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Original Research Article

Strontium ranelate inhibits alveolar bone resorption in diabetic rats with periodontitis by regulating JAK2/STAT3 signaling pathway

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Abstract

Purpose: *To investigate the inhibitory effect of strontium ranelate on alveolar bone resorption in diabetic rats with periodontitis, and the mechanism involved.*
Methods: *Forty-five Sprague-Dawley (SD) rats were allocated to 3 groups, viz, diabetic control, diabetic periodontitis, and diabetic periodontitis + strontium ranelate groups. Diabetes was induced via i.v. administration of streptozotocin (STZ) (45 mg/kg). Then, a rat model of periodontitis was established by ligating the neck of the upper left first molar of each rat with a 0.4-mm orthodontic ligation wire. Strontium ranelate or normal saline was administered by gavage. Four weeks later, various indicators were assessed.*
Results: *There was a significantly higher expression level of Mir-21 in the periodontal tissue of diabetic periodontitis rats than in diabetic control rats. In contrast, this parameter was significantly lower in diabetic periodontitis rats than in periodontal tissues of rats in the diabetic periodontitis + strontium ranelate group, while the translations of JAK2 and STAT3 genes were significantly higher in periodontal tissues of diabetic periodontitis rats ($p < 0.05$). In contrast, there were lower expression levels of JAK2 and STAT3 in diabetic periodontitis group than in diabetic periodontitis + strontium ranelate group ($p < 0.05$).*
Conclusion: *Strontium ranelate increases the expression level of miR-21 and activates JAK2/STAT3 signaling pathway, thereby inhibiting the resorption of alveolus bone in rats with diabetes/periodontitis.*

Keywords: *Diabetic periodontitis, Strontium ranelate, Alveolar bone, MicroRNA-21, JAK2/STAT3*

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INTRODUCTION

Periodontitis is seen regularly in the stomatology department in clinics. It results from chronic inflammation of periodontal support tissues such as cementum, alveolar bone, periodontal membrane, and gum. The symptoms manifested in patients include chronic inflammation-mediated destruction of periodontal tissues and alveolar bone resorption which seriously harm oral health, and may eventually lead to tooth loosening and tooth loss [1].

Studies have found that alveolar bone absorption is the most important pathophysiological change in periodontitis. Metabolic balance in alveolar bone is impaired, and excessive proliferation of osteoclasts causes a higher rate of bone absorption than the rate of bone formation, leading to the destruction of periodontitis bone tissues [2]. Diabetes is one of the several factors that affect the resorption of alveolar bone in periodontitis. Indeed, diabetes aggravates the symptoms of periodontitis, and the resorption of alveolar bone in diabetic periodontitis patients is more serious than that in ordinary periodontitis patients [3].

Ranelate acid strontium is a new anti-osteoporosis drug. It comprises non-radioactive strontium and the organic part i.e., ranelate, both of which promote bone formation by stimulating osteoblast activity, and reduce bone resorption by inhibiting osteoclast activity. These effects reduce periodontitis-induced alveolar bone absorption in orthodontic tooth movement and root resorption [4]. MicroRNA (miRNA) is a highly-conserved non-coding small RNA that is crucial in bone tissue metabolism. It has been reported that Mir-21 is abnormally expressed in periodontitis patients [5]. The Janus kinase/signal transduction and transcriptional activator (JAK2/STAT3) signal route is implicated in the proliferative, migratory, and apoptotic changes in cells, and studies show that Mir-21 regulates the JAK2/STAT3 signaling pathway [6]. At present, not much is known about the influence of strontium ranelate on bone absorption in alveoli in diabetic periodontitis. In this study, the influence of this drug on alveolar bone resorption in diabetic rats was investigated, and the involvement of the JAK2/STAT3 signal route in this process.

EXPERIMENTAL

Animals and reagents

Forty-five male Sprague-Dawley (SD) rats were purchased from Beijing Weitonglihua Experimental Animal Technology Co. Ltd. Strontium ranelate was bought from France Scheer. Streptozotocin (STZ), Mir-21 primer and β-actin primer were products of Sigma Company, USA. Hematoxylin and Eosin (H&E) staining kit, qPCR detection kit, and immunohistochemical sheep anti-rabbit secondary antibody were purchased from Shanghai Biyuntian Company, IL-6, TNF-α, and IL-1β kits were obtained from Shanghai Biyuntian Co. Ltd, while antibodies for JAK2 and STAT3 were products of Abcam Biotechnology Co. Ltd.

Establishment of rat model of periodontitis

Forty-five SD rats were assigned to 3 groups: diabetic control rats, diabetic periodontitis group, and diabetic periodontitis + strontium ranelate group, with 15 rats per group. Diabetes was induced *via* STZ administration *i.v.* (45 mg/kg). Fasting blood sugar determined every other day was above 0.0167 M, indicating that diabetes was effectively induced. Then, the animals were anesthetized with an intraperitoneal injection of 10 % chloral hydrate, and the periodontitis model was established by ligating the neck of the upper left first molar of each rat with a 0.4-mm orthodontic ligating wire. Thereafter, each group was given strontium ranelate or saline at a dose of 900 mg/kg via intragastric route, once a day, continuously for 28 days. This study received approval from the Animal Ethics Authority of Stomatology Key Laboratory of Fujian College and University (approval no. FJCU2020021). It was conducted in line with the "Principles of Laboratory Animal Care" [7].

Sampling and sample preparation

After the completion of intragastric administration, 3 mL of fasting sub-peritoneal venous blood was collected from each rat, after which the rats were put under chloral hydrate anesthesia. Thereafter, the oral cavity of each rat was cut open to remove the maxillary bone and the corresponding periodontal tissue, and half of the periodontal tissue was kept refrigerated at -80 ℃ for further assay. The other half of the periodontal tissue was fixed overnight with a 4 % paraformaldehyde solution, after which it was processed for routine histological analysis, H & E staining, and microscopic examination. In essence, after cutting, dehydration, embedding, and sectioning, the paraffin sections were stained with H & E. Changes in periodontal histomorphology in the rats were determined by examining the stained and sealed sections under a light microscope.

MicroCT analysis

The maxilla was analyzed using a micro-CT scan at a resolution of 20 μm. The parameters analyzed in the trabecular space were bone volume fraction, trabecular population, trabecular breadth, and bone microstructure.

Assay of protein expression levels

Total protein was extracted from periodontal tissue by the preparation of a 10 % homogenate in RIPA buffer at 4 ℃. The homogenate/lysate

was centrifuged, and the protein was quantified using the BCA procedure. Then, equal amounts of protein were resolved using SDS-polyacrylamide gel electrophoresis, followed by transfer to PVDF diaphragms which were subsequently subjected to sequential incubation for 12 h at 4 ^{o}C with 1^{o} immunoglobulins, and thereafter with horse radish peroxidase-linked 2^{o} immunoglobulins at room temperature for 2 h. The results were analyzed using Bio-RAD image laboratory software.

Evaluation of serum levels of pro-inflammatory indices

Serum was obtained from peripheral blood by centrifuging at 3000 rpm for 20 min using a serum separator. Then, serum levels of pro-inflammatory factors were assayed with ELISA kits in strict compliance with the kit instructions. Serum levels of alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P) were measured with an automatic biochemical analyzer.

Determination of Mir-21 expression in periodontal tissues

Total mRNA was extracted from periodontal tissues using TRIzol reagent, and the mRNA was reverse-transcribed into cDNA using the One Step PrimeScript miRNA cDNA synthesis kit. Then, qRT-PCR was performed for Mir-21 using miRNA fluorescence quantitative PCR detection kit, and the cycle was completed according to the kit instructions. After the reaction, the expression of Mir-21 was calculated in the software.

Statistical analysis

Results are presented as mean ± SD. Two-group comparison was done with one-way ANOVA, while multiple groups were compared using LSD test. Statistical significance was assumed at $p < 0.05$.

RESULTS

Histomorphology of periodontal tissues

Histology showed the presence of normal periodontal tissue and intact alveolar bone in the control diabetes rats, with no inflammatory cell infiltration. In contrast, in the diabetic periodontitis group, the periodontal tissue structure of rats was disorganized, with the migration of the epithelium to the root, and there were active osteoclast bone resorption depressions. Resorption was present in the vertical transverse width and height of the alveolar bone, and there were numerous inflammatory cells. In comparison with the diabetic periodontitis group, rats in the diabetic periodontitis + strontium ranelate group showed significant reductions in periodontal histopathology, alveolar bone destruction, and inflammatory cell infiltration.

Bone microstructure

Alveolar bone volume fraction, trabecular number, and trabecular space were significantly reduced in the diabetic periodontitis rats, relative to diabetic control sp, but they were significantly higher in the strontium ranelate group than in diabetic periodontitis rats. The number of bone trabeculae was comparable among the three of them. These results are shown in Table 1.

Serum ALP, Ca, and P levels

Table 2 shows that the serum level of ALP was significantly higher in periodontitis rats with diabetes than in diabetic control but significantly raised in the strontium ranelate group, relative to diabetic periodontitis rats. No marked differences were seen in serum Ca and P concentrations among the three groups.

Table 1: Image features of airway remodeling in each group (n = 15)

Group	Bone volume fraction (%)	Bone trabecular thickness (μm)	Number of bone trabeculae (1/mm)	Bone trabecular gap (μm)
Diabetic control	0.13±0.04	0.47±0.12	2.64±0.76	0.52±0.12
Diabetic periodontitis	0.07±0.02[a]	0.33±0.07[a]	2.26±0.63	0.32±0.12[a]
Diabetic periodontitis+ Strontium ranelate	0.10±0.02[ab]	0.40±0.08[ab]	2.46±0.77	0.42±0.13[ab]
F	16.875	8.5800	1.037	9.847
P-value	0.000	0.001	0.363	0.000

[a]$P < 0.05$, vs diabetic control; [b]$p < 0.05$, vs diabetic periodontitis rats

Table 2: Serum ALP, Ca, and P levels in each group (n = 15)

Group	Ca (mmol/L)	P (mmol/L)	ALP (IU/L)
Diabetic control	2.40±0.34	3.05±0.26	288.16±16.42
Diabetic periodontitis	2.48±0.44	3.12±0.35	326.75±19.12[a]
Diabetic periodontitis +Strontium ranelate	2.25±0.70	2.92±0.31	379.25±30.69[ab]
F	0.768	1.620	59.650
P-value	0.471	0.210	0.000

[a]$P < 0.05$, vs diabetic control; [b]$p < 0.05$, vs diabetic periodontitis rats

Mir-21 expression in periodontal tissues

As presented in Table 3, the expression level of Mir-21 was significantly up-regulated in the periodontal tissue of diabetic periodontitis rats, relative to diabetic controls, and it was significantly higher in the periodontal tissues of rats in the diabetic periodontitis + strontium ranelate group than in diabetic periodontitis group.

Table 3: Mir-21 expression in periodontal tissues of the groups (n = 15)

Group	miR-21
Diabetic control	1.24±0.52
Diabetic periodontitis	2.47±0.54[a]
Diabetic periodontitis + strontium ranelate	3.55±0.70[ab]
F	57.144
P-value	0.000

[a]$P < 0.05$, vs diabetic control; [b]$p < 0.05$, vs diabetic periodontitis rats

Protein expressions of JAK2 and STAT3

The protein expression levels of JAK2 and STAT3 were significantly higher in the periodontal tissue of diabetic periodontitis rats, in comparison with diabetic control, but were significantly higher in the diabetic periodontitis + strontium ranelate group than in the diabetic periodontitis group ($p < 0.05$; Table 4).

Table 4: Comparison of protein expression levels of JAK2 and STAT3 in periodontal tissues of rats amongst the groups (n = 15)

Group	JAK2	STAT3
Diabetic control	0.28±0.04	0.13±0.03
Diabetic periodontitis	0.84±0.21a	0.59±0.17a
Diabetic periodontitis+Strontium ranelate	1.25±0.37ab	0.83±0.35ab
F	58.431	39.387
P-value	0.000	0.000

[a]$P < 0.05$, vs diabetic control; [b]$p < 0.05$, vs diabetic periodontitis rats

Serum inflammatory indices

There were significantly up-regulated levels of serum inflammatory markers in diabetic periodontitis rats than in diabetic controls. However, the levels of these inflammatory indices were significantly lower in diabetic periodontitis + strontium ranelate group than in diabetic periodontitis group ($p < 0.05$; Table 5).

Table 5: Serum levels of inflammatory indexes in each group (n = 15)

Group	IL-6 (µg/L)	TNF-α (ng/L)	IL-1β (pg/L)
Diabetic control	97.86±11.28	50.71±8.22	9.34±1.76
Diabetic periodontitis	180.28±18.04[a]	170.33±17.11[a]	30.28±4.84[a]
Diabetic periodontitis+ Strontium ranelate	150.37±16.09[ab]	121.41±13.14[ab]	16.36±2.13[ab]
F	110.091	305.367	164.567
P-value	0.000	0.000	0.000

[a]$P < 0.05$, vs diabetic control; [b]$p < 0.05$, vs diabetic periodontitis rats

DISCUSSION

Periodontitis is caused by the infection of the gum tissue by pathogenic microorganisms. It is a complex inflammatory disease that results in the generation of a large number of cytokines. The disease easily affects the periodontal connective tissue and alveolar bone structures, causing the opening of the periodontal pocket, destruction of associated ligament, and resorption of alveolar bone, leading to loosening and loss of teeth [8]. Metabolic disorders in patients with diabetes tend to impair bone generation-resorption homeostasis, as well as enhancement of bone resorption, weakening of bone synthesis, and aggravation of alveolar bone resorption in periodontitis patients [9]. The results from H & E staining showed normal periodontal tissue, intact alveolar bone, and absence of inflammatory cell infiltration in diabetic controls. In diabetic periodontitis rats, periodontal tissue structure was disorganized, in addition to migration of the epithelium to the root and active osteoclast bone resorption depressions. Moreover, there were absorptions in the vertical transverse width and height of the alveolar bone, as well as the presence of a large number of inflammatory cells.

Compared with the diabetic periodontitis group, the diabetic periodontitis + strontium ranelate group had significant mitigations of periodontal histopathology, alveolar bone destruction, and inflammatory cell infiltration. These results suggest that strontium ranelate inhibited alveolar bone resorption in rats with diabetic periodontitis. The alveolar bone volume fraction, number of trabecular bones, and trabecular space were significantly lower in diabetic periodontitis rats than in diabetic controls, while the number of trabecular bone and trabecular space in diabetic periodontitis + strontium ranelate group were significantly raised, relative to diabetic periodontitis rats. Strontium ranelate is a dual-effect anti-osteoporosis drug. It is composed of non-radioactive strontium and organic ranelate. Being a bone-friendly element, strontium promotes collagen and bone matrix synthesis and enhances calcium receptor-mediated proliferation of osteoblasts, thereby increasing the rate of bone mineral deposition. Moreover, strontium destroys the cytoskeleton in the closed area of osteoclasts and stimulates apoptosis of osteoclasts; it inhibits osteoclasts and reduces bone absorption, thereby effectively inhibiting alveolar bone absorption in diabetic periodontitis [10,11]. Alkaline phosphatase (ALP) is one of the important enzymes that regulate cell mineralization, and it is an early indicator of cell osteogenic differentiation. In osteoblasts, ALP reduces the concentration of pyrophosphate and promotes bone mineralization [12]. In this study, the serum ALP level in the diabetic periodontitis group was significantly higher than that in the diabetic control group, and the serum ALP level in the diabetic periodontitis + strontium ranelate group was significantly higher than that in the diabetic periodontitis group. Serum Ca and P were comparable in the 3 rat groups. These results suggest that strontium ranelate increased ALP levels, stimulated osteoblast maturation and activity, and enhanced bone formation. Serum levels of Ca and P are affected by the parathyroid hormone, nutrient absorption, dietary habits, and other factors. In this study, it was difficult to obtain significant changes in serum levels of Ca and P due to the low absorption capacity of alveolar bone.

The inflammatory process and resorption of alveolar bone in diabetic periodontitis are affected by complex cytokine signaling. Research on miRNA has attracted a lot of attention in the field of stomatology in recent years. The miRNAs are a group of nucleic acids that modulate cell proliferation, migration and apoptosis by binding to target genes [13]. In particular, Mir-21 is a form of miRNA involved in the regulation of inflammatory response. Although its specific regulatory role in the inflammatory response has not been fully elucidated, studies have shown that miRNA exerts its anti-inflammatory role by targeting JNK and TSG4 [14]. Moreover, *in vitro,* Mir-21 acts as an osteogenic promoter of mesenchymal stem cells of the bone marrow and enhances the osteogenic effect of bone marrow stem cells by regulating downstream target protein Sprouty [15]. Other studies have confirmed that Mir-21 is highly expressed in invasive periodontitis tissues and that the activity and number of macrophages in periodontitis tissues are closely positively correlated with the expression level of Mir-21 [16]. These results suggest that the expression level of Mir-21 is closely related to the severity of periodontitis disease [16]. In addition, studies have found that Mir-21 not only increases the expressions of bone destruction markers but also enhances the proliferation of osteoclasts, suggesting that it may be an important target for the treatment of bone lesions in periodontitis [17]. The relative expression of Mir-21 in the periodontal tissues of the diabetic periodontitis group was significantly higher than that in the diabetic control group, and the expression level of Mir-21 in the periodontal tissues of the diabetic periodontitis + strontium ranelate group was significantly higher than that in diabetic periodontitis group. Therefore, Mir-21 was highly expressed in periodontal tissues of diabetic periodontitis rats, and strontium ranelate up-regulated Mir-21 expression level and inhibited bone resorption in the alveoli of diabetic periodontitis rats.

The JAK2/STAT3 signaling route is a pathway formed by the targeted transduction of various cytokines. The pathway is widely involved in various physiological processes such as oxidative stress and inflammatory response of tissues and organs, and it is closely related to the occurrence and development of immune system diseases, ischemic diseases, and inflammatory diseases [18]. The JAK2/STAT3 signaling pathway is activated in periodontitis and inflammatory bowel disease. An important protein molecule in JAK2/STAT3 signaling is STAT3. This protein is highly expressed and phosphorylated in periodontitis diseases, and it forms a dimer with JAK (JAK-STAT dimer). This dimer activates the transcription and expression of corresponding downstream genes [19]. It has been reported that the relative protein expression levels of STAT3 and JAK2 in Mir-21-transfected cells were significantly reduced, and Mir-21-overexpressed cells targeted inhibition of activation of JAK/STAT signaling pathway, relative to un-transfected controls without Mir-21[20]. Other studies have found that Mir-21

increased the expression of STAT3 by binding to the STAT3 promoter. These studies indicate that Mir-21 is linked closely to the activation of the JAK2/STAT3 signaling pathway [21]. This investigation revealed that protein concentrations of JAK2 and STAT3 in periodontal tissues of the diabetic periodontitis group were significantly higher than the corresponding levels in the diabetic control rats, and the expression levels of these proteins in periodontal tissues of diabetic periodontitis + strontium ranelate rats were significantly raised, relative to diabetic periodontitis rats. Thus, strontium ranelate inhibited alveolar bone resorption in diabetic rats with periodontitis by targeting Mir-21 and activating the JAK2/STAT3 signaling pathway.

The basic pathological change in periodontitis is the inflammatory response of periodontal tissue under the stimulation of local factors. This results in the stimulation of inflammatory cells to release a large number of inflammatory factors such as IL-6, TNF-α, and IL-1β into the blood, resulting in inflammation-mediated alveolar bone destruction [22]. Serum IL-6, TNF-α, and IL-1β in the diabetic periodontitis group were significantly higher than those in the diabetic control group, while the serum levels of these inflammatory factors in diabetic periodontitis + strontium ranelate rats were significantly reduced, relative to the diabetic periodontitis rats. Thus, there were raised serum levels of pro-inflammatory cytokines in diabetic periodontitis rats, while their levels were decreased after strontium ranelate treatment. A study has shown that Mir-21 is up-regulated in macrophages, dendritic cells, neutrophils, and other immune cells [23]. Moreover, it has been reported that Mir-21 inhibited the expressions of IL-6, TNF-α, and IL-1β through targeted activation of the JAK2/STAT3 inflammatory signaling pathway, thereby reducing periodontal inflammation, suppressing bone resorption, and enhancing alveolar bone regeneration [24].

CONCLUSION

Strontium ranelate inhibits alveolar bone resorption in diabetic rats with periodontitis by targeting Mir-21 expression level and activating JAK2/STAT3 signaling pathway. This provides a basis for research and development of drugs for inhibiting alveolar bone absorption in patients with diabetes periodontitis.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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