RESEARCH

Quantitative MRI analysis of salivary glands in sickle cell disease

J Liao^{*1}, N Saito¹, A Ozonoff², H Jara¹, M Steinberg³ and O Sakai¹

¹Department of Radiology, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA; ²Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA; ³Department of Medicine, Boston Medical Center, Boston University School of Medicine, Boston, MA, USA

Objectives: The purpose of this prospective study was to characterize the MR relaxometric features of the major salivary glands in patients with sickle cell disease (SCD).

Methods: 15 patients with SCD (aged 19.8–43.6 years) and 12 controls were imaged with the mixed turbo-spin echo pulse sequence. The major salivary glands were manually segmented and T_1 , T_2 and secular T_2 relaxometry histograms were modelled with Gaussian functions.

Results: Shortened T_1 relaxation times were seen solely in the submandibular glands of patients with SCD (747.5 ± 54.8 ms vs 807.1 ± 38.3 ms, $p < 0.001$). Slight T_2 and secular T_2 shortening were seen in the parotid gland; however, this difference was not significant ($p = 0.07$). The sublingual gland showed no changes under MR relaxometry. There was no difference in glandular volumes, and no correlation was demonstrated between history of blood transfusion and salivary gland relaxometry.

Conclusions: Patients with SCD exhibited changes in quantitative MRI T_1 relaxometry histograms of the submandibular glands.

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Introduction

Sickle cell disease (SCD) is an autosomal recessive haemoglobinopathy that affects 1 in 400 African Americans.¹ The polymerization of deoxy-sickle haemoglobin (HbS) initiates pathophysiological changes that lead to vaso-occlusion, haemolytic anaemia and chronic organ damage.² Vaso-occlusive processes occur in capillaries and restrict blood flow to end organs. This includes the extracranial regions and has been shown to result in cranial and facial bone infarction, as well as sensorineural hearing loss.^{3–5} These complications can be detected by CT or MRI.^{6,7}

MRI is excellent for soft-tissue resolution and can easily visualize the major salivary glands, which consist of the parotid, submandibular and sublingual glands.⁸ The microvascular component of these secretory structures may potentially make them targets for sickle cell vaso-occlusion. Furthermore, the use of transfusion therapy may contribute to end-organ complications. Between 70% and 80% of patients with SCD receive at least one transfusion before the age of 20 years.⁹ In severe instances,

repeated blood transfusions can result in iron overload, which is especially seen in individuals with β -thalassaemia.¹⁰ Iron overload is also becoming an increasingly prevalent complication as closely managed patients with SCD are now living longer. For this reason, regular ferritin testing is recommended in patients with SCD receiving transfusion therapy.¹¹ There have been reports of haemosiderin deposition in the salivary glands of β -thalassaemia patients, and we hypothesize that the same process may occur during the management of SCD.¹¹

To our knowledge, there have been no studies investigating the MR relaxometry characteristics of the salivary glands in the setting of SCD. Our study uses imaging as a non-invasive technique to characterize the effects of this systemic disease on a novel region of interest. We hypothesized that pathological changes from vaso-occlusion and chronic inflammation, as well as iron deposition from repeated transfusion, might be reflected in quantifiable shifts in MR relaxation times.

Materials and methods

This prospective study protocol was approved by the institutional review board of our institution. All subjects

*Correspondence to: Joseph Liao, 86 Saint Botolph St, #13, Boston, MA 02116, USA. E-mail: joseph.h.liao@gmail.com

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consented following National Institutes of Health Insurance Portability and Accountability Act guidelines. The study population consisted of 15 patients with SCD (4 male, 11 female, aged 19.8–43.6 years, mean 30.0 years, SD = 8.5 years) and 12 age-matched healthy subjects (5 male, 7 female; aged 21.7–47 years, mean 34.4 years, SD = 9.4 years). All patients with SCD were self-identified as African American. Three of our controls were self-identified as African American, five as Hispanic, three as Caucasian and one was unspecified. Of the patients with SCD, 13 were homozygous HbSS and 2 were HbS β^0 thalassaemia. Chart review of the HbS β^0 patients revealed typical clinical sequelae of SCD, including vaso-occlusive crises, avascular necrosis of the hips and episodes of acute chest syndrome. Haemoglobin status was confirmed by haemoglobin electrophoresis and peripheral blood leukocyte genomic testing. All patients were followed by haematologists in the sickle-cell clinic of our institution. Patients were residents of the north-eastern USA and enrolled from August 2005 to August 2009. The subjects were referred to MRI for various clinical reasons unrelated to the salivary glands, and the research sequence was added to clinical sequences. Selection criteria for further analyses were (1) MRI study without contrast administration and (2) data sets without artefact from motion and dental fillings.

MRI

All subjects were scanned with the mixed turbo-spin echo (mixed-TSE) pulse sequence in either of two 1.5 T units at our hospital (Intera and Achieva, Philips Medical Systems of North America, Cleveland, OH). Key scanning parameters of this pulse sequence are listed in Table 1. For all scans, the quadrature-body

and quadrature-head coils were used for radiofrequency excitation and signal detection, respectively.

Mixed-TSE is a fast, multislice quadruple time point quantitative (q)MRI pulse sequence that combines the principles of T_1 weighting by inversion recovery and of T_2 weighting by multi-echo sampling, in a single acquisition. This sequence has two inversion times (TI1, TI2) and two effective echo times (TE1_{eff}, TE2_{eff}), thus generating four self-co-registered images per slice, each with different levels of T_1 and T_2 weighting. These four acquired images can be processed to generate qMRI maps portraying the T_1 , T_2 and secular T_2 distributions. The difference between the T_1 and T_2 relaxation rates represents the pure spin-spin interactions and is known as the secular relaxation rate. The associated secular T_2 relaxation time is given by Equation 1:¹²

$$T_2^{(\text{sec})} = T_2 / (1 - T_2 / 2 T_1) \quad (1)$$

In addition to the research sequence, clinical sequences including spin echo T_1 weighted images, gradient and spin echo (GRASE) fat-suppressed T_2 weighted images and gradient echo T_2 weighted images were performed. All studies were reviewed by a neuroradiologist.

Image processing

We performed multispectral qMRI analysis of the T_1 , T_2 and secular T_2 relaxation times in the major salivary glands of patients with SCD, with additional volume studies. The use of T_1 , T_2 and secular T_2 qMRI algorithms in image processing has been described in recent literature.¹³ The parotid, submandibular and sublingual glands were segmented manually using a three-dimensional (3D) slicer (v. 2.6, <http://www.slicer.org/>), a freely available, open-source software package for visualization, registration, segmentation and quantification of medical data. Large vessels coursing through the glands, such as the retromandibular vein and external carotid artery, were excluded from segmentation. T_1 , T_2 and secular T_2 relaxation time histograms for all segmented salivary glands were generated and modelled with Gaussian functions using MathCAD 2001i (PTC, Needham, MA). The intensity of each voxel was quantified and assigned a relaxation time value in milliseconds. The highest voxel frequencies, or peak values, for T_1 relaxation times of all subjects were then recorded and graphed as function of age. The same method was used to generate age-ordered T_2 and secular T_2 spectra.

Average multisubject histograms were created for both subject groups by calculating the mean voxel frequency for every 10 ms increment in relaxation time. Volumes for segmented salivary glands were calculated by multiplying the number of voxels of the segmented salivary glands by the corresponding voxel volumes: $0.94 \times 0.94 \times 3.00 \text{ mm}^3$. The relaxation time peak values, as well as glandular volumes, were then plotted against age.

Chart review

We reviewed all electronic medical records of the patients with SCD between 2000 and 2009 (Centricity

Table 1 Mixed turbo-spin echo (mixed-TSE) pulse sequence parameters

Parameter	Mixed-TSE
Geometry	
Imaging plane	Axial
Acquisition matrix	256×192
Voxel dimensions	$0.94 \times 0.94 \times 3.00$
Interslice gap	Null (two packages)
PE per cent sampling	75%
FOV ^(FE) $\times$ FOV ^(PE) $\times$ mm ²	240×180
Slices	80
Contrast	
Effective echo time (ms)	TE1 _{eff} = 7.142; TE2 _{eff} = 100
Repetition time (ms)	TR = 14 882.18
Inversion times (ms)	TI1 = 700; TI2 = 7 441
Echo train lengths	18 (9 per echo)
Phase encoding orders	Centric first echo and linear second echo
Fat suppression	No
Acquisition	
Averages	NEX = 1
SAR (W kg ¹)	2.7
Scan time (min)	9.5

FOV^{FE}, field of view in the frequency encoding direction; FOV^{PE}, field of view in the phase encoding direction; NEX, number of excitations; SAR, specific absorption rate; TE, echo time; TI, inversion time; TR, repetition time.

Figure 1 Salivary gland segmentation. The parotid (a), submandibular (b), and sublingual (c) glands of a 42-year-old male. Gland segmentation was performed in a three-dimensional slicer using T_2 maps and an axial slice thickness of 3.0 mm. Three-dimensional models were reconstructed for relaxometry analysis and volume calculation

EMR; GE Healthcare). Medical records earlier than 2000 were not available. In that 9 year time period, we recorded the number of hospitalizations for vaso-occlusive events and the total units of packed red blood cells (PRBCs) transfused over all hospitalizations. We then plotted the number of units of PRBCs received for each subject, a marker of disease severity, against the T_1 , T_2 secular and T_2 peak values of their salivary glands. r^2 coefficient values were calculated as a measure of correlation.

Statistical analysis

The Wilcoxon signed-rank test was used in preliminary analyses in order to eliminate distribution assumptions. The T_1 , T_2 and secular T_2 peak values, as well as glandular volumes, were then compared with the SCD and healthy groups. This was accomplished using a linear model fit with generalized estimating equations to account for multiple measurements (left and right gland) per subject.

Results

54 parotid glands (30 SCD, 24 controls), 44 submandibular glands (26 SCD, 18 controls) and 48 sublingual glands (28 SCD, 20 controls) were segmented. The patients ranged in age from 19.8 years to 43.6 years. Sample segmentations of each gland are shown in Figure 1. T_1 , T_2 and secular T_2 histograms were generated for each salivary gland from the segmented qMRI maps (Figure 2). During segmentation, ten submandibular glands and eight sublingual glands were excluded owing to artefacts from either motion or dental fillings.

T_1 , T_2 and secular T_2 peak values of the three salivary glands are shown in Table 2. The parotid glands and sublingual glands did not show any significant change in the patients with SCD in any of the pulse sequences. In the submandibular glands, however, T_1 peak values were significantly shortened by 7.4% in patients with SCD ($p < 0.001$). T_2 and secular T_2 values of the submandibular gland were not significantly different.

Figure 2 Single subject histogram. Graph shows a T_1 relaxation time histogram of the left parotid gland in a 29-year-old female. The abscissa is measured in milliseconds. A monomodal Gaussian distribution is observed with a peak value of 560 ms with normal decay

Table 2 Summary of relaxation time peak values and volumes

Region	Parameter	Controls			SCD			% Change	p-value
		n	Mean	SD	n	Mean	SD		
Parotid	T_1 (ms)	12	578.8	67.9	15	589.7	82.1	1.88	0.74
	T_2 (ms)	12	104.5	11.7	15	94.4	15.3	-9.67	0.07
	Secular T_2 (ms)	12	115.3	15.0	15	102.6	19.1	-11.01	0.07
	Volume (cm ³)	12	23.3	6.2	15	21.4	7.8	-8.15	0.26
SM	T_1	9	807.1	38.3	13	747.5	54.8	-7.38	0.001
	T_2	9	83.9	4.5	13	82.0	7.4	-2.26	0.31
	Secular T_2	9	88.6	5.4	13	86.0	8.2	-2.93	0.24
	Volume	9	7.6	2.0	13	6.7	2.0	-11.84	0.21
SL	T_1	10	735.8	42.5	14	708.8	55.5	-3.67	0.16
	T_2	10	82.8	4.5	14	81.0	7.9	-2.17	0.44
	Secular T_2	10	87.8	3.9	14	85.8	8.7	-2.28	0.42
	Volume	10	2.2	0.5	14	2.4	1.3	9.09	0.74

SCD, patients with sickle cell disease; SL, sublingual gland; SM, submandibular gland.

The bold, italic line represents the statistically significant difference observed in our experiment.

Peak values for individual salivary glands were plotted as a function of age. The T_1 peaks in the submandibular gland (Figure 3a) and the T_2 peaks in the parotid gland (Figure 3b) are shown in contrast to the sublingual gland, which showed the fewest relaxometric changes (Figure 3c). In the case of the submandibular gland, trend lines calculated for the two groups were shown to be roughly parallel. Peak values for both groups exhibited a slight decrease at an average of 10.4 ms per decade of life, but age did not appear to be a factor in the magnitude of T_1 shortening between the two groups at any given age.

In contrast to decreasing T_1 peak values with age, the parotid gland exhibited increasing T_2 peak values with age. The parotid glands of patients with SCD older than 40 years of age exhibited increasing variability in T_2 peak values, to the point of overlap with normal subjects. As a result, SCD T_2 peak values were shown to increase at an average of 11.2 ms per decade of life in comparison with 3.5 ms per decade of life for normal subjects.

Multisubject histograms of T_1 relaxation times are shown in Figure 4. All histogram curves were unimodal. The T_1 shortening in the submandibular gland of patients with SCD is shown again in Figure 4b. A constant distribution between the two groups was observed despite the shortening. The y-axis represents the quantity of voxels for each relaxation time; hence, the area under the curve (AUC) is a function of glandular volume. The peak voxels for the SCD group was decreased by 23.7% in the submandibular gland and 27.5% in the parotid gland. On the other hand, the T_1 multisubject histogram for the sublingual gland showed little difference between the two group with regard to peak relaxation times and voxel count.

Multisubject histograms of T_2 relaxation times are shown in Figure 5. T_2 shortening is seen in the parotid gland in Figure 5a. In contrast to the large decrease in peak voxel frequency shown in the T_1 histogram, the T_2 histogram of the parotid gland showed similar peak heights (SCD = 810.2 vs control = 802.8 voxels, a 0.9%

Figure 3 Glandular changes as function of age. Graphs show histogram peak values of individual glands plotted as a function of age. (a) T_1 peak values in the submandibular gland of subjects with sickle cell disease (SCD) were significantly shortened by 7.4% (747.5 ± 54.8 ms and 807.1 ± 38.3 ms; $p < 0.003$). Trend lines calculated for the two groups were shown to be roughly parallel. Peak values for both groups exhibited a slight decrease at an average of 10.4 ms per decade of life, but age did not appear to be a factor in the magnitude of T_1 shortening between the two groups at any given age. (b) T_2 values of the parotid glands were shortened by 9.7% (94.4 ± 15.3 ms and 104.5 ± 11.7 ms, $p = 0.07$). The distribution of the parotid gland T_2 peaks in SCD patients widened with increasing age. Slight upward trends are observed with increasing age. (c) An example of non-change in the T_1 relaxation times of the sublingual gland is shown

Figure 4 Multisubject T_1 histograms. Graphs show multisubject histograms of T_1 relaxation times in the parotid (a), submandibular (b) and sublingual (c) glands. Multisubject histograms were generated by combining all histograms and dividing them into two groups. These graphs show a T_1 shortening in the submandibular gland, as well as a decreased area under the curve in both the parotid and submandibular glands of patients with sickle cell disease (SCD)

difference). A decrease of 23.5% was instead observed in the width of the SCD curve when measured halfway up the curve. Both the submandibular and sublingual T_2 histograms exhibited considerable overlap between the two groups and were not remarkably different.

Although the difference in AUCs for multisubject SCD histograms suggests a decreased volume of parotid and submandibular glands (Figures 4a,b) and volumetry calculations showed a 12.7% and 14.1% decrease in these two glands in Table 2, these findings were not statistically significant. Within our subject age range, there also appeared to be no age-related trends in glandular volumes.

The patients with SCD underwent a wide range of PRBC transfusions over a span of 9 years (0–47 units PRBCs, mean = 10.6 units) (Figure 6). No significant trends in T_1 , T_2 or secular T_2 peak values were seen with increasing blood transfusions. There were no significant r^2 coefficient values for any of the salivary glands.

Discussion

Numerous radiological findings in the maxillofacial region have been described in the setting of SCD. The bones exhibit decreased radiodensity, as erythroblastic hyperplasia results in medullary expansion and increased marrow space.¹⁴ The inferior border of the mandible can appear thinned and the dentin can become hypomineralized.¹⁵ The majority of the literature focuses on plain film radiography, which primarily outlines bone. The involvement of the maxillofacial soft tissue in SCD, on the other hand, has not been well studied. The major salivary glands are implicated in a wide range of pathologies, including infection, inflammation, autoimmune diseases and neoplasm.¹⁶ To our knowledge, this is the first study to apply MRI to the quantitative measurement of salivary glands in SCD. We identified quantitative shifts in the relaxation times in the salivary glands of patients with SCD. More

Figure 5 Multisubject T_2 histograms. Graphs show multisubject histograms of T_2 relaxation times in the parotid (a), submandibular (b) and sublingual (c) glands. Multisubject histograms were generated by combining all histograms and dividing them into two groups. These graphs show T_2 shortening in the parotid gland, with no change in the voxel frequency between the sickle cell disease (SCD) and control peaks

Figure 6 Blood transfusions. Graphs show T_1 and T_2 peak values of salivary glands in subjects with sickle cell disease as a function of blood transfusions received between 2000 and 2009. Subjects receiving <10 units of packed red blood cells (PRBCs) displayed a wide distribution of peak values. No trend was observed between the salivary gland peak values and the increasing number of blood transfusions received. The parotid gland exhibited the widest variability in peak values. The parotid gland also exhibited shorter T_1 peaks and longer T_2 peaks than the other two glands, which overlapped in both T_1 and T_2 peak values

specifically, we found T_1 shortening in the submandibular glands.

One potential aetiology for the T_1 shortening is an expansion of fatty tissue in the salivary glands. This process has been observed in Sjögren's syndrome, an autoimmune disease implicating the salivary glands. In Sjögren's syndrome, fatty deposition develops alongside the lymphocytic infiltration of the major salivary glands.¹⁷ Lymphocyte-catalysed fat deposition is not uncommon; this phenomenon occurs in other regions of the body as well. In the orbit, T lymphocytes have been shown to induce fibroblasts to differentiate into adipocytes, seen in Graves' disease.¹⁸ In patients with SCD, chronic inflammation or infection may recruit lymphocytes to the salivary glands and induce fibroblast differentiation, leading to a shift in MR signal. Fibrosis, despite being a common consequence in chronic disease states, was ruled out as a potential aetiology. This is because fibrotic tissue would exhibit hypointense T_1 and T_2 weighted images. Lastly, given the small T_1 effect observed and the fact that several physical and physiological processes affect T_2 , it is also plausible that there may exist T_2 variations that are not observed to a significant level.

Microscopic differences between the salivary glands may also account for differences seen between the glands. The parotid gland, for example, has a higher fat content than the other two salivary glands. It also produces pure serous saliva, and is the only salivary gland that contains lymphatic tissue.^{17,19} The two other glands, on the other hand, produce mixed serous and mucinous saliva. The

presence of lymphatic tissue and increased proportion of serous fluid in the parotid gland may explain why, compared with the other two glands, the parotid gland has a lower T_1 peak and a higher T_2 peak.

Another topic we investigated was the potential long-term sequelae of transfusion therapy. In this study, the frequency of blood transfusions did not correlate with the relaxometric MR characteristics of the salivary glands. In the literature, sources have shown a correlation between the number of units of blood transfused and serum ferritin levels.²⁰ Furthermore, the number of transfusions received has been used to monitor the severity of the disease in individuals.²¹ The mean amount of blood transfused in our sample was 10.6 units over a period of 9 years, or an average of 1.2 units per year, which is unimpressive when compared with patients with thalassaemia major, who receive transfusions as often as every 2–4 weeks.²¹ Based on the frequency of blood transfusions observed in our sample, our cohort of patients with SCD most likely lies in the subclinical range of iron overload. Therefore, we were not able to rule out the presence of iron deposition in the salivary glands in more severe cases of SCD.

There were no major age-related trends observed in our study. Our subjects were aged 18–50 years. This is largely owing to the increased morbidity and mortality associated with SCD: the median age at death in the setting of SCD is 42 years for males and 48 years for females.²² In Africa, the median age of death is even lower, at 11 years for males and 12 years for females.²³ Age-related T_2 and secular T_2 relaxometry changes have

been described in the major salivary glands, particularly in the newborn and elderly populations.²⁴ Without patients with SCD in these age categories, however, we were unable to confidently characterize this in SCD.

All patients with SCD in our study were self-identified African American. From a genetic standpoint, this is a term that is not rigorously defined, and as a group our patients had varying degrees of genetic admixture, both of Caucasian and of African origin. This is known from very detailed genetic studies that have been done.²⁵ Because both our SCD and control populations were genetically heterogeneous, our study does not attempt to draw conclusions based on race.

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