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Would Sub-regional Analysis Improve Sensitivity in Knee dGEMRIC?

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Abstract

Purpose: To evaluate if sub-regional analysis could offer higher sensitivity than full-thickness analysis when quantifying dGEMRIC data of the knee.

Materials and methods: A dGEMRIC data set of medial femoral cartilage of the knee, including thirteen patients with osteoarthritis (diseased) and fourteen asymptomatic subjects (control), was reanalyzed with sub-regional analysis, i.e. using two ROIs (regions of interest) representing superficial region and deep region of the cartilage respectively, in addition to full-thickness ROI. Comparisons were made in T_{1pre} (spin-lattice relaxation time without contrast administration), T_{1Gd} (after Gd-DTPA^{2-} administration), and ΔR_1 (the change of relaxation rate) obtained with the three analysis methods.

Results: Differences between superficial region and deep region in T_{1pre}, and T_{1Gd} were clearly observed. Superficial region analysis always provided shortest T_{1Gd} and highest ΔR_1 in both the diseased and the control, but the diseased-control difference in T_{1Gd} and ΔR_1 were quite close with the three analysis methods. Even though superficial region analysis showed slightly higher values of AUC (areas under the curves) of Receiver Operating Characteristic compared to full-thickness analysis, no significant difference in sensitivity was observed for knee dGEMRIC, with either T_{1Gd} ($p=0.802$) or ΔR_1 ($p=0.328$).

Conclusion: For analyzing dGEMRIC of the knee with reduced cartilage thickness due to OA, there is no significant difference in sensitivity between sub-regional analysis and full-thickness analysis.

Keywords: dGEMRIC; Contrast agent; Sub-regional analysis; Knee; Osteoarthritis

Introduction

Spin-lattice relaxation time (T_1) of articular cartilage after contrast administration of Gd-DTPA^{2-} (T_{1Gd}) has been commonly used as a dGEMRIC index to determine relative glycosaminoglycan (GAG) level within articular cartilage [1-3]. It has been argued that tracking ΔR_1, i.e. the change in relaxation rate ($R_1 = 1/T_1$) before (R_{1pre}) and after Gd-DTPA^{2-} administration (R_{1post}), is necessary [4]. A previous report showed that T_{1Gd} and ΔR_1 were similarly effective in differentiating knees with osteoarthritis (OA) from the healthy [5]. To-date, quantification of T_{1Gd} and ΔR_1 has been based on the analysis of regions of interest (ROIs) covering full thickness of cartilage.

It has been reported that the GAG concentration profile in canine articular cartilage was tissue depth dependent [6]. Degeneration of cartilage in aging and osteoarthritis generally progresses from the surface of the cartilage [7]. A recent report on asymptomatic subjects [8] suggested that when performing an analysis of the knee based on the depth of the cartilage, the superficial layer of articular cartilage showed longer T_{1pre}, shorter T_{1Gd}, and hence larger ΔR_1 compared to the deep layer. These reports then put forward a practically interesting question: would dGEMRIC analysis be more sensitive if sub-regional ROI of cartilage, instead of full thickness of ROI, was used to quantify the biomarkers for assessing health status of articular cartilage?

In this study, we reanalyzed a dGEMRIC data set [5] of the knee with sub-regional analysis, i.e. using two ROIs representing superficial region and deep region of the cartilage respectively, in addition to full-thickness ROI. The effectiveness across the three analysis methods: superficial region analysis, full-thickness analysis, and deep region analysis, was compared. Since the ROIs we used did not exactly represent any single anatomical layer, we used the word "region" instead of "layer" in this study to avoid misunderstanding.

Methods

Subjects

We performed a retrospective review of knee dGEMRIC datasets of eighteen patients with OA and fourteen asymptomatic subjects. One knee was imaged for each case. Of the eighteen patients, five patients were excluded from the study due to limited cartilage available in which no more than one ROI could be accommodated. The rest thirteen patients (diseased group, 5 males, average age of 60.8 ± 13.0 years) and the fourteen asymptomatic subjects (control group, 5 males, average age of 29.2 ± 7.4 years) were reanalyzed using ROIs covering superficial region and deep region of cartilage respectively, in addition to full-thickness coverage. OA was diagnosed by clinicians based on clinical symptoms only (n=4), or symptoms along with X-rays (n=8), or symptoms along with MR imaging (n=1). For asymptomatic subjects, there was no symptom with the knee and no history of documented knee disease or injury. The study was conducted in compliance with the

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regulations of the institutional review board and informed consent was obtained from each subject.

Image acquisition

All subjects were imaged before and 90 min after double-dose Gd-DTPA^{2-} (0.2 mmol/kg) administration on a 1.5 Tesla MR scanner (GE Healthcare, Waukesha, WI) with a transmit/receive extremity coil. A two-dimensional inversion recovery fast spin-echo (2D IR-FSE) sequence was used for all exams, except for nine pre-contrast exams (control = 5; diseased = 4) in which a three dimensional Look-Locker (3D LL) sequence was applied. The 3D LL technique was shown to provide accurate T_1 estimates compared to 2D IR-FSE method [9,10]. The 2D IR-FSE scans in single slice were positioned sagittally going through the medial femoral condyle. The nine pre-contrast 3D LL scans were positioned sagittally covering whole joint, but only the slice through femoral medial condyle, which was matched with the position of post-contrast 2D IR-FSE image, was used for analysis. Imaging parameters relevant to spatial resolution were: slice thickness = 3 mm, field of view = 160 mm, Matrix was 384^2 (in plane resolution = 417μm, interpolated to 512^2) for post-contrast imaging, and was 256^2 (in-plane resolution =625μm, interpolated to 512^2) for pre-contrast imaging. Other imaging parameters can be referred to our previous study [5].

T_1 mapping and data analysis

T_1 maps of the medial femoral cartilage were generated using a custom software analysis package (MRIMapper, copyright Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology, 2006) written in MATLAB (The Mathworks; Natick, MA). ROIs were segmented at superficial region, deep region, and full thickness of the medial femoral cartilage respectively to obtain T_1 values of pre- (T_{1pre}) and post-Gd-DTPA^{2-} administration (T_{1Gd}). For better representing the health status of the cartilage, in sub-regional analyses we applied relatively thicker (particular thickness in each case depended on the cartilage available) and larger (covering the weight-bearing area as much as possible) compared to previous report [8]. For control group, the sizes of ROI (in number of pixels) were 129 ± 31, 162 ± 37, 538 ± 113 in pre-contrast images, and 135 ± 37, 154 ± 46, 570 ± 164 in post contrast images, in the order of superficial region, deep region, and full thickness respectively. For diseased group, the corresponding numbers were 85 ± 41, 119 ± 45, 385 ± 170 in pre-contrast images, and 88 ± 34, 121 ± 36, 341 ± 162 in post contrast images. The attention was paid to avoid partial volume effect with adjacent tissues and to make superficial and deep regions parallel to each other as much as possible (Figure 1). The average T_1 value of all pixels within the ROI was used. The change in relaxation rate (ΔR_1) between post- and pre-contrast administration was calculated as $1/T_{1Gd} - 1/T_{1pre}$.

The two tailed t-test was used for statistical analysis. A mixed-effects regression analysis was performed to assess whether the sensitivity varied across the three analyses methods. Unstructured variance-covariance was used to adjust within-subject correlation. A logistic regression was also applied to generate areas under the curves (AUC) of Receiver Operating Characteristic, with corresponding optimal threshold values (best-cut) for separation of the diseased and the control [11].

Results

Table 1 lists the values of T_{1pre}, T_{1Gd}, and ΔR_1 of the medial femoral cartilage obtained with the three analysis methods for each subject. The difference between superficial region and deep region in T_{1pre}, and T_{1Gd} could usually be visualized on T_1 maps (Figure 2). Compared to control group, diseased group always showed statistically significant shorter T_{1Gd} and higher ΔR_1, irrespective of which analysis method was used.

Table 2 and Figure 3 summarized the comparison results across the three analysis methods. Superficial region analysis always provided shortest T_{1Gd} and highest ΔR_1 in both the diseased and the control, which was followed by full-thickness analysis and then deep region analysis (Figure 3a, b), but the differences between the diseased and the control (diseased-control difference) were quite close in the three analysis methods. With T_{1Gd}, average values of diseased-control difference (T_{1Gd} of the control - T_{1Gd} of the diseased) were 123, 126, and 129 ms for superficial region, full-thickness, and deep region analyses respectively. The three variation lines were almost parallel to each other (Table 2 and Figure 3c). With ΔR_1, the corresponding diseased-control differences ($\Delta R_1$of the diseased - ΔR_1 of the control) were 0.97, 0.79, and $0.69 s^{-1}$, and variation line of superficial analysis was slightly steeper compared to other two lines (Table 2 and Figure 3d). Standard deviations with ΔR_1 were much larger compared to T_{1Gd} (Table 1 and Figure 3a, b). In both T_{1Gd} and ΔR_1, superficial region analysis showed slightly higher AUC, followed by full-thickness analysis and then deep region analysis. But all three AUCs are larger than 0.8 or 0.9, indicating excellent or distinguished discrimination [11]. The optimal threshold values are different with the three methods. Mixed-effects regression analysis demonstrated that there were no significant differences across the three analysis methods in differentiation of the diseased from the control (Table 2).

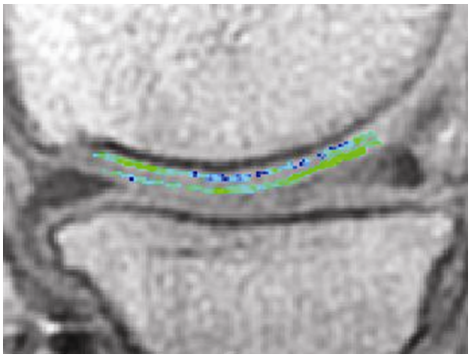

Figure 1: ROI segmentation at deep and superficial regions on medial femoral cartilage.

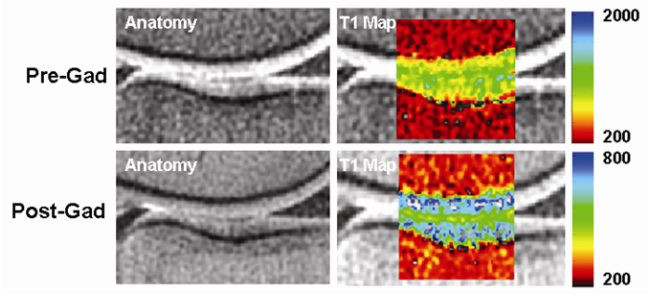

Figure 2: Demonstration of T_1 differences between deep and superficial regions before and after Gd-DTPA^{2-} administration in a healthy subject. Note that in the overlaid T_1 map before contrast administration (Pre-Gad), T_1-superficial is higher than T_1-deep; whereas in T_1 map after contrast administration (Post-Gad), T_1-superficial is lower than T_1-deep

Table 1: T1pre, T1Gd and ΔR1 of femoral cartilage measured with the three analysis methods.

	T_1 pre (ms)			T_{1Gd} (ms)			ΔR_1 (s^{-1})		
Case No.	**Full**	**Super**	**Deep**	**Full**	**Super**	**Deep**	**Full**	**Super**	**Deep**
Diseased group									
1	935	979	908	349	284	368	1.80	2.50	1.62
2	990	929	1090	259	238	287	2.85	3.13	2.57
3	909	912	821	460	373	510	1.07	1.58	0.74
4	967	930	1103	385	364	447	1.56	1.67	1.33
5	963	959	970	490	402	488	1.00	1.44	1.02
6	1003	1012	1027	374	313	414	1.68	2.21	1.44
7	1144	1266	979	255	242	317	3.05	3.34	2.13
8	886	1002	891	404	373	398	1.35	1.68	1.39
9	1450	1725	1173	535	528	567	1.18	1.31	0.91
10	964	1073	816	400	375	459	1.46	1.73	0.95
11	965	1041	869	330	217	465	1.99	3.65	1.00
12	838	896	693	423	279	530	1.17	2.47	0.44
13	893	928	793	425	367	483	1.23	1.65	0.81
Average	**993**	**1050**	**933**	**391**	**335**	**441**	**1.65**	**2.18**	**1.26**
SD (in%)	**156 (16)**	**225 (21)**	**139 (15)**	**81 (21)**	**85 (25)**	**82 (19)**	**0.65 (39)**	**0.78 (36)**	**0.59 (47)**
Control group									
1	925	1017	778	608	499	685	0.56	1.02	0.17
2	949	1030	866	648	632	687	0.49	0.61	0.30
3	894	895	842	540	454	582	0.73	1.09	0.53
4	907	942	841	517	439	580	0.83	1.22	0.54
5	996	1132	859	363	327	357	1.75	2.17	1.64
6	852	848	865	476	419	592	0.93	1.21	0.53
7	901	965	809	524	451	637	0.80	1.18	0.33
8	810	885	720	479	408	499	0.85	1.32	0.62
9	851	921	761	516	496	532	0.76	0.93	0.57
10	883	982	708	518	446	586	0.80	1.22	0.29
11	859	974	764	487	436	549	0.89	1.27	0.51
12	977	1059	865	527	451	585	0.87	1.27	0.55
13	937	1047	876	587	530	617	0.64	0.93	0.48
14	922	1087	844	454	418	487	1.12	1.47	0.87
Average	**905**	**985**	**814**	**517**	**458**	**570**	**0.86**	**1.21**	**0.57**
SD (in%)	**52(6)**	**82(8)**	**57(7)**	**69(13)**	**69(15)**	**85(15)**	**0.30(35)**	**0.35(29)**	**0.35(62)**
P - Diseased vs Control	**>0.05**	**>0.05**	**<0.05**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.01**

* With t-test; Full: full-thickness analysis; Super: superficial region analysis; Deep: deep region analysis

Table 2: The comparison of the three analysis methods.

	with T_{1Gd} (ms)			with ΔR_1 (s^{-1})		
	Super	**Full**	**Deep**	**Super**	**Full**	**Deep**
D-C Difference	123	126	129	0.97	0.79	0.69
D-C best-cut	402	460	530	1.45	0.96	0.74
AUC	90%	87%	89%	95%	94%	88%
***P—Value**	0.802	0.853		0.328	0.092	

Full: full-thickness analysis; **Super:** superficial region analysis; **Deep:** deep region analysis;
D-C Difference: Difference between the diseased and the control; **D-C best-cut:** the best threshold for separation of the diseased and the control; **AUC:** areas under ROC curve;
* with mixed-effects regression analysis

Discussion

The anatomical feature of the depth wise variation of articular cartilage is well known. Native articular cartilage is composed of an extensive extracellular matrix synthesized by chondrocytes. It contains different zones with respect to depth from the articular surface and has a regional organization around the chondrocytes. Its composition varies regionally and zonally in its collagen and proteoglycan contents, and those of other matrix molecules [12]. GAG concentration profile has been reported to vary approximately linearly as a function of the tissue depth in canine articular cartilage [6]. A number of studies have

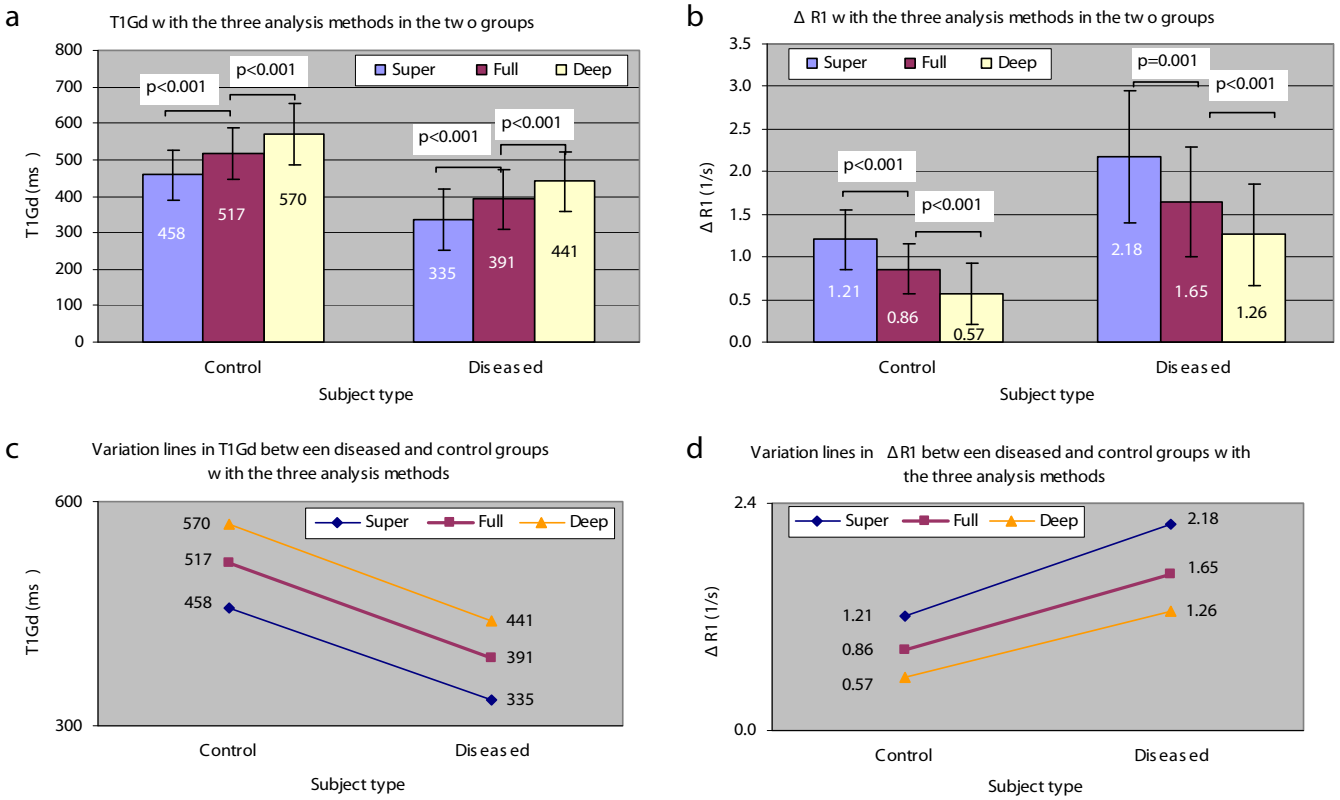

Figure 3: (a) and (b) show the average T_{1Gd} and ΔR_1 of the two groups obtained with the three analysis methods: superficial region analysis provides significantly shortest T_{1Gd} and highest ΔR_1 in both the diseased and the control, followed by full-thickness analysis and deep region analysis; much larger standard deviations were observed with ΔR_1 compared with T_{1Gd}. (c) and (d) demonstrate the variation lines (line connecting the two average values of diseased and control groups) of the three analysis methods. With T_{1Gd} the three lines are almost parallel to each other, indicating the three analysis methods are almost equally effective. With ΔR_1, the line of superficial analysis is just slightly steeper compared to other two lines, but no significant difference was observed because of higher standard deviation.

investigated the spatial distribution of T_2 and $T_{1\rho}$ in articular cartilage [13,14]. A study on asymptomatic subjects has demonstrated the difference between superficial layer and deep layer in T_{1pre}, T_{1Gd}, and ΔR_1 of articular cartilage [8]. But, to our best knowledge, using sub-regional analysis for dGEMRIC for OA and asymptomatic subjects has not been published.

In this study, the variations between superficial region and deep region in T_{1pre} and T_{1Gd} could usually be visualized on the T_1 maps, which was consistent with previous report [8]. The variation in T_{1pre} may reflect the differences in molecular structure and composition between regions. The T_{1Gd} disparity between regions may indicate additional differences in GAG level and other factors, such as transport of contrast to respective regions [8,15].

We had expected that using superficial region analysis, instead of full-thickness analysis, might have advantage for dGEMRIC to get better sensitivity. Because of the depth wise variation of articular cartilage and that the degeneration of cartilage in aging and osteoarthritis generally starts from the surface of the cartilage [7], superficial region analysis could show shorter T_{1Gd} in diseased cartilage compared to full thickness analysis, and hence lead to larger diseased-control differences in both T_{1Gd} and ΔR_1. However, our data did not show obvious increase in diseased-control difference with sub-regional analyses in either T_{1Gd} or ΔR_1 compared to full-thickness analysis. Even though superficial region analysis showed slightly higher AUC values compared to full-thickness analysis, no significant difference in sensitivity across the three analysis methods was observed with either T_{1Gd} or ΔR_1, as shown in Table 2.

It is possible that the negative result observed in this study may be related to the reduced cartilage thickness in subjects with OA. A limitation of the study is lack of staging information on OA patients. However, our recent experience suggests that even OA subjects with grade of KL-2 could exhibit full thickness cartilage loss [16]. It is also interesting that the recent report in healthy subjects [8] shows the medial cartilage thickness to be variable from 1-4 pixel wide. The pathologic changes in these cases could exist not only in superficial region of the cartilage, but also in deeper or even the full thickness of the cartilage. Larger pathologic area involved would lead to less difference between superficial region and deep region. As a result, the diseased-control differences of T_{1Gd} with the three analysis methods were almost identical (123 ms, 126 ms, and 129 ms for superficial region, full-thickness, and deep region analyses respectively). Although the diseased-control difference of ΔR_1, which was influenced by both T_{1Gd} and T_{1pre}, was slightly higher with superficial region analysis ($0.97 s^{-1}$) compared to full thickness analysis, it did not reach statistical significance probably due to the large variance associated. This result suggests that for subjects with reduced cartilage thickness, sub-regional analysis has comparable sensitivity in either T_{1Gd} or ΔR_1 compared to full-thickness analysis. It should be noted that the best-cuts (thresholds) were quite different when using different analysis methods, as shown in Table 2.

The ROIs' size, range and location and in-plane resolution could also affect the result of dGEMRIC. The result presented here was based on our relatively thicker and wider ROIs, under the in-plane resolution similar to the in-plane resolution commonly suggested for dGEMRIC [17]. In the previous study, which was to investigate the transport of Gd-DTPA^{2-} in different layers [8], the authors applied one-pixel thickness ROIs and confined the ROIs to a specific area. In this study we used relatively thicker and wider ROIs to better reflect the health status of cartilage as a whole.

The major limitations of this study are that the number of subjects was small and lack of early stage of OA included. A study with larger subject number including enough patients with early stage of OA is warranted, which may show different trends compared to the present study.

In summary, the depth wise variations in T_{1pre} and T_{1Gd} were clearly observed in both diseased and control group. For analyzing dGEMRIC of knee articular cartilage in OA subjects with reduced cartilage thickness, there was no significant difference in sensitivity between sub-regional analysis and full-thickness analysis.

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