enhance the value and impact of its findings. Firstly, to our knowledge, this is the first study to investigate the potential utility of serum chemerin levels as a diagnostic tool for osteoid osteoma. This novel approach can stimulate further research into the role of chemerin and other potential biomarkers in the diagnosis of osteoid osteoma. Secondly, our study design was prospective and cross-sectional, allowing for a systematic and unbiased selection of patients and controls. This strengthens the internal validity of our findings. Thirdly, we used rigorous methods to collect and analyze serum samples, ensuring the accuracy and reliability of chemerin measurements. The use of the Enzyme-Linked Immunosorbent Assay (ELISA) technique, which is a well-established and highly sensitive method, further strengthens the validity of our findings. Fourthly, we employed comprehensive statistical analysis, including the Receiver Operating Characteristic (ROC) analysis, to determine the cut-off value of serum chemerin levels for diagnosing osteoid osteoma. This enhances the practical application of our findings in clinical settings. Lastly, we had well-defined inclusion and exclusion criteria, ensuring that our study population was representative of patients with osteoid osteoma. We also collected a wide range of patient data, including age, gender, tumor size and localization, treatment methods, and recurrence rates, providing a comprehensive overview of the disease characteristics in our study population.

Our study has several limitations. While the sample size was sufficient for a first pilot study of this nature and demonstrated significant significance, it was relatively small. This can be considered a limitation in the discussion. Therefore, future studies with larger, multicenter cohorts are needed to confirm the findings and strengthen generalizability.

***4.1. Conclusion*:** The results of our research showed that individuals with osteoid osteoma have considerably lower levels of chemerin compared to healthy individuals, indicating that chemerin could be a useful diagnostic biomarker. The ROC analysis demonstrated that chemerin had a good diagnostic ability with an AUC of 0.80, 100% sensitivity, and 62% specificity at a cut-off value of 1.5 ng/ml. Nonetheless, further investigation is necessary to validate these findings and to explore the practical implications of chemerin in the management of osteoid osteoma.

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