The role of interleukin-6 in pathogenesis of chronic periapical lesions

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SUMMARY

Introduction Cytokine network plays an important role in pathogenesis of chronic periapical lesions. The aim of this study was to determine the concentration of interleukin-6 (IL-6) in tissue homogenates of human periapical lesions and correlate its levels with symptomatology and size of the lesions.

Materials and Methods 93 samples of chronic periapical lesions were obtained after extraction of teeth. Samples were divided according to the clinical presentation as symptomatic and asymptomatic, and according to the size as large and small. The concentration of IL-6 was analyzed using ELISA.

Results Statistically significant difference in IL-6 concentration was observed in symptomatic lesions compared to asymptomatic (p<0.001). Analysis showed statistically higher concentration in large symptomatic lesions compared to large asymptomatic lesions (p<0.001), and in small symptomatic lesions compared to small asymptomatic (p<0.05). Higher production of IL-6 was observed in large lesions compared to small but this difference was not statistically significant.

Conclusion Higher concentration of IL-6 in lesions with expressed clinical symptoms as well as in large lesions indicates that IL-6 is an important factor responsible for the progression of lesions and bone resorption.

Keywords: Periapical lesions; cytokines; IL-6

INTRODUCTION

Periapical lesions are inflammatory disorders that develop as a result of an immune response to continuous antigen stimulation from the root canal. Their development and progression to chronic lesions with concomitant bone resorption occur as a result of inability of host defense mechanisms to remove infection [1]. Chronic periapical lesions represent inflamed granulation tissue infiltrated by different inflammatory cells, which produce a variety of mediators. Cytokine network plays an important role in the regulation of non-specific and specific immune responses. Many studies have demonstrated the production of various cytokines in the periapical lesions [2, 3].

Interleukin 6 (IL-6) is a cytokine that influences the antigen-specific immune responses and inflammatory reactions, and has the role of proinflammatory and anti-inflammatory cytokine [4]. IL-6 is the “myokin”, a cytokine produced in the muscles in response to contraction. It increases significantly with exercise, and prior to the occurrence of other cytokines in the bloodstream. IL-6 production is proven in human periapical lesions [5] and in marginal inflammation of periodontal tissues [6]. The literature data suggests that IL-6 is multifunctional cytokine produced by several types of immune cell- monocytes, macrophage, Th-2 cells, activated B cells, and polymorphonuclear cells [7]. Production of IL-6 is carried out under the influence of IL-1, TNF-α and INF-γ, however, it also regulates the secretion of IL-1 and is opposed by some of its effects. IL-6 is secreted by osteoblasts during stimulation of osteoclast formation. IL-6 stimulates the formation of osteoclast precursors and increases the number of osteoclasts in vivo, leading to systematic bone resorption [8]. Along with TNF-α and IL-1, it belongs to the group of major proinflammatory cytokines. Numerous data indicate that IL-6 also has anti-inflammatory activity. The antiinflammatory role of IL-6 is mediated through the inhibitory effects of TNF-α and IL-1 [9].

The aim of this study was to determine the concentration of interleukin-6 (IL-6) in tissue homogenates of human periapical lesions and correlate its levels with symptomatology and size of the lesions.

MATERIALS AND METHODS

The study included 93 patients from the Clinic of Dentistry, Niš, who were diagnosed with chronic periapical lesions using clinical and radiographic methods. The study was approved by the Ethical Committee of the Medical
Faculty, University of Nis, Serbia (no. 01-2066-5). Periapical odnosu na simptomatologiju i veličinu

Table 1. Periapical lesions according to symptomatology and size

|                        | Large lesions | Small lesions | Total |
|------------------------|---------------|---------------|-------|
| Symptomatic lesions    | 23            | 23            | 46    |
| Asymptomatic lesions   | 23            | 24            | 47    |
| Total                  | 46            | 47            | 93    |

Figure 1. Concentration of IL-6 in tissue homogenates of periapical lesions in relation to symptomatology and size

Table 2. IL-6 concentration in symptomatic and asymptomatic lesions

| Symptomatic Lesions | n   | Mean ± SD | Median | Min.–Max. |
|---------------------|-----|-----------|--------|----------|
| Large lesions       | 22  | 1162.40±1002,40 | 884.90 | 8.79-2649.63 |
| Small lesions       | 19  | 759.11±836.24  | 427.30 | 17.28-2423.72 |

RESULTS

All tissue homogenates of periapical lesions showed significant concentration of IL-6 cytokine. Figure 1 shows the concentration of IL-6 in the tissue homogenates of all samples that were analyzed with respect to the size and symptomatology. In symptomatic lesions average concentration of IL-6 was 975.51 pg/ml, while in the group of asymptomatic lesions the average value was 212.04 pg/ml. Analysis of the concentration showed that there was significantly higher concentration of IL-6 in symptomatic lesions (p<0.001). In the group of large lesions, average concentrations of IL-6 amounted to 687.14 pg/ml, while in the group of small lesions average value was 470.92 pg/ml. The difference was observed but not statistically significant.

Table 2 shows the concentration of IL-6 within the groups of symptomatic and asymptomatic lesions. The concentration of IL-6 test for IL-6 was from 0.7 pg/ml, and the concentration of cytokine was analyzed in relation to the size and symptomatology of periapical lesions. Statistical analysis was performed using the Mann-Whitney Rank Sum test in the software Sigmastat and Origin. The results were expressed as mean ± standard deviation. P<0.05 was considered statistically significant.
enec in concentration of IL-6 was also not observed in relation to the size. The average concentration of IL-6 in large asymptomatic lesions amounted to 189.24 pg/ml, while in small asymptomatic lesions it was 232.86 pg/ml.

Figure 2 shows the concentration of IL-6 in the groups of large and small lesions where the statistical significance was analyzed in relation to symptomatology. The average concentration of IL-6 in large asymptomatic lesions amounted to 1162.40 pg/ml, while in large asymptomatic lesions it was 189.24 pg/ml. The difference was statistically significant (p<0.001). The analysis showed significantly higher concentration in small asymptomatic (759.11 pg/ml) compared to small asymptomatic lesions (232.86 pg/ml) (p<0.05).

DISCUSSION

Periapical lesions develop as a result of persistent inflammatory response induced by prolonged exposure of periapical tissue to root canal microorganisms, causing an immune reaction. In this local defense mechanism different inflammatory mediators play a complex and central role in the regulation of immune response. While proinflammatory cytokines, such as IL-1, IL-6, TNF-α, TNF-β, chemokines and Th1 cytokines, promote inflammation in the periapical tissues and activate osteoclastic bone resorption [10, 11], the role of antiinflammatory cytokines is important for suppression of inflammatory processes and repair processes within the periapical lesions [2, 3, 12].

In the early inflammatory cascade IL-1 and TNF-α induce production of IL-6. IL-6 has many molecular forms, and each molecule has a different function if secreted by various cells in different situations. The finding that polymorphonuclear cells in the periapical tissues produce IL-6, which was specified by the Euler et al. [13], suggest that IL-6 can contribute to the tissue injury at the site of inflammation. IL-6 is an integral mediator of the acute phase response to injury and infection that stimulate expression of acute phase protein [14]. Examination of various cytokines, such as TNF-α, IL-6, IL-3, GM-CSF, IL-11, IL-17, IL-18, in human and animal models have demonstrated their potential role in the pathogenesis of osteolytic diseases [2, 15]. It has been shown that inflammatory cytokines IL-6 and TNF-α have the capacity to trigger osteoclastic bone resorption and their role can express synergistically with IL-1, causing activation or osteoclast differentiation and production, as well as secretion of prostaglandins by numerous cell types, including fibroblasts and osteoblasts [2]. Several authors have published the expression of IL-6 production in human periapical granulomas and cysts. Results of our study showed the presence of IL-6 in all tissue samples of periapical lesions that is in accordance with data from the literature [9, 16].

Studies have shown that the level of IL-6 is significantly increased in the infection and pain conditions. In the study of De Jongh et al. [17] important role is attributed to IL-6 in the pathophysiology of pain. Due to this fact, in our study we analyzed correlation between levels of IL-6 and symptomatology. The results of our investigations indicated statistically significant difference in IL-6 production in the symptomatic compared to asymptomatic lesions, while the average concentration of cytokines was higher in the large lesions compared to small, but the difference was not statistically significant.

The study of Gazivoda et al. [18] showed higher production of IL-6 in symptomatic and large lesions primarily emphasizing its proinflammatory aspect. However, experiments on IL-6-deficient mice showed conflicting results, indicating protective effect of this cytokine to bone destruction [14]. These differences may be explained by the fact that IL-6 has both proinflammatory and antiinflammatory role and its final effect depends on the target cells and coordination with additional cytokines.

Inflammatory reaction in patients with apical periodontitis is not limited to periodical region [19]. It is known that dental infection can have negative impact on general health in patients with risk [20]. Blood analysis in patients after endodontic treatment of teeth with apical periodontitis showed the presence of bacteria that originate from root canal [21]. Spreading oral bacteria through the bloodstream is not the only way for mediation-targeted effects of oral focal infections. More significant effect on distant tissues and organs function may be induced by certain cytokines. Although the majority of members of the cytokine superfamily exhibits short-term effects, IL-1, IL-6 and TNF have been shown that locally produced within the tissues of periapical granulomas, can be carried by the bloodstream to distant places. These cytokines can cause acute phase response, which includes fever, increased erythrocyte sedimentation rate, and change in serum proteins synthesized by hepatocytes. Some authors examined elevated levels of acute phase protein in patients with chronic periapical granulomas. Their level was lowered to the normal value after the surgical removal of lesions by apicoectomy [10, 22].

CONCLUSIONS

High concentration of IL-6 in lesions with expressed clinical symptoms, as well as in large lesions, indicate its important pro-inflammatory activity and key role of
strong mediator responsible for the progression of lesion and stimulation of bone resorption in the pathogenesis of periapical lesions.

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Uloga interleukina-6 u patogenezi hroničnih periapaksnih lezija

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KRATAK SADRŽAJ
Uvod Mreža citokina igra značajnu ulogu u patogenezi hroničnih periapaksnih lezija. Cilj studije je bio da se odredi koncentracija IL-6 u tkivnim homogenatima hroničnih periapaksnih lezija i da se proveri korelacija sa simptomatologijom i veličinom lezija. MATERIJAL I METODE Ispitana su 93 uzorka hroničnih periapaksnih lezija dobijenih nakon ekstrakcije zuba. Uzorci lezija su podeljeni prema simptomatologiji pacijenata na simptomatske i asimptomatske, a prema veličini na male i male. Koncentracija IL-6 je ispitivana pomoću ELISA testa, a dobijene vrednosti su analizirane u odnosu na grupe. Rezultati Statistički značajna razlika u koncentraciji IL-6 je uočena u grupi simptomatskih lezija u poređenju sa asimptomatskim (p < 0,001). Analiza je pokazala i statistički značajno veću koncentraciju u velikim simptomatskim lezijama u odnosu na male asimptomatske (p < 0,001) i u malim simptomatskim lezijama u odnosu na male asimptomatske (p < 0,05). Statistički značajna razlika u koncentraciji IL-6 je u otkazu velikim lezijama u odnosu na male, međutim, razlika nije bila statistički značajna. ZAKLJUČAK Velika koncentracija IL-6 u lezijama sa izraženim kliničkim simptomima kao i velikim lezijama ukazuje na njegovu važnu ulogu u progresiji periapaksnih lezija i koštane resorpcije.

UVOD
Periapaksne lezije su inflamatorna oboljenja koja nastaju kao rezultat imunog odgovora na kontinuiranu antigenu stimulaciju iz kanala korena. Njihov razvoj i progresija u hronične lezije sa posledičnim gubitkom kosti nastaju kao rezultat nemogućnosti mehanizama odbrane domaćina da ukloni infekciju [1]. Tako hronične periapaksne lezije predstavljaju inflamirano granulo- ciono tkivo koje zamenjuje normalnu kost, nije postojalo pravi tkivni ekvivalent koji bi služio kao negativna kontrola. IL-6 je citokin koji utiče na antigen-specifične imune odgovore i inflamatorne reakcije. Uistinu, IL-6 je bio prvi makrofagički citokin koga produkuje nekoliko tipova imunih ćelija – monociti, infilirane limfocite, aktivirane B ćelije i polimorfonuklearne ćelije. IL-6 je dokažan u humanima periapeksnim lezijama u inflamirano granulacije hroničnih periapeksnih lezija koje zamenjuje normalnu kost, nije postojalo pravi tkivni ekvivalent koji bi služio kao negativna kontrola. IL-6 je citokin koji produbljava antigen-specifične imune odgovore i inflamatorne reakcije. Uistinu, IL-6 je bio prvi makrofagički citokin koga produbljava antigen-specifične imune odgovore i inflamatorne reakcije. Uistinu, IL-6 je bio prvi makrofagički citokin koga produbljava antigen-specifične imune odgovore i inflamatorne reakcije. Uistinu, IL-6 je bio prvi makrofagički citokin koga produbljava antigen-specifične imune odgovore i inflamatorne reakcije.
ELISA testa za IL-6 je iznosila od 0,7 pg/ml, a koncentracija je prema uputstvu proizvođača. Senzitivnost važnu rolu u dijagnosticama bioloških analiza. Koncentracija IL-6 je iznosila 189,24 pg/ml. Ustanovljena je statistički značajna razlika u koncentracijama IL-6 kod asimptomatskih lezija u odnosu na veličinu. Prosečna koncentracija IL-6 u simptomatskim velikim lezijama je iznosila 687,14 pg/ml, dok je u simptomatskim malim lezijama koncentracija IL-6 iznosila 212,04 pg/ml. Analiza je ukazala na statistički značajnu razliku u koncentracijama IL-6 kod asimptomatskih velikih lezija, dok je u simptomatskim malim lezijama statistički značajna razlika u koncentracijama IL-6 kod asimptomatskih lezija u odnosu na veličinu. Prosečna koncentracija IL-6 kod asimptomatskih velikih lezija je iznosila 232,86 pg/ml. Nije imalo statistički značajnih razlika kod simptomatskih malih lezija.

**REZULTATI**

Ispitivanje koncentracije IL-6 u homogenatima uzoraka tkiva periapeksnih lezija je pokazalo značajnu koncentraciju citokina u svim uzorcima. Na slici 1 prikazana je koncentracija IL-6 u homogenatima tkiva svih uzoraka, analiziranih u odnosu na simptomatologiju i veličinu. U grupi simptomatskih lezija prošća koncentracija IL-6 je iznosila 975,51 pg/ml, dok je u grupi asimptomatskih lezija prošća koncentracija IL-6 iznosila 212,04 pg/ml. Analiza je pokazala značajnu razliku u koncentracijama IL-6 kod asimptomatskih lezija u odnosu na veličinu. Prosečna koncentracija IL-6 kod asimptomatskih lezija u simptomatskim lezijama je iznosila 189,24 pg/ml, dok je u simptomatskim malim lezijama koncentracija IL-6 iznosila 759,11 pg/ml. Nije imalo statistički značajnih razlika kod simptomatskih malih lezija.

**DISKUSIJA**

Periapeksne lezije nastaju kao rezultat peristentnog inflamatornog odgovora indukovanog prolongiranom izloženosti periapeksnim tkiva mikroorganizmima kanala korena, što izaziva imunošku reakciju. U ovom lokalnom mehanizmu odbrane različiti inflamatorni medijatori igraju ulogu centralnu ulogu u regulisanju imunog odgovora. Dok proinflamatorni citokini, kao što su IL-1, IL-6, TNF-α, TNF-β, hemokini i Th1 citokini, propagiraju inflamaciju u periapeksnim tkivima i aktiviraju osteoklastnu koštanu resorpciju [10, 11], uloga anti-inflamatornih citokina je važna za supresiju inflamatornih procesa i procese zarastanja unutar periapeksnih lezija [2, 3, 12].

U ranoj inflamatornoj fazi dugače stvaranje IL-6 indukuju IL-1 i TNF-α. IL-6 ima mnoge molekularne forme i svaki molekul ima drugačiju funkciju kada ga sekretuju različite čelije u različitim situacijama. Nalaz da polimorfonuklearne čelije u periapeksnim tkivima propagiraju IL-6, što je navedeno od strane Eulera i saradnika [13], ukazuje da IL-6 može doprineti tkivoj povredi na mestu inflamacije. IL-6 predstavlja integralni mediator u akutnoj fazi odgovora na povredu i infekciju kada stimulira ekspresiju proteina akutne faze [14]. Ispitivanje različitih citokina, kao što su TNF-α, IL-6, IL-3, GM-CSF, IL-11, IL-17, IL-18, na humanim i animalnim modelima pokazala su njihovu potencijalan ulogu u patogenezi ostetolitičkih oboljenja [2, 15]. Dokazano je da inflamatorni citokini IL-6 i TNF-α imaju kapacitet da aktiviraju osteoklastnu koštanu resorpciju, a svoju ulogu mogu da ostvaruju sinergistički sa IL-1, izazivajući aktivaciju ili diferencijaciju osteoklasta i produktivnost, odnosno sekreciju prostaglandina od strane brojnih čelijskih tipova, uključujući fibrabloaste i osteoblaste [2]. Više autora je objavilo ekspresiju IL-6 u humanim periapeksnim granulomima i cistama. Rezultati ove studije su pokazali prisustvo IL-6 u svim tkivima periapeksnih lezija, što je u skladu sa podacima iz literature [9, 16].

Istraživanja su pokazala da je IL-6 značajno povećan kod infekcija i bolnih stanja. U studiji De Jongh i saradnika [17] važna uloga je bila procesa IL-6 u patofiziologiji bolova. Zbog te činjenice, u ovoj studiji je analizirana korelacija između nivoa IL-6 i simptomatologije. Rezultati ovog istraživanja su ukazali na statistički značaj nu veću produkciju IL-6 u simptomatskim lezijama u odnosu na asimptomatskelezije, dok je koncentracija ovog citokina bila u većim lezijama u odnosu na male, ali ova razlika nije bila statistički značajna.

U istraživanju Gazivode i saradnika [18] učenilo se da je produkcija IL-6 u simptomatskim i velikim lezijama, naglašavajući pre svega njegov proinflamatorni aspekt u ovom oboljenju. Međutim, eksperimenti na IL-6 deficitnom mišu pokazuju suprotne rezultate, ukazujući na efekat zaštite ovog citokina od koštane destrukcije [14]. Ove razlike mogu da se objasnit će činjenicom da IL-6 poseduje i proinflamatorne i antiinflamatorne osobine i da njegov krajnji efekat zavisio od ciljnih čelija i sadašnjih drugih citokina.

Inflamatorne reakcije kod pacijenata sa aepskim parodontitima nisu ograničene samo na periradiksnu regiju [19]. Poznato je da dentalne infekcije mogu imati negativni uticaj na opšte zdravlje pacijenata sa rizikom infekcija od odgovora indukovanog proinflamatornog odgovora u ovom ob Solčnom. Međutim, algoritmi su bili poolovani sa nekim odgovorima na povredu i infekciju kada stimuliraju oksidativni procesi vazikinetičkih oboljenja [2].

**Izvor:** Stomatološki glasnik Srbije. 2018;65(3):126-132

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da izazovu akutnu fazu odgovora koji podrazumeva povišenu telesnu temperaturu, povećanu sedimentaciju eritrocita i promenu u serumskim proteinima sintetisanih od strane hepato-cita. Pojedini autori su pratili povećane nivoe proteina akutne faze kod pacijenata sa hroničnim periapeksnim granulomima. Njihov nivo je snižen na normalne vrednosti nakon hirurškog uklanjanja lezije apikotomijom [10, 22].

ZAKLJUČAK

Veća koncentracija IL-6 u lezijama sa izraženim kljničkim simptomima, kao i velikim lezijama, ukazuje na njegovu važnu proinflamatornu aktivnost i ključnu ulogu snažnog medijatora koji je odgovoran za progresiju lezije i stimulaciju koštane re-sorpcije u patogenezi periapeksnih lezija.