Evolution of Inflammatory Biochemical Markers Within Periodontal Therapy to Patients with Rheumatoid Arthritis

RADU MADALIN BOATCA1, MIHAELA MONICA SCUTARIU1, IOANA RUDNIC1, MARIA ALEXANDRA MARTU STEFANACHE1, LOREDANA HURJUI2, ELENA REZUS1, SILVIA MARTU1

1 Gr. T. Popa University of Medicine and Pharmacy Iasi, Periodontology Department, 16 Universitatii Str., 700115, Iasi, Romania
2 Gr. T. Popa University of Medicine and Pharmacy Iasi, Physiologic Department, 16 Universitatii Str., 700115, Iasi, Romania

The purpose of this study is to analyze outstanding similarities between two of the most common chronic inflammatory diseases, rheumatoid arthritis and periodontal disease. The study evaluated the impact of specific etiological periodontal therapy on systemic inflammatory biochemical markers during of 6 months. The study included 19 patients diagnosed with periodontal disease divided into two groups, one in patients with periodontal disease and rheumatoid arthritis, and another group of patients with periodontal disease but without rheumatoid arthritis. Both groups received specific periodontal therapy and were monitored in terms of the development of biochemical markers levels. The results indicate that the majority values of biochemical markers are improved after the first 3 months and then are maintained after 6 months from moment of therapy initiation. Our study emphasizes that the levels of biochemical markers are clearly influenced by the local periodontal environment and selectively influenced by a systemic inflammatory condition such as rheumatoid arthritis.

Keywords: inflammatory markers, periodontal disease, rheumatoid arthritis

Rheumatoid arthritis is a systemic inflammatory disease with unknown etiology and an autoimmune pathology, characterized by distorting and destructive arthropathy with development of musculoskeletal system, but also with multiple systemic manifestations.

Latest research showed a similarity between periodontal disease and rheumatoid arthritis because of autoimmunity elements that characterize both diseases. As the periodontal disease as well as in rheumatoid arthritis, in terms of the immune response, there are common elements by increasing the number of cytokines, T-lymphocytes and lipid mediators.

In terms of statistical research [1-3] were shown an increase in the prevalence of periodontal disease in patients with rheumatoid arthritis. All investigations in recent years have demonstrated that the diagnosis and treatment of periodontal disease in patients with rheumatoid arthritis emphasized a greatly improved treatment response in these patients.

Studies have shown that salivary levels of certain biomarkers are increased at people who have periodontal disease. In particular, the biological biomarkers associated with different stages of periodontal disease (ex.: inflammation, collagen degradation and bone remodeling) have been suggested to be useful in early recognition of patients with periodontitis. [1-3]

On this context, they have investigated several biomarkers, including interleukin (IL-1b, protein C-reactive, metalloproteinase s matrix (MMP 8 and MMP 9), tissue inhibitor of matrix 1 of metalloproteinase, tumor necrosis factor (TNF)-α, receptor activator of nuclear factor-κ B and pyridinolina reticulate carboxyterminal of type I of collagen telopeptide [4, 5].

Periodontal disease has several clinical and pathogenic characteristics common with rheumatic disease. Periodontal diseases are not only a risk factor for odonto-periodontal complex, but can also be a threat to general health.

There are reports suggesting an increased prevalence of diabetes, atherosclerosis, myocardial infarction, stroke and rheumatoid arthritis in patients with periodontal disease. All forms of inflammatory periodontal disease are associated with chronic inflammation (accumulation of lymphocytes B and T, as well as of monocytes and of neutrophils), resulting the destruction of the periodontal ligament and alveolar bone.

A current approach to etiopathogenesis of rheumatoid arthritis includes generating of initial phenomena which lead to significant synovial inflammation and tissue destruction. All forms of periodontitis disease, are associated with an chronic accumulation of inflammatory cells (accumulation of T and B lymphocytes, as well as monocytes and neutrophils), there by causing tissue edema, endothelial cell proliferation and matrix degradation. [6]

For both diseases, the host response dictated by immunogenetic determines to a large plummet inflammatory responses. In addition, enzymes and cytokines cells which determines the degree of tissue damage in the joints causes pathological processes both in rheumatoid arthritis and periodontal disease. For this reason, therapeutic strategies aimed at modulating these answers are similar.

These results suggest a future support for the utility of clinical biomarker salivary in evaluating periodontal disease in adults, which are healthy, and are necessary additional studies that to delineate the impact of inflammatory systemic and profiles of associated diseases salivary biomarkers and results could then be used for monitoring to healthy and / or unusual about defining stages of disease. [7] In addition, they can provide a demonstration of a relationship between the presence of infection in the mouth.

* email: monascutaru@yahoo.com
and disturbing the haemostatic mechanisms influencing impaired inflammatory markers. It also wants the confirmation of the link between periodontal disease, rheumatoid arthritis and high levels of AAG, CRP and ESR.

On this line were analyzed similarities between those two pathologies, rheumatoid arthritis and periodontal disease. Also was evaluated the specific etiological periodontal therapy pathology (to eliminate the infection at this level) on serological markers of systemic inflammation (CRP, ESR, AAG) in patients with rheumatoid arthritis and periodontal disease. The effects of therapy were analyzed clinically periodontal and biochemically to validate the effectiveness of periodontal treatment.

**Experimental part**

**Material and method**

The study included 19 patients diagnosed with periodontal disease which were divided into groups according to the presence of systemic disease. Test group comprised patients with rheumatoid arthritis and periodontal disease and the control group, patients with periodontal disease but with rheumatoid arthritis. Patients of both groups received non-surgical periodontal therapy (scaling and root planning over, the field closed curettage, root surfacing). To these groups was performed monitoring of biochemical serum for a period of 6 months from the initiation of periodontal treatment and were evaluated significant changes in biochemical markers of inflammatory pathology studied.

Serum samples were collected by venipuncture initially at 3 and 6 months after the completion of treatment. Sampling is done on α jeun (fasting) from venous blood. Serum was obtained by centrifugation for 15 min at 2000 rpm within 1 hour of collection and the samples were stored at -70°C.

Serum levels CRP were analyzed by specific kits and evaluated by an automated high-sensitivity immunoturbidimetric device (Greiner Diagnostic, Gmbh, the detection limit is less than 0.25 mg/L). Blood donation containers consist in vacutainers without anticoagulant with / without separator gel. Postblood donation processing is required in serum separation by centrifugation, the minimum sample volume being 0.5 mL serum. Processing method was immunoturbidimetric - latex. Normal values are generally below 0.5 mg / dL.

**Results and discussions**

Results obtained are obtained by conducting comparative clinical - biological studies on basis of personal data concerning health and periodontal damage to susceptible or affected by chronic periodontal disease with or without rheumatic disease.

CRP has the highest values in the group of patients with chronic periodontitis and rheumatoid arthritis (table 1).

On this line, CRP is generally considered as the most sensitive response marker of infectious acute phase of tasks and / or of inflammation.

In this sense it seems relevant to note that serum CRP on baseline was detected in higher value intervals in patients with periodontal pathology and significant systemic. This is important in providing a correct interpretation of these findings: in the context of infections, doctors found these increased CRP as an indication of a systemic infectious tasks that require appropriate treatment. However more recent longitudinal studies have shown that acute phase response markers such as CRP and / or ESR appear to be predictive for rheumatoid arthritis (table 2) [9,10].

**Table 1**

<table>
<thead>
<tr>
<th>Patients</th>
<th>T0 initial</th>
<th>T1 after 3 months</th>
<th>T2 after 6 months</th>
<th>Friedman</th>
<th>T1-T10 Wilcoxon</th>
<th>T2-T1 Wilcoxon</th>
<th>T2-T0 Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST group</td>
<td>0.90 (1.06)</td>
<td>0.86 (1.11)</td>
<td>0.63 (0.54)</td>
<td>P=0.4293</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CONTROL group</td>
<td>2.07 (1.26)</td>
<td>1.23 (0.77)</td>
<td>0.63 (0.31)</td>
<td>P&lt;0.0000</td>
<td>P=0.0024</td>
<td>P=0.0022</td>
<td>P=0.0015</td>
</tr>
</tbody>
</table>

*The first value is the average and median value in parentheses represents the value from the middle of the range of values, we therefore mean (standard deviation) and median. It is used when data are not symmetrical (unevenly distributed); Mann-Whitney test (U) is used two independent groups and in this case, p = 0.0136; Friedman test (Fr) reveals the extent to which repeated evaluations ranks really different (statistically significant) together; Wilcoxon signed rank test is used to rank the difference of the two samples pairs that is, when the same subjects are evaluated twice.*

**Table 2**

<table>
<thead>
<tr>
<th>Patients</th>
<th>T0 initial</th>
<th>T1 after 3 months</th>
<th>T2 after 6 months</th>
<th>Friedman</th>
<th>T1-T10 Wilcoxon</th>
<th>T2-T1 Wilcoxon</th>
<th>T2-T0 Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST group</td>
<td>24.53 (13.13)</td>
<td>24.07 (13.51)</td>
<td>22.40 (13.13)</td>
<td>P&lt;0.0000</td>
<td>P=0.0106</td>
<td>P=0.0007</td>
<td>P=0.0007</td>
</tr>
<tr>
<td>CONTROL group</td>
<td>37.47 (7.36)</td>
<td>34.67 (9.59)</td>
<td>27.67 (9.60)</td>
<td>P&lt;0.0000</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*The first value is the average and median value in parentheses represents the value from the middle of the range of values, we therefore mean (standard deviation) and median. It is used when data are not symmetrical (unevenly distributed); Mann-Whitney test (U) is used two independent groups and in this case, p = 0.0136; Friedman test (Fr) reveals the extent to which repeated evaluations ranks really different (statistically significant) together; Wilcoxon signed rank test is used to rank the difference of the two samples pairs that is, when the same subjects are evaluated twice.*
α1-Acid glycoprotein is a plasma glycoprotein with a carbohydrate content of about 40%. As an acute phase protein, the results indicated a high level in chronic infections studied in this research (Table 3).

For laboratory results of markers of an acute phase, in test group, the values of ESR, PCR and AAG, they showed no statistical differences after 6 months (0-3, 0-6, and 3-6), but at three months were observed statistically significant difference.

Systemic markers in the control group, CRP (p < 0.0000), ESR (p < 0.0000) AAG (p < 0.0001), showed statistically significant reductions. These differences appeared in the examination periods of 0-3, 0-6, 3-6 months. The differences for systemic parameters were statistically significant between the two groups, CRP and ESR in the evaluation periods of 0-6, 3-6 months, AAG for examination periods of 0-3 and 0-6 months.

Once it has identified a possible link between rheumatoid arthritis and moderate to severe periodontitis it assumes that a proportion of these patients present a pathological disorder common mechanisms operating in these two chronic inflammatory diseases.

In fact, there is remarkable similarity in the pathogenesis of these two pathological conditions, both at the cellular and molecular level [11].

CRP, ESR and AAG have been studied in the context of rheumatoid arthritis because these biomarkers have been associated with biological aspects encountered in the context of periodontal disease, and were found to be significantly increased in this condition, compared to systemically healthy patients [12 13].

These markers were studied in the context of rheumatoid arthritis, chronic inflammatory disorder because this has a positive association with periodontal disease and high levels of these serum mediators occur in patients with rheumatoid arthritis.

These variations were examined by 2 study groups (patients with disease periodontal disease, patients with rheumatoid arthritis and periodontal disease and patients with periodontal disease without rheumatoid arthritis) on the assumption that if rheumatoid arthritis had an influence, levels of biomarkers could be changed.

In this study we have shown blood levels of biomarkers in patients with periodontal disease compared to the healthy group.

Laboratory markers for the outcome of an acute phase, the test group, the values of ESR, CRP and AAG introduce not statistically different at 6 months (0-3, 0-6 and 3-6), but at three months were observed statistically significant difference.

Table 3

<table>
<thead>
<tr>
<th>Patients</th>
<th>T0 initial</th>
<th>T1 after 3 months</th>
<th>T2 after 6 months</th>
<th>Friedman</th>
<th>T1-T10 Wilcoxon</th>
<th>T2-T1 Wilcoxon</th>
<th>T2-T0 Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEST group</td>
<td>91.57 (24.93)</td>
<td>92.11 (27.54)</td>
<td>88.67 (23.95)</td>
<td>p = 0.9955</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CONTROL group</td>
<td>97.67 (10.87)</td>
<td>86.20 (10.56)</td>
<td>78.27 (12.39)</td>
<td>p = 0.0000</td>
<td>p = 0.0011</td>
<td>p = 0.0012</td>
<td>p = 0.0018</td>
</tr>
</tbody>
</table>

* The first value is the average and median value in parentheses represents the value from the middle of the range of values, we therefore mean (standard deviation) and median. It is used when data are not symmetrical (unevenly distributed); Mann-Whitney test (U) is used two independent groups and in this case, p = 0.0136; Friedman test (Fr) reveals the extent to which repeated evaluations ranks really different (statistically significant) together; Wilcoxon signed rank test is used to rank the difference of the two samples pairs that is, when the same subjects are evaluated twice.

Systemic markers in the control group, CRP (p < 0.0000), ESR (p < 0.0000) AAG (p < 0.0001) showed statistically significant reductions. These differences have emerged in the examination periods of 0-3, 0-6, 3-6 months. Differences for systemic parameters were statistically significant between the two groups, CRP and ESR in the evaluation periods 0-6, 3-6 months, AAG for examination periods of 0-3 and 0-6 months.

Inflammatory markers C-reactive protein, erythrocyte sedimentation rate is increased in study groups compared with the control group (CRP 5.02 ± 6.0 vs. 1.56 ± 2.1 (p < 0.01), ESR 4 ± 10, 6 vs. 6, 3 ± 5, 7 (p < 0.001). Statistical analysis shows results with great significance because “p” (statistical significance) has value < 0.01.

CRP has averages values of 0.5 mg / l in the group with periodontal disease - higher than the control group or in the group with periodontal disease with rheumatoid arthritis.

This study highlights that levels of biomarkers ESR, CRP, AAG are obviously influenced by the local environment and periodontal selective systemic inflammatory influenced by a condition like rheumatoid arthritis.

When they compared the results between the two groups were statistically significant, however. Improve periodontal status affect laboratory results (protein in the acute phase) which was found easier to control group, which means that rheumatoid arthritis is a multifactorial disease, which makes getting control of other inflammatory processes in the body to carry out difficult.

The results indicate that the majority of clinical improvements occur within the first 3 months maintaining the 6 month study period.

These results suggest therefore that there is a future scientific support of the clinical utility of biomarkers for evaluating periodontal disease and requires additional studies that to delineate the impact of inflammatory systemic to associated diseases in evaluating profile of biomarkers that could be used to monitor the healthy and / or defining unusual about the stages of disease.

Conclusions

The study emphasizes that the biomarkers levels ESR, CRP AAG, are obviously influenced by the local periodontal environment and selective influenced by systemic inflammatory condition like rheumatoid arthritis. While all studies allege periodontal disease to various systemic inflammatory condition common mechanisms operating in these two pathological conditions, both at the cellular and molecular level.
References

Manuscript received: 13.09.2015