**RESEARCH**

**$T_1$ relaxation time and magnetic resonance imaging of inflamed gingival tissue**

R Schara*,1, I Serša2 and U Skalerič1

1University of Ljubljana, Faculty of Medicine, Department of Oral Medicine and Periodontology, Hrvatski trg 6, 1000 Ljubljana, Slovenia; 2Jožef Stefan Institute, Jamova 39, 1000 Ljubljana, Slovenia

**Objectives:** The aim of this study was to evaluate the use of MRI as a non-invasive method for the characterization of the inflammation and healing processes in periodontal tissues.

**Methods:** For the *in vitro* study, 99 gingival samples were collected during periodontal surgical treatment and $T_1$ relaxation time measurements were performed and correlated to the probing depth measurements recorded at the collection sites. For the *in vivo* study, a group of eight patients with moderate to advanced periodontal disease was examined with pre-contrast and Gd-DTPA contrast-enhanced $T_1$ weighted MRI both before and 3 months after non-surgical periodontal therapy. On the MR images of the 8 patients, 53 regions of interest (ROIs) were selected. For each ROI, the ratio between post- and pre-contrast signal intensity (RSI) was calculated and used as a measure for the degree of inflammation.

**Results:** The *in vitro* $T_1$ relaxation times measurements of gingival samples showed an increase in relaxation times with the increase of probing depth at the sites of tissue removal. The *in vivo* studies demonstrated that the reduction of inflammation and probing peepth in gingival tissues after non-surgical periodontal therapy correlates with a decrease of RSI in $T_1$ weighted MR images. The non-invasively obtained data provide the characteristic ratio $U$, which shows that two distinct types of inflammation occurred in the examined group of patients.

**Conclusions:** The results of MRI provide a new possibility to characterize the type and healing process of periodontal inflammation.


**Keywords:** periodontal diseases; magnetic resonance imaging; magnetic resonance spectroscopy; wound healing

**Introduction**

Periodontal disease is the most widespread chronic infection of mankind. Bacteria associated with dental plaque represent the primary aetiologic factor in periodontal inflammation. It is characterized by the loss of the supporting tissues of the teeth as well as humoral and cellular immune response to bacterial antigens of the microbial dental plaque that accumulates at the dentogingival junction. Periodontal inflammation represents the response of vascular gingival tissues to injury. It is usually protective but, if the causative agent persists, can become chronic with associated tissue damage. The magnitude of the inflammatory response is crucial because an insufficient response can lead to infection, whereas an excessive response can cause morbidity. Plasma cells are common in chronically inflamed sites, including periodontal lesions. Accumulation of plasma cells in inflamed sites is promoted by chronic inflammation, activators of microbial origin and specific antigens. This milieu can be expected to develop in some periodontal lesions and could help explain why gingival crevicular fluid from some sites may contain extraordinary levels of locally produced specific antibodies for certain antigens. Vasculitis occurs within the gingival tissues and immune cells are recruited to the site. Neutrophils, lymphocytes, plasma cells and monocytes/macrophages act to destroy the bacterial pathogens; however, destruction of host tissue can also occur. Alterations in the vascular network occur and many capillary beds are opened. Exudative fluid and proteins swell the
tissues and an influx of inflammatory cells in the connective tissue occurs subjacent to the junctional epithelium. The inflammatory cell infiltrate consists mainly of lymphocytes, macrophages and neutrophils. Exudative and transudative fluid and plasma proteins leave the vessels and travel through the tissues to the gingival crevice. The histopathology of the periodontal lesion is similar to that of the established gingival lesion, with a predominance of plasma cells and a loss of soft connective tissue elements as well as bone resorption. Early diagnosis and therapy improve the prognosis of periodontal disease and so minimizes its influence on the systemic condition. Precise diagnosis is needed for good treatment planning that leads to a successful outcome of the periodontal therapy. The diagnosis and classification of periodontal diseases are usually based almost entirely on clinical and radiological analysis. Diagnostic imaging methods used in dentistry show mainly changes in hard dental and periodontal tissues. However, a diagnostic method that provides qualitative and quantitative data about soft inflamed periodontal tissues is lacking. Such a method could be MRI. In medicine, MRI is used to distinguish pathological tissues from normal tissues in regions where other imaging modalities do not provide sufficient spatial resolution and contrast. In the orofacial region, MRI is used mainly for diagnosing the pathology of the temporomandibular joint, the floor of the mouth, the tongue, salivary glands and paranasal sinuses. In this study we used MRI to characterize the inflamed periodontal soft tissues, to characterize the extent of inflammation and to evaluate the healing of inflammation in gingiva and periodontal ligament after non-surgical periodontal therapy.

As the contrast agent accumulates in inflamed tissues and enhances mainly the signal intensity of those tissues, it is our hypothesis that after the therapy there will be a reduction in inflammation that can be confirmed by a reduction of the ratio of signal intensities (RSI) values in those tissues. Similar results with contrast-enhanced cardiac MRI in areas of myocardial inflammation were identified in up to 70% of patients with biopsy-proven cardiomyopathy.

Materials and Methods

The study was performed in two parts. The first part of the study included 64 patients (39 females and 25 males, mean age 46 ± 11 years) with clinically diagnosed moderate to advanced periodontal inflammation. From those patients, 99 gingival samples were collected during periodontal surgical treatment (modified Widman flap and clinical crown lengthening procedures). The probing depth (PD) at sites of collected tissue was recorded, gingival index of Löe and Silness was determined and biopsies of the gingival tissue were taken (approximately 12 mm³) on the gingival margin at the exact place of the measurement. The samples were temporarily stored at 8°C, dry, in small closed containers (1 ml) and were measured within 3 h, at room temperature, for the T₁ nuclear magnetic resonance (NMR) relaxation time on a Tecmag NMR spectrometer (Houston, TX) with a 2.35 T Oxford (Abingdon, Oxfordshire, UK) superconducting magnet (100 MHz proton frequency). The T₁ relaxation time was calculated by the Origin program (OriginLab Corporation, Northampton, MA) from NMR relaxation data obtained by the standard inversion recovery sequence in which the inversion time was varied from 500 μs to 5 s, in 18 equidistant time increments on logarithmic scale. The T₁ relaxation time was then correlated to the probing depth measured adjacent to the taken gingival sample.

The second part of the study included eight patients with moderate to advanced periodontal disease. T₁ weighted and contrast-enhanced T₁ weighted MR images were obtained after clinical examination which included PD measurements at six sites around all teeth. The patients were motivated and instructed for appropriate oral hygiene, including tooth brushing and interdental flossing. After that, they were treated by non-surgical periodontal therapy, including root scaling and planing under local anaesthesia. The clinical parameters and MR images were taken both before and 3 months after the periodontal therapy. The patients were imaged in the whole body MR scanner (Siemens Magnetom-SP 63, Erlangen, Germany), with a magnetic field strength of 1.5 T. The signal-to-noise ratio (SNR) was optimized by using a dedicated temporomandibular surface radio frequency (RF) coil of 10 cm diameter for NMR signal detection. MR images were acquired in transverse 3 mm-thick slices that offered the best compromise between spatial resolution and SNR for gingival tissue. The slices were positioned based on the sagittal pilot MR images of the head. Pre- and post-contrast images were acquired in the selected slices using the spin-echo T₁ weighted MRI technique with the following parameters: repetition time (TR) = 470 ms, echo time (TE) = 15 ms, imaging matrix 256 × 256, field of view (FOV) 200 × 200 mm, and acquisition time 2 min. Gd-DTPA (Magnevist; Bayer Schering Pharma, Leverkusen, Germany) contrast agent was injected intravenously at a dose of 0.1 mmol kg⁻¹ immediately before each post-contrast T₁ weighted scan.

53 regions of interest (ROIs) were selected manually by the expert in the maxilla and mandible in a slice positioned approximately 3 mm from the gingival margin. The same selected ROI was used for the analysis of pre- and post-contrast T₁ weighted images. Each slice was 3 mm thick. The selected regions were analysed by ImageJ program (NIH Image, National Institute of Health, Bethesda, MD) for their signal intensity before (SI) and after (SI_Gd) administration of the contrast agent. SI was determined by calculating the average pixel intensity from selected ROIs. In each image, signals from selected regions were normalized to the fat tissue signal, which was used as a reference. Additionally, a convenient parameter, the ratio between...
post- and pre-contrast signal intensity RSI = SI_{Gd}/SI for selected ROIs, was introduced. These parameters were used to describe the selected sites in periodontal tissues before and after the periodontal treatment.

Statistical analysis was done by the MedCalc Software (Ghent, Belgium) using the linear regression and correlation. The comparison between the slopes of the two selected groups of inflammation regions was calculated by multiple linear regression. The level of significance was set at the value $P < 0.001$.

The research was approved by the medical ethics committee of Slovenia and written informed consent was obtained from the patients.

Results

$T_1$ relaxation time measurements in vitro show an increase in relaxation time with increased PD (Figure 1) and gingival index. Gingival tissue obtained during crown lengthening (PD up to 3 mm) was in group 0 to 1 and gingival tissue obtained during treatment of periodontal inflammation (PD 4 mm or more) was in groups 2 and 3. $T_1$ relaxation time correlation with the PD can be described by the following model function which consists of a line with two sections of different slope

$$T1(PD) = \begin{cases} k_1PD + T1_0; & PD \leq PD_b \\ k_2(PD - PD_b) + (k_1PD_b + T1_0); & PD \leq PD_b \end{cases}$$

(1)

Here, $T1_0 = T1(PD = 0)$, $PD_b$ is the probing depth at which the slope of the $T_1$ function changes.

The best fit of the model parameters to the $T_1$ vs PD data, which is presented in Figure 1, was obtained at parameters: $k_1 = 50.3 \pm 10.8$ ms mm$^{-1}$, $k_2 = 20.4 \pm 3.8$ mm mm$^{-1}$, and $T1_0 = 850 \pm 37$ ms, while $PD_b$ was at 5 mm. The correlation coefficient $r = 0.957$ and for the line above the break $r = 0.785$. This breaking point correlates with the critical probing depth, above which scaling and root planing are typically insufficient and surgical treatment is also required.

In the in vivo studies we measured signal intensity in selected regions. The signal intensity is a complex function of instrument parameters and tissue parameters such as proton density, $T_1$ and $T_2$. To maximize the contrast within the ROI the instrument parameters, TR and TE must be correlated to in vitro gingival tissue relaxation time measurements. MR images of periodontal tissues in Figure 2 show high signal intensity in regions of soft dental tissues: gingiva, periodontal ligament, dental pulp and cancellous bone. The cortical bone of the jaw and hard dental tissues such as enamel, dentin and cementum show nearly no MR signal and appear as dark region in MR images. For good analysis of $T_1$ weighted MR images, it is important that the inflamed tissues can be well resolved from non-inflamed (clinically normal) tissues (Figure 2a). The reduction of the periodontal inflammation could be observed even better with the use of the contrast agent Gd-DTPA (Figure 2b). The contrast agent penetrates preferentially into the inflamed tissue regions. The resolution is further enhanced when a pre-contrast image is subtracted from a post-contrast image (Figure 2c). After the therapy, the extent and intensity of inflammation in all ROIs decreased. This was quantitatively confirmed with clinical parameters as well as by the RSI measurements of MR images (Table 1). Following the therapy, there was a reduction of inflammation as measured by probing depth and RSI reduction (Table 1).

It was assumed that the signal intensity depends linearly on the probing depth. In Figure 3, there is a summarised presentation of 53 ROIs of 8 patients before and after the periodontal treatment, representing the correlation between the RSI and PD measurements. The slope of the regression line before the therapy is $K = 0.106$ mm$^{-1}$, $P = 0.009$. The correlation coefficient is $r = 0.35$, $P = 0.01$. After the therapy, the slope of the regression line is $K = 0.138$ mm$^{-1}$, $P = 0.002$, the correlation coefficient $r = 0.415$, and $P = 0.001$. The characteristic slope of the line is denoted by the variable $K$ (the proportionality constant between RSI and PD), whereas the intercept of the line with the ordinate is denoted by the variable $N$ (the expected signal intensity at zero probing depth). Linear regression lines in the correlation graphs (Figure 3) were calculated by fitting the model equation $RSI = N + K \times PD$ to the data presented above.

Correlation graphs show that RSI correlates with the PD. Despite the relatively scattered results, it is possible to
conclude that the slope of the regression curve is steeper after the healing treatment, because the extent of the volume contraction in the group data is relatively larger than the corresponding RSI decrease.

Due to the large scattering of the data and very similar intercepts and slopes of the regression lines, the differences are not significant other than the obvious shift of the data after healing to lower PD and RSI values.

Within these 53 collected data, the observed periodontal damage pertains to different stages of development as well as possible type of inflammation. We therefore tried to sharpen the selection of data with respect to the MRI parameters, which finally reflect the heterogeneity of the tissue compartments and the access of the contrast agent molecules as well as the processes that accompany the healing. Thus we divided the data into two groups with respect to the parameter $U$ ($U > 0.2$ mm$^{-1}$ for the first group and $U < 0.2$ mm$^{-1}$ for the second group), which is the ratio between the decrease of the MR signal intensity and PD reduction in the healing process ($U = \Delta \text{RSI}/\Delta \text{PD}$). In Figure 4 we show the scattered graph with the regression lines describing the relations between $\Delta \text{RSI}$ and $\Delta \text{PD}$. Here, significant differences appear in the slopes of the linear regression lines, which in fact represent the dependence of the extents of retraction and the qualitative alteration occurring during the healing process in the selected groups of ROIs.

A large slope means that the size alteration of the inflamed tissue is amply supported by the removal of extracellular fluid, while a small slope means that retraction is accompanied by a reduction of larger proportions of inflamed cells together with extracellular fluid.

Figure 2  MR images acquired before the healing treatment (upper row) and 3 months after the non-surgical periodontal treatment (lower row). Images in column (a) are standard $T_1$ weighted MR images, images in column (b) are $T_1$ weighted MR images after the administration of the MR contrast agent (Gd-DATPA), which accumulates in the inflamed tissue, and images in column (c) were calculated by computerized subtraction of the pre-contrast images from post-contrast images (column (b) minus column (a)). The subtracted image therefore represents only the signal of the contrast agent.

Figure 3  Correlation of the ratio between post- and pre-contrast signal intensity (RSI) and probing depth before and after treatment measured from 53 regions of interest of 8 patients before and after treatment. The slope of the regression line, which was $K = 0.106$ mm$^{-1}$ (grey line) before treatment and increased to $K = 0.137$ mm$^{-1}$ (black line) after treatment, indicates a correlation for both pre- and post-healing measurements that is not statistically significant.

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The slope of the second group (B) with data points characterized with U > 0.2 is significantly larger than the slope of the second group (B) with data points characterized with U < 0.2 values.

Figure 4 ΔPD (probing depth) vs ΔRSI (the ratio between post- and pre-contrast signal intensity) graph with the ratio of healing U = ΔRSI/ΔPD illustrates the extent of the inflamed tissue size retraction as well as the corresponding RSI of the MR images for the ROI. Data points in the graph correspond to the degree of the reduction of PD and RSI values in the healing process. The characteristic slope, of the regression line for the first selected group (A) comprising the data points with U > 0.2 is significantly larger than the slope of the second group (B) with data points characterized with U < 0.2 values.

MRI is the ideal technique to display the soft-tissue abnormalities produced by inflammation. In general, these soft-tissue alterations are recorded by signal intensity changes that reflect the increased water content of the soft tissues, induced by the inflammatory processes. In some cases these changes are non-specific, but in others MRI can be quite helpful in detecting the presence and extent of the inflamed tissue, which helps to provide a better characterization than usually obtained by clinical parameters. It would also be interesting to supplement MRI data with CT scans as these could help to reveal inflammation processes in hard/soft-tissue interfaces.

The research on inflamed lung tissue showed that there was an increase of water content due to oedema and tissue proliferation. The signal intensity of those regions in MR images was further enhanced with the use of a contrast agent that accumulated in the inflamed tissues. There was a linear relationship between the relaxation times and the total water content of the lung samples \( (T_1; r = 0.87; T_2; r = 0.91) \). It was concluded that proton MRI may be helpful in detecting disease such as inflammation in collapsed lung tissue based on differences in relaxation parameters compared with normal lung areas. A decrease of \( T_1 \) relaxation times was observed in an experimental allergic encephalomyelitis analysis of \( \text{in vivo} \) proton MRI; after intravenous injection of Gd-DTPA, a decrease of \( T_1 \) relaxation times was observed. This coincides very well with macrophage activation, but not so well with T-cell infiltration. The T-cell infiltration can be used to distinguish \( \text{in vivo} \) between two components of the lesion: inflammatory infiltrates and vasogenic oedema.

The swelling of gingival tissues occurs by the penetration of infiltrate in the connective tissue and proliferation of epithelium. Periodontal disease is histologically characterized by the degradation of extracellular matrix components associated with a gingival infiltration of inflammatory cell populations.

Our \( \text{in vitro} \) research shows correlation of \( T_1 \) on the PD. It is also evident that in more inflamed tissues the infiltrates producing the swelling show a lower effect on the increase of relaxation time (Figure 1.). Therefore, it can be expected that the amount of “free water” is diminishing as compared with the increased portion of cellular infiltrates in more advanced periodontal tissue inflammation. It would be interesting to also conduct a similar study on tissue samples after the healing; however, this was not possible as this would require post-operative tissue removal.

In our \( \text{in vivo} \) research, the measured parameters SI and SIGd provide a good description of the tissue conditions via the spin lattice \( T_1 \) relaxation rates \( (1/ T_1) = X(1/ T_1)_e + (1–X)(1/ T_1)_i \). Here, the indices signify the relaxation rates: tissue \( (t) \), extracellular fluid \( (e) \) and intracellular fluid \( (i) \). \( X \) represents the volume portion of the extracellular fluid. This relation assumes a fast exchange of water molecules between the two...
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components in a tiny volume segment of tissues. It can be used as a qualitative indication of the average relaxation rates, which are measured in this situation within different local compartments of the tissue. The measured signal intensity SI is proportional to $(1 - \exp(-TR/T_1)) \exp(-TE/T_2)^{23}$ Here, TR and TE are the characteristic times set in the experiment to optimize the measured intensity, and $T_1$ and $T_2$ are the corresponding tissue relaxation times. In our presentation the ratio $RSI = SI_{Gd}/SI$ is used, where $SI_{Gd}$ corresponds to the measured intensity of the signal obtained in gadolinium-contrasted samples and SI corresponds to the measured intensity in samples with no contrast. Since the contrast agent accumulates primarily within the extracellular fluid, we are able to explore the population of the gadolinium accessible part of the tissue. In this way the processes of water and cellular infiltration in the inflamed tissue can be studied.

In our in vivo experiment, the healing process could be monitored by comparing the swelling of the gingival tissues and the corresponding quality of the infiltrate, as well as the infiltrate elimination. These measurements support the present status of knowledge of periodontal disease in different grades of inflammation. The microscopic constituents like cells, extracellular matrix collagen and infiltrated cells in connective tissue samples$^{24}$ are not homogeneously distributed, although the measured relaxation rates represent the average response of the water molecules. At different stages of the development of the disease, damage to the collagen fibres occurs and a progressive infiltration of cells gradually increases. The MRI methods, which are non-invasive, can help to characterize the infiltrate by way of the differences in the relaxation times, which are typical for the cellular and extracellular compartments. The possibility to explore the extracellular space is especially important because the gadolinium complexes can easily reach these parts of the tissue and improve the information on this tissue heterogeneity. In this presentation of the results, we believe that, presently, the comparison between the pre- and post-treatment, which provides valuable information on the processes involved in the infiltration and removal of fluids and cells, can help to distinguish between different types of inflammation in a non-invasive approach. In part, it is possible to draw some conclusions from the SI, PD relations for the particular ROIs in gingiva, though this will require further examination to improve the techniques for this special type of tissue. Quite distinguished processes of healing appear in different ROIs, as shown in Figure 4, where significant differences in the slopes for the regression lines can be observed for the two selected groups of ROIs. It should also be stressed that the ROIs of the same patient can be found in both groups. It illustrates the extent of the inflamed tissue size retraction $\Delta PD$ as well as the corresponding $\Delta RSI$ of the MR images for the ROI. It is interesting that the path of healing reveals at least two significantly different types of inflammation and different processes of healing. If the reduction of the infiltrate maintains a nearly constant ratio between the cells and extracellular fluid, then there is a very small decrease in the $RSI$ values, while on the other hand a typical oedema where the extracellular liquid causes swelling would drastically diminish the $RSI$ value. The two regression lines indicate that we are dealing with two different groups comprising ROIs with different type of inflammation characterized in the healing process.

In conclusion, the results of the study confirm a correlation between clinical parameters and relaxation times of gingival tissues in vitro and signal intensity measurements in vivo. After the therapy the decrease of inflammation in periodontal tissues and the improvement in clinical parameters was also confirmed by signal intensity measurements of MR images. Quantification of MR images by the new parameter $U$ might be a useful tool to characterize inflammation with a reflection on the processes evolving during the healing.

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References


