High-Mobility Group Box 1 Expression in Mandibular Bone Cells of Experimental Periodontitis

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Original Article

High-Mobility Group Box 1 Expression in Mandibular Bone Cells of Experimental Periodontitis

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Abstract

Background: High-mobility group box 1 (HMGB1) was suggested to be associated with the pathogenesis of chronic periodontitis which characterized by alveolar bone loss. HMGB1 was defined as a bone-active cytokine, but the rule of HMGB1 in bone loss of chronic periodontitis is still understood. **Aim:** The aim of this study is to investigate the expression of HMGB1 on osteoblasts and osteoclasts in the mandible of chronic periodontitis. **Methods:** This experimental study was conducted to rats injected by *Porphyromonas gingivalis* into the buccal and lingual subgingival area at a concentration of 2×10^9 CFU/mL three times a week with 2-day apart for 2, 3, 4, and 6 weeks as chronic periodontitis group and injected by normal saline as control group. Analysis of variance was used to examine the differences between groups followed by least significant difference *post hoc* test with the level of significance was <0.05. **Results:** The HMGB1 expression was found in both osteoclasts and osteoblasts of mandibular bone by immunohistochemistry analysis. There was a difference of HMGB1 expression on osteoblasts and osteoclasts of chronic periodontitis. HMGB1 expression was found increased significantly in mandibular osteoblasts of chronic periodontitis, whereas the HMGB1 expression in mandibular osteoclast is higher in 2 and 3 weeks, but it was lower in 4 and 6 weeks. **Conclusions:** This study indicated a potential role for HMGB1 in bone loss of chronic periodontitis. HMGB1 on mandibular osteoclasts and osteoblasts may play different rules in the onset and progression of chronic periodontitis.

Keywords: *Bone loss, chronic periodontitis, high-mobility group box 1, mandibular bone cell, osteoblasts/osteoclasts*

Introduction

High-mobility group box 1 (HMGB1) was a nonhistone chromatin-binding protein that was the most highly expressed of all the high-mobility group family members.[1] HMGB1 is located in the nucleus, but HMGB1 has been reported to be present in the cytoplasm and cell membrane. Nuclear HMGB1 acts as an architectural protein in chromosomes to maintain nucleosome structure and acts as a DNA chaperone and regulates gene transcription.[2] HMGB1 can translocate from nucleus to cytoplasm because of some stressors, including cytokine, chemokine, heat, hypoxia, and oncogene.[2] A recent study showed that HMGB1 can be released into the extracellular by necrotic and damaged cells and can act as a signal of tissue damage and mediates inflammation and tissue regeneration.[3] It has been reported that HMGB1 is a potent pro-inflammatory cytokine that orchestrated in systemic and local inflammation. HMGB1 is involved in the development and contributes to the outcome of some diseases such as bacterial sepsis, diabetes, postischemic brain and heart disease, rheumatoid arthritis, and skin lesions in systemic lupus erythematosus.[2,3]

It was suggested that HMGB1 has a potential role in the pathogenesis of chronic periodontitis. The increased HMGB1 was found in gingiva and gingival crevicular fluid of the patient with chronic periodontitis.[4-6] Expression of HMGB1 can be detected higher in chronic periodontitis patients and decreased after periodontal treatment.[5] Chronic periodontitis is a chronic infectious disease, resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone loss.[7] *Porphyromonas gingivalis* (*P. gingivalis*) has been identified as one of the major periodontal pathogens of chronic periodontitis.[8] The virulence

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factors of these bacteria can contribute to extracellular matrix destruction and modulate inflammatory and immune responses, resulting in deeper tissue destruction and bone resorption.[9] *P. gingivalis* LPS, lipids, and metabolic products can inhibit the differentiation and osteogenesis of osteoblasts, and modulate receptor activator of nuclear factor-kappa B ligand (RANKL) and/or osteoprotegerin (OPG) expression in osteoblasts to stimulate osteoclastogenesis, resulting in bone loss.[10,11]

Alveolar bone loss is a hallmark of periodontitis progression. Mandibular bone cells, osteoclasts, and osteoblasts were the key cells in bone loss in periodontitis. Although HMGB1 was defined as a bone-active cytokine,[12] the rule of HMGB1 in alveolar bone loss in periodontitis was remaining understood. A study by Charoonpatrapong *et al.*[13] found that rat calvarial osteoblast and primary osteoclasts derived from mouse bone marrow cells expressed and released HMGB1. HMGB1 released into the bone microenvironment and induced inflammatory bone loss through the release of RANKL, interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α) by osteoblast.[12] Studies reported that HMGB1 expression was higher in gingiva and periodontal ligament of experimental periodontitis.[14,15] However, the study reported the expression HMGB1 in mandibular bone cells is not found yet. This study conducted to investigate the expression of HMGB1 on mandibular bone cells of experimental periodontitis induced by *P. gingivalis*.

Methods

All experimental procedure was performed under a protocol approved by Committee Ethical of Faculty of Dentistry, Airlangga University (Ethical Clearance Certificate Number 017/HRECC.FODM/II/2017). Forty Wistar –Strain of *Rattus novergicus*, 3–4-month-old male, 200–220 g in weighing, were randomly divided into two equal groups, periodontitis and control group. Throughout the experimental period, rats were housed in plastic cages, fed a standard laboratory diet, and given water *ad libitum*.

Bacterial strain and culture

P. gingivalis (ATCC 33277, MediMark, France) was cultured at 37°C on Trypton Soya Agar plates with 10% sheep blood, supplemented with 0.4 μL/mL Vitamin K and hemin in an oxygen-free atmosphere (80% nitrogen, 10% carbon dioxide, and 10% hydrogen). After 14 days, *P. gingivalis* colonies were selected, and a solution of 2×10^9 CFU/mL in 100 μL of 0,9% sodium chloride was prepared. This solution was prepared immediately before use. Gram's method was used to confirm the purity of the colonies.

Experimental periodontitis

The rat in the periodontitis group was injected by 0.05 mL live-*P. gingivalis* at a concentration of 2×10^9 CFU/mL into buccal and lingual subgingival sulcus area between the left first and second mandibular molar three times a week with 2 days interval for 2, 3, 4, and 6 weeks. The bacterial injection was performed using tuberculin disposable syringe (OneMed, Indonesia) with needle 30Gauge (BD PrecisionGlide™ Needle, USA). The control group was injected by normal saline as periodontitis group protocol. One day after 2, 3, 4, and 6 weeks following injection, five rats in each group were sacrificed. The mandibular specimens were harvested and fixed in normal buffer formalin. Then, the tissues were demineralized in 10% EDTA for 2 months. The demineralized tissues were dehydrated using gradient ethanols, cleared with xylene and embedded in paraffin. Serial sections of 5 mm in thickness were made in the mesiodistal direction for hematoxylin and eosin and immunohistochemical staining.

Immunohistochemical staining

The sections were deparaffinized using xylene, hydrated in gradient ethanols, and then the sections were treated with 3% H_2O_2 for 10 min at room temperature to inhibit endogenous peroxidase activities and washed with 0.01 M PBS 5 min × 2 times. The sections were treated with 5% normal blocking serum (UltraTekHRP, Scytec) for 5 min to block nonspecific background staining and washed with 0.01 M PBS 5 min × 2 times. Then, the sections were reacted with polyclonal antibody HMGB1 (HMG-1, sc-135809, Santacruz Biotechnologi, Inc.) for 1 h at 4°C as recommended by the manufacturer. After washing with 0.01 M PBS 5 min × 3 times, the sections were then incubated with Poly-HRP anti-goat/rabbit IgG (UltraTekHRP, Scytec) for 15 min at 37°C. Afterward, the sections were visualized with 3,3-diaminobenzidine tetrahydrochloride for 10 min (UltraTekHRP, Scytec). 0.01 M PBS instead of antibody served as negative control. The sections were examined and photographed with a light microscope (Nikon E100 J fully equipped digital camera ILCE A7 Sony). The number of osteoblasts and osteoclasts cells with positive the expression of HMGB1 was calculated.

Statistical analysis

Data were presented as mean ± standard deviation One-way analysis of variance was used to examine the differences between groups followed by Least Significant Difference *post hoc* test. The data were considered statistically significant when the *P* value was < 0.05.

Results

The result showed that HMGB1 was expressed in osteoblast as well as in osteoclast of mandibular bone. Immunohistochemical analysis of mandibular osteoblast demonstrated that weak staining of HMGB1 was observed primarily in the cytoplasm [Figure 1], but in the mandibular osteoclasts, the expression of HMGB1 was found in strong staining in cytoplasm and nucleus [Figure 2].

HMGB1 expressed either in the chronic periodontitis model group and control group. The HMGB1 expression

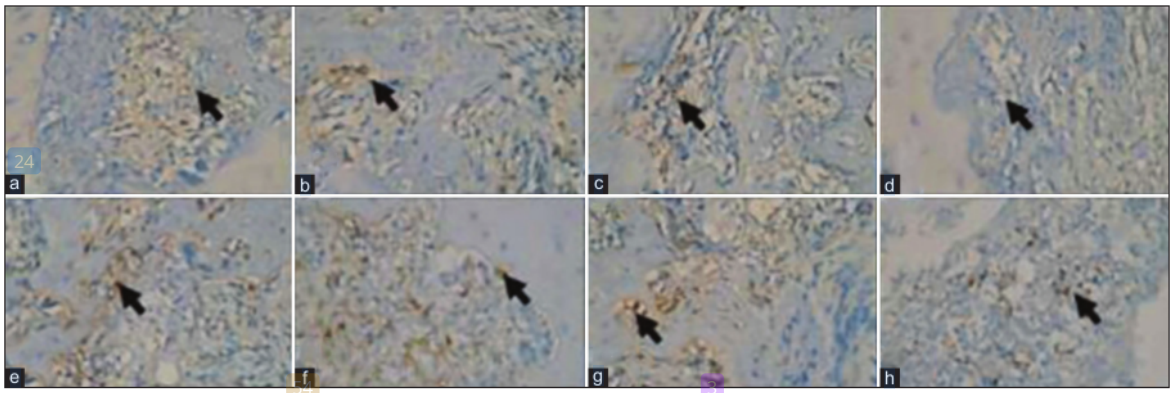

Figure 1: The immunoexpression of high-mobility group box 1 in mandibular osteoblast. High-mobility group box 1 observed in weak staining of the cytoplasm of periodontitis group 2 week (e), 3 weeks (f), 4 weeks (g) and 6 weeks (h) and in control group 2 week (a), 3 weeks (b), 4 weeks (c) and 6 weeks (d)

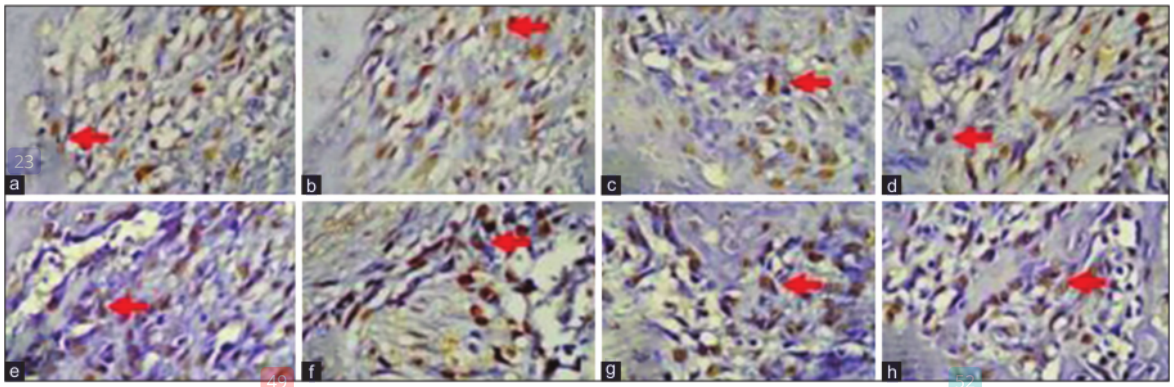

Figure 2: The immunoexpression of high-mobility group box 1 in mandibular osteoclast. Nuclear and cytoplasmic staining of high-mobility group box 1 observed in control group 2 week (a), 3 weeks (b), 4 weeks (c) and 6 weeks (d) and periodontitis Group 2 week (e), 3 weeks (f), 4 weeks (g) and 6 weeks (h)

in mandibular osteoblast of all periodontitis groups was higher significantly than the control group ($P < 0.05$). The HMGB1 expression in osteoblast of the periodontitis group was decreased significantly in line with the time of injection until 4 weeks; however, it increased but not statistically significant ($P = 0.087$) in 6 weeks injection [Figure 3]. A different result found in mandibular osteoclast of periodontitis groups. The HMGB1 expression of mandibular osteoclast in periodontitis group 2 and 3 weeks were higher than control group, but HMGB1 expressions in periodontitis group 4 and 6 weeks were lower significantly than control group ($P < 0.05$). By the time of injection, the HMGB1 expression in osteoclast of periodontitis group was decreased significantly ($P < 0.05$); although; the decreasing periodontitis 6 weeks was not significant periodontitis 4 weeks ($P = 0.121$) [Figure 4]. In all of the periodontitis groups, the expression of HMGB1 in osteoblast was higher significantly than osteoclast ($P < 0.05$).

Discussion

It has been suggested that HMGB1 has a potential role in the pathogenesis of chronic periodontitis.[4,5] The level of gingival crevicular fluid HMGB1 in periodontitis patients has a positive correlation with probing depth and clinical attachment loss.[6] Chronic periodontitis was characterized by alveolar bone loss which is mediated by the host immune and inflammatory response to the microbial challenge.[16] *P. gingivalis* can inhibit the differentiation and osteogenesis of osteoblasts and stimulate osteoclastogenesis and osteoclast activation resulting in bone loss.[9,10] Mandibular osteoclast and osteoblast were the principle cells regulated mechanism of the bone loss in periodontitis. Therefore the expression of HMGB1 on mandibular bone cells should be determined.

This study successfully found the expression of HMGB1 on osteoblasts and osteoclasts of mandibular bone both in the experimental periodontitis and control rats. There was an increase in HMGB1 expression in osteoblast and osteoclast in periodontitis group than in control group. The result of this study supported the potential role of HMGB1 in the pathogenesis of periodontitis. In experimental periodontitis, HMGB1 expression was also reported higher in gingiva and periodontal ligament.[14,15]

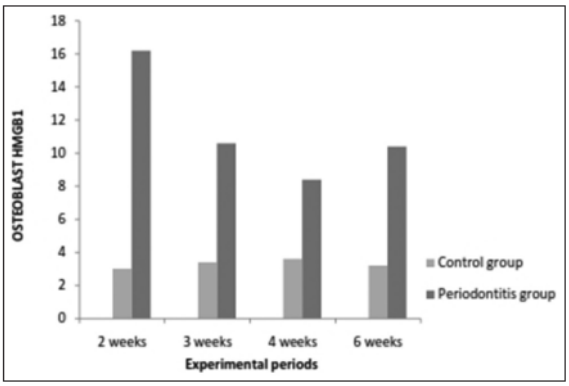

Figure 3: The immunoexpresion of high-mobility group box 1 in mandibular osteoblast of experimental periodontitis different experimental periods. All of periodontitis group showed the higher expression significantly than control group ($P < 0.05$)

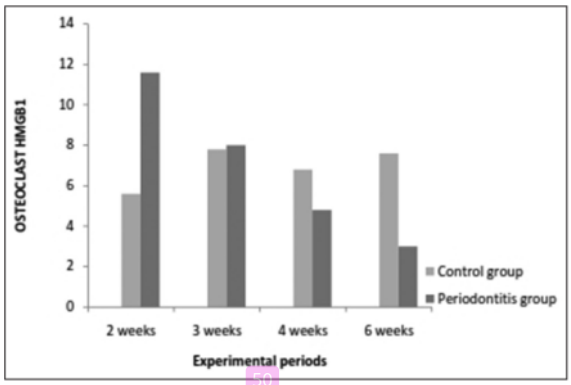

Figure 4: The immunoexpresion of high mobility group box 1 in mandibular osteoclast of experimental periodontitis in different experimental periods. The high-mobility group box 1 expression of mandibular osteoclast in periodontitis group 2 was higher than control group, but high-mobility group box 1 expressions in periodontitis group 4 and 6 weeks were lower significantly than control group ($P < 0.05$)

According to our knowledge, this is the first study reporting the immunoexpression of HMGB1 in mandibular bone cells. In mandibular osteoblast, HMGB1 expression observed mainly in the cytoplasm with weak staining, whereas in mandibular osteoclast, strong staining of HMGB1 observed in the nucleus and cytoplasm. This study was nearly same with the previous study that found HMGB1 expressed in osteoblast lined the trabecular surface of a rat femoral metaphysis and in primary osteoclast derived from mouse bone marrow chondrocytes.[13] The immunoexpression of HMGB1 primarily localized to the nucleus of osteoblasts, but weak staining was observed in the cytoplasm. Primary osteoclasts expressed HMGB1 in the nuclei and in the perinuclear region.[13] HMGB1 was also detected in the nuclei of prehypertrophic chondrocytes and in the cytosol of hypertrophic chondrocytes.[17]

Naturally, the HMGB1 was located in nuclei, but it can translocate to the cytoplasm or perinuclear because of some stressor including cytokine, chemokine, heat, hypoxia, and oncogene.[2,3] Study Morimoto *et al*.[18] found that in healthy gingival tissues, HMGB1 is located mainly in the nucleus of epithelial cells while in inflamed gingival epithelial cells it is located in the perinuclear and in the cytoplasm. *In vitro* study in gingival fibroblast conducted by Feghali *et al*.[19] found that before the induction of LPS *Actinobacillus actinomycetemcomitans* dan *P. gingivalis*, HMGB1 was expressed in the nucleus. After 6 h induction of that LPS, HMGB1 began expressed in the cytoplasm and after 12 h all of the nuclear HMGB1 translocate to cytoplasm. A study in ligature and *Escherichia coli* LPS-induced periodontitis found that HMGB1 was more expressed in the nucleus and cytoplasm of the fibroblast of periodontal ligament than in the extracellular space suggest that periodontal disease could contribute to HMGB1 translocation from the nucleus to the cytoplasm in the epithelial and connective cells.[15] *P. gingivalis* induces translocation of HMGB1 from the nucleus to the cytosol.[20] In this study, it has been suggested that experimental periodontitis induced by *P. gingivalis* increased the HMGB1 expression in osteoblast and osteoclast and might induce translocating that molecule to the perinuclear or cytoplasm. Further study was needed to clarify this assumption.

The higher HMGB1 expression in osteoblast was observed in all of the periodontitis groups than in the control group and in osteoclasts, but HMGB1 expression in osteoclasts of periodontitis group presented higher at 2 and 3 weeks followed by decreased at 4 and 6 weeks than in control group. The study by Nogueira *et al*.[15] found that the expression of HMGB1 in gingiva from ligature induced periodontitis higher at 7 and 14 days following by a decrease at 30 days.

The HMGB1 expression in osteoblast and osteoclast of the periodontitis group was decreased in line with the experimental periods. It was suggested that by the time of periodontitis progression, the HMGB1 translocated from the cytoplasm to the extracellular. According to study Charoonpatrapong *et al*.[13] that osteoblasts and osteoclasts have been released HMGB1 to the bone environment. HMGB1 can be secreted from the cytoplasm to the extracellular actively by stimulated cells or passively by necrotic or damaged cells.[2,3] Although the level of HMGB1 in tissue or gingival crevicular fluid as extracellular HMGB1 was not determined in this study, the increased level of HMGB1 in tissue or gingival crevicular fluid detected periodontitis patient may have come from mandibular osteoblasts or osteoclasts even in the milieu concentration.

This study demonstrated that there was a difference in HMGB1 expression between osteoblasts and osteoclasts in experimental periodontitis and control groups. In the control group, expression of HMGB1 in mandibular osteoblast was lower than in mandibular osteoclast. In contrast, in the

periodontitis group expression of HMGB1 in osteoblast was higher than osteoclast. This result showed that HMGB1 may have a different rule on osteoblasts and osteoclasts during the development and progression of periodontitis. The function of extracellular HMGB1 in periodontal tissue has been explored. Extracellular HMGB1 can act as cytokines or chemokines that involved in inflammation, immunity, cell growth, cell proliferation, and cell death.[2,3] HMGB1 increased cytokine IL-1 β, interferon-gamma, or TNF-α production by macrophages.[21] HMGB1 has been reported to stimulate the proliferation of gingival fibroblasts and the migration of gingival and periodontal ligament fibroblasts.[22] Study Wolf *et al*.[23] also found that HMGB1 increased the proliferation and migration of periodontal ligament cells. Osteogenic differentiation of periodontal ligament cell also increased by HMGB1 which was proven by increased of alkaline phosphatase specific activity and osteopontin expression.[23] HMGB1 also can act as carrier protein for cytokines that have capability to activate the cell to release other cytokines.[21] HMGB1 was secreted actively by chondrocytes acts as chemotactic factor for osteoblasts and osteoclasts and regulates endochondral ossification.[17] HMGB1 promotes the migration of osteoblasts by TLR2/4-dependent signaling pathways that drive the activation of NF-κB. The migration rate of osteoblasts increases 2.3-fold after HMGB1 treatment.[24] The previous study has been demonstrated that HMGB1 molecules have a synergistic effect with RANKL to regulate osteoclastogenesis.[25] Based on previous study, the HMGB1 alters osteoblast expression of RANKL or OPG[26] and participates in osteoclastogenesis process.[25] HMGB1 induced inflammatory bone loss through the release of RANKL, IL-6, and TNF α by osteoblast.[12] RANKL induces HMGB1 release and it is required for RANKL-induced osteoclastogenesis *in vitro* and *in vivo*.[25] In bone fractures, HMGB1 enhances mesenchymal stem cells in bone fracture area to secrete various cytokines and promotes osteogenic differentiation.[27] Systemic administration of anti-HMGB1 neutralizing antibody significantly inhibited periodontal inflammation and bone resorption.[28] However, there was no study reported the function of HMGB1 in mandibular osteoblast and osteoclast of periodontitis.

This finding HMGB1 expression in mandibular bone cells in periodontitis was very meaningful. This would be open the chance of studies to investigate the potential role of HMGB1 in the mechanism of pathogenesis and severity of periodontitis, especially bone resorption. HMGB1 in mandibular bone cells may be a critical biomarker of bone destruction in periodontitis, which can be used for the detection and diagnosis of disease, prediction of response to therapeutic interventions, or prognosis of the outcome.

Conclusions

HMGB1 was expressed at mandibular bone cells, and it increased in experimental periodontitis. It suggested that HMGB1 may be a critical biomarker of periodontitis, especially in bone loss in periodontitis. HMGB1 on mandibular osteoblast and osteoclast may have a different rule in the development and progression of periodontitis. Further studies are necessary to investigate the potential role of HMGB1 in the mechanism of pathogenesis and severity of bone destruction in periodontitis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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