RESEARCH ARTICLE

T_2 relaxation mapping MRI of healthy and inflamed gingival tissue

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Objectives: To investigate the use and reproducibility of MRI transverse relaxation time (T_2) mapping in healthy and inflamed gingivae.

Methods: 21 subjects were recruited into 2 groups: those without evidence of gingivitis ("healthy"; $n = 11$, age 24.0 ± 3.66 years) by visual assessment and those with moderate to severe gingivitis ("gingivitis"; $n = 10$, age 28.9 ± 6.03 years) exhibited across the second mandibular premolar and first mandibular molar buccal gingivae. Subjects were imaged by MRI twice in a single day. Three T_2 weighted turbo spin-echo volumes with $0.25 \times 0.25 \times 0.8\text{-mm}^3$ resolution were acquired at echo times of 16, 32 and 48 ms for T_2 decay fitting. Image analysis was fully blinded; the two imaging sessions were not identifiable as coming from the same subject. Each imaging session had independent regions of interest drawn on the first echo image and applied to the calculated T_2 decay maps.

Results: The coefficient of variation was low and similar in healthy and gingivitis populations: 6.10 and 5.25% populations, respectively, with 5.65% populations across both groups. Bland–Altman analysis revealed no bias (mean -2.93% ; 95% confidence intervals -22.20 to 16.34%) between sessions. The intersession agreement was good ($r = 0.744$, $\rho = 0.568$, intraclass correlation coefficient = 0.68). T_2 mapping did not differentiate healthy from gingivitis groups. The mean T_2 value in the healthy group (63.7 ms) was similar to that of the gingivitis group (65.23 ms) ($p = 0.30$).

Conclusions: Mapping of the T_2 decay in the gingivae was a repeatable process; however, T_2 value alone did not differentiate those with clinical examination-determined gingivitis from those without signs of gingivitis.

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Introduction

Periodontal disease is one of the most common disease conditions in man. It results from accumulation of dental

plaque at the dentogingival junction causing a chronic inflammatory response in the gingival tissues—chronic gingivitis—whereby the dense gingival connective tissue is replaced by the chronically inflamed, immature granulation tissue. The progressive destruction of the periodontal tissues seen in chronic periodontitis is inevitably preceded by gingivitis; however, gingivitis can be managed by effective plaque control measures or may remain self-limiting for long periods of time.^{1,2}

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Assessment of gingival disease is generally carried out by clinical assessment of gingival bleeding, visual signs of gingival inflammation (redness and swelling) or a combination of both of these signs.^{3–6} Various indices of gingivitis have been described that are based on these signs, but inevitably are subjective, only semi-quantitative and their sensitivity to change within the practical limits of a clinical trial has been questioned.⁷ Although many other changes have been reported during the development and progression of gingivitis, including increases in gingival crevicular fluid flow, changes in bacterial flora and increases in gingival crevicular fluid and salivary inflammatory cytokine concentrations,² none of these parameters have been shown to provide reliable objective longitudinal diagnostic information for monitoring of gingival disease.⁷

MRI can provide highly detailed images of soft tissues including the dental pulp, nerves, gingivae, bone marrow and joint structures.⁸ Dental MRI is hampered by difficulty in imaging areas near metal implants or amalgam fillings; however, examination of caries with MRI demonstrated in *ex vivo* and *in vivo* work using the negative contrast from filling the mouth with a contrast gel has shown promise.^{9,10} MRI has recently also been reported for the assessment of apical periodontitis.¹¹

MRI is commonly used to visualize the inflammatory response in a number of tissues throughout the body, including the muscle and mucous membranes in the sinuses and bowel.^{12–14} The two most common

techniques used are T_1 weighted contrast after the administration of a contrast agent and T_2 weighted imaging. A prior MRI study used the first method to assess periodontal inflammation before and after therapy.¹⁵ The relative signal enhancement from the introduction of the gadolinium chelate contrast agent could be related to the reduction in pocket depth in *in vitro* gingival samples. Furthermore, the signal enhancement decreased 3 months after non-surgical intervention in eight subjects with moderate to advanced periodontal disease. T_2 mapping has been extensively tested in a number of other organs and diseases, such as articular cartilage arthritis.¹⁶

Given the prior report assessing periodontal inflammation using contrast-enhanced T_1 imaging, we wished to examine whether MRI without the use of an i.v. contrast agent could quantitatively map inflammation of the gingivae. T_2 mapping results in a continuous numerical value that may be able to track the progression or resolution, rather than the diagnosis, of gingival inflammation. This study is a first step towards determining whether T_2 mapping may be a useful biomarker for gingivitis for use within an interventional clinical trial. This study, therefore, was designed to assess the test–retest reproducibility of quantitative T_2 mapping in the gingivae of subjects with and without examiner-determined gingivitis and to examine the ability of the MRI technique to non-invasively discriminate between clinically assessed “healthy” and “unhealthy” gingivae.

Figure 1 An example data set from a single subject: (a) four axial slices in a representative subject. In the online image, the resulting region of interest (ROI) covering the gingivum between the second premolar and first molar is in green; (b) sagittal and (c) coronal views through the RIO and (d) the resulting T_2 map (scaled 0–100 ms) from the third slice in (a).

Methods and materials

This prospective, parallel-arm study was reviewed by the South Central–Oxford B Research Ethics Committee (14/SC/1147) and was performed in accordance with the ethical standards of the 2000 Declaration of Helsinki. All subjects gave written informed consent prior to inclusion in the study. There were two amendments to the protocol. The first amendment was a name change for the protocol author that did not affect the study procedure. The other amendment added smoking as an exclusion criterion and discussion with the subject of the screening questionnaire. It also clarified the time allowed between screening and MRI visits and removed radiologist review of the MRI scan.

Subjects were aged 18–40 years, in good general health with ≥ 20 natural permanent teeth. Exclusion criteria included current smokers or who had quit within 6 months prior to screening and current users of any form of smokeless tobacco; contraindications to MRI scanning; concomitant medication that could, in the investigator opinion, affect gingival condition; and active caries or periodontitis that could affect study outcomes. No treatment products were employed in this

study. Adverse events and incidents (for the MRI) were collected.

The healthy group was those without any evidence of gingivitis, as determined by visual assessment by the clinical investigator, a registered specialist in periodontology. The gingivitis group was defined as those with moderate to severe gingivitis affecting the buccal gingivae across the second mandibular premolar and adjacent first mandibular molar, on the right or left side. This location was defined as the area of interest in both groups. Moderate to severe gingivitis was characterized by visual examination as having a modified gingival index score of 3 or 4.⁶ The nominated teeth were chosen on whichever side did not contain metal dental work or amalgam fillings that might affect MRI results. Subjects were referred for imaging with one or both sides nominated as free from amalgam fillings or implanted metal. MRI assessment was performed on one side only. The same side was imaged in both imaging sessions.

Within 5 days of the screening visit, subjects attended the imaging site to undergo two imaging sessions. The imaging site was blinded to the subject group; subjects were imaged by MRI twice in a single visit day with

Figure 2 Bland–Altman analysis of intersession reproducibility of *T*₂ mapping (a) and region of interest (ROI) volume (b): although neither show evidence of a bias between sessions, the ROI volume definition was much less repeatable than the *T*₂ value (change in the scale on y-axis can be noted).

Table 1 Repeatability analysis of *T₂* mapping

	Gingivitis group n = 9	Healthy group n = 7	All subjects n = 16
CoV (%)	5.25	6.10	5.62
Bias (%) (95% CI)	−1.62 (from −19.92 to +16.69)	−4.61 (from −26.03 to +16.80)	−2.93 (from −22.20 to +16.34)
ICC (95% CI)	0.76 (0.24–0.94)	0.57 (from −0.23 to 0.91)	0.68 (0.29–0.87)
Pearson's <i>r</i>	0.86	0.62	0.74
Spearman's <i>ρ</i>	0.57	0.64	0.57

CI, confidence interval; CoV, coefficient of variation; ICC, intraclass correlation coefficient.

a break in between during which subjects could consume only water. Subjects brushed their teeth as usual on the morning of the scan, but no oral hygiene was permitted for 1 h before scan time. No interdental cleaning (use of floss, water picks or toothpicks) was permitted on the day of the scan.

Each imaging session was performed on a Siemens 3.0-T clinical MRI scanner (MAGNETOM® Verio; Siemens Healthcare, Erlangen, Germany) using a 4-cm loop coil placed on the cheek surface. Initial localizers confirmed the positioning of the coil over the nominated teeth on the left or right side. Three *T₂* weighted turbo spin-echo volumes were acquired at echo times of 16, 32 and 48 ms for *T₂* decay fitting. 26 0.8-mm-thick slices in a three-dimensional slab were acquired in a 128 × 94 × 208-mm field of view with a 256 × 256 resolution, reconstructed to 0.25 × 0.25 × 0.8-mm (0.05-mm³) voxels.

Image analysis was blinded to the subject and visit in addition to the group. The two imaging sessions were therefore not identifiable as coming from the same subject. Each imaging session had independent regions of interest (ROIs) drawn on the first echo image. ROIs were defined in the superoinferior direction by the surface of the gingivae down to the alveolar bone. The left–right extent of the ROI was bounded by a plane tangent to the surface of the two nominated adjacent teeth (Figure 1).

The three *T₂* weighted volumes were rigid-body co-registered using the “flirt” tool in FSL.¹⁷ At each spatial location in the resulting four-dimensional data (three spatial dimensions, plus one of echo time), the *T₂* and effective proton density (*S₀*) were determined *via* multidimensional least-squares minimization between the data and the equation for signal decay. The equation predefined by the statistical analysis plan in advance of the study was $S = S_0 \times \exp(-T_E/T_2) + C$, where *T_E* represents the 1 × 3 vector of echo times and *C* represents a term capturing non-exponential decay and a rectified noise floor.¹⁸ Upon data review, a *post hoc*

change to remove the noise floor term *C* was made and data refitted with the simplified equation $S = S_0 \times \exp(-T_E/T_2)$.

Statistical analysis

No formal sample size calculation was determined for this exploratory study. Sufficient subjects were to be screened to ensure 22 subjects were recruited, 11 subjects in each group, to ensure that approximately 10 subjects were present in each group, a sample size thought to provide sufficient information to allow an assessment of between-group differences. The per protocol (PP) population was considered the primary analysis population for this exploratory study, defined as all subjects who had at least one MRI assessment and did not have a major protocol violation requiring exclusion from the PP population. The intent-to-treat (ITT) population was defined as all subjects who had at least one MRI scan. An ITT analysis was to be performed if the ITT population was different from the PP population.

As predetermined by the statistical analysis plan, the intraclass correlation coefficient (ICC) with 95% confidence interval (CI) was determined using the method of Lu and Shara.¹⁹ Intergroup differences were analyzed with a one-way ANOVA model, with *T₂* as the response variable and subject group as a fixed effect. Differences between groups were estimated from the models with 95% CIs as well as *p*-values for subject group comparisons. Model assumptions were not found to be violated, so no transformations or non-parametric methods were used. For ease of reporting and visualization, two *post hoc* additions were made to the statistical analysis: reproducibility was determined by the coefficient of variation (CoV), defined as the standard deviation divided by the mean and the intersession correlation by both Pearson linear coefficient and Spearman rank correlation for both ROI volume and *T₂* value, and intersession agreement was analyzed by Bland–Altman analysis.²⁰

Table 2 Repeatability analysis of region of interest volume definition

	Gingivitis group n = 9	Healthy group n = 7	All subjects n = 16
CoV (%)	10.75	19.64	14.64
Bias (%) (95% CI)	−5.27 (from −43.28 to +32.73)	12.11 (from −56.54 to +80.77)	2.33 (from −52.08 to +56.74)
ICC (95% CI)	0.25 (from −0.46 to 0.76)	0.04 (from −0.72 to 0.69)	0.19 (from −0.32 to 0.61)
Pearson's <i>r</i>	0.25	−0.04	0.19
Spearman's <i>ρ</i>	0.18	−0.14	0.106

CI, confidence interval; CoV, coefficient of variation; ICC, intraclass correlation coefficient.

Figure 3 Intergroup comparison of T_2 values in the gingivae in the per protocol population: boxes are indicating 25th, median and 75th percentiles. Whiskers are spanning minimum to maximum values. Intergroup differences are not statistically significant.

Results

Of the 31 screened subjects, 29 subjects were randomized and 21 subjects completed the study, 10 subjects in the gingivitis group (6 females; age 28.9 ± 6.03 years, range 20–38 years) and 11 subjects in the healthy control group (7 females; age 24.0 ± 3.66 years, range 19–31 years). The healthy group was significantly younger than the gingivitis group ($p = 0.035$). Four sessions, one from each of four subjects, were excluded from image analysis owing to excessive subject motion in the raw images. This left seven subjects in the healthy group and nine subjects in the gingivitis group with two data sets for repeatability analysis. The ITT and PP populations were identical for repeatability analysis. For intergroup differences, the PP population in the healthy group reduced to 10 subjects from 11 subjects in the ITT population, as motion corrupted 1 subject's only available data set. The gingivitis group remained identical in both populations.

Using the T_2 equation fits from the predefined analysis plan, poor reproducibility in T_2 measures was noted. The ICC in the PP population was 0.49, with 95% CI of 0.021–0.782, indicating low levels of concordance between the two MRI scans within a subject. The within-subject CoV was 12.46%, with 95% CI of -44.57 to 24.02% and a bias of -10.28% . Pearson's r was 0.569 and Spearman ρ was 0.453.

A *post hoc* decision was made to review the quality of the fits to the signal decay equation. The noise floor term, C , was found to add variability to the fitting. Removing the C term reduced the fitting residual by an average of 69% across all data sets. Data were reanalyzed based on the T_2 values determined using the simplified fitting.

Figure 1 provides an example data set from a single subject. The ROI defined covers the gingivum across four axial slices between the second premolar and first molar. The depth of the gingival ROI was between three and five slices (2.4–4.0 mm) in all subjects. An example of a T_2 map, scaled 0–100 ms, from the third slice in Figure 1 is shown in panel (d) to show the quality of the T_2 fitting.

The CoV of the revised T_2 mapping in the PP population was low and similar in the healthy and gingival groups, 6.10 and 5.25%, respectively. Across both groups, the CoV was 5.62%. Bland–Altman analysis within each group or across all subjects revealed no bias in either T_2 mapping or ROI volume, as the 95% CI spanned zero in all analyses, as seen in Figure 2. The intersession agreement for the T_2 mapping was good, with a Pearson's r of 0.744 and Spearman ρ of 0.568. The ICC of T_2 mapping was also good at 0.68, with limits of agreement from 0.29 to 0.87. Neither group showed different trends in reliability against the group containing all subjects, as shown in Table 1, implying T_2 mapping was equally repeatable in either group.

The intersession agreement for the ROI volumes, however, was poor. ROI volumes were drawn independently on each imaging session by a blinded analyst. The CoV was 14.64% across both groups; however, as seen in Table 2, the ROI definition in the gingivitis group was strikingly more repeatable than that in the healthy group.

Figure 3 shows the mean T_2 values in milliseconds for subjects in the healthy and gingivitis groups, as well as group medians and 25th/75th percentiles for the PP population using the revised T_2 fitting. Within- and between-subject group means and CIs for both the PP and ITT populations are reported in Table 3; as per the predefined T_2 analysis, the revised fitting T_2 values are presented in Table 4. There were no significant differences in T_2 between the two subject groups, in terms of

Table 3 Intergroup differences in T_2 value using the predetermined analysis plan

	Mean T_2 (ms) (SEM)		Mean (95% CI) p value
	Gingivitis (n = 9)	Healthy (n = 10)	
PP (Scan 1)	56.95 (3.626)	53.67 (3.988)	3.28 (from -8.185 to 14.740) 0.5513
PP (Scan 2)	51.11 (2.318)	48.30 (4.090)	2.81 (from -6.920 to 12.538) 0.5476
PP (Scan mean)	54.03 (2.691)	51.87 (3.084)	2.16 (from -6.561 to 10.890) 0.6075
	Mean T_2 (ms) (SEM)		Mean (95% CI) p value
	Gingivitis (n = 9)	Healthy (n = 11)	
ITT (Scan 1)	56.95 (3.626)	55.80 (5.425)	1.15 (from -12.951 to 15.245) 0.8657
ITT (Scan 2)	51.11 (2.318)	48.30 (3.285)	3.07 (from -5.591 to 11.738) 0.4645
ITT (Scan mean)	54.03 (2.691)	50.89 (3.695)	3.14 (from -6.870 to 13.151) 0.5182

CI, confidence interval; ITT, intent to treat; PP, per protocol.
SEM (Standard Error of the Mean).

Table 4 Intergroup differences in T_2 value using the revised T_2 fitting

	<i>Mean T_2 (ms) (SEM)</i>		<i>Mean (95% CI) p value</i>
	<i>Gingivitis (n = 9)</i>	<i>Healthy (n = 10)</i>	<i>Gingivitis–healthy</i>
PP (Scan 1)	66.01 (3.398)	65.95 (3.247)	0.067 (from −10.15 to 10.02) 0.7960
PP (Scan 2)	64.44 (2.028)	61.69 (2.125)	2.751 (from −9.017 to 3.515) 0.9870
PP (Scan mean)	65.23 (2.622)	64.10 (2.065)	1.13 (from −8.097 to 5.843) 0.5887
	<i>Mean T_2 (ms) (SEM)</i>		<i>Mean (95% CI) p value</i>
	<i>Gingivitis (n = 9)</i>	<i>Healthy (n = 11)</i>	<i>Gingivitis–healthy</i>
ITT (Scan 1)	66.01 (3.398)	68.68 (4.366)	2.67 (from −9.196 to 14.45) 0.4050
ITT (Scan 2)	64.44 (2.028)	61.23 (2.099)	3.211 (from −9.399 to 2.977) 0.8171
ITT (Scan mean)	65.23 (2.622)	64.48 (2.592)	0.75 (from −8.556 to 7.072) 0.8173

CI, confidence interval; ITT, intent to treat; PP, per protocol.

Scan 1 results, Scan 2 results or mean scan results for either analysis or population.

Discussion

This work showed that T_2 mapping using MRI in the small gingival tissues between the teeth is possible and reproducible on a clinical MRI system. The ROI definition, although formally defined, did not result in similar volumes between the two scans. These differences, however, are not believed to affect the reproducibility of the mean T_2 values in those ROIs. Although the use of a constant bias term in exponential fitting of magnitude MRI data is common, in this study, it was found to increase the variability of the resulting fits and was thus discarded.¹⁸ The bias term may have been unnecessary, as the noise floor was not reached; the signal-to-noise ratio in the final echo image was well above 3.

Along the spectrum from healthy gums to the development of gingivitis, there are marked changes in the tissues that might be detectable by MRI. The changes include substantial breakdown in the dense fibrous tissue of healthy gingivae, infiltration by inflammatory cells, increased swelling, blood flow and vasodilation near the gingivae surface.

Prior work examining inflammation of the gingivae in periodontal disease used the administration of a gadolinium agent to change the signal level in T_1 weighted images.¹⁵ The relative signal difference between before and after contrast agent administration was found to be potentially an indicator of inflammation and could be related to probing depth. Post-contrast T_1 weighted imaging changes with inflammation primarily from extravasation of the contrast agent owing to increased vessel density and leakiness. Signal enhancement in T_2 weighted imaging, on the other hand, is driven by

extracellular fluid content, or oedema, and cellular swelling in an inflamed tissue.²³

The T_2 values determined here, on the order of 64 ms in the healthy gum, are longer than those found in normal (36 ± 4 ms) or oedematous (40 ± 8 ms) skin dermis.²¹ Lymphoedema was found to significantly increase the T_2 value found in the dermis, but to a smaller extent in the epidermis. Gingivitis is characterized by gingival bleeding and signs of gingival inflammation. Changes in T_2 relaxation time in the gingivum are well described in head and neck cancers, such as melanoma and lymphoma, owing to inflammatory changes.^{22,23}

One limitation to this study is its parallel-arm design. Intersubject differences outside of the process of gingivitis may have added too much variability to detect intergroup differences. It would be informative to perform a longitudinal intervention study with T_2 mapping, before and after treatment for gingivitis. The lack of longitudinal data also means that the sensitivity of T_2 mapping to progression or resolution of gingivitis was not examined.

This study set out to determine whether T_2 mapping can be used as a quantitative indicator of the level of gingivitis without the introduction of an i.v. contrast agent. The amount of oedema or cellular swelling in moderate to severe gingivitis was not of sufficient level for differences to be shown from those of healthy gum tissues using T_2 mapping performed here. However, the process did result in repeatable measurements of T_2 in the gingivum of normal and moderate to severe gingivitis at a very high resolution.

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