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ORIGINAL RESEARCH

Exploring the clinical significance of cuproptosis and bone metabolism factors in tooth eruption disturbances

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Abstract

Background: This study aimed to investigate the clinical significance of cuproptosis and bone metabolism factors in tooth eruption disturbances. **Methods**: Dental follicle tissue and alveolar bone tissue from 10 patients with tooth eruption disturbances were collected as the eruption disturbance group (Group EG). Likewise, corresponding tissues from 10 patients undergoing removal of impacted third molars for orthodontic treatment were collected as the control group (Group CG). Morphological changes in dental follicle cells were evaluated by hematoxylin and eosin (H&E) staining. Protein expression of ferredoxin1 (FDX1), dihydrolipoamide S-acetyltransferase (DLAT), receptor activator of nuclear factor κB ligand (RANKL), and osteoprotegerin (OPG) in dental follicle tissue and alveolar bone tissue was examined by immunohistochemistry (IHC). **Results**: H&E staining of dental follicle tissue in Group EG showed reduced cell volume and condensed nuclei, suggesting impaired osteoblast/osteoclast differentiation. IHC analysis demonstrated that in Group EG, expression of FDX1, DLAT, and RANKL was reduced in the same direction in both dental follicle tissue and alveolar bone tissue, whereas OPG expression was increased. Consequently, the RANKL/OPG ratio was significantly decreased compared with Group CG. **Conclusions**: Excessive stress during tooth eruption may alter cuproptosis by affecting cell morphology, thereby disturbing the balance of bone differentiation factors in dental follicle cells and ultimately contributing to eruption disturbances.

Keywords

Tooth eruption disturbances; Stress; Cuproptosis; Dental follicle tissues; Bone metabolism

1. Introduction

Tooth eruption disturbances refer to teeth that remain unerupted within the jawbone beyond the expected eruption period [1]. Clinically, they are characterized by retained deciduous teeth, delayed eruption of permanent teeth, and tooth impaction. At this stage, the eruptive potential of the teeth is weakened but not entirely lost [2, 3]. After removing the resistance force on the tooth germ crown, such as extracting retained deciduous teeth or removing the overlying bone, eruption may still occur. It is well established that a certain degree of pressure is required during the eruption process to initiate osteoclast differentiation in the dental follicle [4, 5]. However, excessive pressure often leads to eruption disturbances. The prevailing hypothesis suggests that excessive mechanical stress disrupts molecular signaling regulation, thereby impairing the osteoclast differentiation potential of dental follicle cells.

Currently, the nuclear factor kappa B (NF-κB) signaling pathway is recognized as a key regulator of osteoclast activation. It plays a central role in bone remodeling by modulating receptor activator of nuclear factor κB ligand (RANKL)/osteoprotegerin (OPG) (RANKL/OPG) expression, coordinating osteoblast and osteoclast differentiation, and influencing bone matrix formation [6, 7].

Cuproptosis, a recently identified form of regulated cell death, is triggered by dysregulated intracellular copper homeostasis leading to copper overload. Copper has a positive effect on regulating bone metabolism cells, but it exhibits dose-dependent effects. Low doses promote osteoblast growth, while high doses activate signaling pathways for pro-inflammatory gene expression in macrophages. Recent studies have reported that activation of the NF-κB pathway by inflammatory stimuli in the periodontal tissues of patients with periodontitis elevates intracellular copper ion concentration, thereby inducing cuproptosis in a manner correlated with the degree of bone destruction [8]. Moreover, emerging evidence indicates that cuproptosis-related genes exert diverse effects on bone growth and development, suggesting a potential role for cuproptosis in regulating bone remodeling during tooth eruption [9, 10].

The appropriate stress generated during tooth eruption promotes monocytes to enter the dental follicle from peripheral blood and transform into osteoclasts, maintaining the dynamic balance of alveolar bone remodeling to facilitate normal tooth eruption. Therefore, exploring the molecular regulatory mechanism by which dental follicle cells induce osteoclast differentiation under stress is of great significance. Such investigations may advance our understanding of the biological basis of eruption channel formation and provide novel insights into the prevention and management of tooth eruption disturbances.

2. Materials and methods

2.1 Experimental subjects

Dental follicle tissue and alveolar bone tissue were collected from 10 patients aged between 10 and 16 years with tooth eruption disturbances treated in our pediatric stomatology department from January 2024 to June 2025. All the affected teeth met the following inclusion criteria: patients without systemic or bone metabolism disorders; impaired tooth eruption without dental crown, periapical and periodontal tissue diseases; teeth with eruption disturbances that was vertically obstructed, without obvious proximal, distal, mesial or buccolingual displacement; and availability of imaging data or telephone follow-up confirming tooth eruption after establishment of the eruption pathway. The exclusion criteria were as follows: uncooperative patients; patients with systemic diseases or bone metabolism disorders; long-term history of medication/antibiotic use; and teeth with eruption disturbances associated with misaligned positions, as well as dental body, periapical, or periodontal tissues. In parallel, dental follicle tissue and alveolar bone tissue were obtained from 10 patients aged between 10 and 16 years during removal of impacted third molars for orthodontic treatment, and these were included as the control group (Group CG). All participants received information sheets detailing the research objectives, relevant treatment procedures, and participant's requirements. Written informed consent was obtained from each participant's legal guardian. The detection methods used hematoxylin and eosin (H&E) and immunohistochemistry (IHC) staining, with H&E staining mainly used to observe the morphological structure of tissues and cells, while IHC staining is used to detect specific antigens or proteins [11, 12].

2.2 H&E staining of dental follicle tissue specimens

During the surgical extraction of teeth with eruption disturbances and third molars, the dental follicle tissue from above the dental crowns was collected separately, which then was fixed with 4% paraformaldehyde for 24 h and embedded in paraffin blocks. The paraffin blocks were cut into 5 μm thick sections, floated on warm water, and mounted on glass slides. The slides were dried in a constant-temperature oven at 45 ℃ for subsequent use. Before staining, paraffin was removed with xylene, followed by graded ethanol dehydration from high to low concentrations. H&E staining was performed sequentially. The stained sections were dehydrated in absolute ethanol, cleared in xylene, and mounted with neutral resin. Cell morphology was examined under a microscope.

2.3 IHC staining of dental follicle and alveolar bone tissue specimens

Using the same method as H&E, during the surgical extraction of teeth with eruption disturbances and third molars, dental follicle tissue and alveolar bone tissue were collected from above the dental crown. All of these collected tissues were placed into the specimen solution and fixed in 4% paraformaldehyde for 24 h. Dental follicle tissue was directly embedded in paraffin blocks, while alveolar bone tissue was decalcified in sodium formate decalcifying solution (BioGnost d.o.o. Company, OSTEOFAST2, Purity: 100%, OF2-OT-2.5L, Zagreb, Croatia) at 4 °C for 72 h before embedding. Paraffin blocks were sectioned into 5 μm thick slices, floated on warm water, mounted on glass slides, and dried in a 45 ℃ constant-temperature oven. IHC staining was performed following the manufacturer's protocol. Antigen repair was performed using microwave heating. The repair solution was diluted to a ratio of 1 and preheated in a microwave at medium high temperature for about 1–2 minutes. Tissue slices were then placed and filled with the repair solution. After the first medium high temperature repair for 8 minutes, the second repair was repeated for 12 minutes at medium high temperature. After cooling to room temperature, the repair solution was poured out and washed twice with 1× phosphate buffered solution (PBS) for 15 minutes each time. The primary antibodies used were: rabbit anti-FDX1 (Proteintech, No. 12582-1-AP, 1:200, Chicago, IL, USA), rabbit anti-DLAT (Proteintech, No. 13426-1-AP, 1:100, Chicago, IL, USA), mouse anti-RANKL (Proteintech, No. 23408-1-AP, 1:100, Chicago, IL, USA), and rabbit anti-OPG (Proteintech, No. 11534-1-AP, 1:300, Chicago, IL, USA). The secondary antibody was diluted anti-rabbit immunoglobulin G (IgG) (Santa Cruz, No. sc2004, 1:300, Santa Cruz, CA, USA). After IHC staining, sections were counterstained with hematoxylin, dehydrated with graded ethanol, cleared with xylene, and sealed with neutral resin. The expression the target proteins was examined under a microscope (Olympus CX43, Olympus Medical Systems, Tokyo, Japan).

2.4 Statistical analysis

All experimental results are expressed as the mean ± standard error of the mean. The *t*-test method in SPSS 22.0 statistical software (SPSS Incorporated, Chicago, IL, USA) was used for statistical analysis of the data. $p < 0.05$ was considered as statistically significant.

3. Results

3.1 H&E staining

In the eruption disturbance group (Group EG), H&E staining of dental follicle tissues revealed a reduction in dental follicle cell volume and condensation of nuclei, suggesting that the differentiation of dental follicle cells into osteoblast/osteoclast may be limited (Fig. 1).

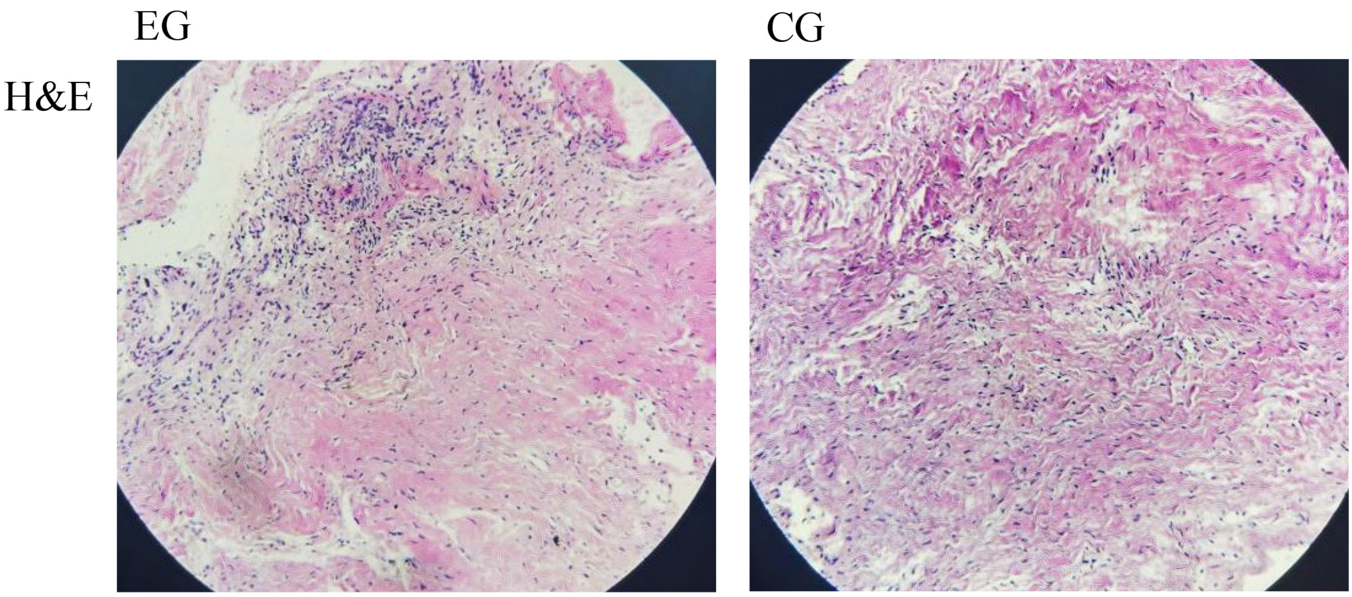


FIGURE 1. Hematoxylin and eosin (H&E) staining showed dental follicle cell volume in the eruption disturbance group (Group EG) was decreased and their nuclei were condensed compared to the control group (Group CG) (×400).

3.2 Cuproptosis and bone metabolism factors in dental follicle specimens

IHC staining of dental follicle tissue was performed according to the immunohistochemistry kit protocol. The expressions of FDX1, DLAT, and RANKL proteins were weakly positive in Group EG, whereas OPG expression was markedly higher compared with Group CG. Statistical analysis of IHC demonstrated that the optical density values of FDX1, DLAT, and RANKL in Group EG were significantly lower, while the optical density value of OPG was significantly higher. Furthermore, the RANKL/OPG ratio in Group EG was reduced compared with Group CG, with all differences reaching statistical significance (Fig. 2).

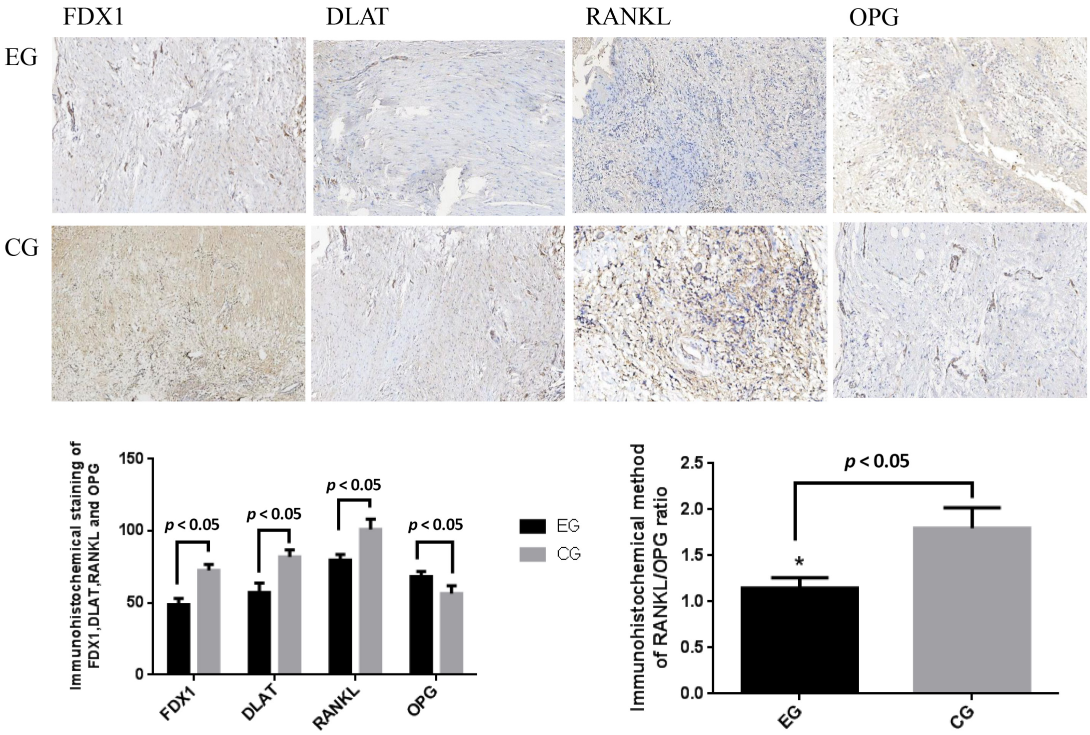
3.3 Cuproptosis and bone metabolism factors in alveolar bone specimens

IHC staining of alveolar bone tissue was performed according to the immunohistochemistry kit protocol. Consistent with the findings in dental follicle tissue, expression of FDX1, DLAT, and RANKL proteins was weakly positive in Group EG, while OPG expression was elevated compared with Group CG. Statistical analysis further indicated that the optical density values of FDX1, DLAT, and RANKL were significantly decreased in Group EG, whereas the optical density value of OPG was significantly increased. Moreover, the RANKL/OPG ratio was significantly lower in Group EG (Fig. 3).

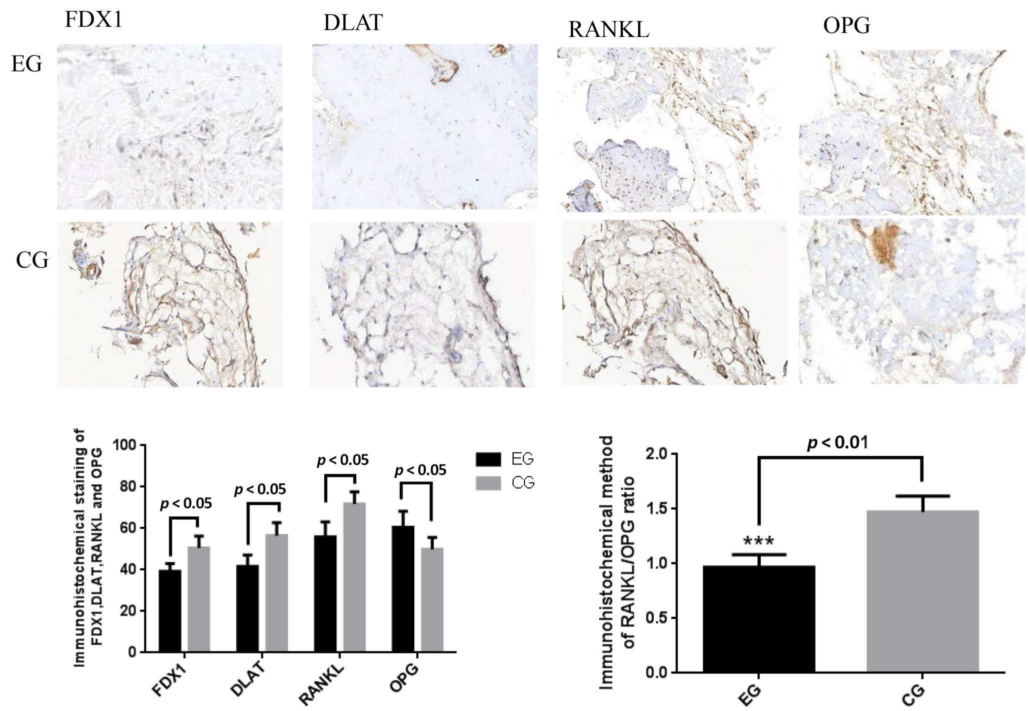
4. Discussion

Excessive stress leading to abnormal osteoblast/osteoclast differentiation in the dental follicle, thereby resulting in tooth eruption disturbances, has become a key research focus in dentistry [13]. Previous studies have demonstrated that under appropriate stress, the expression of monocyte chemokines in dental follicle cells increases, facilitating the migration of monocytes from peripheral blood into the dental follicle. These monocytes then differentiate into osteoclasts, promoting the formation of eruption channels [14, 15]. Therefore, maintaining the dynamic balance of alveolar bone remodeling under certain stress conditions is crucial for normal tooth eruption. Other studies have further suggested that in cases of tooth eruption disturbances, the ratio of osteoblast/osteoclast differentiation factors in dental follicle cells differs significantly compared with the normal eruption group [16, 17]. *In vitro* experiments involving dental follicle tissue from patients with tooth eruption disturbances confirmed that the expression of bone metabolism factors in dental follicle cells was reduced compared to the normal eruption group [18]. Collectively, these findings suggest that excessive pressure on the crown of the tooth germ may impair osteoblast/osteoclast differentiation by altering the molecular signal transduction mechanism of dental follicle cells, ultimately leading to eruption failure. This raises the question: what are the key molecular signaling mechanisms involved in this regulatory process?

The NF-κB pathway is a central signaling cascade in bone remodeling, regulating osteoclast differentiation by modulating the RANKL/OPG ratio, and thereby maintaining bone homeostasis [19]. During the normal eruption process, RANKL expression in the dental follicle is up-regulated, whereas OPG expression is down-regulated. This increases the RANKL/OPG ratio, enabling RANKL to bind to RANK receptors on osteoclast precursors, thereby promoting osteoclast differentiation, maturation and the establishment of eruption pathways [20, 21]. Clinical studies have further demonstrated that in children with delayed tooth eruption or persistent primary teeth, RANKL expression and the RANKL/OPG ratio are significantly lower compared with healthy controls [22, 23]. Consistent with these reports, our study found that both dental follicle and alveolar bone tissue in the eruption disturbances group (Group EG) exhibited reduced RANKL expression, increased OPG expression, and a lower



F I G U R E 2. Immunohistochemical (IHC) staining results of the dental follicle tissue showed reduced expression of ferredoxin1 (FDX1), dihydrolipoamide S-acetyltransferase (DLAT), and receptor activator of nuclear factor κB ligand (RANKL) proteins in the eruption disturbances group (Group EG), while osteoprotegerin (OPG) expression was increased ($\times$400). Statistical analysis confirmed that FDX1, DLAT, and RANKL expression levels, as well as the RANKL/OPG ratio, were lower in Group EG, whereas OPG expression was higher compared with Group CG (*$p < 0.05$). CG: control group.



F I G U R E 3. Immunohistochemical (IHC) staining of the alveolar bone tissue showed decreased expression of ferredoxin1 (FDX1), dihydrolipoamide S-acetyltransferase (DLAT), and receptor activator of nuclear factor κB ligand (RANKL) proteins in the eruption disturbance group (Group EG), with increased osteoprotegerin (OPG) expression ($\times$400). Statistical analysis revealed that the FDX1, DLAT, and RANKL expression levels, and the RANKL/OPG ratio, were significantly lower in Group EG, whereas OPG expression was significantly higher compared with Group CG ($p < 0.05$, ***$p < 0.01$). CG: control group.

RANKL/OPG ratio compared with the control group (Group CG). These results indicate that RANKL, OPG expression, and the RANKL/OPG ratio may serve as valuable biomarkers for evaluating tooth eruption diseases.

Cuproptosis, a recently identified form of programmed cell death, has attracted increasing attention [24, 25]. Its hallmark features include copper-induced protein toxicity mediated by the aberrant oligomerization of thiol-containing proteins in the tricarboxylic acid cycle, along with the destabilization of iron-sulfur cluster proteins. Ferredoxin1 (FDX1) reduces Cu^{2+} to Cu^{+}, thereby promoting the lipoylation of dihydrolipoamide S-acetyltransferase (DLAT) and reducing the stability of iron-sulfur cluster proteins, ultimately leading to cell death. Therefore, FDX1 and DLAT are widely recognized as key markers of cuproptosis [26, 27]. Recent studies have reported that inflammatory activation of the NF-κB pathway in periodontal tissue of patients with periodontitis increase intracellular copper ion concentration, triggering cuproptosis that correlates with the severity of bone destruction. This suggests a potential synergistic interaction between NF-κB activation and cuproptosis in driving inflammation-induced alveolar bone resorption [8, 28]. In addition, other findings have revealed that cuproptosis-related genes play distinct roles in bone growth and development, indicating that cuproptosis may also regulate bone remodeling during tooth eruption [29]. However, to date, no studies have specifically addressed the role of cuproptosis in eruption channels formation or its relationship with bone metabolic factors in eruption disturbances.

In the present study, we examined two key tissues involved in tooth eruption: dental follicle tissue, and alveolar bone tissue adjacent to the crown of the tooth germ. Our findings demonstrated that cuproptosis-related factors were expressed in dental follicle tissue and alveolar bone tissue of both Group EG and Group CG. However, their expression was significantly reduced in Group EG. These findings suggest that during normal tooth eruption, cuproptosis occurs in both dental follicle tissue and alveolar bone tissue; yet, excessive stress on the tooth germ crown may lead to the down-regulation of cuproptosis-related factors. Such down-regulation could impair osteoclast differentiation, thereby disrupting bone remodeling and ultimately leading to eruption disturbances.

5. Conclusions

The dental follicle plays a crucial role in inducing osteoclast aggregation, and differentiation, thereby promoting the formation of tooth eruption channels. However, limited research has explored the molecular regulatory mechanisms by which the dental follicle initiates differentiation, the role of RANKL-induced osteoclast formation, the signaling pathways involved, and whether cuproptosis is implicated. In this study, we first examined the morphology of dental follicle cells in patients with tooth eruption disturbances, followed by an analysis of the relationship between cuproptosis and bone metabolism-related factors in dental follicle and alveolar bone tissues. The aim was to investigate the potential causes of abnormal osteoblast/osteoclast differentiation in the dental follicle under excessive stress, thereby providing a new theoretical and experimental basis for the prevention and treatment of dental eruption disturbances. Based on previous studies, we propose that moderate pressure during tooth eruption may regulate cuproptosis via the NF-κB signaling pathway, inducing differentiation of dental follicle cells to differentiate into osteoclast-stimulating factors, subsequently activating osteoclasts and precisely regulating the eruption process. However, due to the limited number of cases that meet the inclusion criteria for this category, this study has certain limitations. Although we considered the issue of small sample size when conducting statistical analysis and randomly selected multiple slices from each sample to obtain as many datasets as possible, we know that there is indeed a certain degree of bias in the statistical results obtained through this method. We will collect sufficient samples in future studies to obtain more convincing research results and further explore the molecular regulatory mechanisms of dental follicle regulation of bone metabolism affecting tooth eruption.

ABBREVIATIONS

H&E, hematoxylin and eosin; IHC, immunohistochemical; FDX1, ferredoxin 1; DLAT, dihydrolipoyl transacetylase; RANKL, receptor activator of nuclear factor kappa B ligand; OPG, osteoprotegerin; Group EG, experimental group; Group CG, control group; NF-κB, nuclear factor kappa B.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

HQ and JC—designed the research study and analyzed the data. HQ—performed the research and wrote the manuscript. Both authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures of this study were carried out in accordance with relevant guidelines and approved by Lianyungang Affiliated Hospital of Xuzhou Medical University (Approval number: KY-20240227001-01). And the informed consent was obtained from the patient and his parents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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