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Research Progress of Quantitative Magnetic Resonance Imaging in Articular Cartilage

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Abstract

Clinically, articular cartilage damage is a common disease. Its occurrence and development can be caused by factors such as trauma, osteoarthritis (OA), and osteochondritis dissecans. Once this damage occurs, it is difficult to repair. Articular cartilage damage is mainly manifested as joint pain and dysfunction. In the elderly and people who exercise vigorously for a long time, the degeneration and damage of articular cartilage occur to varying degrees. Arthroscopy is considered to be the gold standard for diagnosing articular cartilage diseases. However, it is an invasive examination, which requires a high level of technology for the examiner, and cannot have a thorough understanding of the internal condition of the cartilage. Quantitative magnetic resonance imaging (qMRI) can not only display cartilage morphological changes, but also quantitatively evaluate the biochemical components of cartilage. It has the advantages of non-invasive, good soft tissue resolution, multi-parameter, and multi-plane imaging. It can sensitively monitor the microscopic changes of cartilage with non-invasive quantitative measurements and provide reliable and repeatable imaging biomarkers.

Keywords

Quantitative Magnetic Resonance Imaging, Articular Cartilage Damage, Non-Invasive, Biomarker

定量磁共振成像在关节软骨中的应用研究进展

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摘　要

在临床上，关节软骨损伤是一种常见病，其发生发展可由外伤、骨性关节炎(osteoarthritis, OA)以及剥脱性骨软骨炎等原因造成，而且这种损坏发生后很难修复。关节软骨损伤主要表现为关节疼痛及功能障碍，关节软骨的损伤以及退变都不同程度地发生在老年人及长期剧烈运动的人群中。关节镜检查被认为是诊断关节软骨病变的金标准。但由于其有创检查的性质，对检查者的技术水平要求很高，且无法深入了解软骨的内部情况。定量磁共振成像(quantitative magnetic resonance imaging, qMRI)既可显示软骨形态学变化，又可以定量评估软骨的生化成分，由于该技术具有无创、良好的软组织分辨力、多参数、多平面成像的优势，它能以非侵入性的定量测量来敏感地监测软骨的微细变化，提供可靠和可重复的成像生物标志物。

关键词

定量磁共振成像，关节软骨损伤，无创，生物标志物

1. 引言

近年来，随着影像学事业的快速发展，产生了诸多能够对软骨的生化成分进行定量分析的新兴技术[1]，其中，在最近影响最大的是：定量磁共振成像(quantitative magnetic resonance imaging, qMRI)技术，它既具备传统磁共振能够显示软骨形态学变化的优点，又能够创新性地定量评价软骨的生化组成变化。它能够以非侵入性的定量测量方式来监测软骨的微细变化，而且敏感性很高，因此它可以提供既可靠又可重复的成像生物标志物[2] [3]，近年来凭借着这些优势越来越受到临床医生的重视。

2. 关节软骨的生理学特征

ECM 主要由 80%的水和 20%的胶原蛋白及聚蛋白多糖(proteoglycan, PG)组成[4] [5]。关节软骨是一个充满水的分子网格，网格内富含胶原蛋白及 PG。该网格作为软骨组织的结构框架，在正常时排列有序从而限制形态上可变的软骨结构进行横向扩展，起到承载拉力以及剪力的作用[6]。关节软骨的主要作用是保持关节面湿润，从而使关节润滑，减少了剧烈运动过程中对骨性关节面的磨损，因此在保护骨性关节面上起到了巨大的作用。由于软骨内没有血管走形，因此软骨细胞只能以基质的扩散作用从软骨膜血管获取营养；而且软骨内也没有分布神经和淋巴管，因此软骨一旦损伤便难以再生[7]。

3. 软骨形态学的定量评估

现阶段来说，用于对软骨进行量化的定量磁共振序列主要还是 3.0T 的 T_1 加权稳态扰相梯度回波采集序列(spoiled gradient recalled acquisition in steady-state, SPGR)以及小反转角激励(fast low angle shot, FLASH)。二者的优势体现在诊断效率上，它们在目前使用的定量磁共振机上几乎是随时可以使用的，因此不需要额外的软件干预，这对于操作技术人员来说无疑提供了巨大的方便，且对于临床医生来说大大提高了诊断效率。

3.1. 软骨体积

因软骨组织的三维结构体特性，qMRI 可高精确、可重复的测量膝关节软骨体积，现阶段得到的软骨体积数值较可靠。有文献报导，3.0T 磁共振成像的随机误差约为 2.5%~3.2% [8] [9]。与 X 线检查相比，MRI 可在其显示关节间隙变窄之前敏感地检测到软骨体积损失的变化，相关文献报导其数值大概为 11%~13% [10]。此外还需要有一定技术水平的技术人员运用专业的软件来对大量的图像进行重建、分割，才能更精确地测量软骨体积。

3.2. 软骨厚度

实际操作过程中，软骨厚度测量较软骨体积测量会节省大量时间，临床实验证明：在评估软骨损失和测量软骨体积方面，1.5T 系统相比于 3.0T 成像系统具有几乎相同的敏感性，其统计学结果显示无明显差异[11]。由于自然老化，正常的软骨厚度也会以每年 0.3%~0.5%的速度减少[12]。一项超过 12 个月的研究报导显示，对于那些在影像资料上已发生改变的膝关节骨关节炎患者，股骨内侧髁中央软骨的厚度若减少至 54 μm，则患者将会遭受经常性的疼痛[13]。

3.3. 软骨形态与危险因素

形态学 qMRI 研究表明肥胖是影响软骨病变的独立危险因素，体重的增加将会导致更严重的软骨退变。适度的体育锻炼有利于软骨量增加和骨关节炎发病率的降低，但长期剧烈运动将可使软骨容积减少[14]。除去最主要的危险因素肥胖，软骨形态学定量测量研究还显示，软骨量的减少与软骨下骨髓病变、半月板撕裂与挤压、维生素 D 缺乏、膝关节对位不齐以及吸烟等都有关。

4. 软骨生化成分的定量评估

现阶段，用于定量评估软骨生化成分的 MR 技术主要包括：$T_1\rho$、T_2 mapping、DWI、dGEMRIC、^{23}Na-MRI、gagCEST 等成像技术[1] [15] [16] [17] [18]。

4.1. $T_1\rho$

MRI 旋转框架内自旋晶格弛豫(the spin-lattice relaxation in the rotating frame, $T_1\rho$)成像技术是最近几年来发展迅速的新兴技术，它的应用原理是能够感受作为关节软骨的主要成分的水中的氢原子和大分子物质间的微弱流动，因此可以间接反映软骨基质蛋白多糖(PG)的含量变化[19]。Bolbos 等[20]采用 $T_1\rho$ 技术定量评估了软骨基质中 PG 的含量变化后得出结论：$T_1\rho$ 磁共振成像技术可在 OA 早期观察到关节软骨基质中 PG 的损失[21]。$T_1\rho$ 值会随着年龄的变化而变化，有研究者通过动物实验组织学验证了这与 PG 的丢失有相关性[22]。通过软骨组织的切片番红 O 染色可以发现，软骨成分越少，$T_1\rho$ 值则越高。Regatte 等[23]研究表明 $T_1\rho$ 成像还可敏感地检测到牛软骨基质中 PG 的丢失，并对其进行量化。由于其对 PG 含量敏感，无需高磁场等优势，$T_1\rho$ 成像成为 dGEMRIC 的一种替代方法[24] [25]。

4.2. T_2 Mapping

获得 T_2 图的过程可通过定量磁共振机中的 T_2 mapping 序列，T_2 指的是磁共振扫描时横向磁化弛豫衰减至 37%最大信号强度时所需要的时间，当我们应用 T_2 mapping 序列进行扫描时，便可以得到相关量化后的指标。因为 T_2 值与水的含量以及胶原蛋白的含量、排列方向相关，所以 Domayer 等认为 T_2 图可反映出与软骨胶原成分变化相关的信息[26]。而且有相关文献表明，T_2 值与关节软骨组织学退变中应用最广的 Mankin 评分系统也有统计学意义上的相关性[27]。目前，T_2 值可作为研究软骨生化结构的影像学标

志[28] [29] [30]，因为它对软骨胶原生化成分的改变有着很高的敏感性，这也使得 T_2 mapping 成为现阶段一种极具潜力的检测软骨的技术。但是当 T_2 图中的胶原蛋白的排列方向与基线(B0)成 55˚角时，将使得 T_2 值增加[31]，这也就是我们常说的“魔角效应”，这严重影响了关节软骨诊断的精确性，使 T_2 mapping 序列的发展受到了限制。

4.3. DWI

关节软骨中有高达 80%的水含量，DWI 可根据软骨内各组分水含量不同而呈现出不同的扩散特性。[32] [33] [34]。

4.4. dGEMRIC

1996 年初，有关于软骨延迟动态成像技术(delayed gadolinium-enhanced MRI of cartilage, dGEMRIC)的相关报导首次出现在人们的视野中[35]。自那以后，该序列在临床上的应用也越来越多。钆喷酸葡胺(gadolinium-diethylenetriaminepentaacetic acid, Gd-DTPA)作为一种影像学对比剂，在该序列中的应用主要是以日常所用的双倍剂量经静脉注射，使得其在磁共振扫描时能够多次反转并反馈给恢复序列，从而采集并建立与软骨相关的 T_1 图曲线，测定 T_1 值，进而对软骨的生化成分进行定量测量。有很多研究证明了 T_1 在关节软骨病变的检测中具有很大的优势[36] [37] [38]，但应用该序列时需要向患者体内注射对比剂，且对比剂渗透时间很长，这就使得在操控时易产生误差，这也是导致该技术后来在临床中的应用并不普及的主要原因。

4.5. ^{23}Na-MRI

^{23}Na 谱成像最早见于 1988 年，这是一种用来评估关节软骨中蛋白多糖含量变化的非侵入性技术[39]。因为在关节软骨的退变过程中蛋白的丢失会释放大量的钠离子，故其主要成像原理是通过钠离子在关节软骨中的分布差异来显示蛋白多糖含量减少的区域，经磁共振波谱成像对健康软骨和病变软骨中的钠离子进行定量测量，对比其分布情况，通过蛋白多糖的含量变化检测软骨病变程度[40] [41]。Newbould 等[42]通过研究证明：^{23}Na-MRI 在 3.0 T 磁共振成像系统中具有可重复性。但由于 ^{23}Na-MRI 多为高场强，需要特殊的发射接收线圈和软件来进行后期处理，所以在临床应用中受到了极大的限制。

4.6. gagCEST

近年来，一种基于磁化转移技术以及化学交换理论的新型成像技术：GAG 化学交换饱和转移(glycosaminoglycan chemical exchange saturation transfer, gagCEST)成像技术逐渐出现在人们的视野中。在此技术中，位于 GAGs 酰胺和羟基上的非共振质子被 RF 脉冲饱和，然后这些质子产生相互作用，并且通过化学交换转移至周围的水分子当中，进而在周围水的输出图像中产生对比度。相比较 dGEMRIC 而言，gag CEST 技术不需要注射外源性对比剂，被认为是测量周围水中与 GAG 含量相关的质子含量的非侵入性生物标记物[16] [43] [44] [45]。Brinkhof 等[15]发现与健侧踝突的健康软骨相比较，受损软骨组织中的 GAG 含量有显著的差异。但 Singh 等[17]在其研究中发现，gag CEST 可能在 3.0T 磁场下无法准确定量病变或者健康的软骨组织中的 GAG 含量，所以目前在临床中的使用也受到了限制。

5. 小结

大量研究证明了 qMRI 技术是现阶段临床最佳的无创检查手段，但由于不同地域所使用的仪器不尽相同，各级技术人员也存在着水平的差异，如何优化序列选择以及诊断标准的确立的问题亟待解决。总而言之，qMRI 联合生物标记物对于早期诊断关节软骨损失及评估术后软骨修复情况等方面有着良好的应

用前景。

参考文献

[1] Bruno, F., Arrigoni, F., Palumbo, P., *et al*. (2019) New Advances in MRI Diagnosis of Degenerative Osteoarthropathy of the Peripheral Joints. *La Radiologia Medica*, **124**, 1121-1127. https://doi.org/10.1007/s11547-019-01003-1

[2] Guermazi, A., Roemer, F.W., Alizai, H., *et al*. (2015) State of the Art: MR Imaging after Knee Cartilage Repair Surgery. *Radiology*, **277**, 23-43. https://doi.org/10.1148/radiol.2015141146

[3] Link, T.M., Neumann, J. and Li, X. (2017) Prestructural Cartilage Assessment Using MRI. *Journal of Magnetic Resonance Imaging*, **45**, 949-965. https://doi.org/10.1002/jmri.25554

[4] Mansour, J.M. (2003) Biomechanics of Cartilage, Kinesiology: The Mechanics and Pathomechanics of Human Movement. Lippincott Williams and Wilkins, Philadelphia, 66-79.

[5] Chaudhari, A.M., Briant, P.L., Bevill, S.L., Koo, S. and Andriacchi, T.P. (2008) Knee Kinematics, Cartilage Morphology, and Osteoarthritis after ACL Injury. *Medicine & Science in Sports & Exercise*, **40**, 215-222. https://doi.org/10.1249/mss.0b013e31815cbb0e

[6] Burstein, D., Gray, M., Mosher, T., *et al*. (2009) Measures of Molecular Composition and Structure in Osteoarthritis. *Radiologic Clinics of North America*, **47**, 675-686. https://doi.org/10.1016/j.rcl.2009.04.003

[7] Bay-Jensen, A.C., Hoegh-Madsen, S., Dam, E., *et al*. (2010) Which Elements Are Involved in Reversible and Irreversible Cartilage Degradation in Osteoarthritis? *Rheumatology International*, **30**, 435-442. https://doi.org/10.1007/s00296-009-1183-1

[8] Xing, W., Sheng, J., Chen, W.H., *et al*. (2011) Reproducibility and Accuracy of Quantitative Assessment of Articular Cartilage Volume Measurements with 3.0 Tesla Magnetic Resonance Imaging. *Chinese Medical Journal*, **124**, 1251-1256.

[9] Eckstein, F., Charles, H.C., Buck, R.J., *et al*. (2005) Accuracy and Precision of Quantitative Assessment of Cartilage Morphology by Magnetic Resonance Imaging at 3.0T. *Arthritis & Rheumatology*, **52**, 3132-3136. https://doi.org/10.1002/art.21348

[10] Jones, G., Ding, C., Scott, F., *et al*. (2004) Early Radiographic Osteoarthritis Is Associated with Substantial Changes in Cartilage Volume and Tibial Bone Surface Area in Both Males and Females. *Osteoarthritis Cartilage*, **12**, 169-174. https://doi.org/10.1016/j.joca.2003.08.010

[11] Kornaat, P.R., Reeder, S.B., Koo, S., *et al*. (2005) MR Imaging of Articular Cartilage at 1.5T and 3.0T: Comparison of SPGR and SSFP Sequences. *Osteoarthritis Cartilage*, **13**, 338-344. https://doi.org/10.1016/j.joca.2004.12.008

[12] Hudelmaier, M., Glaser, C., Hohe, J., *et al*. (2001) Age-Related Changes in the Morphology and Deformational Behavior of Knee Joint Cartilage. *Arthritis & Rheumatology*, **44**, 2556-2561. https://doi.org/10.1002/1529-0131(200111)44:11<2556::AID-ART436>3.0.CO;2-U

[13] Eckstein, F., Cotofana, S., Wirth, W., *et al*. (2011) Greater Rates of Cartilage Loss in Painful Knees than in Pain-Free Knees after Adjustment for Radiographic Disease Stage: Data from the Osteoarthritis Initiative. *Arthritis & Rheumatology*, **63**, 2257-2267. https://doi.org/10.1002/art.30414

[14] Roos, E.M. and Dahlberg, L. (2005) Positive Effects of Moderate Exercise on Glycosaminoglycan Cotent in Knee Cartilage: A Four-Month, Randomized, Controlled Trial in Patients at Risk of Osteoarthritis. *Arthritis & Rheumatology*, **52**, 3507-3514. https://doi.org/10.1002/art.21415

[15] Brinkhof, S., Nizak, R., Khlebnikov, V., *et al*. (2018) Detection of Early Cartilage Damage: Feasibility and Potential of gagCEST Imaging at 7 T. *European Radiology*, **28**, 2874-2881. https://doi.org/10.1007/s00330-017-5277-y

[16] Kogan, F., Hargreaves, B.A. and Gold, G.E. (2017) Volumetric Multislice gagCEST Imaging of Articular Cartilage: Optimization and Comparison with T1rho. *Magnetic Resonance in Medicine*, **77**, 1134-1141. https://doi.org/10.1002/mrm.26200

[17] Singh, A., Haris, M., Cai, K., *et al*. (2012) Chemical Exchange Saturation Transfer Magnetic Resonance Imaging of Human Knee Cartilage at 3T and 7T. *Magnetic Resonance in Medicine*, **68**, 588-594. https://doi.org/10.1002/mrm.23250

[18] Franklin, S.P., Stoker, A.M., Lin, A.S.P., *et al*. (2019) T1ρ, T2 Mapping, and EPIC-μCT Imaging in a Canine Model of Knee Osteochondral Injury. *Journal of Orthopaedic Research*, **38**, 368-377. https://doi.org/10.1002/jor.24450

[19] 李智慧. MRT1ρ 成像技术在关节软骨中的研究进展[J]. 国际医学放射学杂志, 2012, 35(6): 557-561.

[20] Bolbos, R.I., Ma, C.B., Link, T.M., *et al*. (2008) *In Vivo* T1ρ Quantitative Assessment of Knee Cartilage after Anterior Cruciate Ligament Injury Using 3 Tesla Magnetic Resonance Imaging. *Investigative Radiology*, **43**, 782-788. https://doi.org/10.1097/RLI.0b013e318184a451

[21] Tsushima, H., Okazaki, K., Takayama, Y., *et al*. (2012) Evaluation of Cartilage Degradation in Arthritis Using T1ρ Magnetic Resonance Imaging Mapping. *Rheumatology International*, **32**, 2867-2875. https://doi.org/10.1007/s00296-011-2140-3

[22] Fenty, M.C., Dodge, G.R., Kassey, V.B., *et al*. (2012) Quantitative Cartilage Degeneration Associated with Spontaneous Osteoarthritis in a Guinea Pig Model. *Journal of Magnetic Resonance Imaging*, **35**, 891-898. https://doi.org/10.1002/jmri.22867

[23] Regatte, R.R., Akella, S.V., Borthakur, A., *et al*. (2002) Proteoglycan Depletion-Induced Changes in Transverse Relaxation Maps of Cartilage: Comparison of T2 and T1rho. *Academic Radiology*, **9**, 1388-1394. https://doi.org/10.1016/S1076-6332(03)80666-9

[24] Witschey, W.R., Borthakur, A., Fenty, M., *et al*. (2010) T1rho MRI Quantification of Arthroscopically Confirmed Cartilage Degeneration. *Magnetic Resonance in Medicine*, **63**, 1376-1382. https://doi.org/10.1002/mrm.22272

[25] Wang, Y., Wluka, A.E., Jones, G., *et al*. (2012) Use Magnetic Resonance Imaging to Assess Articular Cartilage. *Therapeutic Advances in Musculoskeletal Disease*, **4**, 77-97. https://doi.org/10.1177/1759720X11431005

[26] Domayer, S.E., Kutscha-Lissberg, F., Welsch, G., *et al*. (2008) T2 Mapping in the Knee after Microfracture at 3.0T: Correlation of Global T2 Values and Clinical Outcome-Preliminary Results. *Osteoarthritis Cartilage*, **16**, 903-908. https://doi.org/10.1016/j.joca.2007.11.014

[27] Bittersohl, B., Miese, F.R., Hosalkar, H.S., *et al*. (2012) T2* Mapping of Hip Joint Cartilage in Various Histological Grades of Degeneration. *Osteoarthritis Cartilage*, **20**, 653-660. https://doi.org/10.1016/j.joca.2012.03.011

[28] Mosher, T.J., Smith, H.E., Collins, C., *et al*. (2005) Change in Knee Cartilage T2 at MR Imaging after Running: A Feasibility Study. *Radiology*, **234**, 245-249. https://doi.org/10.1148/radiol.2341040041

[29] Dunn, T.C., Lu, Y., Jin, H., *et al*. (2004) T2 Relaxation Time of Cartilage at MR Imaging: Comparison with Severity of Knee Osteoarthritis. *Radiology*, **232**, 592-598. https://doi.org/10.1148/radiol.2322030976

[30] Bolbos, R.I., Zuo, J., Banerjee, S., *et al*. () Relationship between Trabecular Bone Structure and Articular Cartilage Morphology and Relaxation Times in Early OA of the Knee Joint Using Parallel MRI at 3T. *Osteoarthritis Cartilage*, **16**, 1150-1159. https://doi.org/10.1016/j.joca.2008.02.018

[31] Moshe, T.J., Smith, H., Dardzinski, B.J., *et al*. (2001) MR Imaging and T2 Mapping of Femoral Cartilage: *In Vivo* Determination of the Magic Angle Effect. *AJR*, **177**, 665-669. https://doi.org/10.2214/ajr.177.3.1770665

[32] Mlynarik, V., Sulzbacher, I., Bittsanský, M., *et al*. (2003) Investigation of Apparent Diffusion Constant as an Indicator of Early Degenerative Disease in Articular Cartilage. *Journal of Magnetic Resonance Imaging*, **17**, 440-444. https://doi.org/10.1002/jmri.10276

[33] Mamisch, T.C., Menzel, M.I., Welsch, G.H., *et al*. (2008) Steady-State Diffusion Imaging for MR *In-Vivo* Evaluation of Reparative Cartilage after Matrix-Associated Autologous Chondrocyte Transplantation at 3 Tesla-Preliminary Results. *European Journal of Radiology*, **65**, 72-79. https://doi.org/10.1016/j.ejrad.2007.09.015

[34] 刘斯润, 朱天缘, 陈汉方, 等. MR 扩散加权成像诊断膝关节骨关节病髌骨软骨病变的价值[J]. 中华放射学杂志, 2006, 40(10): 1098-1101.

[35] Burstein, D. (2014) Delayed Gadolinium-Enhanced MRI of Cartilage. In: Kim, Y.J. and Mamisch, T.C., Eds., *Hip Magnetic Resonance Imaging*, Springer, New York, 33-41. https://doi.org/10.1007/978-1-4614-1668-5_3

[36] Sur, S., Mamisch, T.C., Hughes, T., *et al*. (2009) High Resolution Fast T1 Mapping Technique for dGEMRIC. *Journal of Magnetic Resonance Imaging*, **30**, 896-900. https://doi.org/10.1002/jmri.21869

[37] Zheng, S. and Xia, Y. (2010) The Impact of the Relaxivity Definition on the Quantitative Measurement of Glycosaminoglycans in Cartilage by the MRI dGEMRIC Method. *Magnetic Resonance in Medicine*, **63**, 25-32. https://doi.org/10.1002/mrm.22169

[38] Trattnig, S., Burstein, D., Szomolanyi, P., *et al*. (2009) T1(Gd) Gives Comparable Information as Delta T1 Relaxation Rate in dGEMRIC Evaluation of Cartilage Repair Tissue. *Investigative Radiology*, **44**, 598-602. https://doi.org/10.1097/RLI.0b013e3181b4c236

[39] 李五根, 龚洪翰. 膝关节软骨的 MRI 研究基础与进展[J]. 江西医学院学报, 2009, 49(12): 128-131.

[40] Shapiro, E.M., Borthakur, A., Gougoutas, A., *et al*. (2002) 23Na-MRI Accurately Measures Fixed Charge Density in Articular Cartilage. *Magnetic Resonance in Medicine*, **47**, 284-291. https://doi.org/10.1002/mrm.10054

[41] Wheaton, A.J., Casey, F.L., Gougoutas, A.J., *et al*. (2004) Correlation of T1rho with Fixed Charge Density in Cartilage. *Journal of Magnetic Resonance Imaging*, **20**, 519-525. https://doi.org/10.1002/jmri.20148

[42] Newbould, R.D., Miller, S.R., Tielbeek, J.A., *et al*. (2012) Reproducibility of Sodium MRI Measures of Articular Cartilage of the Knee in Osteoarthritis. *Osteoarthritis Cartilage*, **20**, 29-35. https://doi.org/10.1016/j.joca.2011.10.007

[43] Ling, W., Regatte, R.R., Navon, G., *et al*. (2008) Assessment of Glycosaminoglycan Concentration *in Vivo* by Chemi-

cal Exchange Dependent Saturation Transfer (gagCEST). *Proceedings of the National Academy of Sciences of the United States of America*, **105**, 2266-2270. https://doi.org/10.1073/pnas.0707666105

[44] Kogan, F., Hariharan, H. and Reddy, R. (2013) Chemical Exchange Saturation Transfer (CEST) Imaging: Description of Technique and Potential Clinical Applications. *Current Radiology Reports*, **1**, 102-114. https://doi.org/10.1007/s40134-013-0010-3

[45] Li, X. and Majumdar, S. (2013) Quantitative MRI of Articular Cartilage and Its Clinical Applications. *Journal of Magnetic Resonance Imaging*, **38**, 991-1008. https://doi.org/10.1002/jmri.24313