PERIOSTIN AS A MARKER OF PERIODONTAL STATUS. A NARRATIVE REVIEW

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Abstract

Periostin is a protein of the extracellular matrix, which belongs to the fasciclin-1 protein family, located on chromosome 13 and has 835 amino acids in its composition. Periostin is an inducer of fibrinogenesis and acts by stimulating the production of type I collagen. The excess production of periostin was observed in the processes of tissue regeneration of the injured organs and later associated with pathological fibrosis.
In the oral cavity, periostin is present in various tissues, serum, saliva and in the crevicular fluid and is absent in enamel, dentin, cementum, dental pulp, and deep alveolar bone.
Periostin participates in the processes of cell adhesion, migration, and proliferation, stimulating tissue regeneration. The expression of periostin in the crevicular fluid decreases as the severity of the periodontal disease increases. Periostin is detectable in saliva of patients with chronic periodontitis, its expression being negatively influenced by inflammatory processes. The values of the periodontal indices are correlated with the values of periostin in the crevicular fluid, observing lower values of the protein in conditions of inflammation, volumetric reduction of the dental support and in the presence of the microbial factor. Studies demonstrate records of the lowest values of periostin in patients presenting both chronic periodontitis and type II diabetes, compared to patients only affected periodontally and those showing no signs of periodontal disease. Therefore, periodontal diseases associated with general diseases majorly decrease the expression of periostin. The presence of TNF-alpha in the tissues has the effect of decreasing the expression of periostin, which is an indicator of the progression of periodontal disease. Periostin has a role in regulating the number of osteoclasts and in the rate of collagen degradation during the processes of ligament remodeling and bone resorption necessary in orthodontic treatment, delays in tooth movements being observed in experimental animals with no periostin. The presence of periostin in the endothelium of blood vessels from the periodontium indicates a probable role that this protein has in the processes of angiogenesis and repair of injuries.
Periostin can represent a valuable biomarker in the diagnosis of periodontal disease and the assessment of its severity.

Keywords: *Periostin, biomarker, periodontal disease, gingival crevicular fluid*

Introduction

Healthy periodontal status is essential in supporting the teeth and fulfilling their functions, integrating the dental structures with the rest of the body [1-4].
The term "periodontal disease" encompasses a wide variety of inflammatory conditions, which are multifactorial in nature, and result in the progressive destruction of the periodontal support, over time [5-18].
Periostin is a protein of the extracellular matrix, which belongs to the fasciclin-1 protein family, first mentioned in literature under the name osteoblast-specific factor-2 [19]. The term "periostin" derives from the words "periosteum" and "periodontal ligament" [20]. In the genomics of the

human body, this protein is located on chromosome 13 and has 835 amino acids in its composition [21].
Periostin is discharged by fibroblasts and is therefore present in collagen-rich fibrous connective tissues that are continuously subjected to mechanical stress, such as periosteal tissues, periodontal ligament, tendons, heart valves, and skin.
Initially, periostin was studied for its structural role, maintaining the normal activity of the connective tissue. From a functional point of view, periostin is involved in bone remodeling, with a role in cell migration and adhesion [22].
Periostin is an inducer of fibrinogenesis and acts by stimulating the production of type I collagen. A tight, tissue-like structure is formed by crossing of the collagen fibers. The excess production of periostin was observed in the processes of tissue regeneration of the injured organs and later associated with pathological fibrosis, the function of the organ being affected. In order to better understand the mechanism of fibrosis, research has been conducted on periostin and clinical applications have been initiated to treat fibrosis by blocking its action [20].

1. Location and systemic functions

High levels of periostin were observed during skin wound repair, in the granulation tissue underlying the wound edges and at the dermo-epidermal junction in injured mice. The absence of periostin in subjects with injuries compromises the processes of repair and re-epithelialization of wounds and affects the proliferation and migration of dermal fibroblasts necessary for healing [19].
Periostin is necessary in the adaptation of the bone mass and in its architecture. Some studies have shown that periostin-deficient mice show bone defects, such as dwarfism, bone dysplasia, or defects similar to those in Marfan syndrome [23].
In the heart, periostin plays a substantial role in the cardiovascular differentiation of the heart valves and the cardiac skeleton. In general, the presence of periostin is beneficial in cardiovascular physiology. Following cardiac injuries, such as those of a myocardial infarction, periostin acts by differentiating bone marrow cells into cardiac fibroblasts, and by mobilizing them, the affected tissue will be grafted through scarring. [19]
High levels of periostin have been detected in tumors such as lung carcinoma, breast cancer, carcinomas of the head and neck, ovarian cancer, adenocarcinoma of the pancreatic duct. This protein participates in tumor development, by promoting cell adhesion and encouraging the mobility of tumor cells during the interaction with $\alpha\gamma\beta3$ and $\alpha\gamma\beta5$ integrins. Different studies have shown that increased levels of periostin are correlated with an increase in angiogenesis and metastasis. [19]
In allergic reactions, the amount of periostin is stimulated by type 2 inflammatory cytokines. In allergic airway reactions, periostin guides and facilitates the infiltration of granulocytes that support inflammation, and accumulate in the thickened basement membrane of bronchial epithelial cells in patients with asthma [19,24].
In airway inflammation, periostin is involved in both tissue remodeling and mucus production. Thus, periostin represents a valuable biomarker, its levels being linked with the severity of the disease, prognosis and responsiveness to treatment in conditions such as atopic dermatitis, asthma, and pulmonary fibrosis. [24]

2. Location and functions in the oral cavity

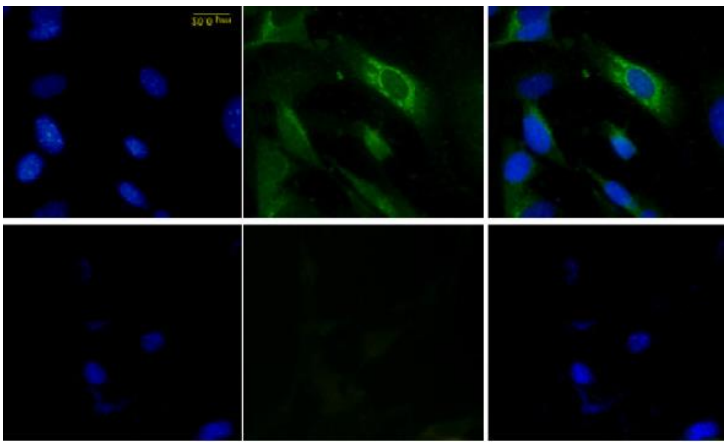
In the oral cavity, periostin is present in various tissues, serum, saliva and in the crevicular fluid and is absent in enamel, dentin, cementum, dental pulp and deep alveolar bone [25-29]. The importance of periostin in oral health is underlined by the fact that, in adult tissues, it is located in the

fibroblasts of the periodontal ligament and in the alveolar bone [30].
Being a protein of the extracellular matrix, it contributes to maintaining bone homeostasis, which is of great importance in maintaining the integrity of the periodontal ligament and the neighboring alveolar bone [30]. Periostin is found on the alveolar bone surface, and this fact suggests its role in the functional regulation of osteoblasts. In mice with a lack of periostin, the height of the alveolar ridge is greatly reduced, and the periodontal space is enlarged, which indicates a weak ligament anchoring of the tooth in the alveolus [19].
Periostin supports occlusal forces or those triggered by tooth eruption to which desmodontium is subjected, this protein being involved in periodontal remodeling in response to mechanical stress. Periostin is expressed by immature osteoblasts, so it participates in cell differentiation processes, which favor bone regeneration. The migration of fibroblasts and osteoblasts to the areas that require repair is encouraged by the presence of periostin, thus fulfilling the role of periodontal tissue regeneration by increasing cellular activity [31].
In orthodontic rehabilitation, the alveolar bone is subjected to biomechanical challenges, and the presence of periostin is essential so that the movement forces do not alter the collagenous tissue and the consequent bone remodeling of the periodontium.
The existence of periostin in periodontal components keeps under control the number of osteoclasts and the level of collagen degradation during orthodontic tooth movement [30]. During embryogenesis, periostin was detected at the interface between the internal adamantine epithelium and preodontoblasts, in the dental papilla and in the mesenchymal tissue around the cervical loop and the dental follicle.
Periostin has a role in dental development and is possibly correlated with the storage and organization of other extracellular matrix adhesion molecules [19].
In several studies, the lack of periostin is associated with enamel and dentine matrix defects, abnormal organization of the alveolar bone, and inflammatory infiltrate of neutrophils, all of which lead to a defective and unstable tooth structure [32].

3. The link between periostin and periodontal status

In order to understand the connection between periostin and periodontal status, and the role of this protein in physiopathological processes, we used the Google search engine and the PubMed and Google Scholar databases, where we entered the following keywords: "periostin", "periodontal disease", "periodontal inflammation", "periodontium", "periodontitis". Following the searches, a number of 31 experimental studies were found, from which 12 studies were eligible for the chosen topic.
In the study carried out by Cobo T. et al, when analyzing the immuno-fluorescence and Western-blot tests, it was observed that periostin is an exogenous protein, being discharged by cells (Figure 1).
The presence of periostin increased the ability of MC3T3-E1 cells to attach to different proteins of the extracellular matrix, such as type I collagen, fibronectins, laminins, tenascins and vitronectins. The expression of periostin is increased following tissue injuries, this protein being involved in the first phases of bone fracture repair, in the differentiation of osteoblasts and in the formation of new bone tissue. The high amount of periostin also interferes with the migratory ability of osteoclasts, resulting in a slower cellular activity. From the analysis of the data and the RT-PCR test, it appears that the low gene periostin level alters the functions related to bone remodeling, independent of other stimuli, such as mechanical stress or the presence of inflammatory cytokines [19].

Figure 1.



Immunolocalization of periostin in MC3T3-E1 cells using nuclei highlighting (blue) by 4', 6-diamino-2-phenylindole (DAPI) staining and Alexa-488 antibodies (green) [16]

After performing the RT-PCR test, Horiuchi K. et al, highlighted the fact that the volume of messenger ribonucleic acid (mRNA) of periostin is highly expressed in osteoblasts and in their precursor cell lines. The immuno-histological tests showed that, in the femoral bone, the periostin is present in the periosteum, but is absent in the endosteum and in the bone matrix. Also, through the immuno-histological analysis, in the dental tissue by fluorescent staining, expressions of periostin with localization and distribution in the periodontal ligament and in the composition of the extracellular matrix were observed (Figure 2) [33].

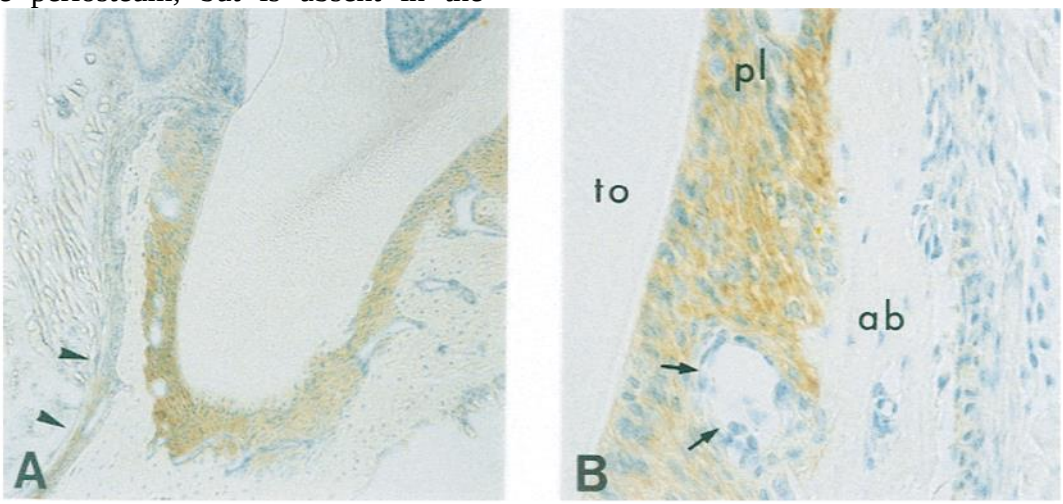


Figure 2. Mandibular bone, of murine origin, immunostained for the detection of periostin (magnification A x100, B x400). The staining (orange) is strongly positive in the periodontium and periosteum of the alveolar bone (arrows A), and less obvious in the endothelium of blood vessels (arrows B).
to=tooth, pl=periodontal ligament, ae=alveolar bone[33]

The study carried out by Padial-Molina M. et al on experimental animals, had significant results in understanding the importance of periostin expression in teeth. Comparing the control group, with the groups that had periodontal disease induced after two and four weeks, the volume and consistency of the bone were significantly reduced (Figure 3).

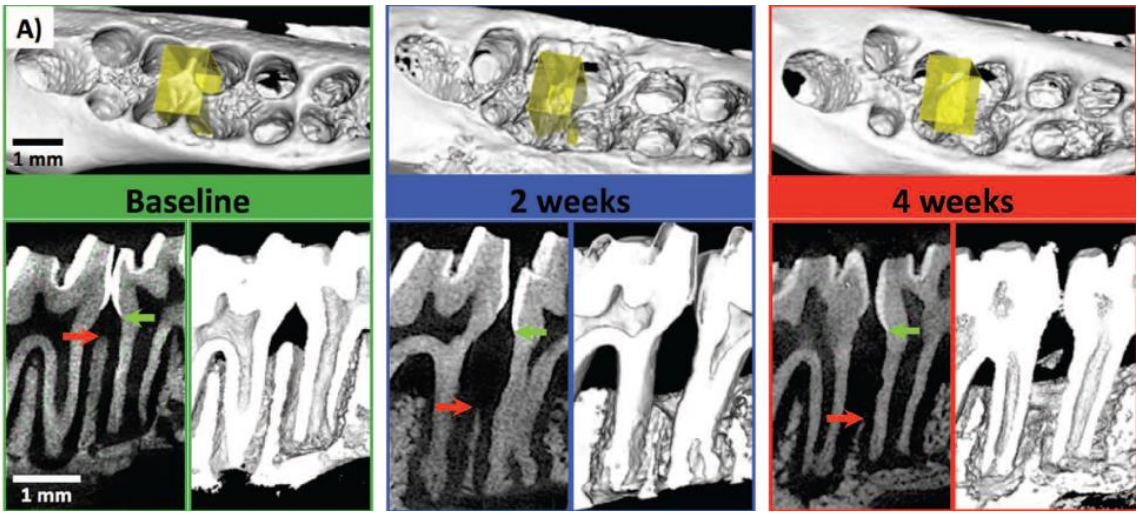


Figure 3. Micro-CT analyzes of alveolar bone resorptions in the 3 studied groups: green - control group, blue - group of periodontal diseases induced after 2 weeks, red - group of periodontal diseases induced after 4 weeks.
Yellow cubes - the areas of interest, green arrows - the enamel-cement junction, red arrows - the ridge of the alveolar bone [34]

In the immunofluorescence test, the intensity of the fluorescent levels of periostin was lower as a result of the inflammatory process, induced by the gingival ligatures in the groups with periodontal disease, while in the groups with healthy periodontium, the fluorescent intensity of the periostin was considerably higher.

Through the immuno-fluorescence method, significant differences were also recorded between the two groups of subjects with induced periodontal disease, the periostin level being lower in the areas with advanced tissue modifications [34].

The presence of periostin is essential for osteoclasts, so that these cells fulfill their function of alveolar bone resorption, therefore, in mice without periostin, the results of orthodontic treatment are much delayed due to these defects in the processes of bone resorption and remodeling [35].

Takayama and Kudo observed in the group of mice without periostin, on the dental radiographs, defects of the dental structures in incisors, followed by pathological eruptions, and resorption of the alveolar bone, in molars, although their dental structure has a relatively normal appearance [36].

Jamesha F.I. et al, observed in patients with aggressive periodontitis, that periostin levels in crevicular fluid were the lowest. The highest values of periostin expression were recorded in patients without periodontal diseases (Table 1.1.).

This paper also highlighted the fact that periostin can represent a valuable biomarker of inflammation and that the early diagnosis of periodontal disease would be possible and simple to perform, by determining the concentration of periostin in the crevicular fluid of patients, this analysis method being a minimally invasive, easy and fast procedure [25].

Table.1. Comparison of periodontal indices between the studied groups

	Grup I + II	Grup I + III	Grup II + III
MA	semnificativ	nesemnificativ	semnificativ
PI	semnificativ	semnificativ	nesemnificativ
mSBI	semnificativ	semnificativ	nesemnificativ
CAL	semnificativ	semnificativ	nesemmnificativ
Periostin	semnificativ	semnificativ	-

group I - healthy participants, group II- patients with chronic periodontitis, group III- patients with aggressive periodontitis. MA ("mean age") - average age, PI ("plaque index") - bacterial plaque index, mSBI ("modified sulcular bleeding index") - modified sulcular bleeding index, CAL ("clinical attachment loss") - loss of clinical attachment.

In relation to periodontal indices, periostin levels are lower in patients with high values of periodontal parameters, such as gingival index and clinical attachment loss. On the other hand, in the group of patients without systemic and periodontal diseases, the highest values of periostin expression in the sulcular fluid were recorded [37].

Sophia K. et al found the lowest periostin levels in patients with generalized periodontitis (group III), and the highest values in periodontally healthy participants (group I). The group of patients with gingivitis had lower periostin expression values compared to group I, but higher than group III [31].

Following the evaluations by the ELISA method, Esfahrood et al noted that the periostin values were significantly lower in the saliva with periodontitis compared to the salivary levels of the participants in the control group (Figure 4) [38].

Figure 4. The quantitative difference of periostin (pg/ml) expressed between the control

Sample	Healthy controls (*n*=20)	Patients with periodontitis (*n*=25)	*P**
Periostin (pg/ml)	505.05±78	140.5±68.6	0.03

*Significant correlation $P \leq 0.05$. *P* – *P* value; *n* – number

group and the group of patients with periodontal disease [38]

Menendez-Diaz I. et al observed that the pattern of periostin distribution in the periodontal ligament is fibrillar, matching the arrangement of fibroblasts. The distribution of periostin in the adult periodontal ligament and in the gingiva was observed along the entire section, without differences in the localization and intensity of the immuno-staining between the segments or between the periodontal ligaments of the different types of selected teeth. [39]

Histological analyzes of tissues collected from patients with healthy periodontium during surgical procedures highlight strong periostin immunoreactivity signals and its localization in the underlying specialized connective tissue, immediately below the epithelial junction. The distribution of periostin is fibrillar, similar to the fibrillar structures of the periodontal ligaments between the alveolar bone and the root surface of the teeth. Hematoxylin-eosin (HE) staining of samples from

periodontally healthy patients did not indicate the presence of inflammatory infiltrate, but only physiological characteristics of the epithelium, junctional epithelium and connective tissue. Conversely, when evaluating the tissue samples of patients with periodontal inflammation, the presence of chronic inflammatory infiltrate was visible (Figure 5). Also, in this group, reduced levels and a diffuse distribution of periostin were revealed in the area close to the functional epithelium. [40]

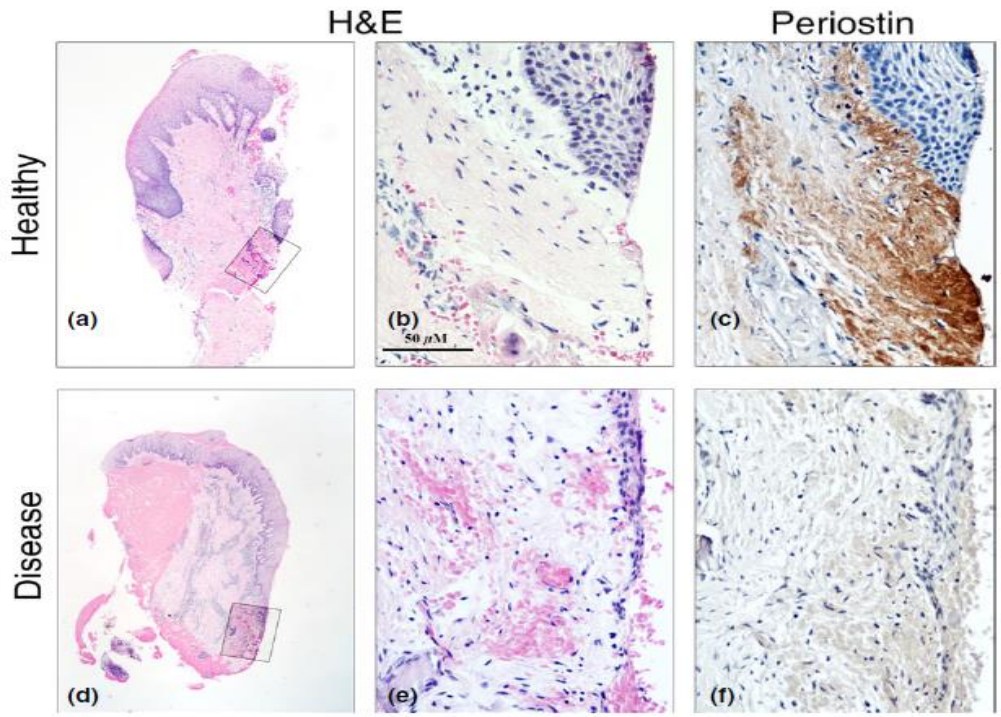


Figure 5. Images with histological analysis of tissue from the control group (a, b, c) and the group with periodontal diseases (d, e, f)
HE staining (a, b, d, e) and periostin expression (c, f) [40]

Xu H.N. et al, demonstrated in a mixed clinical and laboratory study that the tension of applied orthodontic forces increased the expression of periostin levels in periodontal ligament cells. Immunohistochemical analysis resulted in the diffuse distribution of periostin from the periodontal ligaments in healthy mice.
Conversely, in mice with orthodontic treatments, an increase in the intensity of periostin expression in the periodontal ligament was demonstrated in the first 4 days, followed by a decrease in fluorescence intensity from day 6 (Figure 6), which suggests that periostin was involved in the periodontal ligament remodeling process induced by applied external forces [41].
In patients of the experimental group, who benefited from orthodontic treatment, a significant increase in the levels of periostin in the periodontal ligament and an increase in the expression of periostin mRNA in the extracted teeth was observed, compared to the control group, not subjected to orthodontic treatment, in which the values were more reduced.
By the analysis methods used, the authors came to the conclusion that periostin is more expressed, following the applied external tension forces, and that this protein can play a role in stimulating the synthesis

of type I collagen, contributing to the remodeling of the periodontal ligament during orthodontic treatments [41].

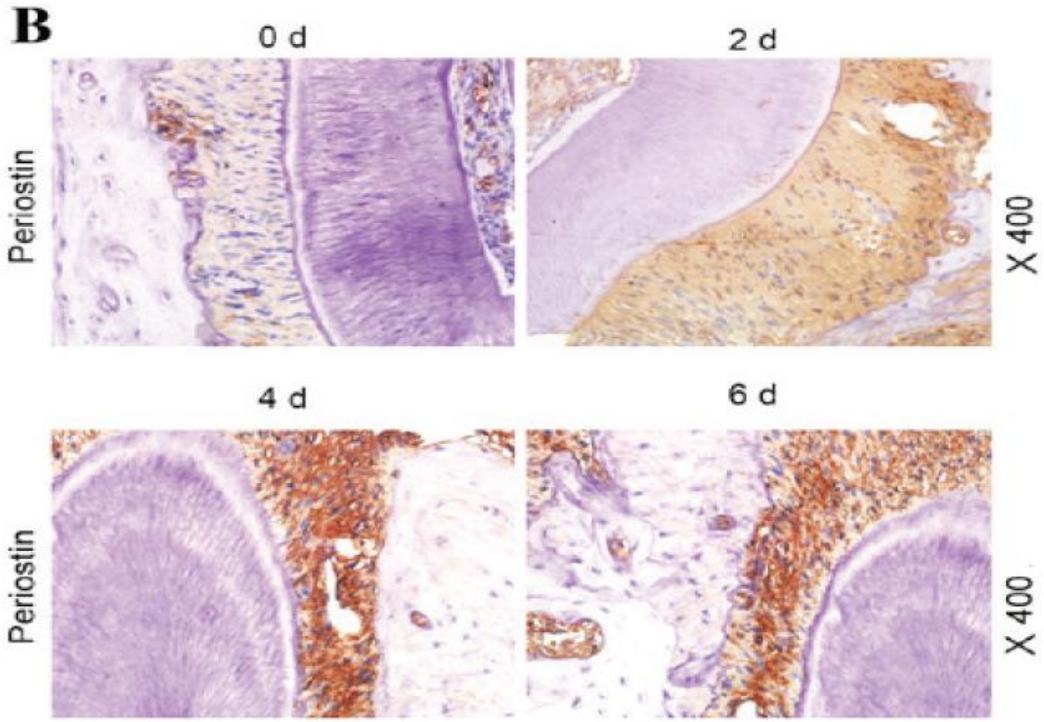


Figure 6. Immunohistological staining of the upper molars subjected to orthodontic forces on day 0, 2, 4 and 6. Magnification of the samples - X400 [41]

In relation to periodontal disease and the influence of other systemic conditions, the study by Radhika et al resulted in a major reduction in periostin expression in patients who had both periodontitis and type II diabetes compared to patients who only had periodontitis, without other associated systemic diseases. This indicates that the aggregated inflammatory states encourage the decrease in periostin expression and in the progression of periodontal disease [37]. Researchers state that periostin is an indispensable factor in periodontal stability, and is reduced due to of the inflammation caused by periodontal disease. This protein may represent a new biological marker in the diagnosis of periodontal disease in cases where it is suspected [34].

Following the evaluation of several studies, articles and results regarding periostin and its involvement in periodontal disease, the following can be concluded:

• periostin participates in the processes of cell adhesion, migration and proliferation, stimulating tissue regeneration;

• the expression of periostin in the crevicular fluid decreases as the severity of the periodontal disease increases;

• periostin is detectable in saliva of patients with chronic periodontitis, its expression being negatively influenced by inflammatory processes;

• the values of the periodontal indices are correlated with the values of periostin in the crevicular fluid, observing lower values of the protein in conditions of inflammation, volumetric reduction of the dental support and in the presence of the microbial factor;

• the presence of TNF-alpha in the tissues has the effect of decreasing the expression of periostin, which is an indicator of the progression of periodontal disease;

• periostin levels increase in tissue repair and healing processes, as observed in studies that followed the evolution of changes from orthodontic treatments, both in experimental animals and in patients;
• through its involvement in post-surgical tissue repair and healing processes, the role of periostin in cell proliferation is confirmed;
• the presence of periostin in the endothelium of blood vessels from the periodontium indicates a probable role that this protein has in the processes of angiogenesis and repair of injuries;
• periostin has a role in regulating the number of osteoclasts and in the rate of collagen degradation during the processes of ligament remodeling and bone resorption necessary in orthodontic treatment, delays in tooth movements being observed in experimental animals with no periostin

4. Conclusions

Studies demonstrate records of the lowest values of periostin in patients presenting both chronic periodontitis and type II diabetes, compared to patients only affected periodontally and those showing no signs of periodontal disease.

Therefore, periodontal diseases associated with general diseases majorly decrease the expression of periostin.

Periostin can represent a valuable biomarker in the diagnosis of periodontal disease and the assessment of its severity.

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