ULTRASHORT TIME-TO-ECHO MRI TO EVALUATE ENDPLATE CHANGES – A LITERATURE REVIEW

Laurila Kari-Pekka
Syventävien opintojen tutkielma
Lääketieteellinen tutkinto-ohjelma
Lääketieteellinen tiedekunta
Oulun yliopisto
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Ohjaaja: Osmo Tervonen

OULUN YLIOPISTO
Lääketieteellinen tiedekunta
Lääketieteen tutkinto-ohjelma

ABSTRACT

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Back pain is a major health concern in the world. Several causes for the pain origins are known but often the root of the problem remains unspecified. Magnetic resonance imaging has long been the standard technique of imaging the spine but the correlation between MRI findings and the causes of the pain often cannot be found. The interest has been rising for previously radiologically undetectable intervertebral disk structures that physiologically seems to have the capability to cause pain. One of them, cartilaginous endplate, a connection point between vertebral body and intervertebral disk is also a nutrition and innervation pathway for the intervertebral disk. Ultrashort time to echo MRI technique has been developed to image low T2 value tissues such as cartilaginous endplate.

This literature review found 16 articles focusing on ultrashort echo time MRI imaging of cartilaginous endplate. Some articles studied the possibility to detect endplate with ultrashort time to echo. Other studies found correlation between ultrashort echo time MRI findings on cartilaginous endplate and vertebral disk degeneration or back pain. One study formed an automated method for computer to detect endplate MRI findings and another one created a standardization method for them. All articles concluded that larger and more profound studies with larger sample size are required to find the final consensus and the clinical relevance on the matter.

Key words: endplate, intervertebral disk, back pain, MRI, ultrashort time to echo, UTE

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1. INTRODUCTION

Low back pain has been the leading cause of disability in the world. Many studies have shown that 70-85% of all people have back pain at some time in their life. According to studies prevalence of back pain ranges from 15% to 45% annually. In the UK low back pain has been the most common reason to be absent from work. Similar results have been in Sweden where 11-19% of all sick days has been with people diagnosed with back pain. Back pain can be divided into acute, sub-acute and chronic back pain. Acute back pain (<6 weeks) is considered as self-limiting with over 90% recovery rate. Subacute pain is defined as pain lasting between 6 and 12 weeks. In some cases (2-7%) people develop chronic back pain. Low back pain is as common for women and men. Commonly back pain occurs between ages 30 and 50. Overall prevalence increases until ages 60-65 and then declines. (Vos et al 2012, Andersson GBJ 1999, Deyo et al 2001, Hoy et al 2010)

Studies suggests that back pain can originate from several spinal structures, including ligaments, facet joints, vertebral periosteum, paravertebral musculature and fascia, annulus fibrosus, blood vessels and spinal nerve roots. In minority of cases (5-15%) the spesific cause for back pain such as osteoporotic fracture, spondylolisthesis, spinal stenosis, infection or neoplasm can be found. In the rest 85-95 % of cases the specific cause of back pain remains unspecified. It is a difficult task to diagnose back pain because of the complex structure of the spine supported by ligaments and muscles with moving parts that all can be the origin of pain. (Andersson GBJ 1999, Deyo et al 2001)

Lumbar disc degeneration is considered to be one of the underlying causes for low back pain. Intervertebral disk (IVD) is a fibro-cartilaginous structure consisting of three histologically distinct components. 1. The nucleus pulposus (NP): center of the disk consisting of proteoglycan and water held together by a network of collagen type II and elastin. Nucleus pulposus has three main functions: To withstand downward force of body weight, to serve as pivot point for spine movement and bind vertebral bodies together. Nucleus pulposus is not vascularized nor innervated. 2. The annulus fibrosus (AF): Surrounds the nucleus pulposus. Has much higher collagen content than nucleus pulposus. Its function is to contain the nucleus pulposus in pressure. Annulus fibrosus is also well innervated. 3. Endplate separates the nucleus pulposus and annulus fibrosus from vertebra bone. Endplate can be histologically separated to thinner (~0.1 mm) calcified endplate and thicker (~1 mm) cartilaginous endplate (CEP). Endplate functions are believed to serve as an attachment point

of IVD and vertebral body, offer support for AF and to serve as a nutrient pathway to center of intervertebral disk. (Vos et al 2012, Andersson GBJ 1999, Deyo et al 2001, Cheung & Al Ghazi 2008, Kenneth et al 2008, Dosik et al 2016)

As previously stated, low back pain can origin from multiple different anatomical areas and disk degeneration is considered only one of them. Disc degeneration is believed to occur when structural failure (disk prolapse, endplate damage, annulus tears, internal disc disruption) with disk components combines with aging signs (decrease in water content and disk height). Combination of these events can lead to fissuring or fragmentation of NP and AF which eventually can lead to disk herniation. For example a posterolateral herniation can cause nerve root impingement which is a known cause for typical ischiatic back pain radiating to legs and pelvis.

Prolapsed IVD and endplate Modic changes that are seen on conventional MRI imaging are assumed to be causes of disk degeneration and have shown a significant correlation with low back pain. Controversy for the relation between disk degeneration and back pain also exist because the same previous MRI findings can also be found from asymptomatic individuals. (Kenneth et al 2008, Samartzis et al 2015)

1.1 Role of endplate

Endplate plays an important role on IVD health. Normally blood vessels in IVD are restricted to outer layers of annulus fibrosus. The innermost IVD structure the nucleus pulposus is dependent on endplate and AF ability to transfer nutrients in and cell waste products out of nucleus pulposus by diffusion. Endplate also serves as a connector for vertebral bone and annulus fibrosus. It is thought that damage to endplate can begin a cascade of events that leads to disk degeneration and/or disk herniation. (Adams & Roughley 2006)

Pain sentient nociceptive nerves (mostly branches from sinuvertebral nerve) go through endplate and into 1-3mm of annulus fibrosus. Nerves do not usually reach nucleus pulposus in a healthy IVD. Previous pain provocation studies have shown that even a mild mechanical stimulation of annulus fibrosus and endplate can provoke a severe back pain. The role of endplate damage has gathered more interest lately. Previously human endplate damage could only be analyzed by histologically from surgically removed tissue samples or cadavers. New

methods of imaging tissues could give new possibilities to analyze the relevance of endplate. (Adams & Roughley 2006)

Mechanical endplate damage or endplate nutrient transport blocking has been shown to cause disk degeneration with animal models. The time between detectable endplate damage and disk degeneration varies from one week on mice to several years on humans. Endplate imaging has become a point of interest when we are trying to figure out the cause of disk degeneration, especially in its early phases. (Adams & Roughley 2006, Samartzis et al 2015)

1.2 Basics of MRI imaging

Magnetic resonance imaging (MRI) has become the standard imaging diagnostic tool for chronic back pain. With conventional MRI techniques the anatomy of lumbar spine can be evaluated. With variable parameters (repetition time, echo time, spin-lock time) T1-, T2-, and T1ρ-weighings can be achieved and many spinal structures can be observed, unlike images from standard x-ray film or computer tomography**.** T2-weighted MRI sequence shows a positive correlation (stronger signal/brighter image) with water content. Nucleus pulposus is full of water attracting proteoglycan and is shown bright in T2-weighted images. Degenerative disk is usually low of proteoglycan content and consequently low of water therefore is shown as darker in T2 MRI. Another commonly used MRI signs of disk degeneration are called Modic signs/changes. They are various vertebral bone changes seen in conventional MRI imaging. Studies have shown association between Modic changes and low back pain although there are also studies that show the contrary results. (Hwang et al 2016, Samartzis et al 2015)

Conventional MRI imaging uses mostly two types of techniques to acquire image. They are called T2- and T1-weighting. To understand the difference between these techniques one must understand a bit about the physics of magnetic resonance imaging. This is a simplified explanation of the technique. MRI uses protons' (mostly protons from H2O or hydrogen) tendency to react to external magnetic and electric fields. MRI machine first aligns those protons into the same spin and energy state via magnetic field. Then a radio frequency (RF) pulse is introduced to the protons and their spin and energy state changes. After turning off the RF pulse the protons return to their lowest (previous magnetized) energy-state and give up all their excess energy. We can then measure the released energy with a receiver and form an image. Proton precession into lower energy state is a three-dimensional event with three

axis(x, y, z). By measuring the z-axis decay-energy we get T1-weighted image (or longitudinal relaxation) and by measuring the x-y axis decay energy we get T2-weighted image. Different tissues have different T1- and T2 relaxation times. Proton interactions with the surrounding tissues affect the T1- and T2 relaxation times. We can then differentiate the tissues from each other by choosing the angle we measure (T1 or T2) and/or the time when we read the data or "take the image". For human tissues T2 relaxation time is always 5-10 times shorter than T1 relaxation time. (Hashemi et al 2018)

1.3 Why don't we see the endplate?

In layman's terms the more solid the tissue is the shorter its T2 values are. Althought tendons and ligaments are soft tissue, their biochemical composition and interaction with water makes their T2-relaxation times very short. Conventional MRI techniques are capable to acquire T2 image from tissues with time to echo (TE) values between 10-80ms. Lower T2 value tissues produce little to no signal to acquire image and therefore appears dark. For cartilage endplate the T2 value is approximately 2.9ms (2-4ms in some references) and therefore unable to be imaged with conventional MRI techniques. (Siriwanarangsun et al 2016)

A new imaging technique called ultrashort time to echo (UTE) has been developed to detect ultralow T2 value tissues. There are few known ways to perform this short T2 echo time reading. One method uses short radiofrequency (RF) pulses to destroy the long T2 components and only short T2 components are left. Another method is to combine both RF pulses and image subtraction techniques to acquire image. This review will not go deeper into the physics of UTE but it is key to know that UTE can detect T2 components as low as 0.1–0.008ms and therefore it is possible to use to image cartilaginous endplate. UTE MRI requires stronger field strength, at least 3tesla (T). Most medical MRI scanners use 1.5T field strength that is enough for conventional imaging but not enough for UTE technique. (Hall-Craggs et al 2003, Hwang et al 2016, Samartzis et al 2015)

2. MATERIALS AND METHODS

The goal of the literature review is to assess the current scientific literature and studies on imaging of spine cartilaginous endplate structure. The feasibility of using UTE imaging of the spine is also a point of interest in this review. Another interest is the clinical relevance of UTE disk signs and if UTE MRI imaging could be a new standard imaging method in the future for patients with low back pain.

Literature search was conducted via Ovid medline, Science direct, Spine journal and Google scholar using variations of following keywords: ultrashort time to echo, UTE, MRI and endplate.

Criteria for selecting studies for this review were the following: Magnetic resonance imaging on spine and/or cartilaginous endplate that includes ultrashort echo time sequencing. Both in vivo and ex vivo studies were included. All research done with animals and humans were included. Although this literature review is mostly focused on lower back pain all studies that uses UTE MRI to image any part of the spine were included.

Exclusion criteria were the following: conventional MRI imaging of spine (studies that does not include endplate or UTE-sequence), UTE sequence usage on other anatomical parts other than spine and lastly UTE imaging studies that did not include endplate were excluded.

2.1 Search results

Final article search was done 15.4.2021. Total of 90 articles were found. By further assessing abstracts and reading articles 69 were excluded. Five of those 21 remaining articles were about UTE imaging that did not include imaging of endplate or spine and so they also were excluded. Seven of the remaining 16 articles were clinical studies (including in vivo and ex vivo human studies), three were animal studies and six focused on theory, technique and physical aspect of UTE imaging. One article had used both human cadavers and in vivo patients.

3. ARTICLE ANALYSIS

Broadly analyzing the articles could be categorized into three groups:

1. Theory and review articles: These articles focused on theory side and practical aspects of using UTE MRI technique.

2. Animal studies: These articles used animals or animal cadavers in their studies in order to find correlation between UTE disk signs and disk degeneration/Modic changes.

3. Human studies: Human patients or cadavers were used. Some of these studies also attempted to find or form a clinical practice/grading system using UTE MRI.

This literature review will use this 3-group categorization. Next chapter further analyzes each article in these categories respectively.

3.1 Theory and review articles

3.1.1 UTE imaging in the musculoskeletal system (Chang et al 2014)

Chang et al published an article in 2014 where they reviewed and assessed the possibilities of UTE imaging. In the article they first profoundly go through imaging techniques of UTE as well as different image manipulation possibilities to acquire optimal image contrast. UTE image captures signals from short T2 and long T2 components and by subtracting the long T2 value image from UTE image we are left with only short T2 data. Other contrast enhancing methods the article suggests are preparation pulses, off-resonance saturation and phase difference usage. Quantitative imaging techniques are also presented. The article then discusses about different applications of UTE on musculoskeletal system; articular cartilage, bone, knee meniscus, temporomandibular join, tendons, ligaments and entheses and finally the intervertebral disk.

In the intervertebral disc-section they first go through the anatomical and molecular composition of IVD and CEP. Then the article discusses the imaging part of IVD and that UTE allow the visualization of structures that can not be seen in conventional techniques; annulus fibrosus, longitudinal ligaments, CEP (uncalcified and calcified).

Article concludes that the challenges of UTE for clinical uses are hardware limitations, software availability and validation studies (however studies are being made and so far have been encouraging). (Chang et al 2014)

Reviewer comments: This article is a summary of current data of UTE and its mainly focused on UTE technical aspect.

3.1.2 Novel diagnostic and prognostic methods for disc degeneration and low back pain (Samartzis et al 2015)

In 2015 Samartzis et al published large multinational article where they explore the current methods imaging spine of patients suffering lower back pain. First the article goes through why disc degeneration is thought to be one of the causes of LBP, how the disc is innervated and the pain mechanics in IVDs. Article go through epidemiological studies of LBP and emphasizes that most larger studies provide some evidence that LBP is associated with disk degeneration. It is further discussed in the article that it is currently difficult to apply this knowledge to single patients because disk degeneration is also found in asymptomatic patients. Modic I and Modic II changes are also discussed as potential MRI findings in discogenic pain, although controversy on this issue is also discussed.

Article discusses the usage of computer tomography for patients suffering from LBP and comments that CT fails to demonstrate the cause of back pain unless a significant spinal nerve root compression is observed. Limitations of conventional MRI with early disc degeneration is addressed.

Article then goes through four different MRI imaging techniques that could be used to image discovertebral complex; T1ρ MRI, chemical exchange saturation transfer (CEST) MRI, sodium MRI and ultrashort time to echo (UTE) MRI. Only UTE is mentioned to be able to differentiate endplate from adjacent structures. (Samartzis et al 2015)

3.1.3 Conventional and ultrashort MRI of articular cartilage, meniscus and intervertebral disc (Bae et al 2010)

Bae et al published a review article in 2010 where they discussed UTE MRI technique and its usage in different musculoskeletal structures; articular cartilage of human knee, knee meniscus and intervertebral disc. Article briefly goes through the techniques of UTE imaging

and different quantitative techniques are introduced; UTE T2, UTE T1rho, bi-component UTE.

UTE imaging of IVDs: Article points out that at that time AF and CEP had not been evaluated enough with conventional MRI imaging mainly because of short T2 times of those tissues. Short gradient echo-technique is discussed as a potential technique but weaker resolution and increased slice thickness are the downsides. This technique is suggested for imaging AF. Article discusses that UTE MRI technique is used to image shorter TE times than AF and that CEP is fully visible with this technique. An image of UTE MRI of the IVD is also provided in the article. (Bae et al 2010)

3.1.4 Ultrashort time to echo magnetic resonance techniques for the musculoskeletal system (Siriwanarangsun et al 2016)

In 2016 Siriwanarangsun et al published a review article about current advancements of UTE MRI. Main anatomical focus areas are the IVD, meniscus and cortical bone. In the beginning the articular cartilage layers are discussed as well as their importance and function. Short T2 time for calcified cartilage tissue is mentioned as a challenge for imaging with conventional MRI techniques. Article refers to other studies to point out that UTE T2 MRI could be useful for CEP imaging.

Article briefly discusses about the structure, function and importance of IVD and more specific the cartilaginous endplate. In the imaging standpoint, article refers to multiple previous studies that show UTE MRI as a potential imaging technique to not only visualize CEP but also show abnormal morphology (signal loss, thinning, thickening and irregularity). (Siriwanarangsun et al 2016)

Reviewer comments: Review article that combines the knowledge of previous studies.

3.1.5 Quantitative magnetic resonance imaging of the lumbar intervertebral discs (Hwang et al 2016)

Hwang et al published an article in 2016 about techniques for imaging the IVDs. Limitations of conventional MRI imaging of CEP is discussed. CEPs short T2 time characteristic and low contrast of gradient echo imaging technique is mentioned. Article references previous studies for the UTE technique used to image CEP. According to the article UTE MRI can

achieve time to echo as low as 0.008ms. CEP image contrast can be enhanced by using digital image subtraction technique by suppressing long T2 signals and preserving short T2 signals. Other techniques to suppress long T2 signals of CEP are also mentioned: a) inversion nulling of water b) nulling of water and fat (called adiabatic inversion recovery) c) long T2 water saturation technique. References are mentioned to original articles. Article also mentions the possibility to change repetition time (TR) and flip angle and with that method T1 image differences could be used to image CEP. In addition, article discusses about MR relaxation fitting and image post-processing techniques. Article concludes that UTE MRI shows a unique contrast of IVD structures and offers new opportunities to diagnose and characterize IVD problems. Article has well detailed UTE images where CEP is clearly visible as a narrow white band. (Hwang et al 2016)

3.1.6 UTE MRI of the osteochondral junction (Bae et al 2014)

In 2014 a short review article was published by Bae et al about imaging osteochondral junction of a knee and spine with UTE MRI. Article analyzed the anatomical structure of disco-vertebral junction and more specifically the CEP. CEPs importance as nutrition passageway to AF and NP is also briefly discussed.

The invisible nature of CEP for conventional MRI is discussed. T2 time to echo value of CEP is mentioned to be less that 5 milliseconds and subchondral bone shorter than 1ms. UTE MRIs minimum TE is suggested to be as short as 8 µs and such could be used to image directly tissues mentioned before. 2D and 3D UTE MRI techniques are introduced with image acquisition methods.

Article points out that although uncalcified CEP can be imaged with conventional gradient echo sequence the image contrast can be suboptimal. UTE MRI is mentioned to be able to reveal the entire disk and CEP with medium to high signal intensity. With UTE MRI subtraction technique, abnormal (signal loss, thickening or irregularity) osteochondral junction is more easily detected. Article uses multiple images to point out that UTE subtraction technique reveals two high signal layers in osteochondral junction. Further histological analysis confirmed those layers to be both uncalcified and calcified endplate layers and not disc tissue (AF or NP) or subchondral bone.

On end comments article mentions that more studies are required to find out how pathology of disco-vertebral junction is related to back pain and spine health. (Bae et al 2014)

3.2 Animal studies

3.2.1 A computational measurement of cartilaginous endplate structure using ultrashort time-to-echo MRI scanning. (Jin et al 2017)

In 2017 Jin et al published a study where they formulated an automatic CEP segmentation method. This ex vivo study was done using 12 cadaveric goat lumbar spines from L2 to L6 vertebral levels. Imaging was done with a 3 Tesla scanner using UTE MRI technique. Imaging parameters are available in the article. Total of 24 IVDs were scanned and later histologically analyzed. Histological analyze was done to 10 IVDs and they measured the mean thicknesses of CEP and compared to those thicknesses measured from UTE MRIs.

Results: In the article they in details describe the methods they use to locate the cartilaginous endplate from images and how they analyzed its properties (morphology, thickness, signal intensity). Computer used algorithm was compared to manual segmentation done by a radiology. The result showed a good agreement with manual and automatic analyzing. CEP abnormalities were found with the automated analyze. Histological analyze of the thickness also significantly correlated with automated segmentation (p-value 0.002). Processing time for the computer was 59.2 seconds compared to radiologist estimated one hour analysis time.

Overall this study proposes useful and fast method of automated analyze of CEP. Article points out two limitations of the automated method: a) Outer edges of CEP were not always reliably detected, b) Annulus fibrosus showed similar signal intensities than CEP and could be hard to differentiate from endplate. (Jin et al 2017)

Reviewer comments: Using a goat spine is first step. Further studies with human patients are needed.

3.2.2 Collagen composition and content dependent contrast in porcine annulus fibrosus achieved by using double quantum and magnetization transfer filtered UTE MRI (Eliav et al 2013)

Eliav et al published a study in 2013 where they used a double quantum and magnetization transfer filtered ultra-short echo time (DQF-MT-UTE) MRI to get information of connective tissue. Imaging was done to porcine annulus fibrosus. Study suggested that this imaging method could be used to differentiate collagen type I and II in the annulus fibrosus. (Eliav et al 2013)

Reviewer comment: Endplate was not mentioned but this study was included for using UTE MRI technique and used to image soft tissue (collagens) that endplate also consists of.

3.2.3 Three-dimensional ultrashort echo time (3D UTE) magnetic resonance imaging (MRI) of the normal and degenerative disco-vertebral complex at 4.7 T: a feasibility study with longitudinal evaluation (Dallaudière et al 2021)

An article was published by Dallaudière et al where they studied the possibility to use 3D UTE MRI to evaluate normal and degenerative IVDs. Study was done with five rats. For each rat mechanical damage was made to one IVD with a needle in ultrasonic guidance. 3D-T2-FS (RARE) and 3D-UTE MRI sequenced were used when imaging the rats spines. Imaging was done with a 4.7 Tesla scanner. Imaging was done every week for two and a half months for each rat. Image analysis was done by a radiologist and a physicist. After imaging, rats were euthanized and histological samples were made from disco-vertebral complexes (DVC).

They analyzed control DVCs that they acquired from the same rats with 3D T2-FS MRI. They found out that NP was well visualized but AF and CEP could not be differentiated from each other. With 3D UTE sequence they could differentiate all structures from each other (NP, AF, CEP) where nucleus pulposus was shown as low signal, annulus fibrosus as hyperintense. Low signal CEP was possible to identify next to the high signal AF.

With pathological DVCs the CEP could not be differentiated using 3D T2-FS. 3D UTE showed NP and AF hyperintense same as in control samples. CEP remained unchanged in damaged DVCs compared to control DVC.

Histological evaluation showed NP disruption and AF fibrillar disorganization with loss off height with pathological DVCs. No CEP defects were found.

In the discussion section they suggest that 3D UTE MRI could be used to image the anatomy of DVCs and distinguish early discitis from chronic discopathy. Limitations of the study was discussed. Low sample size was mentioned as one of them and the artificially created discitis without CEP alteration as second one. Limitations of how far this kind of animal study and its results can be used to humans is also discussed.(Dallaudière et al 2021)

3.3 Clinical studies

3.3.1 UTE DISK Sign on MRI (Pang et al 2017)

In 2017 Henry Pang et al did a cross sectional study for 108 human subjects taken from Hong Kong Disc Degeneration Cohort. They acquired common characters from the study population (age, sex, weight, BMI, smoking) and lower back pain data using Oswestry Disability Index (ODI for short). In the study they reimaged the subjects with 3 tesla MRI scanner using T2W, T1-rho and UTE techniques. Total imaging count was 540 lumbar discs. Imaging parameters for each technique can be found from the article.

In the study they formulated a new disk phenotype that they called UTE disc sign (UDS for short). It was defined as “hyper- or hypointense band located within the disc”. Two individuals analyzed the MRI images independently. They calculated the number of discs with UDS from L1/L2 to L5/S1 and summation gave the grade from 0 to 5.

In the results they analyzed the association between UDS and various spine imaging phenotypes. UDS was found in 71 discs out of 540. Mean UDS grade was 0.6. Most notable results were that disc generation, disc displacement and Modic changes were more prevalent (p-value <0.001) in discs that had UDS. They did not find correlation with UDS and endplate abnormalities, high-intensity zones (HIZ) or spondylolisthesis. Assessing the patient characteristics, they found out that age had a positive correlation with UDS. Weight, height, BMI, smoking or sex did not have a correlation. They also found out UDS score was positively and significantly correlated with ODI score (p-value <0.001) compared to T2W MRI disc generation score.

In the discussion section they also noted that T1-rho MRI showed less proteoglycan content within the discs that showed UDS signs. In the conclusion they suggest that UDS could have potential implications in diagnostics, therapeutic and prognostic fields with patients

suffering from LBP. Further, larger studies are needed is where they conclude the article. (Pang et al 2017)

Reviewer comments: This was the first study to give a new clinically usable and seemingly significant method of imaging spine and assessing the relevance of the finding. To put some critique, the study does not classify what disc/spine structures UDS consisted of. Only that they were analyzed using UTE MRI. They also acknowledged that T2W MRI was not sufficient to fully analyze Modic changes and that Modic changes were only noted.

3.3.2 3D Ultrashort TE MRI (Kim et al 2018)

Kim et al has published 2018 a study where they evaluated the possibility of using 3D UTE MRI to image CEP and its possible defects. The study had total of 78 living human (70 patient and 8 healthy volunteers). Imaging was done using 3 tesla MRI scanners. T2W, subtracted 3D UTE and 3D UTE sequences were used. They scanned spine from C2 to C7 vertebral bodies and their adjacent discs.

Two radiologists did the MRI image evaluations. Radiologists had three-point system when analyzing the healthy volunteers. CEP: 1. CEP is not separately visualized from body endplate. 2. CEP is separately visualized, but not clear. 3. CEP is clearly visualized.

For the patient group the same radiologists did a more thorough analyze of CEP morphology and compared first echo UTE with subtraction UTE images. CEP abnormalities were categorized into four parts: irregularities, thickening, thinning and defects. Second review of the same patient images were done by the same radiologists after 4 months, learning bias was taken to account by removing patient information.

Results: In the volunteer study they found out that CEP was better visualized from adjacent tissue with subtracted 3D UTE than first-echo 3D UTE. T2W SE images did not show difference with CEP from the adjacent tissues such as the bony endplate. In the patient study they recorded 135 CEP findings. All intra- and interobserver agreements for CEP abnormalities were statistically significant.

Conclusion: Article concluded that 3D UTE sequence is a feasible method to image CEP and its abnormalities. Also, CEP abnormalities may be associated with disk degeneration in T2W images. However, they pointed out that only one UTE method (first echo or subtracted)

might not be feasible enough. In an example they showed that NP signal changes could cause thinning abnormalities show as thickening in subtracted 3D UTE sequence.(Kim et al 2018)

Reviewer comments: Analyzing phase was described well and biases were well thought out. Clinical relevance of endplate abnormalities is not established in this study.

3.3.3 Ultrashort time-to-echo MRI of the cartilaginous endplate (Law et al 2013)

Law et al published an in vivo human study using UTE MRI imaging of the spine. Their goal was to assess the feasibility of UTE MRI technique to image CEP.

Nine human subjects were recruited from the Hong Kong Degenerative Disc Disease Cohort Study. Seven of them with known disk degeneration and two volunteers without. Imaging was done with a 3 tesla MRI scanner using 3D UTE and 3D T2W techniques. They scanned the discs between T12 and S1. Two observers analyzed the images.

Results: They found out that 34% of CEPs had defects. Most CEP defects were found from IVD levels T12/L1, L1/L2 and L4/L5 ($p<0.001$). Study also found a negative correlation between BMI and age with CEP defects. CEP defects and IVD degeneration also had a statistic significant association. They also pointed out that degenerated discs with no CEP defects were found from throughout the lumbar region. (Law et al 2013)

Reviewer comments: More clinical studies are needed. Small sample size

3.3.4 The relationship between endplate pathology and patient reported symptoms for chronic low back pain depends on lumbar paraspinal muscle quality (Bailey et al 2019)

Bailey et al did a cross sectional cohort study in 2019 where they studied the relationship between CEP damage and adjacent paraspinal muscle (PSM) quality and their association with patients suffering from chronic lower back pain (CLBP). For the study they acquired 52 living subjects. Of those subjects 38 suffered from CLBP and 14 were asymptomatic controls.

Imaging was done with 3 tesla MRI scanner. They performed T1- and T2-weighted MRI sequences and fat fraction measurement for muscle segmentation. 3D UTE was used for endplate imaging.

Results: Their statistical analyze showed that CEP damage and disk degeneration had a statistic significant correlation with chronic lower back pain. Also, the more damaged CEP IVDs were found the more likely subject was to have CLBP. They also found out that L4/L5 IVD had the most CEP defects and it was the only level where CEP damage and CLBP were significantly associated. At L4/L5 IVD level the PSM muscle quality with CEP defects were associated with CLBP. Paraspinal muscle fat fraction was also found out to be higher when adjacent CEP damage was present.

In the study they conclude that CEP defects were more predictive of lower back pain than disc degeneration or Modic changes. (Bailey et al 2019)

3.3.5 Evaluation of human cartilage endplate composition using MRI (Wang et al 2020).

Wang et al published 2020 a study where they examined the relationship between CEP composition and disk degeneration. They acquired 13 cadavers and seven healthy human subjects into the study. Test subject ages varied between 25-73 years. Imaging was done with 3 tesla MRI scanner. 3D UTE T2W and traditional T1ρ mapping were used. Additional normal T2W MRI imaging was done to acquire the Pfirrmann gradings for the discs. UTE imaging was done in order to locate endplate and T1ρ was used to identify nucleus pulposus. Imaging was done to L4/L5 and L5/S1 IVDs. 16 IVDs from cadavers and 7 IVDs in vivo were analyzed.

Results: In the study they found out that UTE T2W relaxation times varied systematically within the CEP, highest values were found centrally of the CEP and lowest posteriorly and that it would suggest that CEP composition would be varying regionally. They also found out that within the youngest age group the low CEP T2W values also had lower nucleus pulposus T1ρ- values proposing to a more serious disc degeneration. More so with mild to moderate Pfirrmann grade (II and III) discs. In the older group that had grater Pfirrmann grades (III to IV) they did not find association between CEP T2W values and NP T1ρ values.

This study suggested that T1ρ MRI with UTE T2W MRI could be used to determine the severity of disc degeneration in the younger age group, although larger studies are still needed. (Wang et al 2020)

3.3.6 CT-like images based on T1 spoiled gradient-echo and ultra-short echo time MRI sequences for the assessment of vertebral fractures and degenerative bone changes of the spine (Schwaiger et al 2021)

In 2021 Schwaiger et al published a study where they compared conventional CT imaging to 3D T1W spoiled gradient echo (T1SGRE) and UTE MRI for detection of vertebral fractures and/or bone and soft tissue changes.

Total of 30 patients were included in the study from 79 potential subjects. CT and MRI imaging was done within three days of each other. MRI was done with a 3T scanner. Parameters are found for both CT and MRI imaging. Two radiologists independently analyzed the images. All other patient data was hidden from analyzers and they were done in randomized order.

Results: Overall the focus in the study was to assess vertebral fractures, vertebral body changes and intervertebral disc height and annulus fibrosus diameter. Bony or cartilaginous endplate was not examined or discussed in the result section; hence this literature review will not go more into details of the results. In the discussion section CEP was only mentioned to be a possible imaging target of UTE MRI. (Schwaiger et al 2021)

3.3.7 Ultrashort echo time (UTE) MRI of the spine in thalassemia (Hall-Craggs et al 2004)

Hall-Craggs et al published a case study in 2003 where they examined the use of UTE MRI to image lower thoracic and lumbar spine of three patients diagnosed with thalassemia. Three healthy control males were also scanned. The background of this study was that that back pain is a common symptom in adult patients with homozygote thalassemia and IVD narrowing and severe disc degeneration has been observed in thalassemia. Fat suppressed (FS) and long T2 suppressed (FLUTE) UTE MRI technique, fat suppressed UTE MRI and conventional T1/T2W MRI were used. Study analyzed the results case by case. This literature review will focus the findings on the endplates from the article.

In the first case the FLUTE UTE MRI showed high signal bands parallel to the endplates. Second or third case does not mention endplates. In the discussion section they point out that these parallel bands have not been described before in studies. Potential causes of these high signal bands are suggested. a) Increased iron deposition in the IVDs through endplates

caused by thalassemia, b) Increased fibrous connective tissue in thalassemia, c) calcification. (Hall-Craggs et al 2004)

Reviewer comment. Although this study used UTE MRI to scan the spine its main interest was out of this literature review area of interest.

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4. COMMENTS

From the articles it seems that there is enough both histological and radiological studies to confirm that CEP can be identified and analyzed with UTE MRI imaging. An automated computer performed CEP analytic program has already been developed, although its clinical usage is still unknown. One study has formed a grading system for UTE MRI imaged CEP called UDS. The animal studies and especially human clinical studies still seems to have trouble finding the final correlation between CEP defects, disk degeneration and their correlation with back pain. All clinical articles conclude that more profound and larger sample size studies are required to gain more knowledge on the subject.

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