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Do Cartilage T2 Relaxation Time Measurements over 8 Years Predict if Patients Benefit from Weight Loss? Longitudinal Data from the Osteoarthritis Initiative

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Abbreviations

ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
ANOVA	Analysis of variance
BLOKS	Boston Leeds Osteoarthritits Knee score
BMEP	Bone marrow edem pattern
BMI	Body Mass Index
BML	Bone marrow lesion
CDC	Center for Disease Control and Prevention
CEST	Chemical Exchange Saturation Transfer
CV	Coefficient of Variation
DESS	Dual echo steady state
dGEMRIC	Delayed gadolinium-enhanced MRI of cartilage
ECM	Extracellular matrix
FS-3D	Fat-suppressed three-dimensional fast spoiled gradient-recalled
SPGR	echo
FSE	Fast spin echo
GAG	Glycosaminoglycan
GLCM	Gray level co-occurrence matrix
HIPAA	Health Insurance Portability and Accountability Act
IA	Intraarticular
IGF	Insulin-like growth factor
KL	Kellgren- Lawrence
MESE	multiecho spinecho

MOAKS	MRI Osteoarthritis Knee score
MRI	Magnetic resonance imaging
NIH	National Institute of Health
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
p.a.	posterior anterior
PACS	Picture archiving and communication system
PASE	Physical activity score of the elderly
PG	Proteoglycan
PPI	Proton pump Inhibitor
QA	Quality assurance
RMSE	Root mean scare error
ROI	Region of Interest
SNR	Signal to noise ratio
T	Tesla
TNF	Tumor Necrosis Factor
WHO	World Health Organisation
WL	Weight loss
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORMS	Whole-Organ Magnetic Resonance Imaging Score

1. Introduction

Osteoarthritis (OA) is the most common joint disease that affects millions of elderlies and is a major cause of long-term disability. The World Health Organization (WHO) estimates, that 9.6% of men and 18% of women over the age of 60 years are affected by OA. Due to increased life expectancy and ageing populations, it is supposed to be the fourth leading cause of disability by the year 2020 (Woolf & Pfleger, 2003). OA is among the leading causes of total years lost due to disease at the global level meaning that an average 50 to 84 year old non-obese individual with knee OA will lose 1.9 quality adjusted life years due to disability (Lopez & Murray, 1998; Losina et al., 2011). This results in an enormous economic burden costing billions of dollars each year due to treatment and indirect costs (Bitton, 2009; March & Bachmeier, 1997). Studies focusing on knee OA identified risk factors including age, female gender, heavy physically demanding work, previous traumatic knee injury, repetitive knee bending activities and overweight/obesity (Blagojevic, Jinks, Jeffery, & Jordan, 2010; Felson, 1990). As indicator for weight, the body mass index (BMI) is one of the most significant risk factors for OA. Obese individuals with a BMI $\geq$ 30 kg/m^2 have an up to 7 times greater risk for developing symptomatic OA compared to individuals with normal weight (BMI < 25 kg/m^2) (Blagojevic et al., 2010; Lee & Kean, 2012). The prevalence of obesity is increasing in our population and it is considered as an "upcoming" epidemic problem. According to the WHO, European overweight and obesity estimates from 2008 show that in 46 out of the 51 countries for which data were available, more than 50% of the adult population ($\geq$ 20 years old; both genders) were overweight and that in 40 countries more than 20% were obese (Europe, 2008). Consequently, there

will be an increasing number of patients with obesity-related OA, which creates the necessity to develop effective therapies and preventive strategies.

In general, obesity is associated with a higher prevalence and severity of early degenerative changes in the knee (Laberge et al., 2012). Cartilage degeneration is associated with compositional and structural changes of the extracellular matrix (ECM), degradation of the fibrillar collagen network and an altered content of proteins, proteoglycans and water (Heinegard & Saxne, 2011; Maldonado & Nam, 2013). Individuals should be diagnosed and treated at early stages, before damage of the hyaline cartilage is irreversible. Previous studies have demonstrated weight loss being an effective method to reduce joint loading, improve function and pain and decrease low-grade inflammation (Aaboe, Bliddal, Messier, Alkjaer, & Henriksen, 2011; Christensen, Astrup, & Bliddal, 2005; Messier, Gutekunst, Davis, & DeVita, 2005; Richette et al., 2011). Therefore, treatment of obese or overweight individuals at early stages of OA is most beneficial.

Magnetic resonance imaging (MRI) is the standard technique to assess cartilage pathology without an intervention. Both morphological and compositional techniques are available that allow to either analyze focal cartilage defects or quantitatively characterize the cartilage matrix. Compositional techniques are particularly interesting as they are able to depict structural changes in the cartilage even before they are seen on radiographs. Different modalities of quantitative measurements are available, whereas most experience is available for T2 relaxation time measurements. Studies have shown that the T2 measurements closely correlate with the collagen molecular structure and cartilage hydration (F. Eckstein, Burstein, & Link, 2006). Therefore T2 relaxation time measurements are sensitive to early degenerative processes of the cartilage matrix and might even be able to predict the onset of radiographic OA before

irreversible damage has occurred (F. Eckstein, Cicuttini, Raynauld, Waterton, & Peterfy, 2006; Liebl et al., 2014; Urish et al., 2013).

A previous study focused on the progression of T2 relaxation times in a group of obese individuals loosing over 10% of their weight over a period of 48 months compared to a group of obese individuals with constant weight (Serebrakian et al., 2014). Thereby, it was demonstrated that the T2 relaxation times increase significantly less in the weight loss group indicating slowed progression of degenerative changes in comparison to the group with stable weight. Yet, until today it remains unknown whether there is a correlation between the amount of weight loss and the positive impact on cartilage composition and clinical findings as well as the changes over a longer period of time.

2. Objectives

The purpose of this project was to analyze if the degree of weight loss was associated with slower progression of degenerative disease of the knee over an 8-year follow-up period. The predictor variable was the amount of weight loss (5-10% weight loss, >10% weight and no change (<3 weight loss)). Outcome measures included longitudinal changes over 48 months and 96 months in T2 relaxation time measurements including texture and laminar analysis of cartilage acquired with 3.0 Tesla MRI. Additional outcome measures were physical activity scores (PASE), Kellgren-Lawrence (KL) scores, Western Ontario and McMaster University (WOMAC) pain score and Whole-Organ Magnetic Resonance Imaging Score (WORMS).

The ultimate aim of this study was to identify individuals that would benefit most from weight loss regarding onset and progression of OA and which degree of weight loss was needed to have a protective effect on joint status, since this information would have a major impact on preventive strategies and treatment of OA in clinical practice.

3. Background

3.1 Definition of Osteoarthritis

Osteoarthritis is a multifactorial and heterogeneous disease. The American College of Rheumatology describes it as slowly progressive joint disease typically seen in middle-aged to elderly people.

Pathophysiological it is characterized by loss of articular cartilage within the synovial joints, associated with hypertrophy of the bone, joint space narrowing, thickening of the articular capsule and joint enlargement (Pereira et al., 2011).

3.2 Epidemiological aspects

In the United States of America arthritis is the most common cause of disability among adults and the American Center for Disease Control and Prevention (CDC) estimated that 52.5 million adults are diagnosed with arthritis (Centers for Disease & Prevention, 2013). With 27 million adults being affected, Osteoarthritis is the most common type of arthritis meaning that nearly one in two people may develop symptomatic knee OA in their lifetime (Lawrence et al., 2008; Murphy et al., 2008). By 2030 up to 67 million Americans at the age of 18 years or older are projected to have doctor diagnosed arthritis (Hootman & Helmick, 2006).

This in return causes an immense economic burden and raises new challenges for the Healthcare utilization. In 2004 there have been about 744 000 hospitalizations and 78 million ambulatory care visits with a primary diagnosis of arthritis (Sacks, Luo, & Helmick, 2010). Around 750 000 total knee replacements were performed in the

years 2010 and 2011 primarily due to Osteoarthritis (G, 2011). As a result, there are increasing costs for the society and economy by covering treatments, rehabilitations, work incapacities and long-term disabilities. CDC estimated a total of 128 billion dollars of direct and indirect medical expenditures related to arthritis ("National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003," 2007). Considering those numbers, the changing age distribution and rising prevalence of obesity, OA has become a major concern of the health care system.

3.3 Etiology

Osteoarthritis can be caused by a variety of diseases and conditions. In general it can be categorized into primary and secondary forms whereas the primary or idiopathic form of OA occurs in intact joints and is not triggered by any inciting agent (Taruc-Uy & Lynch, 2013). The age plays an important role in the development of OA, as the wear and tear on the joints causes damage to the cartilage and induces abnormal repair mechanism (Sandell, 2012). Several conditions including primary generalized OA, erosive OA and chondromalacia patellae are recognized as subsets of primary OA. Some studies suggest that genetic predisposition plays another role in primary OA (Herrero-Beaumont, Roman-Blas, Castaneda, & Jimenez, 2009).

Secondary OA results from conditions that change the microenvironment of the cartilage. This can be caused by repeated trauma or after surgical intervention to the joint structures, due to congenital abnormalities or malformations, due to malposition (varus/valgus) of the joints or permanent excessive load, due to metabolic disorder (e.g. rickets, hemochromatosis, chondrocalcinosis, ochronosis), due to endocrine disorder

(e.g. acromegaly, hyperparathyroidism, hyperuricemia) or due to infections (Heinegard & Saxne, 2011; Michael, Schluter-Brust, & Eysel, 2010; Taruc-Uy & Lynch, 2013).

The development of OA is characterized by a combination of biochemical, cellular and mechanical processes. Characteristics include cartilage damage, changes in the subchondral bone, osteophyte formation, muscle weakness and inflammation of the synovial tissue and tendon (Grynpas, Alpert, Katz, Lieberman, & Pritzker, 1991). Normally healthy cartilage is in a dynamic equilibrium between constant anabolic processes (regulated by e.g. insulin-like growth factors (IGF) I and II) and catabolic processes (regulated by e.g. interleukin-1, tumor necrosis factor (TNF) alpha and proteinases) (Michael et al., 2010). This mechanism gives cartilage the ability to regenerate to a certain level. If this equilibrium is off balance due to excessive catabolic processes, as they are present in OA, the cartilage will lose its ability to regenerate and will progressively lose substance. However, during active remodeling, the composition and structure of the ECM are changing. The content of proteoglycans (mainly aggrecan) decreases whereas the collagen synthesis elevates (a change of collagen type II to type I has been shown). Those compositional changes affect the mechanical stability of the ECM network as well as they reduce elasticity and the ability to store elastic energy, which causes fibrillation and fissure formation (Maldonado & Nam, 2013; Taruc-Uy & Lynch, 2013). Additionally, inflammation plays an important role very early in the development of OA. For instance, post-traumatic inflammation can affect synovial cells as well as chondrocytes in the cartilage causing them to produce cytokines (e.g. Interleukin (IL) 1 and proteinases). Those mediators impair further regeneration and elevate the rate of cartilage degeneration (Heinegard & Saxne, 2011).

Recent studies have provided evidence that subchondral bone alterations are

strongly associated with cartilage loss and damage in OA (Intema et al., 2010). Subchondral sclerosis is considered as a feature of late-stage OA whereas thinning of the subchondral plate with increased porosity and deteriorated trabeculae is mostly seen in early-stage OA. Despite those numerous alterations detected in the subchondral bone there is still a lack of clear understanding of the mechanisms explaining these phenomena (G. Li et al., 2013).

3.4 Risk factors

3.4.1 Age and Gender

Age is one of the crucial risk factors for OA. All aging related biological, mechanical and structural changes are associated with a transition stage of pre-OA (Andriacchi, Favre, Erhart-Hledik, & Chu, 2015). This assumption is supported by the fact that the risk of developing knee OA increases substantially above the age of 45 years and the general disease incident increases with an age past the age of 75 years (Cooper et al., 2000; Felson et al., 1987).

Considering gender, females in general are at a higher risk regarding the prevalence and incidence of OA. Especially post-menopausal women tend to demonstrate more severe OA of the knee (Prieto-Alhambra et al., 2014; Srikanth et al., 2005). Due to those observations several studies have been set up to link hormonal factors (e.g. estrogen deficiency) to the development of OA but the results have been conflicting and further research still needs to be done (Hannan, Felson, Anderson, Naimark, & Kannel, 1990; Nevitt et al., 1996; Wluka, Cicuttini, & Spector, 2000).

3.4.2 Body mass index and nutritional factors

Numerous studies have proven that a high BMI is an important risk factor in the development of OA (Blagojevic et al., 2010; Coggon et al., 2001). The increased joint load provokes early degenerative changes and increases the prevalence of cartilage and meniscal legions (Laberge et al., 2012). Moreover, it has been shown that the dietary intake plays an important role too. Malnutrition leading to vitamin D, C or selenium deficiency can decrease the bone strength and increase the risk of disease progression (Y. Zhang & Jordan, 2010).

3.4.3 Joint injury, malalignment and physical activity

Injuries to the joint in particular trans-articular fractures, meniscal tears and anterior crucial ligament (ACL) injuries severely increase the risk of OA (Blagojevic et al., 2010; Gelber et al., 2000; Y. Zhang & Jordan, 2010). Osteoarthritis in young adults is most commonly the result of previous injury to the knee (Roos, 2005).

Malalignment of the knee as potential risk factor is still in discussion although newer studies suggest that both varus (knock-kneed) and valgus (bow-legged) alignment increase the risk of development and progression of knee OA (Andriacchi et al., 2015; Tanamas et al., 2009; Y. Zhang & Jordan, 2010). Older studies are contradictory regarding those results and considering the amount of studies and their respective cohorts further investigations are needed (Tanamas et al., 2009).

Physical activity is only under certain circumstances seen as risk factor for OA. The amount and type of exercise are of importance whereas permanent activities with high impact such as marathon running or professional soccer playing pose a risk for the

development OA. Exercises with low impact in a moderate mode have shown not to increase the risk for OA (Blagojevic et al., 2010; Cheng et al., 2000).

3.5 Symptoms and clinical examination

The most common clinical symptom is pain, mainly described as exacerbated by activity and relieved by rest. In advanced stages pain may occur also during rest. It can be deep, not well-localized and is usually of insidious onset (Hunter, McDougall, & Keefe, 2008). Patients may experience a reduced range of motion in knee flexion and extension as well as pain upon knee rotation. There might be discomfort or dysfunction associated with certain movements such as kneeling, squatting, or going up or down stairs (Kean, Kean, & Buchanan, 2004). The symptoms of OA severely disturb the daily life and reduce the life quality. Studies have shown that there is a high prevalence of depressive symptoms among older adults with OA (Sale, Gignac, & Hawker, 2008).

During physical examination the BMI and body weight should be assessed as well as the joint range of motion, the location of tenderness, crepitus with movement of the joint, muscle strength, ligament stability, pain on active and passive range of motion, bony enlargement or deformities of the joint, joint effusion and the gait (Hunter et al., 2008).

The American College of Rheumatology created reliable clinical diagnostic criteria as seen in the graph below.

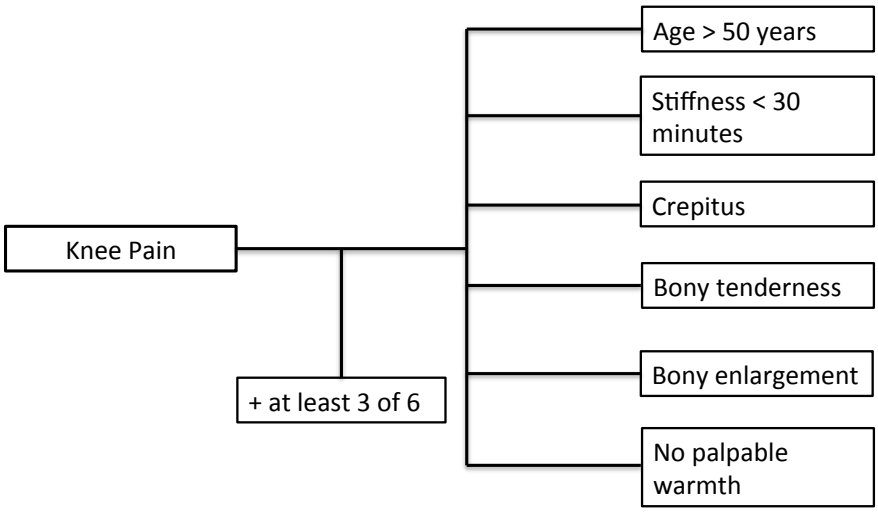

Figure 1: Criteria for the clinical diagnosis of osteoarthritis by the American College of Rheumatology. Rheumatology.org, 2014

It is important that the diagnosis of OA in clinical practice is made based on the patient history and physical examination. Radiographic findings are to confirm the diagnosis and rule out other conditions. Yet there is no significant correlation between the radiographic findings and the associated knee pain sensed by the patient (Hannan, Felson, & Pincus, 2000).

3.6 Radiological assessment of OA

3.6.1 Radiography and KL - Score

Despite the recent development of new imaging techniques, the radiograph still represents the most accessible and cost-effective tool in the evaluation of OA. The Kellgren-Lawrence (KL) score developed in 1957 still represents the most used evaluation tool for Osteoarthritis (Kellgren & Lawrence, 1957) (Chart 3.1). It is based on anterior/posterior x-rays views and the following radiological changes were considered to be evidence of osteoarthritis: The formation of osteophytes on the joint

margins, periarticular ossicles, the narrowing of joint cartilage associated with sclerosis of subchondral bone, small pseudocystic areas usually located in the subchondral bone and altered shape of the bone ends (Kellgren & Lawrence, 1957).

KL-Score	Disease Grade	Radiological signs
0	No changes	No radiographic features of osteoarthritis
1	Doubtful	Possible joint space narrowing and osteophyte formation
2	Mild	Definite osteophyte formation with possible joint space narrowing
3	Moderate	Multiple osteophytes, definite joint space narrowing, sclerosis and possible bony deformity
4	Severe	Large osteophytes, marked joint space narrowing, severe sclerosis and definite bony deformity

Table 1: Radiological features of Osteoarthritis and their corresponding stages defined by Kellgren und Lawrence 1957.

Criticism of this score states that it is characterizing the progression of osteoarthritis of the knee as a linear process, combining osteophyte and joint space narrowing measurements. Therefore, the Osteoarthritis Research Society International created an Atlas focusing on individual radiographic features of OA. They recommend the use of separate scales to evaluate joint space narrowing and osteophyte formation in different compartments (Altman & Gold, 2007; Altman, Hochberg, Murphy, Wolfe, & Lequesne, 1995).

3.6.2 Ultrasound

Ultrasound has an established role in the assessment of OA especially in smaller joints it shows the ability to examine e.g. inflammatory features. In the knee it is also used to asses meniscal extrusions but the application of ultrasound to large joints still is a challenge due to the inherent challenges of ultrasound to visualize deeper portions

of the joint and based on the fact that sound waves are not able to pass through bony structures (Iagnocco, 2014; Roemer & Guermazi, 2014; Yanagisawa et al., 2014). However it is a good tool to evaluate the efficiency of the treatment of clinically significant knee OA (Vojtassak & Vojtassak, 2014).

3.6.3 Magnetic resonance imaging (MRI) of the knee

Magnetic resonance imaging is the most suitable tool in the assessment of cartilage (Van Dyck et al., 2015). Due to developments over the last two decades it has become standard in clinical practice regarding the evaluation of cartilage damage (Link, Stahl, & Woertler, 2007). Its high spatial resolution and ability to depict detailed soft tissue structures makes MRI a superior tool in the assessment of knee cartilage compared to conventional radiography and ultrasound technology (D. J. Hunter et al., 2011). Figure 3.2. nicely illustrates the differences between radiography and MRI. The limitations of MRI are the high costs and relatively long examination times with up to 45 min depending on the amount of sequences used (Oei et al., 2009).

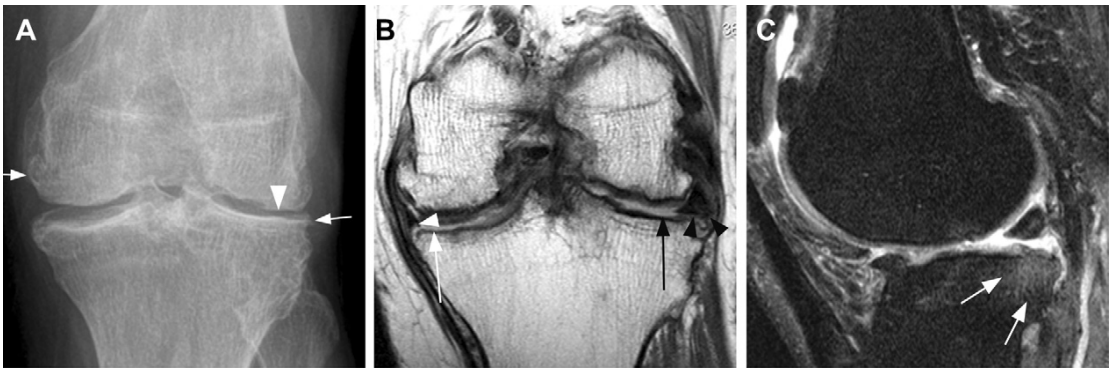

Figure 2: Shortcomings of radiography in regard to visualization of different joint tissues in knee OA. (A) AP radiograph of a Kellgren Lawrence grade 3 knee exhibits definite joint space narrowing of the lateral tibio-femoral compartment (arrowhead). In addition, there are definite marginal osteophytes at the lateral tibial plateau and the medial femur (arrows). (B) Corresponding coronal intermediate-weighted image shows diffuse cartilage loss at the medial (white arrow) and lateral (black arrow) tibial plateaus. In addition, there is partial maceration of the body of the medial meniscus (white arrowhead) and extrusion of the body of the lateral meniscus (black arrowheads), both factors contributing to radiographic joint space narrowing. (C) Corresponding sagittal IW fs image exhibits a subchondral BML of the posterior part of the lateral tibial plateau (arrows), a finding that cannot be visualized by X-ray. These images exemplify the challenge of evaluating the diagnostic performance of a novel, superior methodology using the established method as a reference. Radiography is not able to visualize several articular tissues and thus should not be used as a reference when testing the performance of MRI to evaluate these tissues. From F.W. Roemer, A. Guermazi / Osteoarthritis and Cartilage 20 (2012) 1440-1446 (Roemer & Guermazi, 2012).

The following part gives a short overview over the different kinds of MR scanners as well as the most common sequences used for imaging of the articular structures.

There are different types of scanners available but those using high field 1.5 Tesla (T) and 3 Tesla are most commonly used. Various studies have shown the advantage of 3.0 T compared to 1.5 T scanners due to the fact that their signal to noise ratio is almost linear and the use of quantitative procedures with 3 Tesla machines creates more precise and reliable images (Barr et al., 2007; Jan S. Bauer et al., 2008; J. S. Bauer et al., 2006; Felix Eckstein et al., 2005; Link et al., 2006). In the last years the research regarding ultra-high field magnetic resonance imaging using 7 Tesla and higher has become more apparent suggesting that in future 7 Tesla machines should be used in clinical practice. The signal-to-noise ratio (SNR) is a lot higher than with 3 Tesla generating images with higher spatial resolution, which may improve the diagnostic quality of images. Additionally, the scan time would be shorter reducing the risk for patient motion artifact and patient discomfort (Chang et al., 2014; Jordan, Saranathan, Bangerter, Hargreaves, & Gold, 2013; Welsch et al., 2012). There are still limitations for the use of 7 T scanners. Specific radiofrequency coils must be developed for each body compartment as well as standardized scan protocols (Chang et al., 2014).

Specific sequences for cartilage

A pulse sequence is a pre-selected set of defined radio frequency and gradient pulses, usually repeated many times during a scan, wherein the time interval between pulses and the amplitude and shape of the gradient waveforms will control nuclear magnetic resonance (NMR) signal reception and affect the characteristics of the MR images (Softways, 2015). Different pulse sequences make it possible to evaluate the same image in various ways regarding the diagnostic information we want to get

(Ballinger, 2015). Common MRI sequences for cartilage include standard spin echo (SE), gradient-recalled echo (GRE), fast SE sequences and three-dimensional SE and GRE sequences which can be T1-, T2 weighted, intermediate- or proton density-weighted (Crema et al., 2011). But in order to evaluate the tissue adequately different combinations and multiple sequences have to be used. Those combinations affect the contrast and spatial resolution of the tissue.

Following sequences are used to examine different aspects of the cartilage. One of the most commonly sequences used is a T2 and intermediate-weighted two-dimensional fast spin echo (*2D fast SE)* sequence which provides an excellent contrast between fluid and cartilage. Proton density-weighted images are also capable of showing surface cartilage defects as well as internal cartilage abnormalities, but intermediate-weighted sequences have the advantage of combining the contrast advantage of proton density-weighted sequences with that of T2 weighted sequences having a higher overall signal intensity in cartilage therefore allowing a better

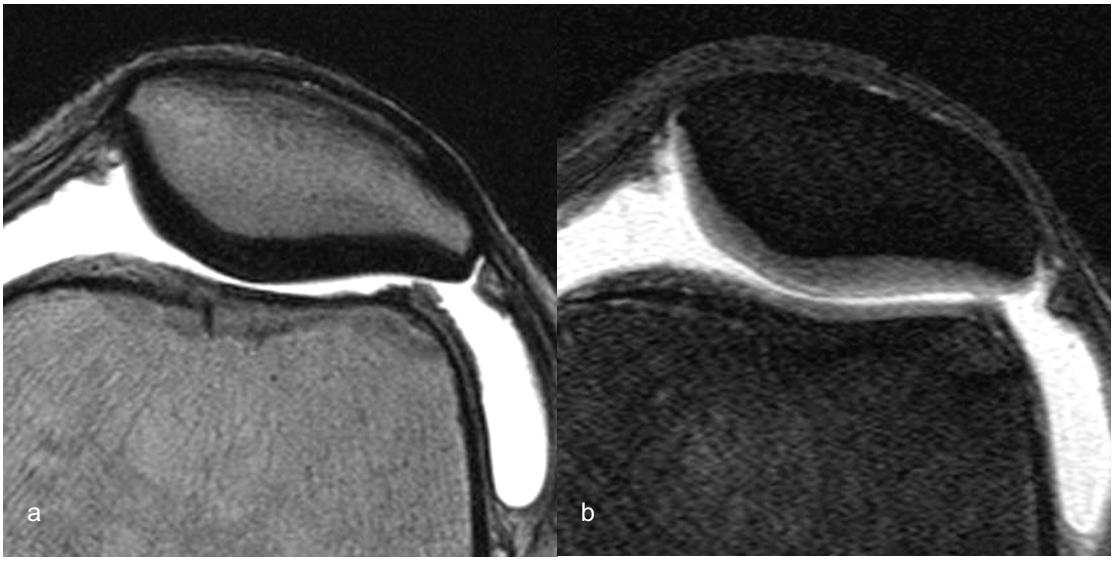

Figure 3: (a) Axial 2D T2-weighted non–fat-suppressed fast SE image provides excellent contrast between cartilage surfaces and synovial fluid, but the cartilage is poorly depicted with diffuse low signal intensity, and there is no contrast between cartilage and cortical bone. (b) Axial 2D intermediate-weighted fat-suppressed fast SE image shows excellent contrast among cartilage surfaces, synovial fluid, and subchondral bone, as well as variation of signal intensity within the cartilage.(Crema et al., 2011)

differentiation between cartilage and subchondral bone(Crema et al., 2011; Link, 2010).

The intact articular cartilage has lower signal intensity as compared to the bright fluid signal intensity, increasing the conspicuity of the focal surface lesions. The three-dimensional GRE sequences are also used to analyze the cartilage because they decrease blurring as well as partial volume artifacts and have a shorter acquisition time but are not ideal for assessing the subchondral bone. On the other hand, it has been shown that 3D fast SE sequences provide an equal diagnostic performance regarding the morphological evaluation of cartilage compared to the standard 2D fast SE and also provides a good depiction of subchondral bone structure while reducing the acquisition time (Kijowski, Blankenbaker, Munoz Del Rio, Baer, & Graf, 2013; Kijowski et al., 2009).

Three-dimension spoiled gradient recalled echo imaging with fat suppression (3D-SPGR) is the currently considered standard technique for morphological assessment of cartilage structure because it offers an excellent imaging quality and contrast of cartilaginous defects (Braun & Gold, 2012).

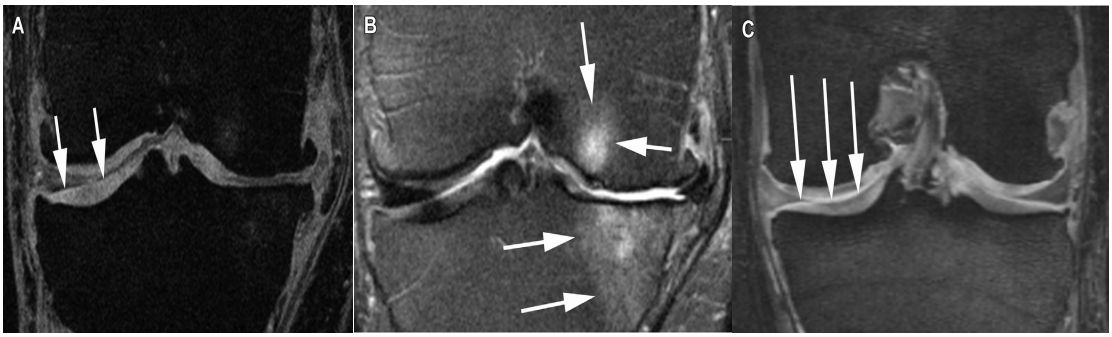

Figure 4: Comparison of different MRI sequences for assessment of cartilage. A. Coronal 3D FLASH image depicts the articular cartilage with high signal. Medial tibial cartilage coverage is preserved in this patient (arrows). B. Corresponding proton density- weighted fat suppressed image shows mixed signal intensity in the preserved cartilage medially. Note, in addition subchondral BMLs are superiorly depicted when compared to the FLASH sequence (arrows). C. Example of the DESS sequence, which depicts cartilage also with high signal intensity and is commonly used for cartilage segmentation (arrows). F.W. Roemer, A. Guermazi / Osteoarthritis and Cartilage 22 (2014) 2003-2012 (Roemer & Guermazi, 2014).

On the downside 3D SPRG sequences have a longer acquisition time, are vulnerable to susceptibility artifacts and are relatively unreliable regarding the contrast between cartilage and joint fluid. In three dimensional dual-echo steady-state (DESS) sequences two or more gradient echoes are acquired with each group of two echoes separated by a refocusing pulse and with data combined from both echoes used to obtain higher T2* weighting for high signal intensity in both cartilage and synovial fluid (Braun & Gold, 2012; Crema et al., 2011). Those sequences are useful in evaluating the internal derangement of the knee, especially in advanced cartilage lesions (Dongola & Gishen, 2004). Initial studies of cartilage morphology have been performed using newer sequences like the driven equilibrium Fourier transform (*DEFT*) imaging. It provides high contrast between cartilage and synovial fluid without loss of cartilage signal. Small surface irregularities and fissures have been best delineated with DEFT sequences compared to SPGR and FSE sequences (Yoshioka et al., 2004).

3.6.5 Semiquantitative Assessment scores WORMS, BLOKS and MOAKS

The whole-organ magnetic resonance imaging scoring system is an instrument for performing semiquantitative multi-feature assessments of the knee using conventional MRI. It incorporates 14 different articular features, which are relevant to the functional integrity of the knee and plays an important role in the pathophysiology of Osteoarthritis. For the evaluation of the cartilage, fat-suppressed T2-weighted FSE images and the FS-3D SPGR images are used which are widely available and easy to implement into most of the hospitals. It offers a high inter-reader agreement and therefore presents a reliable tool in the overall assessment of the knee joint.(C. G. Peterfy et al., 2004) An alternative scoring system is represented by the Boston Leeds

Osteoarthritis Knee Score (BLOKS). It uses a more complex system to evaluate the bone marrow lesions which adds quite the effort when reading it. In general, both scoring systems show a high level of reliability.(Lynch et al., 2010) A newer scoring system published by Hunter *et al.* was developed after analyzing the limitations of WORMS and BLOKS. The MRI Osteoarthritis knee score (MOAKS) is another semiquantitative score which has a refined system evaluating bone marrow lesions including sub-regional assessment and meniscal abnormalities compared to older scores. Moreover, the new score omits some areas of redundancy in cartilage and BML scoring of WORMS and BLOKS. (David J. Hunter et al., 2011)

3.6.6 Quantitative MRI for Cartilage

In order to develop preventive strategies for OA, techniques had to be developed which are sensitive and specific for detecting early changes of cartilage degeneration. Those changes are characterized mainly by changes in hydration and macromolecular structure within the matrix, in particular in the proteoglycan (PG) and collagen network. Therefore recent MRI techniques are focusing on sensitizing the measurement of water proton signals to the macromolecular contents and structures in the matrix based on energy and magnetization exchange between bulk-water protons and protons associated with macromolecules (X. Li & Majumdar, 2013).

Those techniques include methods based on relaxometry (delayed contrast-enhanced MRI of cartilage-dGEMRIC, T2 and $T1_\rho$ quantification), methods based on magnetization transfer measurement (chemical exchange saturation transfer (CEST)) and non-proton-based methods (sodium imaging). For ease of understanding, some of those techniques will be described in detail.

Delayed contrast-enhanced MRI of cartilage (dGEMRIC)

Glycosaminoglycans (GAG) are macromolecules present in the cartilage matrix. They possess negatively charged side chains that provide a negative fixed charged density to the cartilage. dGEMRIC is based on the principle that the negatively charged paramagnetic contrast agent gadolinium diethylene triamine pentaacetic acid ($Gd\text{-}DTPA^{2-}$) distributes in the cartilage in an inverse relationship to the GAG content. In normal cartilage, $Gd\text{-}DTPA^{2-}$ is repelled by the abundant negatively charged GAG, whereas in conditions of GAG loss, more $Gd\text{-}DTPA^{2-}$ will be distributed within the cartilage matrix. The concentration of $Gd\text{-}DTPA^{2-}$ can be calculated from pre- and post-contrast T1 values (Kurkijarvi, Nissi, Kiviranta, Jurvelin, & Nieminen, 2004; Tiderius, Olsson, Leander, Ekberg, & Dahlberg, 2003). The dGEMRIC measurements have been validated in clinical studies, corresponding to reference standard measurements for GAG histology and biochemistry(Crema et al., 2014), however there are limitations of this technique, which need to be taken into consideration. The injection of contrast media and the long delay of MR scan after injection are challenges for the widespread clinical application.

$T1_\rho$ Relaxation Time Quantification

T1rho describes the spin-lattice relaxation in the rotating frame (Singh et al., 2014). It is related with the energy changes between proton spins and the environment. T1ρ measurements can be used to probe the slow-motion interactions between motion-restricted water molecules and their local macromolecular environment. The extracellular matrix in the articular cartilage provides a motion-restricted environment to water molecules (Stahl et al., 2009). Therefore, an increased T1ρ relaxation time could indicate loss of PG and a disruption of the collagen matrix in articular cartilage

(Schooler et al., 2014). This type of cartilage quantification can provide valuable information related with biochemical changes in cartilage matrix. It provides a large dynamic range and sensitive detection of PG loss at early stages of cartilage degeneration. Additionally, it does not require any contrast media or special hardware, which makes it suitable to be used in clinical applications (X. Li & Majumdar, 2013).

T2 Relaxation Time Quantification

The transverse relaxation time T_2 measures the decay in phase coherence between the individual nuclear spins and is sensitive to the structure and orientation of the collagen fibrils in connective tissues (e.g. articular cartilage) in the external magnetic field. It reflects the ability of free water proton molecules to move and to exchange energy inside the cartilaginous matrix (X. Li & Majumdar, 2013). In 1997, Dardzinski *et al.* examined the spatial variation of in vivo cartilage T2 in young asymptomatic adults and found a reproducible pattern of increasing T2 that was proportional to the known spatial variation in cartilage water and was inversely proportional to the distribution of proteoglycans (Dardzinski, Mosher, Li, Van Slyke, & Smith, 1997). Due to its strong anisotropy, articular cartilage has a laminar appearance in MRI, which is also called the magic angle effect (Wang & Xia, 2011).

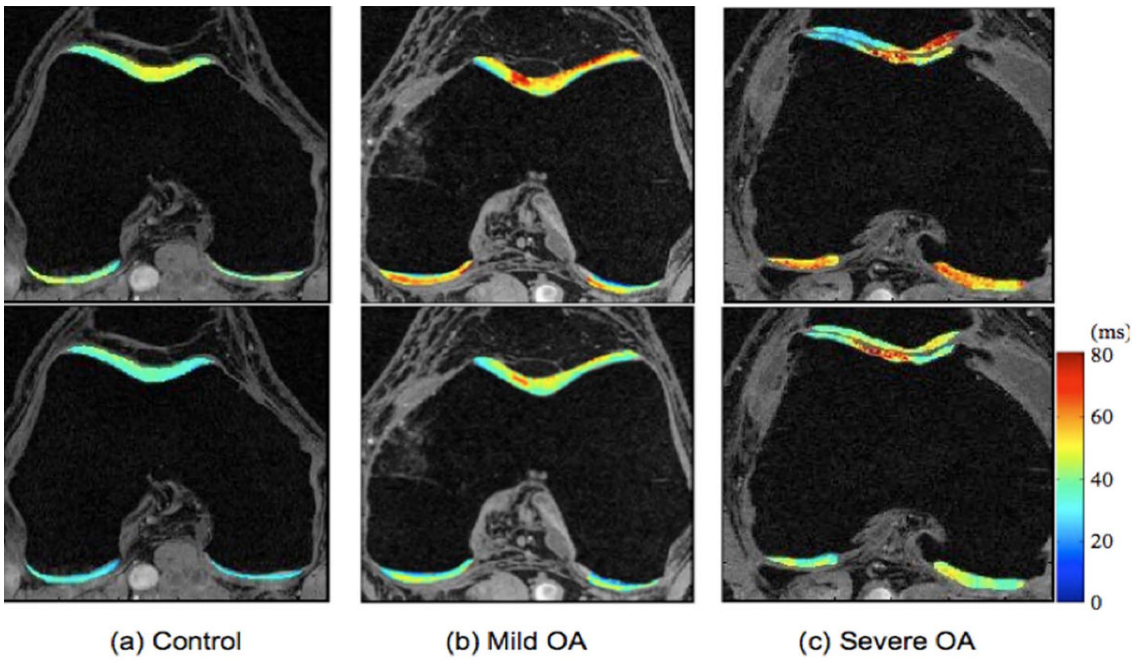

Figure 5: T1ρ and T2 maps of a healthy control (a), a subject with mild OA (b) and a subject with severe OA (c). Significant elevation of T1ρ and T2 values were observed in subjects with OA. T1ρ and T2 elevation had different spatial distribution and may provide complementary information associated with the cartilage degeneration. Li, X. and S. Majumdar, Quantitative MRI of articular cartilage and its clinical applications. J Magn Reson Imaging, 2013. 38(5): p. 991-1008. (X. Li & Majumdar, 2013)

Due to its sensitivity to the fibril orientation the interpretation can be challenging especially in clinical situations where the angular orientation of the tissue to the magnetic field cannot be controlled in the same way as for in vitro studies. Nevertheless recent reviews found promising results that T2 is a reliable measurement in assessing noninvasively early cartilage degeneration, reflecting changes of the biochemical composition of the articular cartilage (Baum, Joseph, Karampinos, et al., 2013; F. Eckstein, Burstein, et al., 2006). Therefore, T2 values might be able to predict the onset of radiological OA before radiographic changes are apparent (Liebl et al., 2014).

3.7. Treatment

Before discussing different treatment modalities for OA, we should remember that cartilage damage and loss of cartilage is an irreversible process, as up to now there is no possibility to regain lost cartilage. Therefore, most treatments focus on symptomatic relieve and its initiation is based on the symptom's severity, duration and impact on the functional status of the patient. Treatment options can be classified into pharmacological, non-pharmacological, surgical and alternative approaches. To achieve an optimal result, patients usually receive a combination of these treatment options. The American College of Rheumatology created detailed guidelines regarding the treatment of Arthritis in each joint separately as it can be seen in the table below using the knee as an example.

Non-pharmacological recommendations for the management of knee OA excluding surgical procedures.	**Pharmacological recommendations for the initial management of knee OA**
Aerobic/land-based exercise Aquatic exercise Weight loss Self-management programs Manual therapy in combination with supervised exercise. Psychosocial interventions Medially directed patellar taping Medially wedged subtalar strapped insoles (for those with lateral-compartment OA) Laterally wedged subtalar strapped insoles (for those with medial-compartment OA) Thermal agents Walking aids, as needed Tai Chi programs Traditional Chinese Acupuncture Transcutaneous electrical stimulation	Acetaminophen Oral NSAIDs Topical NSAIDs Tramadol Intra-articular corticosteroid injections No recommendations regarding the use of intra-articular hyaluronates, duloxetine, and opioid analgesics;

Table 2: Data from Hochberg M, Altman R, April KT, et al. American College of Rheumatology 2012: recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64(4):465–74. (Hochberg et al., 2012)

3.7.1 Non-pharmacological Treatment

One of the main limbs of non-pharmacological treatment is the participation into regular physical activity. It has been shown that almost any kind of moderate physical activity provides significant benefits in the treatment of OA (Esser & Bailey, 2011). In contrast to that inactivity and disuse of the affected joint have shown to accelerate impaired joint mechanisms which may result in a more rapid cartilage degeneration due to cartilage softening and matrix dysfunction (Hagiwara et al., 2009). There are many studies regarding the type and intensity of physical activity but mostly it is recommended to do aerobic or cardiovascular, low impact exercises like cycling, swimming or simple walks to improve function and reduce pain (Esser & Bailey, 2011). Resistance/strength training also plays an important role as it has positive effects regarding pain and physical function. The aim of this training is to reduce muscular disbalances and to strengthen the muscles responsible for the functionality of the joint (Christensen et al., 2005; Lange, Vanwanseele, & Fiatarone Singh, 2008). Another well-researched treatment modality is weight loss for overweight and obese patients. Weight loss as small as 5% - 10% can significantly improve disability and reduce circulation proinflammatory cytokines, which normally promote cartilage degeneration (Christensen et al., 2005; Christensen, Bartels, Astrup, & Bliddal, 2007; Richette et al., 2011). It is well known that massive weight loss improves symptoms like pain, function and decreases low-grade inflammation but newer studies prove that weight loss also has beneficial structural effects on the knee cartilage. Additionally, it is suggested that sustained weight loss over a longer period of time shows less progression in cartilage degeneration compared to a control (Bliddal, Leeds, Stigsgaard, Astrup, & Christensen, 2011; Serebrakian et al., 2014). Other non-pharmacological treatments recommended

by the ACR include lifestyle changes, psychosocial interventions, joint bracing, walking aids and different forms of Tai Chi and Yoga as well as acupuncture.

3.7.2 Pharmacological Treatment

The Osteoarthritis Research Society International (OARSI) set up recommendations regarding the pharmacological treatment including surgical procedures, intra-articular injections and oral analgesic medication (W. Zhang et al., 2008). For initial pain relieve Acetoaminophen (up to 4g/day) is prescribed as oral analgesic. If the patient receives adequate pain relief it can be administered on a permanent basis but in case of insufficient pain relieve and/or presence of inflammation the use of non-steroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose avoiding long-term use. Patients with increased gastrointestinal risk should receive a PPI (proton pump inhibitor) or misoprostol additionally for gastroprotection. IA (Intra articular) injections with corticosteroids are used for the treatment of moderate to severe pain in hip and knee OA. Indicated when the pain relieve through oral analgesic drugs is insufficient or when there are signs of local inflammation as well as joint effusion. IA injections with hyaluronate mostly have the same effects although they are characterized by delayed onset and prolonged action time. Regarding the guidelines, treatment with glucosamine and/or chondroitin sulphate may provide symptomatic relief as well as structure-modifying effects in symptomatic knee OA. If there are no positive effects after 6 months the use should be discontinued. As a last resort the use of opioids can be taken into consideration although it should only be used in exceptional situations e.g. when all other treatment options have failed. At this point most patients probably would benefit from surgical treatment. Patients

have several surgical options including osteotomy, joint lavage, arthroscopic debridement, unicompartmental or total knee replacement and as last ratio joint fusion. Which procedure the patient would benefit from the most must be evaluated separately in every case regarding his age, mobility and other symptoms.

4. Materials and Methods

4.1. Osteoarthritis Initiative (OAI)

Due to the rising awareness of the burden of OA, the National Institutes of Health (NIH) launched the Osteoarthritis Initiative as an ongoing multi-center, longitudinal, observational study focusing primarily on knee OA. The purpose of this study was the development of a public archive of data, biological samples and joint images (x-ray and magnetic resonance) in order to support investigation of the natural history of, and risk factors for, knee OA onset and progression using both traditional measures of disease as well as data on novel biomarkers developed from the study. The data was collected on an annual basis from a very well clinically characterized population of individuals divided into two groups: Individuals with clinically significant knee OA who are at risk of disease progression (progression cohort) and individuals who are at high risk of initiation of clinically significant knee OA (incidence cohort). Pertinent risk factors are knee symptoms in a native knee in the past 12 months, overweight, previous knee injury or surgery, Heberden's nodes, frequent knee bending activity or a family history of total knee replacement.

Between February 2004 and May 2006, the OAI enrolled 4796 men and women of all ethnic groups aged between 45 and 79 years. The study was conducted by four clinical centers (Ohio State University, Columbus; University of Maryland, Baltimore; University of Pittsburgh; Memorial Hospital of Rhode Island, Pawtucket;) and the data-coordinating center (University of California, San Francisco). Informed consent was obtained from all subjects and the study was HIPAA compliant. Study protocols, amendments and informed consent documentations were approved by the local institutional review boards. The following OAI datasets were used (available for public

access at http://www.oai.ucsf.edu): baseline imaging dataset 0.E.1, 48 month follow-up imaging dataset 6.E.1, 96 month follow-up imaging dataset 10.E.1, clinical datasets at baseline 0.2.2, 12 month follow-up 1.2.1, 24 month follow-up 3.2.1 and 48 month follow-up 6.2.2, 82 month follow-up 8.2.1 and 96 month follow-up 10.2.1.

4.2. Subject selection

As illustrated in Figure 4.1, we selected subjects with a baseline body mass index ≥25 kg/m^2 from the progression as well as the incidence cohort with right knee MRI T2 mapping sequences available at baseline, 48 months and 96 months. Subjects without BMI data at one of the eight annual time points were excluded. The same applied to individuals with a baseline Kellgren-Lawrence score larger 3 and the diagnosis of rheumatoid arthritis during one of the follow-ups. To avoid longitudinal changes in joint structure and clinical symptoms due to the trajectory of weight loss we analyzed the rate of change in BMI over 7 years using a linear regression model. Based on the root mean square error (RMSE) of the individual's regression line we categorized the weight change of the subjects into "steady" weight and "uneven" weight change. All patients with an "uneven" weight loss have been excluded from the overall study group. It was defined as an RMSE for weight change above the 95th percentile of the RMSE. Additionally, we excluded all subjects with the development of cardiac failure, cancer and/or other severe diseases during the 96-month study period that might have been causing weight loss using the Katz comorbidity questionnaire.

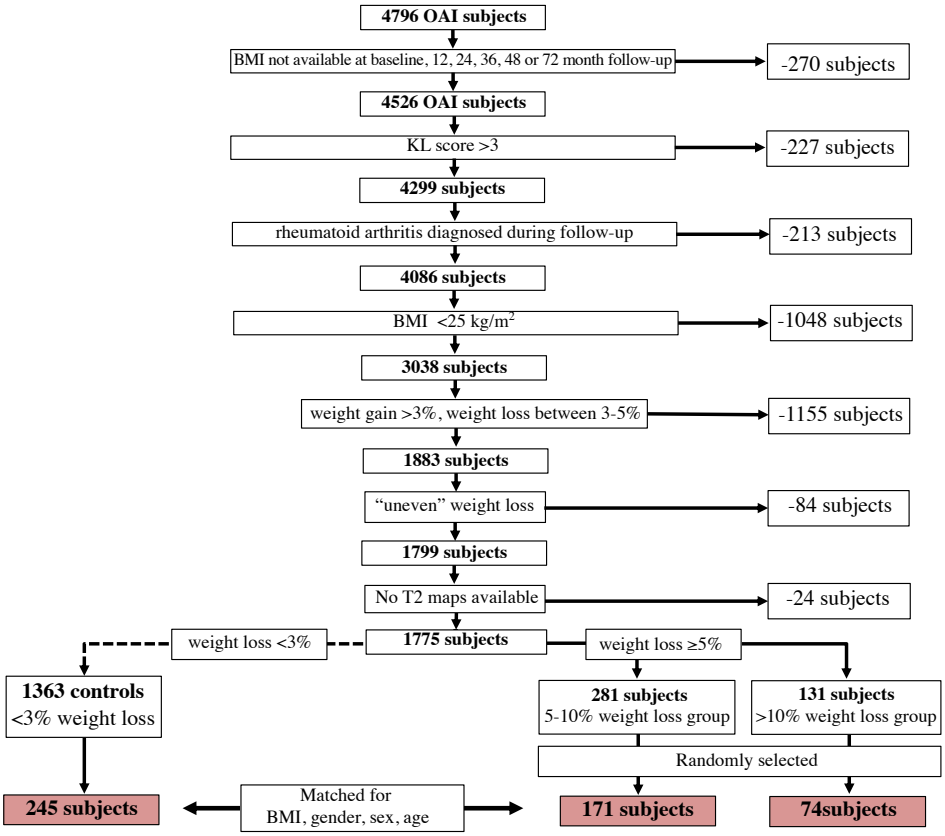

Figure 6: Subject selection process.

After excluding all subjects with previously listed exclusion criteria three groups were identified and selected regarding the amount of weight change over 72 months: moderate (BMI decrease of 5-10%), large amount of weight loss (BMI decrease of >10%) and stable weight (BMI changes <3%). From the moderate weight loss group, we randomly selected 169 subjects and from the >10% weight loss group 71 subjects. Subjects were frequency matched on baseline BMI and KL (BMI in 2.5 kg/m^2 strata, KL in strata of 0/1 and 2/3) to randomly selected subjects from the reference group with stable weight (n=250). Subject characteristics are shown in Table 4.1.

	All	stable weight [1]	weight loss 5-10%[1]	weight loss > 10%[1]	*P*-value 5-10% weight loss vs. stable weight group	*P*-value >10% Weight loss group vs. stable weight group
n	490 (100%)	245 (51.0%)	171 (34.5%)	74 (14.5%)		
Age (years; mean ± SD)	62.4 ± 9.1	62.2 ± 8.8	62.5± 9.4	62.8 ± 9.7	1.0 [3]	1.0 [3]
Sex (females;n (%))	296 (60.4%)	155 (50.5%)	104 (33.9%)	48(12.6%)	0.8 [2]	0.7 [2]
Baseline BMI (kg/m2; mean±SD)	30.3 ± 3.5	30.2 ± 3.5	30.2± 3.5	30.5 ± 3.5	1.0 [3]	1.0 [3]
Baseline KL Score						
KL = 0 (n (%))	194 (39.6%)	102(41.2%)	67 (39.1%)	26(35.2%)		
KL = 1 (n (%))	206(42.0%)	100 (40.0%)	75 (43.8%)	34 (45.1%)		
KL = 2 (n (%))	58 (11.8%)	28 (12.0%)	21 (12.4%)	7 (9.9%)		
KL = 3 (n (%))	32 (6.5)	15 (6.8%)	8 (4.7%)	7 (9,9%)		

Table 3: Subject characteristics. [1] Groups are matched for age, sex, baseline BMI and baseline KL Score, [2] Pearson's chi-squared test.

4.3. Clinical Scores

4.3.1. Physical Activity in the Elderly Scale (PASE)

The Physical Activity in the Elderly Scale is an established questionnaire assessing the physical activity in multiple domains of older adults. It was shown to be reliable and validated for the use in persons with knee OA (Martin et al., 1999). The questionnaire includes questions about household chores or job-related physical activity. As knee bending and lifting is associated with a higher risk for knee

OA(Coggon et al., 2000; Cooper, McAlindon, Coggon, Egger, & Dieppe, 1994; Felson et al., 1991), the PASE also evaluates occupational as well as non-occupational knee bending, squatting and stair climbing. The scale range of the PASE is 0-400 whereas higher scores stand for more activity and lower scores for less activity. Activities contained in the PASE score include strenuous, moderate and light sports as well occupational and housework physical activities.

4.3.2. Western Ontario and McMaster University Index (WOMAC)

The Western Ontario and McMaster University (WOMAC) Osteoarthritis Index is a standard tool for clinicians assessing knee pain, stiffness and knee-related physical function in patients with osteoarthritis of the knee (Bellamy, 2005; Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988). It is a survey based on self-report, which was thoroughly validated and recommended by the OARSI (Baum et al., 2012; Kretzschmar et al., 2015). The survey uses a pain score (range 0-20) as base and additional scores assessing stiffness (range 0-8) and functional disability (score range 0-68). Lastly the questionnaire also analyses the physical performance such as the climbing of stairs, standing up from a sitting or lying position, getting in and out of a car, bending, standing, walking, shopping, lying in bed as well as various other heavy and light household duties.

4.4. OAI Image acquisition protocols

4.4.1. Knee joint radiography

Radiographs acquired by the OAI mainly focused on the OA of the tibiofemoral joint arguing that the patellofemoral joint is comprehensively imaged via MRI. As a guideline the “fixed flection” knee radiographic protocol was used providing bilateral

standing x-rays in the posterior-anterior (PA) projection (Felson et al., 1997; C. Peterfy et al., 2003). The knees were positioned with a knee flexion of 20 to 30 degrees and the feet internally rotated by 10 degrees. To achieve a precise and comparable positioning a plexiglass positioning frame (SynaFlexerTM, CCBR-Synarc, San Francisco, USA) was used. Both knees were imaged together on 14 x 17-inch film using a focus-to-film distance of 72 inches. Afterwards all images were assessed by two experienced radiologists and graded in consensus according to the KL-score.

4.4.2. MR Imaging

The goal of the OAI was to acquire reliable imaging biomarkers and therefore they used four dedicated 3 Tesla MR systems (Trio, Siemens Medical Solutions, Erlangen, Germany) one located at each research facility to conduct this multi-center study. In order to have a high standard and avoid bias, all scanners underwent regular independent quality assurance (QA). For the QA the OAI used standardized phantoms, image protocols and special analysis in order to ensure that the images between the centers as well as in between the different time points were comparable. More information about the specific phantoms and quality assurance settings can be found in the OAI MR protocol.

MRI sequences used in the OAI

There are specific sequences used by the OAI to acquire images that are most suitable for the evaluation of the joint structures. Every sequence has a certain focus and detailed information regarding the slice thickness, number of slices and acquisition time. Imaging parameters are shown in Table 4.2. Subject positioning and scan set up can be found in detail in the OAI MRI Operator's Manual available on the website (http://www.oai.ucsf.edu) (C. G. Peterfy, Schneider, & Nevitt, 2008).

Coronal intermediate weighted turbo spin echo sequence (COR IW TSE)

This sequence provides a good overview over the image and is used to evaluate the joint alignment, cartilage morphology, cysts and sclerosis, the meniscal bodies as well as the collateral ligaments.

Sagittal three-dimensional dual echo stead state with water excitation (SAG 3D DESS WE).

This sequence is used to assess the volume and thickness of the total joint cartilage. Additionally, it can provide information about osteophytes subarticular bone cysts and bone attrition. It is not so sensitive in evaluating the bone marrow. This sequence is also run in coronal and axial plane.

	3-plane	2D TSE	3D DESS	2D TSE	3D FLASH	2D MSME	Thigh Loc.	Thigh Axial
Weighting	**T1W**	**Int**	**T2***	**Int**	**T1W**	**T2 Map**	**T1W**	**Int**
Plane	3-plane	Coronal	Sag	Sagittal	Cor	Sagittal	2-plane (Coronal, Axial)	Axial
Fat Sat	No	No	WE	Yes	WE	No	No	No
Matrix (phase)	256	307	307	313	512	269	256	384
Matrix (freq)	512	384	384	448	512	384	512	512
No. of slices	21	41	160	37	80	21	12	15
FOV (mm)	200	140	140	160	160	120	400	500
Slice thickness (mm)	5	3	0.7	3	1.5	3	10	5
Skip (mm)	1	0	0	0	0	0.5	0; 300	0
Flip Angle (deg)	40	180	25	180	12	n/a	60	180
TE/TI (ms)	5	29	4.7	30	7.57	10, 20, 30, 40, 50, 60, 70	5	13
TR (ms)	10	3850	16.3	3200	20	2700	10	600
BW (Hz/pixel)	250	352	185	248	130	250	250	199
Chemical Shift (pixels)	1.8	1.3	0	0	0	1.8	1.8	2.2
NAV (NEX)	1	1	1	1	1	1	1	1
Echo train length	1	7	1	5	1	1	1	1
Phase Encode Axis	A/P, R/L	R/L	A/P	S/I	R/L	A/P	A/P, R/L	A/P
Phase Partial Fourier (8/8 = 1)	1	1	1	1	1	1	1	1
Readout Partial Fourier (8/8 = 1)	1	1	1	1	1	1	1	1
Slice Partial Fourier (8/8 = 1)	1	1	0.75	1	0.75	0.75	1	1
Options:		elliptical k-space filter and large FOV filter	elliptical k-space filter, elliptical sampling, large FOV filter	elliptical k-space filter and large FOV filter	elliptical scanning, elliptical k-space filter, larger FOV filter	elliptical k-space filter and large FOV filter		elliptical k-space filter and large FOV filter; ascending slice order, 2 concatenations, no FlowComp, std shim
Distance Factor (%)	50	0	0	0	0	16	0; 300	0
Phase Oversampling	0	20	0	40	0	0	0	0
Slice Oversampling	0	0	10	0	0	0	0	0
Phase Resolution	50	80	80	70	100	70	50	62.5
Averaging Technique	Short Term	Short Term	Short Term	Short Term	Short Term	Short Term	Short Term	Short Term
Gradient Rise Time	Fast	Fast	Fast	Fast	Fast	Fast	Normal	Normal
RF Amplitude	Normal	Normal	Fast	Normal	Fast	Normal	Low SAR	Normal
X-Resolution (mm)	0.391	0.365	0.365	0.357	0.313	0.313	0.781	0.977
Y-Resolution (mm)	0.781	0.456	0.456	0.511	0.313	0.446	0.781	0.814
Calc time (min)	2.7	3.4	11.0	4.7	10.2	9.1	1.5	3.8
Scan time (min)	***0.5***	***3.4***	***10.6***	***4.7***	***8.6***	***10.6***	***1.5***	***6.4***

Table 4: Details of the OAI Knee imaging protocol.

Sagittal intermediate weighted two-dimensional fast spin echo sequence with fat suppression (SAG IW 2D FSE FS)

This sequence is particularly useful in evaluating the cartilage morphology and the presence or extent of sub chondral bone cysts and attrition due to the fact that with fat suppression, subarticular marrow can be displayed more clearly. Furthermore, it is used in the assessment of the anterior and posterior femoral and tibial osteophytes. The effusion volume can be measured as well.

Coronal T1 weighted three-dimensional fast low angel shot sequence with water excitation (COR T1W 3D FLASH WE)

This sequence is used to quantitatively measure the cartilage thickness and to segment the volume. The image should cover both femoral condyles as well as the tibia plateau. Additionally, it can be used to identify medial and lateral osteophytes on the femur and tibia, subarticular marrow oedema and cysts in the coronal plane although one has to keep in mind that the marrow assessment is less sensitive compared to sequences with a fat suppression.

Sagittal T2 weighted two-dimensional single excitation multiecho-spinecho sequence (SAG T2 2D MESE)

It was included into the OAI imaging protocol to allow quantification of cartilage T2 relaxation times. As discussed in chapter 3.6.6 those numbers relate to the collagen integrity. In this project T2 relaxation time values were calculated by using the SAG T2 2D MESE sequence with seven echo times (TEs 10ms, 20ms, 30ms, 40ms, 50ms, 60ms, and 70ms). Furthermore, this sequence can be used to assess the cartilage

morphology, anterior and posterior meniscal horns, the cruciate ligament, osteophytes and subchondral bone cysts (C. G. Peterfy et al., 2008).

4.5. Image Assessment

4.5.1. Qualitative Image Evaluation

In this project only images of the right knee have been assessed after transferring them to the picture archiving and communication system (PACS). The images were evaluated separately by two musculoskeletal radiologists (B.S. and A.G.) with more than 5 years of work experience. In case of different scoring results, the images were reviewed by an experienced third radiologist to find a consensus. There have been no time restraints and during their readings the radiologists have been blinded regarding the patient history. For scoring, a modified version of the WORMS has been used. It has been well established and used in several previous studies performed by our study group (Baum, Joseph, Nardo, et al., 2013; Laberge et al., 2012). In contrast to the original 15 WORMS regions the cartilage was assessed only in the following 6 compartments: patella, trochlea, medial/lateral femur and medial/lateral tibia. Cartilage lesions were graded using a standard 8-point scale. Meniscal lesions were graded separately in the medial and lateral aspects of the anterior, body, and posterior portions of the meniscus using a 4-point WOMRS scale. In total, 10 different joint structures were graded separately including cartilage, ligaments, osteophytes, popliteal cysts, loose bodies, menisci, bone marrow edema like lesion (BME), alteration of the articular surfaces, subarticular cysts and synovitis or effusion. Intrasubstance degeneration was added to the WOMRS classification in order to allow quantification of early degenerative disease. Finally, the values were summed (WORMS SUM) up and maximum (WORMS Max) scores were calculated for each joint structure to

express the severity of focal knee lesions. A maximum score greater 0 in any joint structure was defined as the presence of a lesion. E.g. A meniscal WORMS Max < 1 indicates a small tear or worse whereas a WORMS Max >1 in the cartilage indicates that the patient has at least one partial thickness defect (Laberge et al., 2012).

In our 96-month longitudinal analysis we defined progression as any change to a previously intact knee including new meniscal or cartilage lesions or existing lesions that had worsened. Any changes in signal intensity, morphology or any other progression was detected by identifying additional or worsening lesions from baseline to the 96-month follow-up. Progression to a higher grade was detected using a WOMRS Max "delta > 0" analysis.

4.5.2. Quantitative Image Analysis

As described in chapter 4.4.2 T2 maps were generated using the sagittal two-dimensional multiecho-spinecho (MESE) images of the right knee. All images were analyzed with a Sun Workstation (Sun Microsystems, Oracle Corporation, Redwood Shores, CA, USA). T2 maps were computed using a monoexponential decay model (Figure 4.2) that works on a pixel-by-pixel basis by using six echoes (TE = 20 to 70 ms) and with three parameter fittings accounting for noise as described by Joseph *et al.* (Joseph et al., 2011).

$$S(TE)^2 = S_0{}^2 e^{-\frac{2 * TE}{T_2}} + B^2$$

Figure 7: S is the signal intensity at a given echo time (TE), S_0 is the signal intensity at TE = 0 ms and B is the estimated noise at a given TE,

In general, articular cartilage shows a multiexponential T2 decay with a short and long T2 component. Unfortunately, it is not possible to receive validated measurements (in microseconds) without specialized software. Therefore, in this study we used the mono-exponential decay model. In order to improve signal-to-noise ratio we excluded the first echo (10ms) from our calculations because this has previously been shown to be effective (Raya et al., 2010).

Semi-automatic cartilage segmentation of lateral femur, lateral tibia, medial femur, medial tibia and patella compartments was performed, using an in-house, spline-based software based on MATLAB (MathWorks, Natick, Massachusetts) and an interactive display language routine (mrsc_image, IDL, Research Systems, Boulder, USA). Additionally, we were able to calculate the mean cartilage thickness of all regions of interest (ROI) for each compartment (Liebl et al., 2014). The cartilage segmentation has been performed and graded by two trained medical researchers (G.C.F. and M.S.) in consensus under supervision of two experienced radiologists (T.M.L. and A.G.) using the first echo of the MSME sequence.

ROI's were only drawn on artifact-free slices with well-defined boundaries of the cartilage. Examples of different types of artifacts are shown in figure 4.4. The trochlea was not segmented because of the interfering flow artifacts from the popliteal artery, which could lead to an unexpected alteration of the T2 values. Figure 4.3 shows manually drawn ROIs outlining the cartilages.

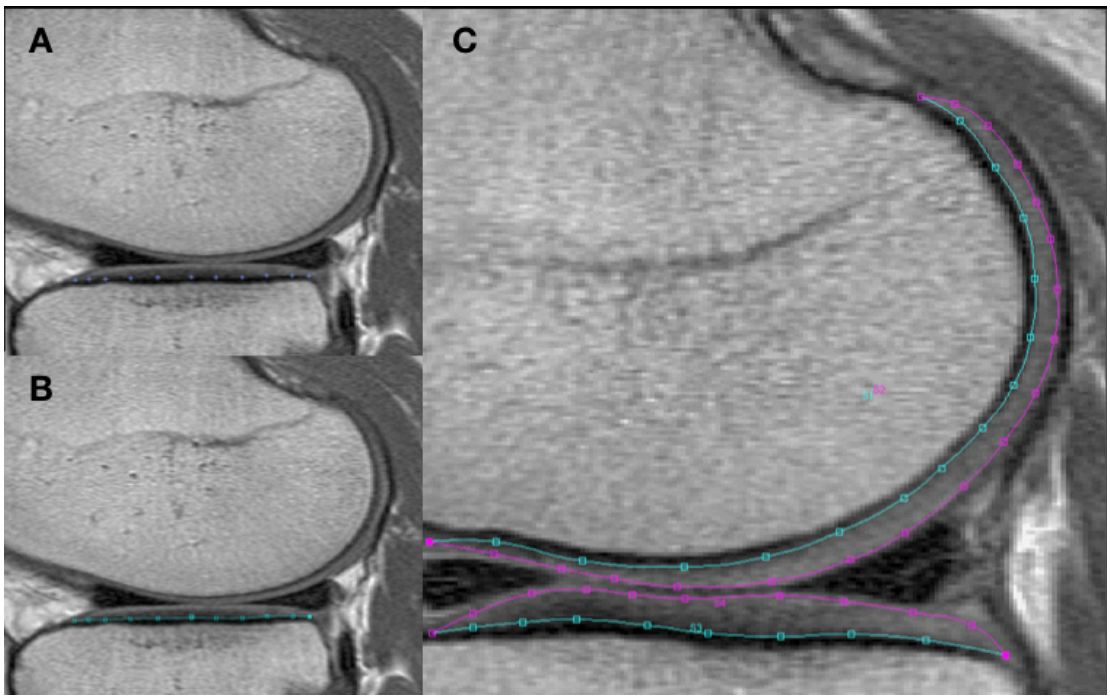

Figure 8: Segmentation procedure. A: Dots are drawn along the bone layer excluding the chemical shift. Afterwards they are connected to a spline (B). The segmentation program creates a corresponding spline at the articular layer, which needs to be adjusted into the right position. This is done for each slice in each compartment. C shows an example of the ROIs of the femoral und tibial compartment.

Furthermore, we performed an automatic laminar analysis, which subdivided the segmented compartments into a superficial and deeper cartilage layer of equal thickness (Carballido-Gamio, Joseph, Lynch, Link, & Majumdar, 2011). Basically, the software splits the whole cartilage into two layers and the superficial layer is oriented to the articular surface and the deeper layer is connected to the bone surface. The laminar analysis allows us to provide a more sensitive assessment of T2 relaxation time measurements and better characterizes cartilage degenerative changes. This is particularly useful for the interpretation of longitudinal data. It is important to keep in mind that for correct interpretation the cartilage thickness should not show significant cartilage thickness changes over time (Carballido-Gamio, Blumenkrantz, Lynch, Link, & Majumdar, 2010).

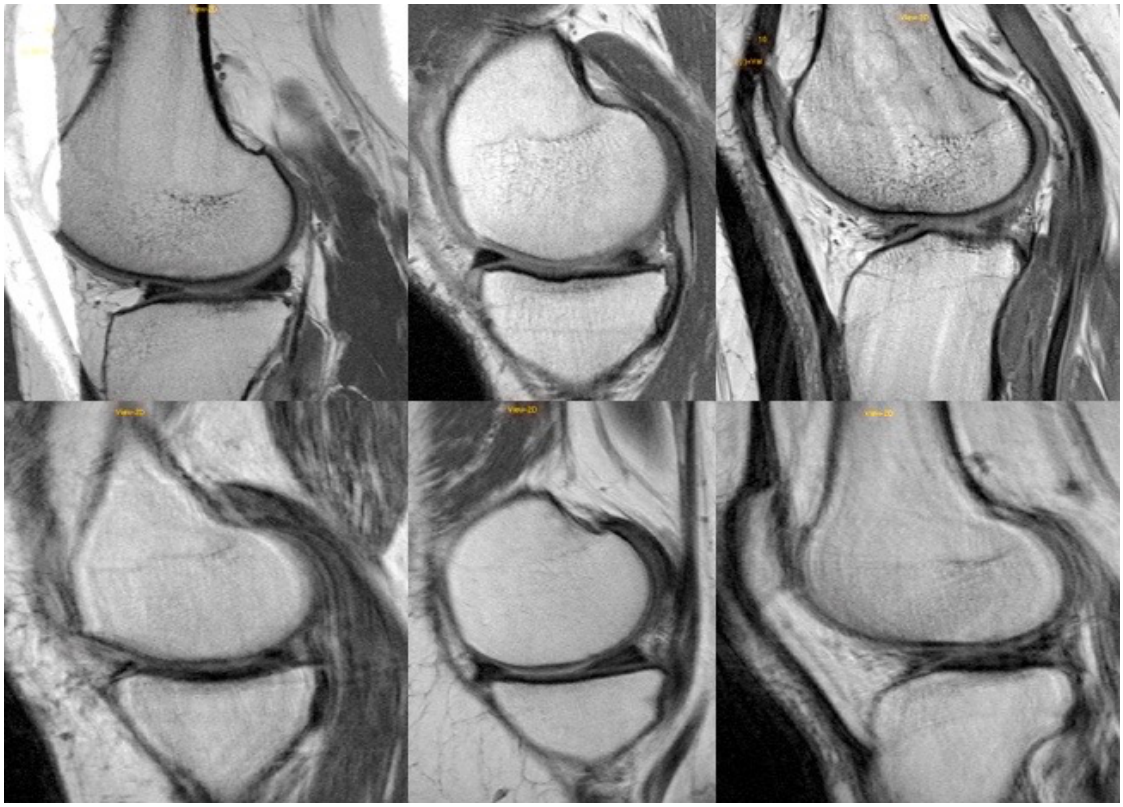

Figure 9: Examples of artifact. A is showing a wrapping artifact, B + E show blurriness, C shows the typical pulsation artifact of A. popliteal and D + F show motion artifacts due to the movement of the patient during image acquisition. For quality assurance those images have been excluded from segmentations.

To prove this, we calculated the distance between the cartilage-bone interface and the closest point on the articular surface for each region, which represents the thickness. Afterwards the average thickness of each slice was calculated.

In order to receive more information regarding the cartilage morphology an exploratory analysis of the cartilage texture has been done. As described by Joseph *et al.* (Joseph et al., 2011) the texture analysis is done on a slice-by-slice technique using a grey-level co-occurrence matrix (GLCM) analysis to evaluate the spatial distribution of cartilage T2 values. In this study we focused on only four of the GLCM parameters, two from the contrast group (contrast and homogeneity), and one parameter each from the orderliness group (entropy) and the statistics group (variance). The contrast represents the differences of values of neighboring pixel, meaning that high GLCM

contrast indicates a high probability of neighboring pixels with large differences in T2 value (Bucknor et al., 2015a). The homogeneity decreases exponentially inversely from the contrast value and expresses the similarity of neighboring pixels. Therefore, higher GLCM values reflect high similarity between neighboring pixels (Carballido-Gamio et al., 2011; Haralick, Shanmugam, & Dinstein, 1973). GLCM variance is a measure of the dispersion of pixel values around the mean T2 value, meaning that high variance reflects a high number of pixels with T2 co-occurrences dispersed from the mean T2 value (Hall-Beyer, 2007; Joseph et al., 2011). The entropy measures the orderliness regarding the distribution of pixel value co-occurrences and therefore high GLCM entropy indicates that pixel pairs with the same T2 value are less likely to be found (Carballido-Gamio et al., 2011; Haralick et al., 1973; Joseph et al., 2011; Mosher, Dardzinski, & Smith, 2000).

4.6 Statistical Analysis

Statistical analysis was performed on SPSS Version 22, software (International Business Machines Corp, IBM, NY, USA) using a two-sided 0.05 level of significance. For the identification of patient characteristics and evaluation of the differences between the groups (stable weight, 5-10% weight loss and > 10% weight loss) a one-way analysis of variance (ANOVA) and a chi-square test were used.

To analyze the changes in T2 relaxation times between the different weight loss groups over the time period of 96 months a linear mixed model was used. With the linear mixed model, we were able to calculate the rate of change for each group over 8 years. Additionally, the linear mixed model compared the rate of change of the weight loss groups (5-10% and >10% weight loss) to the weight stable group and calculated the

intergroup differences in the rate of change. These differences in the slope (rate of change) have been calculated for each department separately and for a mean T2 relaxation time representing the cartilage of the whole knee with all 5 compartments. Depending on whether the slope behaved non-linearly or linearly the mixed model has been adjusted to fit to the trend by either adjusting the fixed effects for the quadratic relation of time by time or the relation of time by group. The same statistical technique has been used for the analysis of the laminar T2 relaxation time values, GLCM texture parameters, cartilage thickness, WORMS and the clinical scores WOMAC and PASE. Finally, for confirmatory purpose the > 10 %weight loss group and the 5 – 10% weight loss group have been fused to one weight loss group (>5% weight loss). Afterwards the linear mixed model, as described was used to compare the slopes of the weight stable group and the weight loss group.

4.7 Reproducibility

To ensure the reproducibility and reliability of the collected data every reader had to assess 10 randomly selected cases twice during the time of data acquisition. The selected cases were identical for both readers. T2 measurements were calculated on a percentage basis as the root mean square average of the single coefficients of variation (CV) to assess the reproducibility error as previously described (Gluer et al., 1995).

Inter-reader reproducibility was assessed between the two readers (M.S. and G.C.F.) in 10 patients and was 1.66% over all compartments. CVs for single compartments were as follows: 1.28% for the lateral femur, 1.11% for the lateral tibia, 1.29% for the medial femur, 2.01% for the medial tibia, and 2.42% for the patella. For intra-reader reproducibility analysis, the reader G.C.F segmented the same 10 cases

after at least 30 days. Intra-reader CVs were calculated for each compartment using these repeated measurements and compartment specific and overall CVs were as follows: 1.01% for the lateral femur, 1.08% for the lateral tibia, 1.00% for the medial femur, 1.63% for the medial tibia, 1.54% for the patella, and 1.35% overall compartments.

5. Results

5.1 Subject Characteristics

An overview of the subject characteristics is given in Table 4.1. No significant differences in the mean age, baseline BMI or gender frequencies between the groups have been detected. Also, no significant difference between any of the groups was found for KL scores ($p > 0.05$).

5.2. Semiquantitative Analysis

5.2.1 WORMS and KL Scoring Results by Gender

When analysing the WORMS Sum scores, we were not able to detect any significant differences in between the different weight-loss groups over the period of 8 years as shown in Table 5.1. Nevertheless, when taking a closer look at the WORMS sub-scores (Table 5.2 -5.7) there was a significantly slower progression in multiple compartments in the >10% WL-group with less progression regarding meniscal defects of the body and the posterior medial meniscus. Interestingly enough, there also was a slower progression of bone marrow edema pattern and subchondral cyst formation in the lateral femur condyle. In the 5 -10% weight-loss group a significantly slower progression of defects was found in the following compartments: cartilage lesions of the lateral tibia, subchondral bone cysts in the lateral tibia and lateral femur condyles.

Sum scores	Group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Sum Cartilage	Control				
	> 10 % WL loss	.006263	.779	-.037521	.050046
	5-10 % WL loss	-.012881	.353	-.040103	.014341
Sum BMEP	Control				
	> 10 % WL loss	-.008813	.385	-.028731	.011106
	5-10 % WL loss	-.007648	.226	-.020032	.004736
Sum Menisci	Control				
	> 10 % WL loss	-.006187	.508	-.024527	.012152
	5-10 % WL loss	-.008053	.166	-.019455	.003349

Table 5: Rate of change of WORMS Sum scores for cartilage lesions, bone marrow edema and meniscal lesions.

Menisci	Group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
MenMedAnt	Control				
	> 10 % WL loss	.001276	.366	-.001493	.004046
	5-10 % WL loss	.001701	.923	-.001637	.001807
MenMedBody	Control				
	> 10 % WL loss	.010236	**.018**	.001761	.018712
	5-10 % WL loss	-.002580	.337	-.007850	.002689
MenMedPost	Control				
	> 10 % WL loss	.008395	**.046**	.000151	.016640
	5-10 % WL loss	.002061	.430	-.003065	.007187
MenLatAnt	Control				
	> 10 % WL loss	.006850	.082	-.000882	.014582
	5-10 % WL loss	-.001504	.539	-.006311	.003303
MenLatBody	Control				
	> 10 % WL loss	.001288	.732	-.006081	.008657
	5-10 % WL loss	-.002261	.333	-.006842	.002321
MenLatPost	Control				
	> 10 % WL loss	-.004115	.236	-.010917	.002688
	5-10 % WL loss	-.002537	.239	-.006766	.001693

Table 6: Rate of change of WORMS score for meniscal lesions. Less progression of meniscal lesions has been found in the body and posterior medial meniscus of the > 10 weight loss group.

Ligaments	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
ACL	Control				
	> 10 % WL loss	.001683	.612	-.004823	.008188
	5-10 % WL loss	-.001293	.531	-.005338	.002751
PCL	Control				
	> 10 % WL loss	.000566	.600	-.001553	.002685
	5-10 % WL loss	-.000718	.285	-.002036	.000599
MCL	Control				
	> 10 % WL loss	-.000208	.864	-.002601	.002184
	5-10 % WL loss	.000848	.264	-.000639	.002335
LCL	Control				
	> 10 % WL loss	.001276	.366	-.001493	.004046
	5-10 % WL loss	0.00174	.923	-.001637	.001807
Patella tendon	Control				
	> 10 % WL loss	.005044	**.003**	.001726	.008361
	5-10 % WL loss	.001182	.261	-.000881	.003245
Popliteal tendon	Control				
	> 10 % WL loss	-.000499	.583	-.002282	.001284
	5-10 % WL loss	-.000464	.412	-.001572	.000645

Table 7: Rate of change of WORMS score for the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), lateral collateral ligament (LCL), Patella tendon and popliteal tendon.

Cartilage Lesions	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
CartLesP	Control				
	> 10 % WL loss	.004562	.573	-.011318	.020441
	5-10 % WL loss	.001004	.842	-.008868	.010877
CartLesT					
	> 10 % WL loss	.006354	.409	-.008729	.021437
	5-10 % WL loss	.002807	.557	-.006577	.012191
CarLesMFC	Control				
	> 10 % WL loss	.005405	.411	-.007493	.018302
	5-10 % WL loss	-.001132	.782	-.009151	.006887
CarLesLFC	Control				
	> 10 % WL loss	-.010478	.056	-.021214	.000258
	5-10 % WL loss	-.006540	.055	-.013215	.000135
CarLesMT	Control				
	> 10 % WL loss	.004794	.407	-.006544	.016132
	5-10 % WL loss	-.000409	.909	-.007459	.006640
CarLesLT	Control				
	> 10 % WL loss	-.004219	.462	-.015474	.007036
	5-10 % WL loss	-.008629	**.016**	-.015627	-.001632

Table 8: Rate of change of WORMS score for cartilage lesions of the knee: patella, trochlea, medial femur condyles, lateral femur condyles, medial tibia lateral tibia.

Bone marrow edema pattern	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Patella	Control				
	> 10 % WL loss	-.000371	.930	-.008629	.007886
	5-10 % WL loss	.003016	.249	-.002118	.008150
Trochlea					
	> 10 % WL loss	-.002408	.582	-.010981	.006165
	5-10 % WL loss	.002780	.307	-.002553	.008114
Medial femur condylus	Control				
	> 10 % WL loss	.000395	.899	-.005680	.006469
	5-10 % WL loss	-.002660	.167	-.006437	.001116
Lateral femur condylus	Control				
	> 10 % WL loss	-.005467	**.038**	-.010622	-.000311
	5-10 % WL loss	-.004319	**.008**	-.007524	-.001113
Medial tibia	Control				
	> 10 % WL loss	-.000119	.970	-.006379	.006141
	5-10 % WL loss	-.000962	.628	-.004854	.002930
Lateral tibia	Control				
	> 10 % WL loss	-.000792	.778	-.006303	.004719
	5-10 % WL loss	-.005491	.002	-.008917	-.002064

Table 9: Rate of change of WORMS score for bone marrow edema pattern.

Subchondral cysts	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval

				Lower Bound	Upper Bound
Patella	Control				
	> 10 % WL loss	-.003140	.420	-.010773	.004492
	5-10 % WL loss	-.000222	.927	-.004968	.004523
Trochlea					
	> 10 % WL loss	.001327	.738	-.006447	.009100
	5-10 % WL loss	-.001335	.588	-.006168	.003498
Medial femur condylus	Control				
	> 10 % WL loss	.001332	.575	-.003327	.005991
	5-10 % WL loss	-.000730	.621	-.003626	.002167
Lateral femur condylus	Control				
	> 10 % WL loss	-.004186	**.029**	-.007949	-.000422
	5-10 % WL loss	-.003442	**.004**	-.005782	-.001102
Medial tibia	Control				
	> 10 % WL loss	-.000119	.587	-.004129	.007296
	5-10 % WL loss	-.000962	.265	-.001534	.005569
Lateral tibia	Control				
	> 10 % WL loss	-.003103	.220	-.008070	.001863
	5-10 % WL loss	-.004342	**.006**	-.007429	-.001254

Table 10: Rate of change for WORMS score of subchondral cysts.

	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Effusion	Control				
	> 10 % WL loss	-.002076	.389	-.006799	.002648
	5-10 % WL loss	-.002154	.150	-.005091	.000783
Loose bodies					
	> 10 % WL loss	.000412	.770	-.002356	.003181
	5-10 % WL loss	-.000537	.541	-.002258	.001184

Table 11: Rate of change of the WORMS score for Effusion und loose articular bodies.

5.3. Quantitative Analysis

5.3.1 Change in T2 relaxation time and weight loss

Table 5.8 shows the differences in slope regarding the progression of T2 values in between the different weight loss groups over 8 years, whereas the weight stable group (< 3% weight loss) is used as comparative control. In the global T2 we were able to detect a significant deceleration in the over > 10% WL-group compared to the controls. Moreover, a significant deceleration was also seen in the medial and lateral Tibia as well as in the Patella, not only in the > 10% WL-group but also in the >5-10% WL-group. Figure 5.1 nicely illustrates the slower progression of cartilage T2 numbers in the >10 % WL-group compared the control group.

Compartment	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Mean	Control				
	> 10 % WL loss	-0,0325550	**.023**	-0,060632	0,004478
	5-10 % WL loss	-0,0085050	.298	-0,024543	0,007534
Lateral Femur	Control				
	> 10 % WL loss	-0,0126390	.466	-0,046646	0,021367
	5-10 % WL loss	-0,0100480	.292	-0,028765	0,00867
Lateral Tibia	Control				
	> 10 % WL loss	-0,0345060	**.016**	-0,062648	-0,006364
	5-10 % WL loss	-0,016065	**.043**	-0,031652	-0,000479
Medial Femur	Control				
	> 10 % WL loss	-0,0164850	.401	-0,054966	0,021997
	5-10 % WL loss	-0,00125	.904	-0,021538	0,019039
Medial Tibia	Control				
	> 10 % WL loss	-0,0290740	**.040**	-0,05685	-0,001298
	5-10 % WL loss	-0,0155240	**.031**	-0,029656	-0,001391
Patella	Control				
	> 10 % WL loss	-0,0476110	**.010**	-0,083897	-0,011324
	5-10 % WL loss	-0,0211940	**.040**	-0,041464	-0,000925

Table 12: Differences in slope regarding progression of T2 values. [1] Non-linear data.

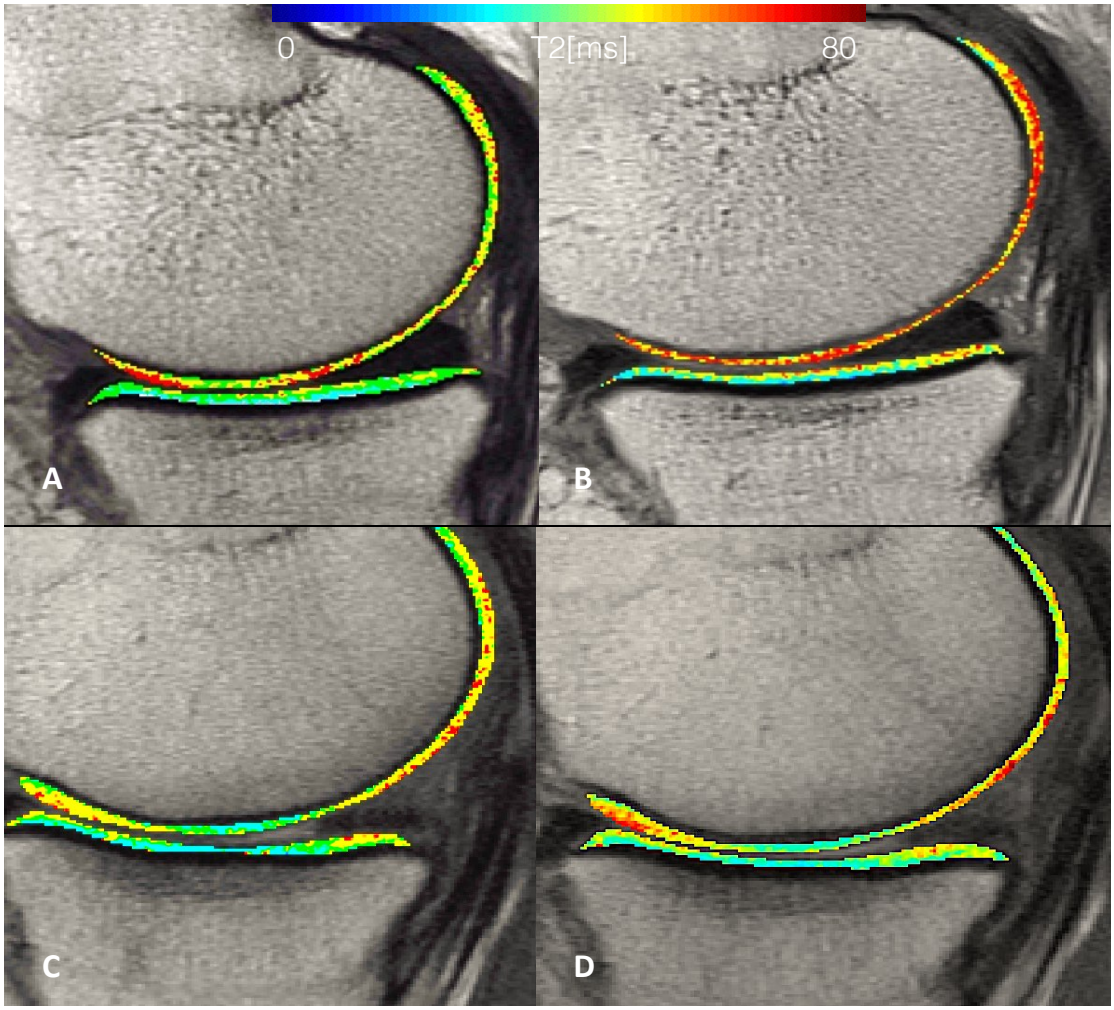

Figure 10: Representative T2 maps of the medial tibia from a control (A, B) and a subject from the over 10 % WL group (C, D) at baseline (left) and 96 months follow up (right). Note the distinct increase of T2 values in the control group compared to the weight loss group depicting a slower cartilage degeneration.

The results of the laminar sub-analysis support the results of the previous analysis. In the mean T2 a significant deceleration was detectable in the bone layer (p=0.023) as well as in the articular layer (p=0.045) of the >10% weight loss group. As described in Table 5.9, the over 10 % WL-group showed significant differences in slope in bone and articular layer of the patellar compartment as well as the lateral tibia. In the medial tibia only the bone layer of the > 10% WL-group showed a significant deceleration. The 5 - 10 % weight loss group showed a significant difference in slope in the bone layer of the medial and lateral tibia as well as the patella.

Compartment	Layer	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
					Lower Bound	Upper Bound
Mean	Articular layer	Control				
		> 10 % WL loss	-.033583	**.045**	-.066387	-.000780
		5-10 % WL loss	-.009613	.314	-.028351	.009126
	Bone layer	Control				
		> 10 % WL loss	-.031245	**.023**	-.058219	-.004270
		5-10 % WL loss	-.008670	.269	-.024079	.006739
Medial Tibia	Articular layer	Control				
		> 10 % WL loss	-.022847	.238	-.060820	.015126
		5-10 % WL loss	-.017352	.078	-.036673	.001969
	Bone layer	Control				
		> 10 % WL loss	-.035110	**.007**	-.060571	-.009650
		5-10 % WL loss	-.015583	**.018**	-.028537	-.002628
Lateral Tibia	Articular layer	Control				
		> 10 % WL loss	-.042868	**.028**	-.081068	-.004669
		5-10 % WL loss	-.017653	.102	-.038809	.003504
	Bone layer	Control				
		> 10 % WL loss	-.025625	**.026**	-.048177	-.003072
		5-10 % WL loss	-.014643	**.022**	-.027133	-.002152
Patella	Articular layer	Control				
		> 10 % WL loss	-.048412	**.031**	-.092314	-.004509
		5-10 % WL loss	-.019389	.121	-.043913	.005135
	Bone layer	Control				
		> 10 % WL loss	-.046265	**.006**	-.079257	-.013273
		5-10 % WL loss	-.021229	**.024**	-.039658	-.002799

Table 13: Laminar sub-analysis of the patellar compartment and the overall T2.

Figure 5.2 illustrates the T2 values for the patellar compartment over three time points comparing the weight stable group with the > 10% weight loss group. It nicely shows the progression of weight stable group in comparison to the > 10 % weight loss group.

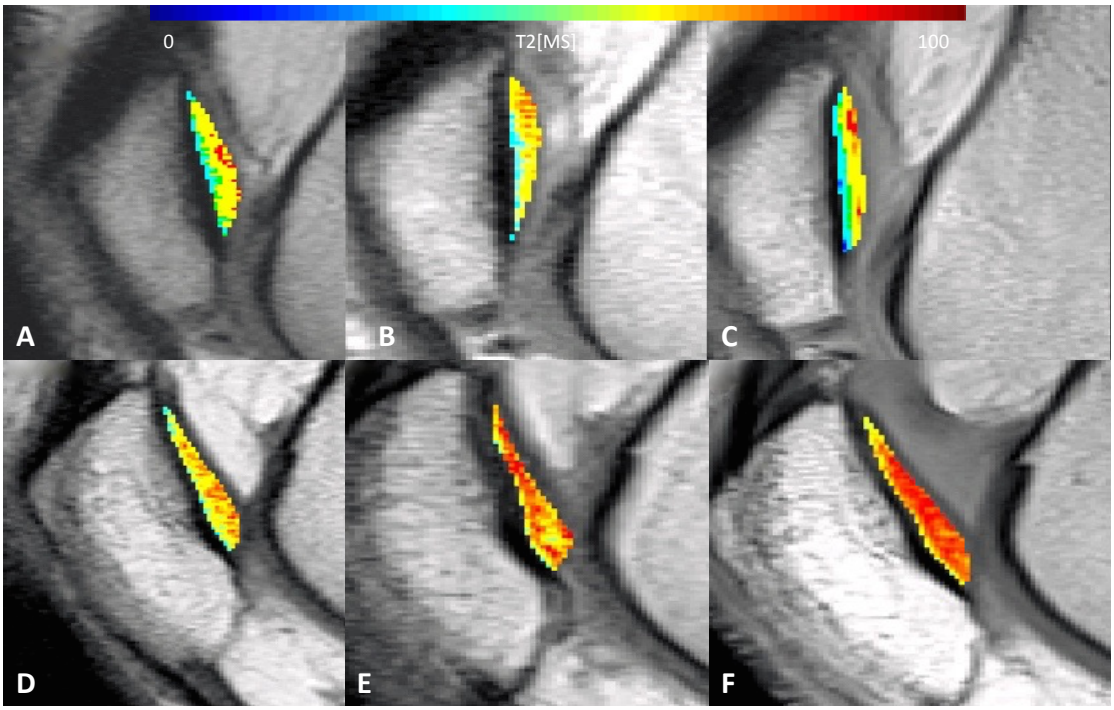

Figure 11: T2 values of the patellar compartment. A, B, C = Baseline, 48-month, 96-month follow-up of the >10% Group, C, D, E = Baseline, 48-month, 96-month follow-up of the control Group

5.3.2 Change in GLCM and weight loss

Regarding the texture analysis the >10% weight loss group showed a significant increase (p=0.006) in homogeneity in the overall, medial and lateral tibia as well as patella (Table 5.10 – 5.13). Furthermore, in the 5-10% WL-group a significant increase in homogeneity was seen in the lateral tibia as well as a significant deceleration of variance in the medial and lateral tibia as well as patella.

Texture Mean T2	Weight-loss group	Difference in Slope compared to controls	P-Value	95% Confidence Interval	
				Lower bound	Upper bound
Variance	Control				
	> 10 % WL loss	-.546204	.082	-1.162.977	.070568
	5-10 % WL loss	-.422398	**.019**	-.774723	-.070074
Entropy	Control				
	> 10 % WL loss	-.003591	.062	-.007368	.000187
	5-10 % WL loss	-.000856	.436	-.003014	.001301
Homogenity	Control				
	> 10 % WL loss	.000498	**.006**	.000141	.000854
	5-10 % WL loss	.000173	.095	-3.023201	.000377
Contrast	Control				
	> 10 % WL loss	-1.027.341	.058	-2.088.420	.033739
	5-10 % WL loss	-.848601	**.006**	-1.454.731	-.242471

Table 14: Texture analysis of the patellar compartment.
***No significant differences in the thickness (rate of change over 8 years)**

Texture Patella	Weight-loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Variance	Control				
	> 10 % WL loss	-.374346	.256	-1.020.613	.271921
	5-10 % WL loss	-.256377	.164	-.617388	.104635
Entropy	Control				
	> 10 % WL loss	-.003222	.243	-.008632	.002188
	5-10 % WL loss	-.001296	.400	-.004318	.001726
Homogenity	Control				
	> 10 % WL loss	.000478	**.038**	2,72E+01	.000930
	5-10 % WL loss	.000245	.057	-7.45200	.000497
Contrast	Control				
	> 10 % WL loss	-.451086	.386	-1.472.533	.570361
	5-10 % WL loss	-.473098	.104	-1.043.688	.097493

Table 15: Texture analysis of the overall compartments.
[1] Non-linear Data
***No significant differences in the Thickness (rate of change over 8 years)**

Medial tibia					
				Lower Bound	Upper Bound
Variance	Control				
	> 10 % WL loss	-.652217	.120	-1.473.852	.169418
	5-10 % WL loss	-.539733	**.011**	-.957782	-.121684
Entropy	Control				
	> 10 % WL loss	-.002723	.204	-.006932	.001486
	5-10 % WL loss	-.001357	.214	-.003499	.000784
Homogenity	Control				
	> 10 % WL loss	.000466	.050	6.756303	.000932
	5-10 % WL loss	.000222	.067	-1.5498501	.000459
Contrast					
	Control				
	> 10 % WL loss	-1.167.609	.123	-2.652.237	.317020
	5-10 % WL loss	-.946652	**.014**	-1.702.033	-.191270

Table 16: Texture analysis of the medial tibia.
***No significant differences in the thickness (rate of change over 8 years)**

Texture Lateral tibia	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Variance	Control				
	> 10 % WL loss	-.446394	.061	-.914208	.021419
	5-10 % WL loss	-.327056	**.013**	-.586150	-.067962
Entropy	Control				
	> 10 % WL loss	-.004487	**.048**	-.008941	-3.248601
	5-10 % WL loss	-.002968	**.018**	-.005435	-.000501
Homogenity	Control				
	> 10 % WL loss	.000626	**.041**	2.548601	.001226
	5-10 % WL loss	.000338	**.047**	4.966600	.000670
Contrast	Control				
	> 10 % WL loss	-.615112	.075	-1.291.263	.061039
	5-10 % WL loss	-.477988	**.012**	-.852467	-.103508

Table 17: Texture analysis of the lateral tibia.
***No significant differences in the thickness (rate of change over 8 years)**

5.3.3 T2 relaxation times of combined weight loss group

As displayed in Table 5.14 the combined weight loss groups (weight loss > 5 %) showed a significant deceleration in the medial and lateral tibia as well as in the patella compared to the weight stable group (< 3% weight loss). Interestingly enough, no statistical significance was reached in the overall T2, although a statistical trend can be seen.

Compartment	Weight loss group	Difference in Slope compared to Controls	P-Value	95% Confidence Interval	
				Lower Bound	Upper Bound
Mean	Control				
	>5 % weight loss	-.012686	.097	-.027681	.002308
Lateral Femur	Control				
	>5 % weight loss	-.012017	.187	-.029859	.005825
Lateral Tibia	Control				
	>5 % weight loss	-.018846	**.013**	-.033678	-.004014
Medial Femur	Control				
	>5 % weight loss	-.005546	.574	-.024917	.013825
Medial Tibia	Control				
	>5 % weight loss	-.017524	**.011**	-.031036	-.004012
Patella	Control				
	>5 % weight loss	-.025693	**.009**	-.044819	-.006568

Table 18: Results for the combined weight loss groups. Group includes patient with weight loss greater than 5 %. The control group includes patients with stable weight (< 3% weight loss)

5.4 WOMAC and Physical activity score

Analysis of the WOMAC clinical outcome scores for pain, stiffness and disability showed significant deceleration of the values in the > 10 % weight loss groups in all 3 scores (Pain p=0.037, Stiffness p=0.018, Disability p=0.019). In the physical activity score for elderly only the 5-10% weight loss group showed a significant increase in the slope for activity (p=0.017). Illustrated in Table 5.15.

Value	Weight loss group	Difference in Slope Compared to Controls	P-value	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
	Control				
WOMAC	> 10 % loss	-.016723	.037[1]	-.032433	-.001014
Pain	5 - 10 % loss	.002027	.729	-.009425	.013478
	Control				
WOMAC	> 10 % loss	-.009670	.018[1]	-.017699	-.001641
Stiffness	5 - 10 % loss	-.000394	.895	-.006247	.005459
	Control				
WOMAC	> 10 % loss	-.063284	.019[1]	-.116000	-.010569
Disability	5 - 10 % loss	-.002102	.915	-.040557	.036352
	Control				
PASE	> 10 % loss	-.307333	.191	-.767778	.153111
	5 - 10 % loss	.408058	.017[1]	.073946	.742171

Table 19: Results of the analysis of WOMAC and PASE scores.
[1] Nonlinear data

6. Discussion

6.1. Interpretation of the quantitative results

In this study, we analyzed the effects of different degrees of weight loss on cartilage degeneration represented by MRI T2 relaxation times and structural deterioration of cartilage, menisci and bone marrow measured by the Whole-Organ Magnetic Resonance Imaging Score. Additionally, we looked at different effects of weight loss regarding the physical activity and other clinical symptoms represented by the Western Ontario and McMasters Universities osteoarthritis index and the physical activity scale for the elderly. In general, a significant slower progression of T2 values was seen in patients losing weight compared to subjects with stable weight suggesting less progression of cartilage degeneration in subjects losing weight. When we divided the subjects into two groups regarding the amount of weight loss, the group with weight loss of over 10 % of their body had the greatest benefit regarding cartilage degeneration over time suggesting that a larger amount of weight loss is more beneficial for cartilage health than is moderate or no weight loss.

Our results are supported by a study from Anandacoomarasamy *et al.* who looked at changes in cartilage degeneration in groups who underwent surgical and non-surgical weight loss measured by MR-based dGEMRIC and showed that the amount of weight loss has a significant effect on the progression of cartilage degeneration. (Anandacoomarasamy et al., 2012) Another study by Serebrakian *et al.* who was looking at subjects over 48 months and found slower progression in the medial femoral condyle, lateral femoral condyle and in the patella as well as globally across all compartments (Serebrakian et al., 2014). Different to previously mentioned studies, our study looked at longitudinal changes over a period of 8 years with a large cohort of

almost 500 patients and used advanced MRI biomarkers. To our knowledge we also were the first to take a look at the amounts of weight loss needed to reduce cartilage degeneration measured by T2 relaxation times. Both groups showed significant slower progression of cartilage degeneration in the medial tibial compartment suggesting that weight loss is most protective for the weight-bearing regions. Less progression of cartilage degeneration has been seen in the lateral tibia and patella as well suggesting that over a longer period of time all compartments of the knee benefit from weight loss. As proof of concept this study also analyzed the T2 values fusing the 5-10% weight loss group together with the > 10 % weight loss group to assess whether weight loss in general has a significant impact regarding the progression of cartilage degeneration. As expected, significance was reached in the medial and lateral tibia as well as in the patellar compartment. Laminar analyses were performed because of its sensitivity to detect changes in between the different layers of cartilage. Significant changes were found in the deep and superficial layer of the medial and lateral tibia as well as the patella in the > 10% weight loss group. Interestingly enough, in the 5-10% WL group significant changes have been seen only in the deep cartilage layer suggesting that bone adjacent cartilage is the first to have a positive benefit from weight loss. This assumption is supported by the fact that only the deep layer of the >10 % WL group showed significant slower degeneration although the overall T2 has been significant too. This circumstance shows once more the superiority of laminar analysis in detecting changes in cartilage composition in between the groups, compared to using solely mean T2 values as used in previous studies (Serebrakian et al., 2014).

Our study also showed that weight loss is associated with the progression of the Whole-Organ Magnetic Resonance Imaging Score (WORMS) sub-scores over 96 months. A

previous study by Gersing *et al*. already analyzed longitudinal morphological changes but only over a period of 48 months. To our knowledge we were the first to look at the association between weight loss and progression of morphologic knee joint abnormalities, including cartilage and meniscal defects, as well as BMEP bone marrow edema pattern, over a period of 96 months. We saw significant less progression of meniscal degeneration in the over 10 % weight loss group especially in the medial meniscus. To our knowledge there is so far no other study that found an association between weight loss and meniscal degeneration but out findings most likely are explained by the changes in the knee joint loading. In general, the meniscus acts as shock absorber and provides load bearing in the joint (Fithian, Kelly, & Mow, 1990). Weight loss reduces the joint loading as well as the shear stress on the menisci and most likely also affects degenerative processes over time. Additionally, meniscal lesions alter the knee joint kinematics and shift the mechanical stress distribution towards the surrounding structures, including the cartilage. Hunter *et al*. previously found out that a meniscal malposition or damaged meniscus is associated with increased cartilage loss (Hunter et al., 2006). Therefore, one might assume that reduced joint leading reduces stress on the menisci slows down degenerative processes in the menisci as well as in the cartilage which would be in line with our previous mentioned results.

In our study we were also able to show less progression of bone marrow edema patterns (BMEP) and subchondral cyst formation in participants with substantial weight loss compared with stable-weight participants. Once more we assume this is most likely caused by the reduced joint loading which is in line with previous studies who showed a strong association between weight gain and increased progression of morphological abnormalities in the knee (Bucknor et al., 2015b; Hunter et al., 2006).

At last, our study showed a significant slower progression of WOMAC sub-scores in patients losing over 10% of their body weight compared to the control group indicating that weight loss has a significant positive effect on clinical symptoms. Taking a closer look at the sub-scores, weight loss has a significant effect on stiffness, disability as well as pain. Reduced stiffness and disability are most likely caused by increased physical activity and reduced joint loading but regarding pain there is quite an inconsistency in the literature. On the one hand Teichtahl *et al*. found an association between weight gain and knee pain as well as increased cartilage loss (Teichtahl et al., 2015) which is supported by a study by Baum *et al*. who found out that there is a significant association of knee cartilage lesions and knee pain in overweight and obese patients with elevated cartilage T2 values (Baum et al., 2012). Several other studies also showed an interrelation between morphological changes and knee pain (Burnett et al., 2015a, 2015b). On the other hand, there are several studies that show no significant connection between morphological changes and pain (Kornaat et al., 2006; Phan et al., 2006; Wildi et al., 2010). Therefore, given the inconsistency in previous studies we need to be careful when evaluating the clinical relevance regarding the interrelation of weight loss, morphological knee changes and WOMAC sub-scores. Nevertheless, we were able to show that the amount of weight loss is associated with the improvement of the WOMAC score and that larger weight loss produces better clinical outcomes and the patients benefit more from it as it has been shown already by several earlier studies (Bliddal et al., 2011; Christensen et al., 2005; Richette et al., 2011). Surprisingly enough, the 5-10 % weight loss group showed significant increase in the physical activity score (PASE) while the >10% weight loss group showed a decrease in activity over the 8 years. This might be explained by the method of weight loss which was used to achieve a certain amount of weight loss.

6.2. Limitations

There are several limitations to this study. First of all, this was a retrospective study of patients with weight loss included in the OAI initiative and we did not include the methods of weight loss (exercise, diet, bariatric surgery *etc.*) into our analysis. This may have introduced confounding effects into our analysis that cannot be estimated because different types of weight loss may have different effects on the joint structures and clinical scores. A recent study by Gersing *et al.* showed that there are indeed differences regarding the weight loss regimens and showed that diet as well as diet and exercise are associated with significant slower cartilage degeneration. Exercise alone did not have a significant effect. Other confounders might be the amount of exercise or medication taken which we did not take into account in this study. Moreover, the WOMAC and PASE scores have been self-reported and no other data was available e.g. histological specimen or arthroscopic image. Regarding the laminar analysis one limitation is that the deep and superficial cartilage layers analyzed do not correlate with the three physiologic layers of cartilage: tangential, intermediate, and radiate. Although the two layers were used instead of three layers because of limited resolution, it is possible that the deep and superficial layers analyzed herein also have limited resolution.

Moreover, because most participants reported their right leg to be the dominant leg, we assessed the MR imaging examinations for the right leg only, which may have introduced a bias to the analyses as well. In addition, only participants in whom MR imaging could be performed were included in the OAI Osteoarthritis Initiative study; thus, participants who had issues with fitting into the MR imaging bore or the MR

imaging knee coil because of their body size were excluded from this study, which may have caused a selection bias.

Finally, WORMS Whole-Organ Magnetic Resonance Imaging Score has limited sensitivity in the detection of subtle changes of cartilage defect sizes over time because changes may not be reflected by an increase in the WORMS Whole-Organ Magnetic Resonance Imaging Score subscale if they are too subtle to cause a difference in the score. Biochemical metrics (e.g. T2 or T1ρ mapping) are more sensitive regarding these subtle changes. The additional evaluation with quantitative assessment, such as cartilage volumetry, and biochemical metrics may yield more detailed information on cartilage degenerative disease.

In summary, our study showed that mild to moderate weight loss is associated with less progression of cartilage degeneration measured by T2 as well as meniscal degeneration and other morphological and clinical osteoarthritic changes. In particular, greater weight loss in obese and overweight subjects has resulted in the biggest impact regarding the progression of degenerative processes emphasizing once more the relevance of lifestyle interventions in obese and overweight individuals regarding joint degeneration as detected with MR imaging.

7. Summary/Abstract

Objective

To analyze the long-term effects of different degrees of weight loss on degenerative processes in the knee as well as on the clinical symptoms over a period of 96 months. The aim was to identify individuals that would benefit most from weight loss regarding onset and progression of osteoarthritis.

Methods

We included 490 participants (Mean age 62.4 years ± 9.1, 296 women) of the osteoarthritis initiative who were obese (BMI > 30 kg/m(2) or overweight (BMI > 25, < 30) and had mild to moderate or risk factors for osteoarthritis, respectively. Subjects were divided into groups regarding the amount of weight loss (a) weight loss of more than 10% (n =74), (b) weight loss of 5%-10% (n =171), or (c) stable weight (n = 245) over 960 months. Participants were frequency-matched for age, sex, baseline body mass index, and Kellgren-Lawrence score. We used MR-based T2 values to examine the longitudinal changes in cartilage composition together with laminar and texture analysis at baseline, 48-months and 96-months. Additionally, we analyzed the MR images and assessed the cartilage, menisci and other knee structures using the modified Whole-Organ Magnetic Resonance Imaging Score (WORMS). Questionnaires were used to assess the development of clinical symptoms and general mobility of the participants. Progression of the sub-scores was compared among the weight loss groups by using a random mixed model.

Results

Over 96 months the WL group with over 10 % weight loss showed a significantly slower increase in mean (averaged over all compartments) cartilage T2 ([-0.032 [-0,06, 0.004] ms/year; $P = 0.023$) as well as global deep ([-0.032 [-0,06, 0.004] ms/year; $P = 0.023$) and articular cartilage T2 ([-0.031 [-0,06, 0.004] ms/year; $P = 0.023$) compared to the controls suggesting slower cartilage deterioration. The 5-10% WL could only show a slower increase in the medial and lateral tibia as well as the patella compartment. Compared to the SW group, slower increase in WORMS sub-scores (medial meniscus and LFC BMEP) was observed in the over 10 % WL groups ($P = 0.046$ and $P = 0.038$, respectively). Regarding the WOMAC scores the over 10% WL group showed a significant slower increase in all sub-scores whereas the 5-10% WL showed a significant increase in the PASE score.

Conclusion

Our study suggests that WL is significantly associated with slowed cartilage degeneration over a period of 96 months. Weight loss of over 10 % of the body weight shows the biggest benefit not only regarding the morphological degeneration of knee structures, but also concerning the clinical symptoms suggesting that greater weight loss is more beneficial than moderate or no weight loss.

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11. Publications

Oral presentations and conference posters

1. Alexandra S. Gersing M.D., Gabby B. Joseph, Ph.D., Benedikt J. Schwaiger, M.D., Ursula R. Heilmeier, M.D., **Georg Feuerriegel** Martin Solka, John Mbapte Wamba, M.D., Charles E. McCulloch, Ph.D., Michael C. Nevitt, Ph.D., and Thomas M. Link, M.D., Ph.D." Weight loss is associated with slower cartilage degeneration over 96 months in obese and overweight subjects: data from the Osteoarthritis Initiative" Abstract RSNA Chicago 2015

2. A. S. Gersing, **G. Feuerriegel**, J. Zarnowski, B. J. Schwaiger, G. B. Joseph, J. Brandao Guimaraes, L. Facchetti, N. Chancheck, U. Heilmeier, P. M. Jungmann, M. C. Nevitt, C. E. McCulloch, T. M. Link; Univ. of California San Francisco, San Francisco, CA, "Association of Weight Loss with slower cartilage degeneration over 96 Months in overweight subjects: Data from the Osteoarthritis Initiative", Abstract OARSI 2016

3. A. S. Gersing, **G. Feuerriegel,** J. Zarnowski, B. J. Schwaiger, G. B. Joseph, J. Brandao Guimaraes, L. Facchetti, N. Chancheck, U. Heilmeier, P. M. Jungmann, M. C. Nevitt, C. E. McCulloch, T. M. Link; Univ. of California San Francisco, San Francisco, CA, "Association of Weight Loss with slower cartilage degeneration over 96 Months in overweight subjects: Data from the Osteoarthritis Initiative" Poster Nr. 930 OARSI 2016

4. **G.C. Feuerriegel**, A.S. Gersing, B.J. Schwaiger, J. Zarnowski, P.M. Jungmann, C.E. McCulloch, M.C. Nevitt, E.J. Rummeny, T.M. Link; "Weight loss regimens in obese and overweight individuals impact cartilage degeneration: 96-month data from the Osteoarthritis Initiative", Oral presentation at the european congress of radiology in Vienna 2017

5. A Gersing,**G Feuerriegel**,D Holwein, A Suchowierski, P Karampinos, P Baum, D Schwaiger, P Imhoff, P Kirschke, P Rummeny, P Jungmann „Zusammenhang zwischen quantitativer Qualität des regenerativen Knorpelgewebes und subchondraler Knochenstruktur, gemessen mit 3T MRT, nach autologer Chondrozyten-Transplantation mit Spongiosaplastik" March 2017 RöFo - Fortschritte auf dem Gebiet der R 189(S 01):S1-S124 DOI: 10.1055/s-0037-1600363

6. Alexandra S. Gersing, **Georg Feuerriegel**, Christian Holwein, Achim Suchowierski, Dimitrios C. Karampinos, Thomas Baum, Benedikt J. Schwaiger, Andreas B. Imhoff, Jan S. Kirschke, Ernst J. Rummeny, Pia M. Jungmann, "Cartilage Repair Tissue Composition Assessed with 3-T MRI Correlates with Trabecular Bone Remodeling in Patients with Spongiosa-augmented Matrix-induced Autologous Chondrocyte Implantation" Semin Musculoskelet Radiol 2017; 21(S 01): S1-S5 DOI: 10.1055/s-0037-1600887

7. J Zarnowski [1], D Gersing [2], D Schwaiger [2], **G Feuerriegel** [3], J Guimaraes [2], L Facchetti [2], N Chancheck [2], P Link [2] [1]Klinikum Rechts der Isar, Institut für diagnostische und interventionelle Radiologie, München [2]Department of Radiology and Biomedical Imaging, University of California, San Francisco [3]Institut für diagnostische und interventionelle Radiologie, Klinikum rechts der Isar, München. „Gewichtsreduktion übergewichtiger und adipöser Patienten ist mit einer verlangsamten Knorpeldegeneration assoziiert über einen Zeitraum von 96 Monaten: Verlaufsdaten aus der Osteoarthritis Initiative“. March 2016, RöFo - Fortschritte auf dem Gebiet der R 188(S 01) DOI: 10.1055/s-0036-1581676

Journal Papers:

1. Gersing AS[1], Solka M[2], Joseph GB[3], Schwaiger BJ[4], Heilmeier U[5], **Feuerriegel G**[6], Nevitt MC[7], McCulloch CE[8], Link TM[9]. “Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative. **Journal paper** in Osteoarthritis Cartilage. 2016 Jul;24(7):1126-34. doi: 10.1016/j.joca.2016.01.984. Epub 2016 Jan 30

2. Förschner PF, Beitzel K, Imhoff AB, Buchmann S, **Feuerriegel G**, Hofmann F, Karampinos DC, Jungmann P, Pogorzelski J. „Five-Year Outcomes After Treatment for Acute Instability of the Tibiofibular Syndesmosis Using a Suture-Button Fixation System” Journal paper in Orthop J Sports Med. 2017 Apr 27;5(4):2325967117702854. doi: 10.1177/2325967117702854. eCollection 2017 Apr.

3. Alexandra Gersing, Benedikt J Schwaiger, M.D.; Michael C Nevitt, Ph.D.; Julia Zarnowski; Gabby B Joseph, Ph.D.; **Georg Feuerriegel**; Pia M Jungmann, M.D.; Julio B Guimaraes, M.D.; Luca Facchetti, M.D.; Charles E McCulloch, Ph.D.; Thomas M Link, M.D., Ph.D, ”Weight Loss Regimen in Obese and Overweight Individuals is Associated with Cartilage Degeneration: 96-Month Data from the Osteoarthritis Initiative.” Osteoarthritis and Cartilage. OAC9022, Pending Review

4. Alexandra S. Gersing, **Georg Feuerriegel**, Christian Holwein, Achim Suchowierski, Dimitrios C. Karampinos, Bernhard Haller, Thomas Baum, Benedikt J. Schwaiger, Andreas B. Imhoff, Jan S. Kirschke, Ernst J. Rummeny, Klaus Woertler Pia M. Jungmann, “T2-relaxation time of cartilage repair tissue is associated with bone remodeling after spongiosa-augmented matrix-associated autologous chondrocyte implantation” Osteoarthritis and Cartilage, OAC8642, Pending Review

5. Sarah Schlaeger, Stephanie Inhuber, Alexander Rohrmeier, Michael Dieckmeyer, Friedemann Freitag, Elisabeth Klupp, Dominik Weidlich, **Georg Feuerriegel**, Florian Kreuzpointer, Ansgar Schwirtz, Ernst J. Rummeny, Claus Zimmer, Jan S. Kirschke, Dimitrios C. Karampinos, and Thomas Baum “Association of paraspinal muscle water-fat composition with isometric strength measurements” Journal of European Radiology, 06/2018 Ms. No. EURA-D-18-00611R2

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