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Tissue ~~Engineered Medical Products –~~ engineered medical products — MRI ~~Evaluation~~ evaluation of ~~Cartilage –~~ cartilage — Part 1: Clinical ~~Evaluation~~ evaluation of ~~Regenerative Knee Articular Cartilage Using Delayed Gadolinium-Enhanced~~ regenerative knee articular cartilage using delayed gadolimium-enhanced MRI of ~~the Cartilage~~ cartilage (dGEMRIC) and T2 ~~Mapping~~ mapping

~~TS stage~~

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Foreword

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This document was prepared by Technical Committee ISO/TC 150, *Implants for surgery*, Subcommittee SC 7, *Tissue-engineered medical products*.

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Introduction

Tissue-engineered cartilage has shown desirable results for the repair of cartilage defects, and histologic findings indicate that the repaired tissue has a hyaline-like cartilage structure. Kang H.J. et al., Zheng M.H. et al. and Behrens P. et al. reported that the histologic change after matrix-associated autologous chondrocyte implantation/transplantation (MACI/MACT) () [1-3] was a hyaline-like cartilage. The knee articular cartilage couldcan also be repaired or regenerated via other tissue engineering approaches using other seed cells such as mesenchymal stem cells or even by tissue regeneration free of external seed cells [4-6]. MACI and other approaches lead to a maturation of the cartilage matrix over time with the development of an organized collagen architecture. For long-term follow-up of regenerative cartilage, clinical scores and morphological evaluations are commonly used. Furthermore, histological evaluation from arthroscopic biopsies provides a gold standard for morphological and biochemical assessments of regenerative cartilage tissue. However, this process is invasive and unacceptable for patients after cartilage repair surgery. Magnetic resonance (MR) is a noninvasive technique that can be used for the evaluation of a cartilage microstructure. Xu X and other researchers reported that MR-based biochemical imaging techniques, such as delayed gadolinium-enhanced MRI of the cartilage (dGEMRIC) and T2 mapping, show the capability of evaluating the biochemical character of articular cartilage [7-12]. The T2 relaxation time is sensitive to the content of effective hydrogen atoms, and thus to the concentration of collagen, the main component of cartilage extracellular matrix [13]. Besides, the orientation changes in the collagen network of articular cartilage produce the depthwise T2 anisotropy through the magic angle effect [14]. The dGEMRIC technique enables an indirect estimation of the fixed charge density (FCD) of cartilage, which mainly arises from the aggregated proteoglycan biomacromolecules [15]. Since both collagen and proteoglycan components are important for determining the functional characteristics of cartilage, a combination of T2 mapping and dGEMRIC techniques provides a better evaluation of articular regenerative cartilage. Therefore, standardization of T2 mapping and dGEMRIC techniques is needed for the evaluation of regenerative articular cartilage.

This document is intended to guide the clinical biochemical evaluation of regenerative articular cartilage with MR. dGEMRIC and T2 mapping are recommended for the clinical evaluation of regenerative cartilage. These techniques have been used for patients who received tissue-engineered cartilage implantation or transplantation (MACI/MACT). The validation data from different hospitals wereare provided in this document as an annexAnnex A.

This document provides general principles for imaging and the measurement method of T2 mapping and dGEMRIC of knee cartilage using 1,5 T or 3,0 T MRI equipment. These techniques are also applicable for other articular cartilage, such as the ankle joint, hip joint, and shoulder joint, but the imaging parameters should be adjusted and modified for better image quality.

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Tissue ~~Engineered Medical Products –~~-engineered medical products — MRI ~~Evaluation~~evaluation of ~~Cartilage –~~cartilage — Part 1: Clinical ~~Evaluation of Regenerative Knee Articular Cartilage Using Delayed Gadolinium-Enhanced~~evaluation of regenerative knee articular cartilage using delayed gadolimium-enhanced MRI of ~~the Cartilage~~cartilage (dGEMRIC) and T2 ~~Mapping~~mapping

1 Scope

This document provides a principle to determine the parameter settings and operating methods for the evaluation of the composition and structure of articular cartilage by dGEMRIC and T2-mapping MRI in humans with a typical example of the methods; each are distinct MRI technologies that allow for noninvasive observation of soft tissue characteristics.

The methods provided in this document are intended for application in the evaluation of the clinical effects of tissue-engineered cartilage or other cartilage regeneration products used in the knee joint, and are also applicable for the evaluation of regenerative cartilage in other joints, although some modification of parameters is needed.

This document ~~recommends~~describes a longitudinal evaluation of the water content, the glycosaminoglycan (GAG) concentration, and the concentration and orientation of collagen ~~fibers~~fibres in regenerative cartilage when using dGEMRIC and T2-mapping techniques in 1,5 T or 3,0 T magnetic resonance imaging equipment.

~~3~~2 Normative references

~~The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.~~

~~ISO/TR 16379:2014, *Tissue-engineered medical products — Evaluation of anisotropic structure of articular cartilage using DT (Diffusion Tensor) MR Imaging*~~

~~ISO/TS 21560:2020, *Tissue-engineered medical products — General requirements of tissue-engineered medical products*~~

There are no normative references in this document.

~~4~~3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain ~~terminological~~terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at ~~https://www.iso.org/obp~~https://www.iso.org/obp

— IEC Electropedia: available at ~~http://www.electropedia.org/~~https://www.electropedia.org/

3.1
pulse sequences
train of programmed radio frequency pulses and gradient pulses~~, in MRI, it is a time protocol for encoding images to obtain k-space data~~

Note 1 to entry: In MRI, it is a time protocol for encoding images to obtain k-space data.

3.2
number of averages
NA
number of repeated acquired identical MR signals from the same ~~programed~~programmed pulse sequence

3.3
voxel
three-dimensional cuboid representing the minimum unit comprising a three-dimensional image

3.4
pixel
two-dimensional cuboid representing the minimum unit comprising an image

3.5
field of view
FOV
width and height of an imaged region ~~(expressed in cm by cm or mm by mm)~~

Note 1 to entry: It is expressed in cm by cm or mm by mm.

3.6
matrix
array of scalars arranged in frequency encoding direction and phase encoding direction in a two-dimensional MR image ~~(~~

Note 1 to entry: It is typically expressed in number of pixels in frequency encoding direction by number of pixels in phase encoding direction~~).~~

Note ~~1~~2 to entry: In MRI, the scalars in the array are called pixel of the matrix.

3.7
~~**in-plane resolution**~~
~~capability of the sensor to observe or measure the smallest object clearly with distinct boundaries, given by = FOV/matrix size (typically expressed in mm by mm)~~

~~**3.8**~~
slice thickness
thickness of the imaging plane ~~(~~

Note 1 to entry: It is expressed in cm or mm~~).~~

3.98
signal-to-noise ratio
SNR
a single number obtained by dividing the image signal by the image noise

3.109
region of interest
ROI
a user-defined area on an image in which parameter of interested is calculated

3.1110
echo time
TE
the time from the centercentre of the 90-degree excitation RF-pulse to the centercentre of the echo.

Note 1 to entry: It is expressed in ms).

3.1211
repetition time
TR
time interval for repetition of the basic unit of magnetic resonance pulse sequences (expressed in ms)

Note 1 to entry: It is expressed in ms.

3.1312
proton density-weighted image
PDWI
magnetic resonance image reflecting the concentration of protons in tissue

3.1413
matrix-associated autologous chondrocyte implantation/transplantation
MACI/MACT
procedure involving expansion of autologous chondrocytes and seeding the cells onto a three-dimensional biomaterial scaffold

3.1514
scaffold
support or structural component or delivery vehicle, or matrix, consisting of synthetic and/or naturally-derived material(s), for modulating the biological properties (including, but not limited to, adhesion, migration, proliferation, and differentiation) or transport of administered and/or endogenous cells and/or binding/transport of bioactive agents

Note 1 to entry: Biological properties include (but are not limited to) adhesion, migration, proliferation, and differentiation.

[SOURCE: ASTM F2312-11:2020, Clause 4]

3.15
gradient recalled3.16
gradientrecalled echo

GRE
MR sequence that generates ~~gradients~~gradient echoes as a consequence of echo refocusing

~~3.17~~
3.16
delayedgadolinium enhanced MRI of the cartilage
dGEMRIC
pre-contrast and post contrast T1 mapping of cartilage

3.~~18~~17
longitudinal relaxation time
T1
~~the~~ time taking for the longitudinal magnetization to recover approximately 63 % of its initial value after being flipped into the magnetic transverse plane by a 90° radiofrequency pulse

Note 1 to entry: It is expressed in ms.

3.18
transverse relaxation time
T2
time taking for the magnetic resonance signal to irreversibly decay to 37 % of its initial value after being flipped into the magnetic transverse plane by a 90° radiofrequency pulse ~~(expressed in ms)~~

~~3.19~~
Note 1 to entry: It is expressed in ms.

3.19
~~**transverse relaxation time**~~
~~**T2**~~
~~the time taking for the magnetic resonance signal to irreversibly decay to 37% of its initial value after being flipped into the magnetic transverse plane by a 90° radiofrequency pulse (expressed in ms)~~

~~3.20~~
T1 mapping
two-dimensional spatial distributions of T1 value of tissue

3.~~21~~20
T2 mapping
two-dimensional spatial distributions of T2 value of tissue

3.~~22~~21
R1
longitudinal relaxation rate calculated as 1/T1

~~5~~4 Principles

Articular cartilage is a type of hyaline cartilage that is characterized by an extracellular matrix that contains a fine network of collagen and proteoglycan ~~etc. ([16]).~~. In regenerative articular cartilage, it is important to evaluate whether the implanted tissues regenerate to hyaline or hyaline-like cartilage with

time. MRI is a noninvasive technique that can provide an indirect method for assessing the composition and microstructure of articular regenerative cartilage, including content and organization of the collagen network and the proteoglycan, as the main component in the extracellular matrix [12,17].

Delayedgadolinium enhanced MRI of the cartilage (dGEMRIC) is a technique pertinent to the T1 relaxation-time measurement that uses the negative ionic charge of gadopentetate dimeglumine ($Gd\text{-}DTPA^{2-}$) to map the fixed charge density of the cartilage GAG. $Gd\text{-}DTPA^{2-}$ is repelled by negatively charged GAGs and is therefore negatively related to the local proteoglycan concentration. Consequently, $Gd\text{-}DTPA^{2-}$ accumulates in areas of low GAG content, and a cartilage will have a shorter T1 relaxation time in these regions. The ability to measure spatial variations in the cartilage GAG concentration in vitro with dGEMRIC has been validated biochemically and histologically using both bovine and human cartilage. The feasibility of using dGEMRIC in vivo has also been demonstrated, and the interpretation of MR images as representing a GAG distribution is supported by literature evidence [18-21]. The GAG is a component of normal hyaline cartilage that is critical to its mechanical strength. Thus, as a noninvasive method of indirectly monitoring the GAG concentration in cartilage, dGEMRIC is a potentially useful method for assessing regenerative cartilage.

T2 mapping usually involves imaging at several echo times along the T2 decay curve [22] and T2 relaxation time of different tissues can be calculated after data processing. In cartilage, changes in the T2-relaxation times are dependent upon the quantity of water and the integrity of the proteoglycan–collagen matrix. T2 relaxation time mapping provides an indirect assessment of the collagen structure and orientation as it relates to the free water content. The presence of unbound water molecules slows the loss of transverse magnetization following an RF pulse, such that regions of cartilage with more free water have higher T2 relaxation times. In healthy cartilage, the collagen matrix traps and immobilizes water molecules. When this structured matrix breaks down, the extra space is filled with free, unbound water, and leads to elevated T2 relaxation times. The correlation between T2 relaxation time mapping and the collagen content has been validated, both in vitro and in vivo [23,24]. The T2 value of cartilage is a dipolar interaction due to the slow anisotropic motion of water molecules in the collagen matrix and varies as a function of the collagen arrangement in the static magnetic field [14,25], the strength of this interaction is orientation-dependent and reaches its minimum at an angle of 54,7 (between the static field and the axis of interacting protons, the so-called “magic angle”. Consequently, T2 changes along cartilage thickness are reported to follow the orientational changes in the collagen fibril network. Using appropriate arrangement of the articular surface with respect to the B0 field the resulting laminated appearance in T2 maps approximately corresponds to the histological collagenous zones: the superficial zone (orientation of collagen fibrils parallel to the articular surface), the transitional zone (random fibril orientation) and the deep or radial zone (fibrils perpendicular to the articular surface and perpendicular to the bone), which reveals the spatial collagen architecture in articular cartilage. This spatial variation is a marker for hyaline-like matrix organization after cartilage repair.

MACI/MACT uses biomaterial scaffolds (natural or synthetic materials) as a carrier and seeds cells of autologous chondrocytes. The repaired tissue may be able tocan develop an organized collagen network, which is the basis for histological characterization of normal hyaline articular cartilage over time [1-3,26,27]. It is possible to longitudinally evaluate the water content, the GAG concentration, and the concentration and orientation of collagen fibersfibres in regenerative cartilage after MACI/MACT by using the dGEMRIC and T2 mapping techniques.

In this document, T2 mapping and dGEMRIC data obtained from subjects who received MACI using different MRI equipment are included in the Annex A.

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