Clinical and Instrumental Evaluation of the Effectiveness of Surgical Treatment of Chronic Generalized Periodontitis Using RANK-RANKL-OPG Biomarkers

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Abstract

The problem of clinical and instrumental evaluation of the surgical treatment effectiveness of chronic generalized periodontitis using RANK-RANKL-OPG biomarkers is discussed in the article. Currently, the important role of Pro - and anti-inflammatory cytokines in the regulation of the immune-inflammatory response has been established [2]. Progressive destruction of bone tissue in patients with periodontal diseases is associated with a combination of cytokines IL-1β, IL-6, TNF and prostaglandins E2. The use of Alhadaya in complex therapy with surgical treatment will allow to control the level of biomarkers of bone inflammation, which will allow to use this method for the diagnosis of periodontal diseases and as the outcome of treatment, in addition to traditional research method (clinical, functional, x-ray, densitometric).

Keywords: *Dentistry, periodontitis, biomarker, RANK-RANKL-OPG.*

Introduction

According to WHO (World Health Organization), periodontal tissue pathology ranks 2nd in the structure of dental morbidity and is the main cause of premature tooth loss[1]. Chronic generalized periodontitis (CGP) develops under the influence of local and general factors, the leading of which is considered bacterial. The impact of periodontal pathogens on the tissues of the periodontal complex triggers a number of responses from the body, leading to the development of inflammation. Currently, the important role of Pro - and anti-inflammatory cytokines in the regulation of the immune-inflammatory response has been established[2]. Progressive destruction of bone tissue in patients with periodontal diseases is associated with a combination of cytokines IL-1β, IL-6, TNF and prostaglandins E2 [3]. These cytokines can activate osteoclastogenesis and bone resorption by osteoclasts. The increased migration of macrophages under the influence of cytokines and their constant presence in tissues exacerbates the destructive processes in the periodontium. It is known that there is a close relationship between the immune and bone systems. The study of the mechanisms of bone resorption associated with the development of periodontitis, Paget disease, osteoporosis, rheumatoid arthritis, multiple myeloma and metastatic bone tumors highlighted the importance of deeper research in the field of osteoimmunology [4].

A breakthrough in understanding the process of bone remodeling was the discovery of a signaling system consisting of the nuclear factor kß activator receptor (RANK), its ligand (RANKL), and osteoprotegerin (OPG) [5]. RANKL is a transmembrane protein – a representative of the family of tumor necrosis factors that plays a key role in osteoclastogenesis, differentiation, activation, and apoptosis of osteoclasts [6]. An important preparatory stage of osteoclast formation is the activation of RANKL, which occurs by binding to RANK located on osteoclast precursors. OPG, being a natural receptor trap for RANKL, competes with RANK for binding to

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RANKL [7]. By blocking this process, OPG suppresses bone resorption, giving priority to bone formation. Disorders of the balance of the RANK/RANKL/OPG system were also detected in various osteopathies, as well as in periodontitis. A significant increase in the content of RANKL in the periodontal pocket fluid is registered in the early stages of the disease [8]. In moderate to severe chronic generalized periodontitis, mixed saliva contains a high content of specific markers of bone remodeling-osteoclast activating factor (RANKL) and osteoprotegerin (OPG), which are absent in saliva in healthy individuals[9]. However, until now there are no clear correlations between the success of surgical treatment and the presence or absence of biomarkers of RANK-RANKL-OPG inflammation, so it seems relevant to conduct such a study.

The aim of the study is to increase the effectiveness of surgical treatment of chronic generalized periodontitis according to the RANK-RANKL-OPG biomarkers.

Materials and Method

To achieve this goal, 65 patients with severe chronic generalized periodontitis have been examined. The average age of patients was 35.43±0.68 years. To determine the quality of treatment, biomarkers of inflammation such as RANK-RANKL-OPG have been used.

The state of bone metabolism has also been examineded by determining the content of local regulators in blood plasma - sRANKL, osteoprotegerin (OPG) and sclerostin by enzyme immunoassay, according to the attached instructions.

In the formation, differentiation and activity of osteoclasts, the main role is played by the cytokine system RANKL-RANK-OPG. RANKL is a ligand of the Kappa nuclear factor activator receptor (antigen 254, TNF-1L). RANKL is produced by osteoblastic cells and interacts with the Ranktransmembrane receptor of osteoclasts and their precursors. When RANKL interacts with RANK, the signal activates intracellular cascade mechanisms and affects the NF-kB-nuclear factor Kappa b, which, with the help of TRAF receptors, goes from the cytoplasm to the nucleus and increases the expression of the nfatc1 protein, which is a specific trigger that triggers the transcription of intracellular genes that form the processes of osteoclastogenesis. OPG (osteoprotegerin) is a soluble (false) receptor for RANKL, synthesized by vascular stroma and endothelial cells. OPG is a blocker of RANKL-RANK interaction and, as a result, inhibits osteoclast formation and bone resorption. Sclerostin is a regulator of the canonical Wnt/β-catein signaling pathway of osteoblastogenesis. It is produced by osteocytes and mineralized hypertrophied chondrocytes, binds to LPR-5 (lipoprotein receptor 5), which is a Wnt-coreceptor, which leads to the destruction of the ubiquitin-proteosomal mechanism of β-catenan in the cytoplasm and a decrease in Wnt signaling with a decrease in osteogenesis.

The soluble receptor-activator of factor b was determined by a set of reagents "sRANKL" of Biomedica Medizinprodukte Gmb H and Co K G "(Germany), the osteoclast inhibitor factor – osteoprotegerin (OPG) by a set of reagents" Osteoprotegerin", sclerostin – " Sclerostin "of The same company on a semi-automatic analyzer"Uniplan". All patients gave their voluntary written consent to participate in the experiment. Statistical data processing has been performed using the program STATISTICA 6.0.

Results

Before the surgical treatment of chronic generalized periodontitis, all the patients underwent a study of biomarkers in the blood (the RANK-RANKL-OPG system). So, as an inhibitor of RANKL, we recommend the drug Alhada (black cumin oil). Alhada was appointed on 1 capsule 2 times a day for 6 months. No serious side effects found during patient follow-up. Thus, during the collection of anamnesis and catamnesis of patients, it was found that in 2 patients during the collection of apampesis vitae, chronic kidney disease of stage 2 was detected. Since patients with reduced renal function are particularly susceptible to hypocalcemia, which is accompanied by an increase in the level of parathyroid hormone, such patients were prescribed in addition to Alhadaya and vitamins of group D (calcium D3 nicomed) 1 tablet 3 times a day.

Discussion

Immediately after the use of Alhadaya and surgical treatment of chronic generalized periodontitis, the gums are pale pink, moderately moistened. The depth of the gingival furrow is 0.28±0.003 mm after treatment, there is no mobility of the teeth. The CPR index before treatment was 24.1±1.41, while after surgical treatment and the influence of Alkhaday it was 11.3±0.56 ($p \leq 0.05$). The hygiene index (HI) before treatment was 73.2±2.08, while after complex surgical treatment with Alhadaya

was 45.1±2.12 (p≤0.05). The bleeding index (PBI) before treatment was 2.1±0.05, while after treatment it was 0.8±0.33 (p≤0.01). The gingival index (GI) is 1.9±0.06 before treatment and 0.7±0.15 (p≤0.01) (after complex application of Alhadaya and hirrugic treatment).

After a General analysis of blood mineral metabolism, the total calcium level before treatment was 2.31±0.01 mmol/l, while after treatment it was 2.12±0.01 mmol/l (p≤0.05). Ionized calcium was 1.24±0.041 mmol/l before treatment, and after 1.12±0.007 mmol/l (p≤0.05). Parathyroid hormone before treatment was 56.7±2.14 PG/l, and after treatment 41.5±1.26 PG/l (p≤0.01). Calcitonin before treatment was 2.7±0.24 ng/l, and after treatment-4.3±0.23 ng/l (p≤0.001). Osteocalcin 5.5±0.57 ng/l before treatment, and after treatment 12.5±0.39 ng/l (p≤0.001).

The RANKL content before treatment was 0.23±0.005 pmol/l (p≤0.001) after treatment, the RANKL content was 0.14±0.003 pmol/l (p≤0.001). OPG before treatment was 4.35±0.004 pmol/l (p≤0.001), after treatment was 3.51±0.003 pmol/l (p≤0.001). Sclerostin before treatment was 297±0.4 pmol/l, after treatment was 210±1.2 (p≤0.05).

Osteoprotegerin (OPG) is a soluble receptor for RANKL. It is synthesized by osteoblastic type cells, as well as β-lymphocytes, vascular stroma and endothelial cells. OPG is a competitor to the interaction of RANKL with RANK and therefore, as a consequence, inhibits the formation of osteoclasts and bone resorption.

Sclerostin is produced by osteocytes and mineralized hypertrophic chondrocytes. It binds to the LRP-5/6 receptor, which is a coreceptor of the Wnt/β-catenin signaling system necessary for the stimulation of osteoblastogenesis and osteoblast functions, and has an inhibitory effect

Conclusions

Thus, osteoblasts express a high level of the nuclear factor activator receptor ligand Kappa beta and osteoprotegerin in the patients with chronic generalized periodontitis with reduced bone mineral density . The use of Alhadaya in complex therapy with surgical treatment will allow controlling the level of biomarkers of bone inflammation, which will allow to use this method for the diagnosis of periodontal diseases and as the outcome of treatment, in addition to traditional research method (clinical, functional, x-ray, densitometric).

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