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## Correlation of chronic periodontitis progression and sTREM-1 and E-cadherin salivary levels

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### Abstract

**Introduction:** Triggering receptor expressed on myeloid cells-1 (TREM-1) was reported to be up-regulated in various inflammatory diseases as well as in periodontal disease. The important role of E-cadherin against bacterial invasion has already been established in the junctional epithelium. This study aimed to evaluate the potential value of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and E-cadherin as salivary diagnostic markers in patients with progressive chronic periodontitis.

**Material and method:** A total of 79 subjects 41 females and 38 males, divided into 4 groups: healthy group (HG), early generalized chronic periodontitis group (EGP), moderate generalized chronic periodontitis group (MGP) and advanced generalized chronic periodontitis group (AGP), were included in the study. Enzyme-linked immunosorbent assay (ELISA) test was used for quantification of sTREM-1 and E-cadherin in the saliva samples. Clinical and periodontal parameters were recorded and statistical analysis, using SPSS version 25.0, was performed.

**Results:** Elevated salivary sTREM-1 levels were evident in EGP, MGP and AGP compared to the HG. Statistically significant differences in sTREM-1 concentrations were found between HG and AGP. Salivary E-cadherin was found to be up-regulated during the progression of periodontal disease and statistically significant differences were found between HG and MPG.

**Conclusion:** Salivary sTREM-1 may be considered a new biomarker in chronic periodontitis progression. E-cadherin, although detected, does not seem to have diagnostic value at salivary level in chronic adult periodontitis.

**Keywords:** Chronic periodontitis; Saliva; sTREM-1; E-cadherin; Inflammatory marker

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### Introduction

Adult periodontitis is the most prevalent chronic inflammatory disease in humans [1] As an infectious disease that affects supporting tissues of the teeth, periodontitis is the leading cause of tooth loss, particularly in the elderly [2] Periodontal disease is at the moment a problem of most adults. Currently it is estimated that severe chronic periodontitis affects 5-20% of any population [3] Periodontal disease results from a complex interplay between the microbiota and the host immune-inflammatory response, and is influenced by genetic and environmental factors [4] Although bacterial infection is the primary cause in triggering periodontal

disease, the persistence and dysregulation of the host immune and inflammatory responses are mainly responsible for the destruction of the periodontal tissues [5,6].

The triggering receptor expressed on myeloid cells-1 (TREM-1) is a recently discovered cell-surface protein, a member of the immunoglobulin superfamily that is expressed by neutrophils and a subset of monocytes and macrophages [7,8] Its expression is up-regulated by ligation of bacterial products to toll-like receptors [7] Individual microbial components, such as lipopolysaccharide (LPS), peptidoglycan, heat-inactivated Gram-positive bacteria, Gram-negative bacteria or fungi can cause up-regulation of

cell surface-localized TREM-1 by monocytes, as well as release in its soluble (s)TREM-1 form. In this way sTREM-1 may act as a biological marker of bacterial infection as has been shown for sepsis, pneumonia and bacterial meningitis [7].

The triggering receptor expressed on myeloid cells 1 (TREM-1) has already been identified as an important receptor involved in the innate inflammatory response [9]. Even though the role of TREM-1 in monocyte activation and secretion of pro-inflammatory molecules has been established in a number of microbial diseases, little is known about the regulation of its expression during host cell infection in periodontal disease [1]. E-cadherin is a calcium-dependent cell-cell adhesion molecule with pivotal roles in epithelial cell behavior, tissue formation, tumor cell migration, and suppression of cancer [10]. E-cadherin, a subclass of cadherin found in stratified squamous epithelium, plays a crucial role in maintaining the structural integrity and function of both adherence and desmosomal epithelial intercellular junctions at the base of the gingival sulcus. In the junctional epithelium, E-cadherin, which is a key molecule involved in forming adherence junctions and desmosomes, is known to play an important role against bacterial invasion [11].

Maintaining the integrity of the epithelial barrier could be considered the primary immunological function of E-cadherin, which is intended to remove potentially damaging agents from the tissues. In addition, E-cadherin can actively regulate innate immunity functions at the epithelial level by releasing cytokines and chemokines, and modulates the transepithelial passage of innate and acquired immune system cells [12]. The reduction of E-cadherin was observed in inflamed gingival tissue [11]. Previous studies have shown that E-cadherin expression is uniformly present in healthy periodontitis, and the decrease in protein expression was evident in the basal areas of the oral gingival epithelium of patients with periodontitis. This suggests that E-cadherin's expression plays a role in the progression of chronic periodontitis [13]. The overall purpose of this study was to evaluate the existence of chronic inflammation markers, the E-cadherin adhesion molecule and the sTREM-1 cell surface receptor in saliva of patients with chronic periodontitis and observe the changes of these markers in the progression of periodontal disease.

## Materials and Methods

### Study population

Study subjects were selected from the department of General and Maxillofacial Surgery, Sibiu University Hospital, Romania, from May to October 2016. A total of 79 subjects (n=79; 38 males and 41 females; age ranging from 29 to 76 years, mean age of 54.30 years) were divided into four groups, viz., healthy group (HG), early generalized chronic periodontitis group (EGP), moderate generalized chronic periodontitis group (MGP) and advanced generalized chronic periodontitis group (AGP). The purpose of the study was completely explained to each subject, before entering the study and informed consent was obtained from each patient. Complete medical and dental histories were taken from all

subjects. None of the patients were smokers and none of them underwent any nonsurgical or surgical periodontal treatment within the past 12 months. Subjects with diabetes, osteoporosis, chronic coronary, respiratory and kidney diseases as well as pregnant women were not included in the study. Selection of the patients was made according to the clinical and radiographic criteria proposed by the 1999 International World Workshop for the Classification of Periodontal Diseases. The subjects for sampling were selected at random from individuals scheduled for a routine oral examination. All patients, included in periodontitis groups, presented clinical signs of periodontal disease, such as: halitosis, gingival recession, periodontal pockets or tooth loss in advanced stages of the disease. The clinical attachment loss (CAL) was measured, classifying the severity of the disease in slight: CAL 1-2 mm, moderate: CAL 3-4 mm and severe: CAL 5 mm or more. At the screening stage, to determine the clinical periodontal status, all subjects had a clinical periodontal examination, including the measurement of pocket depth and CAL, by one examiner. The early generalized chronic periodontitis group (EGP) consisted of 13 patients, 7 females and 6 males between the ages of 29 and 58 years (mean of 48 years) that had a maximum of 2 mm CAL. The moderate chronic periodontitis group (MGP) consisted of 23 patients 17 females and 6 males between the ages of 42-74 (mean of 56 years). They had moderate alveolar bone loss and CAL of max 4 mm. The advanced chronic periodontitis group (AGP) consisted of 23 patients 8 females and 15 males, between the ages of 52-76 years (mean age 60 years). They had severe alveolar bone loss, CAL of  $\geq 6$  mm and probing depth of gingival sulcus (PD) of  $\geq 4$  mm, in multiple sites of all four quadrants of the mouth. The healthy group (HG) consisted of 20 patients, 9 females and 11 males, ranged in age from 29-52 years, with a mean age of 42 years, who exhibited no CAL, PD of 1-2 mm, no clinical inflammation or sulcular bleeding and no radiographic evidence of bone loss.

### Collection of saliva samples

Samples of unstimulated saliva were collected between 9-12 am. The donors did not brush teeth for 12 h and abstained from food and drink intake for 2 h prior to donating saliva. Study participants were asked to rinse their mouth with water at least 5 minutes before donating saliva. Saliva samples were collected for about 10 minutes from each patient in sterile plastic containers (Eppendorf tubes). Participants were first ask to swallow, then to bow their heads forward and let saliva flow into the sterile tubes. Saliva samples were stored at -40 degrees Celsius for further analysis. Compromised saliva samples were excluded from the study.

### Biochemical analysis

Determination of salivary concentration of E-cadherin (Assay Biotech) and sTREM-1 (Hycult Biotech) were analyzed by enzyme-linked immunosorbent assay (ELISA), for quantification of these proteins in the saliva samples. Manufacturers' guidelines were followed for each assay and 96-well plates, precoated with appropriate antibodies, were used. The detection thresholds for E-cadherin were 187.5; 375; 750; 1500; 3000; 6000 pg/ml

and salivary concentration of sTREM-1 was performed using the following standard concentrations: 31.3; 62.5; 125; 250; 500; 1000; 2000 pg/ml.

### Statistical analysis

Statistical analysis was performed using SPSS, version 25.0. The comparison of age and gender in the CP groups and control group were analyzed using Chi-Square test, comparison between the study groups and salivary E-cadherin and sTREM-1 testing between the groups were performed, using Fischer analysis,  $p < 0.05$  was considered to be statistically significant. Parametrical Pearson rank correlation analysis was used to analyze the correlation between saliva E-cadherin and sTREM-1 for healthy and chronic periodontitis groups and  $p < 0.05$  was considered to be statistically significant.

### Results

Mean concentration of sTREM-1 increases with age, reaching it's peak in the 61-70 years age group, but there are no statistically significant differences between the age groups ( $p = 0.483$ ,  $p > 0.05$ , Fischer test) (Figure 1).

Mean concentration of E-cadherin decreases with age, reaching it's minimum concentration in the 41-50 years age group and increases in the advanced age groups, the difference between the age groups being statistically significant ( $p = 0.016$ ,  $p < 0.05$ , Fischer test) (Figure 2).

Mean concentration of sTREM-1 is higher in the early generalized chronic periodontitis group (EGP) than in the healthy group (HG). The difference between the healthy group (HG) and the early generalized chronic periodontitis group (EGP) is not statistically significant ( $p = 0.206$ ,  $p > 0.05$ , Fischer test). Also sTREM shows higher concentrations in the moderate generalized chronic periodontitis group (MGP) than in the healthy group (HG), the differences not being statistically significant ( $p = 0.117$ ,  $p > 0.05$ , Fischer test). In the advanced generalized chronic periodontitis group (AGP) sTREM-1 concentrations are higher than in the healthy group (HG), the differences being statistically significant ( $p = 0.009$ ,  $p < 0.05$ , Fischer test), (Figure 3).

Mean concentration of E-cadherin is higher in the early generalized chronic periodontitis group (EGP) than in the healthy group (HG). The difference between the healthy group (HG)

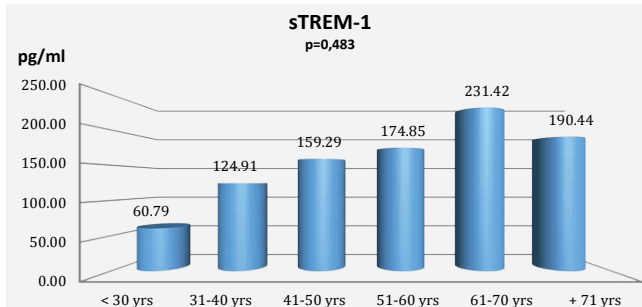


Figure 1 Mean concentration of sTREM-1 on age groups.

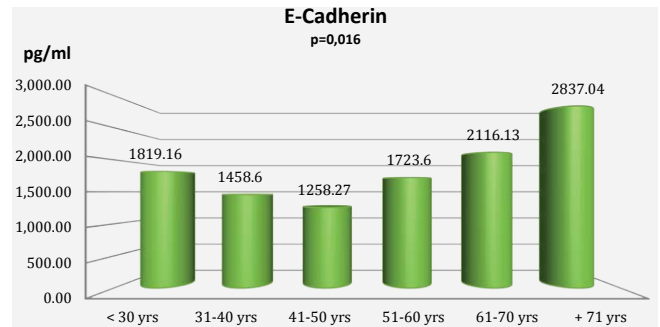


Figure 2 Mean concentration of E-cadherin on age groups.

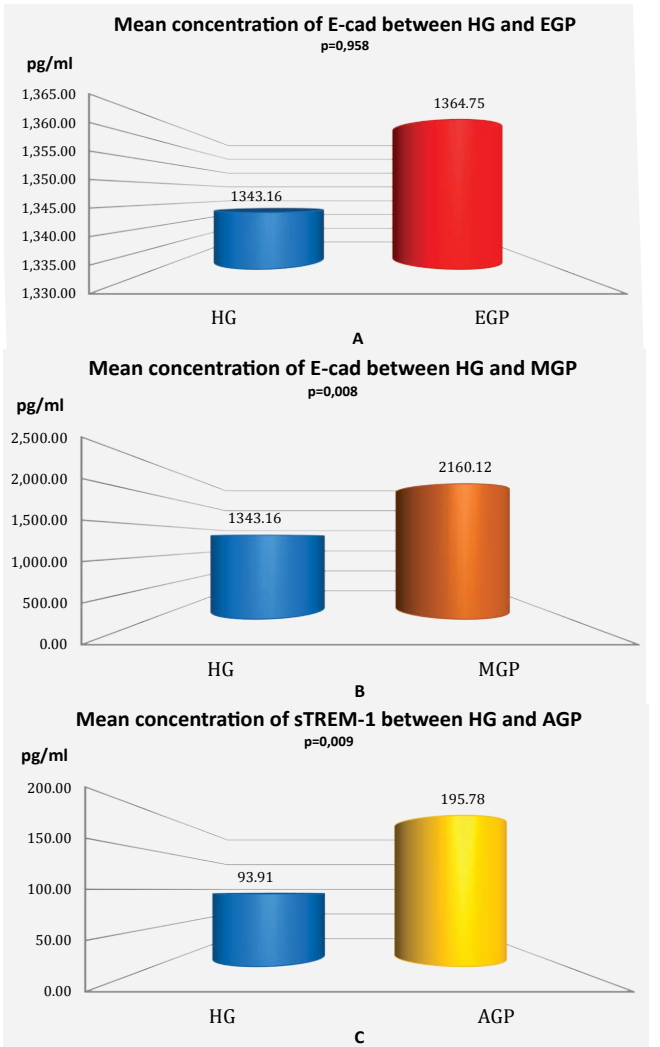


Figure 3 Mean concentration of sTREM-1 between healthy and periodontitis groups: A) Mean concentration of sTREM-1 testing between HG and EGP. B) Mean concentration of sTREM-1 testing between HG and MGP. C) Mean concentration of sTREM-1 testing between HG and AGP.

and the early generalized chronic periodontitis group (EGP) in E-cadherin testing is not statistically significant ( $p = 0.958$ ,  $p > 0.05$ ,

Fischer test). Also E-cadherin shows higher concentrations in the moderate generalized chronic periodontitis group (MGP) than in the healthy group (HG), the differences being statistically significant ( $p=0.008$ ,  $p<0.05$ , Fischer test). In the advanced generalized chronic periodontitis group (AGP) E-cadherin concentrations are higher than in the healthy group (HG), the differences are not statistically significant ( $p=0.060$ ,  $p>0.05$ , Fischer test), (Figure 4).

There are no significant correlations between sTREM-1 and E-cadherin according to Pearson analysis in chronic periodontitis patients (Figure 5).

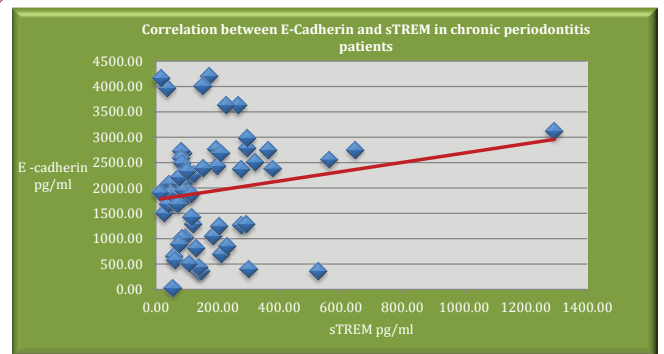


Figure 5 Pearson rank correlation analysis between sTREM-1 and E-cadherin in chronic periodontitis patients.

## Discussion

Individual microbial components, such as lipopolysaccharide (LPS) and peptidoglycan, can cause up-regulation of cell surface-localized TREM-1 by monocytes, as well as release in its soluble (s) TREM-1 form [1]. Periodontal pathogens have been shown to trigger systemic inflammatory responses and that sTREM-1 released during infections may be a useful marker in the pathogenesis of periodontal disease [14]. Some authors demonstrated a good correlation of sTREM-1 with the severity of periodontal disease [1,15,16].

One of the purposes of our study was to correlate salivary level of sTREM-1 with the progression of periodontal disease. Previous studies showed significantly higher levels of sTREM-1 in the crevicular fluid of patients with periodontal sites compared to healthy patients and demonstrated that periodontal pocket depth was positively correlated with high concentrations of sTREM-1. Therefore sTREM-1 could be a marker of periodontal tissue destruction [17]. Also, high concentrations of sTREM-1 were found in the crevicular fluid of patients with chronic periodontal disease compared to the control group and sTREM-1 correlated positively with the presence of periodontal pathogens such as *P. gingivalis*, *T. denticola* and *T. forsythia* in subgingival plaque, enhancing the association of this inflammatory marker with chronic periodontitis [14].

By comparing mean concentrations of sTREM-1 with clinical parameters of periodontal disease, our study revealed notable differences between salivary levels of sTREM-1 in subjects with periodontal disease compared to healthy subjects. Healthy subjects show low concentrations of sTREM-1 while subjects with moderate (MGP) and advanced stage of periodontal disease (AGP) show elevated concentrations. The difference in sTREM-1 concentration between stages of chronic periodontitis is not statistically significant ( $p=0.211$ ,  $p<0.05$ , Fischer test) but there

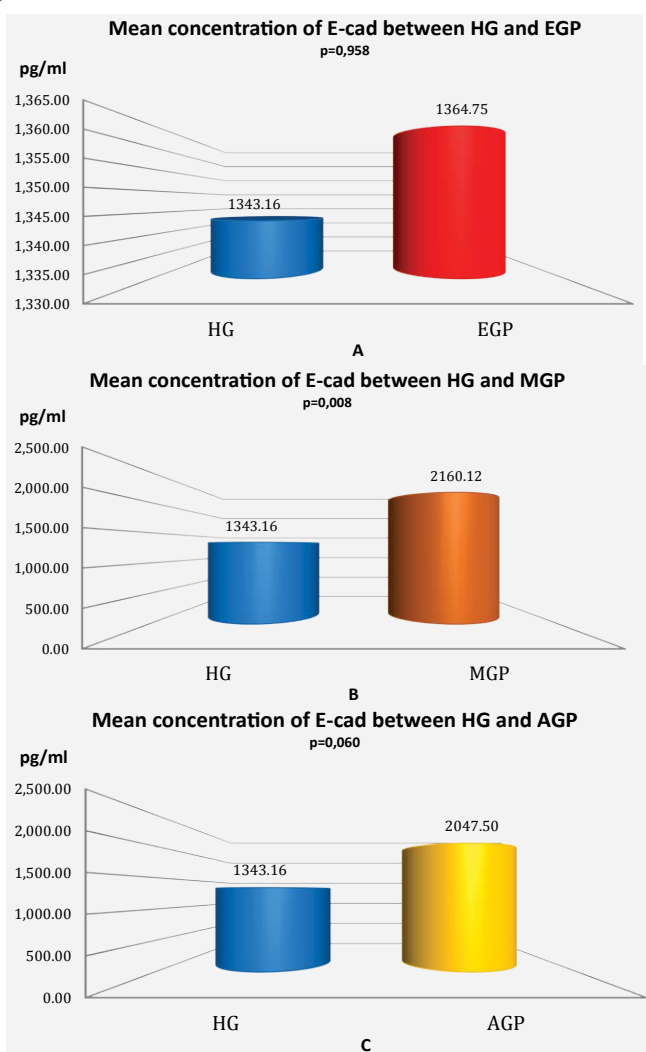


Figure 4 Mean concentration of E-cadherin between healthy and periodontitis groups: A) Mean concentration of E-cadherin testing between HG and EGP. B) Mean concentration of E-cadherin testing between HG and MGP. C) Mean concentration of E-cadherin testing between HG and AGP.

is an obvious increase in sTREM-1 levels in advanced stages of the disease compared to early stage. We found statistically significant differences ( $p < 0.009$ ) between sTREM-1 levels in advanced periodontitis patients compared to healthy ones. Our results indicate increased salivary concentrations of sTREM-1 during the progression of periodontal disease. Our research is in consonance with other studies that have shown higher salivary levels of sTREM-1 in periodontal disease patients compared to healthy subjects, strengthening the value of this molecule as a biomarker of periodontal disease and associating periodontal infection with a systemic inflammatory response [16].

Regarding sTREM-1 concentrations in different age groups, we found increased levels of this molecule along with advancing age, reaching its highest concentration in the 61-70 years age group and decreasing levels in the 70+ years age group. sTREM-1 analysis in elderly shows that there were no significant differences between sTREM-1 levels in patients with periodontitis compared to healthy patients. These data support the presence of an altered inflammatory response in the advanced age group (over 70 years), in which the bacterial challenge has limited impact [18].

E-cadherin provides intercellular adhesion between epithelial cells, its adhesive role requiring that these structures remain stable [19]. The structural integrity and functionality of the gingival junctional epithelium have been studied in connection with the inflammatory changes associated with periodontitis. E-cadherin expression has been studied in various regions of the gingival epithelium, between healthy subjects and those with periodontal disease, given the important role of E-cadherin in cell adhesion at the junctional epithelium. It has been shown that E-cadherin has reduced expression in the epithelium of the periodontal pockets, these changes indicating an important disruption of the epithelial structure and an altered ability of the gingival epithelium to function as an effective barrier against penetration of microbial products into tissues [20].

Our study aimed to evaluate salivary concentrations of E-cadherin along with progression of periodontal disease and to establish an association between E-cadherin and sTREM-1 in patients with chronic periodontitis. From our knowledge there are no studies that observed the salivary level of E-cadherin in the progression of periodontal disease or a possible correlation of this adhesion molecule with cell surface receptors (sTREM-1) in periodontal disease.

Previous studies have shown that subgingival plaque and periodontal bacteria such as *P. gingivalis* [21] or *A. actinomycetemcomitans* [22] can destroy junctions in the gingival epithelium, thereby compromising the structural integrity of gingival tissue and favoring bacterial invasion and chronic infection [23]. Also, human gingival cells exposed to certain periodontal pathogens showed low E-cadherin levels in patients

with periodontal disease. Significant reduction of E-cadherin levels in gingival tissue in patients with periodontal disease, compared to healthy subjects, could be a result of the invasion of periodontal pathogens and the progression of periodontal disease [24].

Our data suggest increased salivary E-cadherin levels along with the progression of periodontal disease. Increased concentrations of E-cadherin are obvious in moderate and advanced stage of periodontal disease compared to the control group. The differences in E-cadherin concentrations between clinical stages of the disease are statistically significant ( $p = 0.027$ ;  $p < 0.05$ ; Fischer test), with evident high levels of this molecule in advanced stages of the disease, reaching its highest concentration in the moderate clinical stage of chronic periodontitis. Healthy subjects show low concentrations of E-cadherin while subjects with medium and advanced stage of periodontal disease show high concentrations.

Therefore, salivary E-cadherin cannot be considered a marker of inflammation in periodontal disease due to its increased salivary levels along with the progression of chronic periodontitis, since its expression should be altered in periodontal lesions [25]. Salivary E-cadherin analysis is not relevant in patients with periodontitis and only its expression in gingival epithelial tissue can be considered a marker of the disease.

We also observed statistically significant differences in E-cadherin concentrations between age groups ( $p = 0.016$ ,  $p < 0.05$ , Fischer test). Decreasing levels of E-cadherin are obvious until the age of 50 while in older ages E-cadherin concentration increases. The mean E-cadherin concentration is at its lower level in the 41-50 years age group and reaches its higher level in the 71+ years age group. Other studies observing E-cadherin systemic levels did not show significant correlations between E-cadherin and age [26], only one other study revealed a low E-cadherin expression in the group of younger patients under 50 with gastric cancer [27].

Pearson analysis regarding correlation between sTREM-1 and E-cadherin in healthy and periodontitis patients, in our study, showed no statistically significant correlations ( $p = 0.194$ ;  $p < 0.05$  in patients with periodontal disease and  $p = 0.168$ ,  $p < 0.05$ , in healthy subjects) between the two, meaning that interdependence of these two molecules might not be important in chronic periodontitis.

## Conclusions

Salivary levels of sTREM-1, analyzed in patients with chronic periodontitis, strengthens the value of this molecule as a biomarker of periodontal disease. More than that, sTREM-1 may be considered an inflammatory marker in chronic periodontitis progression. Also, sTREM-1's detection in saliva of patients with periodontal disease may support an influence of periodontal infections on the systemic inflammatory response.

Salivary E-cadherin does not appear to be significant as an inflammatory marker in the pathology of chronic periodontitis

and it is likely to be relevant only in gingival epithelial tissues of periodontal sites. There is no evidence of any interdependence between the cell adhesion molecule (E-cadherin) and the cell surface receptor (sTREM-1) at salivary level in periodontal disease.

However further studies on more homogenous groups and correlations with other biomarkers are required, in order to demonstrate that salivary levels of these molecules may be used as indicators of chronic periodontitis progression.

## Ethical Approval

This study was approved by the Ethical Committee of the

School of Medicine, Lucian Blaga University (Protocol no: 5532/26.11.2015).

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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