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Impact of different amounts and regimes of weight loss on cartilage health in obese and overweight individuals: 96-month Data from the Osteoarthritis Initiative

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1

INTRODUCTION

Osteoarthritis (OA) is a degenerative musculoskeletal condition, progressively impairing the joint function. Characteristically, the hyaline articular cartilage is destroyed, along with degenerative changes of related joint structures such as menisci, subchondral bone and ligaments. [115]

Demographical data signify the rising medical and social importance of osteoarthritis as two major risk factors – obesity and age – show a worldwide increase. [18]

Global ageing, due to higher life expectancy, decreasing infant mortality and increasing health and educative standards, can be impressively seen in Germany, where life expectancy has risen from 67.1 years to 75.6 years in men and from 72.7 years to 81.3 in women in only 40 years. [84] Accordingly, projections for 2050 claim that the 65+ year old population in the United States (US) will grow from 13.7% to 20.9%, with its highest peak in the 85+ group. [123]

Worldwide, the number of people over 60 years is going to double until 2050 and triple until 2100.[167] While age is a non-influenceable risk factor for the development of OA, overweight on the other hand is strongly modifiable and preventable.

Worldwide obesity is a widespread health concern, with a substantially increasing presence in our society:

Over the past 30 years, the global prevalence for overweight and obesity increased by more than 8%, from 28.8 to 36.9% in men and 29.8 to 38.0% in women. [118]

Current health data show that over one third of the adult population in the American society and nearly one fifth of the children are obese. [147]

Simultaneously, over half of the adult population in Germany is overweight, showing rising tendencies for body mass indices related to obesity (BMI $\geq$ 30 kg/m^2). [106]

This development is causing a considerable impact on our health care system, as obesity-related diseases and economic costs are escalating. [92] Direct medical costs and indirect costs caused by the loss of manpower and working potential result in a huge economic expenditure, which is supposed to double every decade. [28 172]

In addition, high amounts of visceral fat cause a dysfunction of the lipid and glucose metabolism, which are reinforcing atherosclerotic changes and hypertension and ultimately leading to cardio- and cerebrovascular events, both being the most common death causes among industrialized countries. [63 73]

Various research results emphasize the degenerative effect of weight gain on the cartilage health, describing that a 10 pound weight gain is increasing the risk for osteoarthritis by 40%. [23] [53] Accordingly the beneficial effect of weight loss interventions is described, which is not only reducing the risk for OA and disability, but also improving clinical performance and decreasing pain. [53] [33]

Although several studies hint at the advantages of weight loss on the cartilage integrity [150], no studies have so far evaluated the effect of different amounts and methods of weight loss on the knee joint using modern biochemical imaging techniques in ***a multi-perspective long-term*** design. This study offers an important research potential, as our demographical development needs qualitative prevention strategies for diseases due to the prospectively greater demand of the health care system in the future.

2

AIM OF THE PROJECT

This study investigates the longitudinal evolution and progression of osteoarthritis, depending on continuous obesity or significant weight loss, in overweight and obese individuals over a period of 8 years. Additionally, the long-term impact of different amounts and regimes of weight loss on knee cartilage health is studied.

As the pathophysiology of osteoarthritis is a complex interaction of biochemical, systemic and mechanical processes, a multi-layered approach is used to understand the longitudinal development of the disease:

The quantitative measurement of cartilage T_2 relaxation times reflects the biochemical cartilage composition, supported with laminar and texture analysis.
Clinical questionnaires give an insight into the quality of life over time. Lastly, a supplementary weight loss questionnaire further evaluates the chosen method for weight reduction.

The specific aim is to investigate whether weight loss can prevent or decelerate the progression of osteoarthritis over 96 months in previously overweight and obese patients. Furthermore, the chosen method for weight-loss will be studied in a subgroup analysis to understand which weight-loosing pathway is most reasonable and recommendable for patients.

Altogether weight-loss offers a potentially highly effective, non-invasive and economically convenient therapeutic resource with no side effects and high feasibility for patients suffering from both onerous, disabling, straining and chronic diseases - obesity and osteoarthritis.

3

BACKGROUND

3.1

EPIDEMIOLOGY AND PREVALENCE

Osteoarthritis (OA) is the most common musculoskeletal disorder worldwide, gradually leading to structural changes, chronic pain and malfunctioning of the entire joint, mostly occurring in weight-bearing joints such as the knee, followed by the hip, hand joints and spine. [20] [111] The World Health Organisation (WHO) describes that nearly one quarter of the global population is affected by OA and forecasting data indicate the rising importance of diagnosing and treating osteoarthritis as already 27 million adults in the US and 35-40 million Europeans estimatedly suffer from OA. [90] [111] [173]

In regard to symptoms, over 10% of men and 13% of women over 60 years suffer clinically from stiffness, swelling, soreness or chronic pain in the US. Prospectively over half of the American population is estimated to suffer from symptomatic osteoarthritis of the knee by the age of 85, effecting enormous socioeconomic consequences, as OA is the leading cause of disability, loss of independence and working ability among the elderly population. [3] [116] Economically, OA causes costs in the US ranging in double-digit billions of dollars per year, which are composed of hospitalization costs due to joint replacement surgeries, direct and indirect patient costs as well as sick leave and rehabilitation costs. [24] [115]

Similarly to the US, the health report from the European Union estimates that 1 in 10 adults over 60 years is encountering clinically significant problems due to osteoarthritis. [20] [164]

Moreover, death incidents are twice as high in patients diagnosed with OA compared to the general population, whereas deaths caused by side effects of pain medication or joint replacement surgery were not included into this calculation, suggesting an even higher incident number. [121] [143] [166]

The morbidity burden caused by OA is tremendous, as it is ranked the 8th highest burdening disease in the European states. Being listed amid severe firstly ranked health conditions such as cardio- and cerebrovascular diseases, motor vehicle accidents or oncological diseases, signifies the huge impact and burden of osteoarthritis on the populations everyday life. [164]

3.2

RISK FACTORS

Osteoarthritis is a multifactorial degenerative disease, influenced by biomechanical, genetic and systemic risk factors.

Increased age, postmenopausal female gender and overweight are key risk factors for the development of OA. [51] [146] [156]

Especially an increased BMI is associated with a higher incidence and progression of knee osteoarthritis [134] and leads additionally to an altered distribution of muscular forces, increasing the muscular strain of quadriceps and hamstrings in early stance phase, whilst gastrocnemii forces are elevated in late stance, effecting a higher compression during gait. [66] Altogether, this increases the joint load and causes higher tibiofemoral shear forces, thus reinforcing inflammative processes and accelerating osteoarthritis.

Systemically, visceral obesity is linked to tissue inflammation, hyperinsulism and consequently the development of type-2-diabetes or metabolic syndrome. [44] This connection is of tremendous importance, as both obesity-related diseases are not only increasing the risk but also the severity of OA. [29] [88] Recent data signifiy the association between metabolic syndrome and OA, as they show a 5-fold increased risk of developing a metabolic syndrome, if already suffering from OA.

A common pathophysiological pathway, which leads to metabolic abnormalities and a systemic inflammation, is suggested within this study. [129] Additionally, new studies theorize that type-2-diabetes can directly promote cartilage degeneration, having effects on a molecular level and thus changing the chondrocyte metabolism. [29] [141]

Additional predisposing factors for OA include congenital abnormalities, varus-/valgus-malalignment and increased knee bending activities or occupational stress, altogether leading to an overuse of the joint and increasing the wear of cartilage. [69] Traumatic events, such as previous knee injury e.g. anterior crucial ligament tear or meniscal extrusion lead to muscle and tendon weakening, joint laxicity and focal cartilage defects, increasing the risk for developing OA almost 4-fold. [18] [69] [154]

Lastly, genetical susceptibility is discussed, as huge studies have identified several gene variants that are linked to osteoarthritis. DNA regions coding proteins for bone and cartilage regulation, as well as different collagenous and non-collagenous extracellular matrix components such as Aggrecan are involved in this context. Also, the expression of

inflammatory enzymes such as leukines or hormone receptor genes has been discovered, broadening the view on OA as a genetically influenced disease. [40 54 181]

3.3

PATHOPHYSIOLOGY AND CLINICAL SYMPTOMS

An osteoarthritic joint is characterized by the loss of articular cartilage and pathological changes in other joint features such as menisci, ligaments, subchondral bone and bone marrow.[76] Traditionally, osteoarthritis was perceived as a degenerative "wear-and-tear" disease with the main pathological feature of hyaline cartilage loss.

Nowadays the complex interaction of several joint structures in regard to symptoms and disease progression has led to a change of paradigm with OA being viewed as a whole-organ disorder with multi-tissue pathologies. [104 139]

Injured menisci[2], characterized by tears, cysts or extrusion lead to a higher loss of cartilage volume and are associated with a progression of symptoms due to a decreased shock absorption.[9 162] Pathologies concerning the ligaments and tendons are strongly weakening the mechanical stability, altering the tibiofemoral load distribution and increasing sliding and shear forces, altogether accelerating the progression of osteoarthritis.[55] In regard to the knee joint, injuries concerning the crucial ligaments are often seen in both, the general population and younger patient groups. Especially traumatic injuries during competitive sports are common in young athletes, causing rotatory instability and accelerating osteoarthritis, thus widening the focus of osteoarthritis prevention, diagnostics and therapy to younger age groups. [2 100]

Changes in the subchondral bone and bone marrow, such as osteophytes, cysts, chronic edema, fibrosis, necrotic lesions or microfractures are often found in affected joints and show a high correlation with the progression of OA, its clinical symptoms and the risk of joint replacement surgery. [36 52 96 161 162]

Lastly, synovitis and effusion around the joint space play an important role in the pathophysiology of osteoarthritis as several studies have shown a significant correlation between the presence of synovitis, knee pain and severity of OA. [10 72 112]

Typical changes include a higher stromal vascularity, synovial membrane thickening and an inflammatory cell infiltration with macrophages, mast cells and T cells. [98 112] Experimental studies with mice suggest that an activation and infiltration with synovial macrophages produces higher amounts of matrix metalloproteinases, which are potentially leading to

cartilage damage through molecular mechanisms, offering a potential pharmacological target. [19 98 104]

Clinically, all those affected structures lead to a complex of symptoms such as chronic pain, swelling, reduced mobility and stiffness of the joint. Especially the combination of restricted physical functioning, limited self-supply, disability and dependency on relatives or social care can be the consequence of severe osteoarthritis and be a huge burden leading to mental health issues. [4 90 153] Not only are OA symptoms often associated with greater depressive symptoms, but depression itself can vice versa worsen clinical symptoms and negatively influences the outcome of different treatment interventions. [43]

3.4

HISTOLOGY AND BIOCHEMISTRY

The articular joint surface is covered with hyaline cartilage, a hypocellular, aneural tissue with no intrinsic vascular or lympatic supply and therefore highly depending on diffusion of synovial fluid for nutritive organisation. [21] Altogether this is leading to a low regenerative potential with high irreversibility if damage occurs. [16 25 104 176]

Biochemically, the cartilage tissue is built of 1-10% chondrocytes and over 90% matrix.

The chondrocytes form the cellular component of cartilage and are embedded into the extracellular matrix (ECM), which is constituted of water, the main component with a share of 60-80%, and structural macromolecules with a share of 20-40%. The macromolecules are constituted of 50% collagene fibers, 30-35% connective proteins such as Anchorin and Chondronectin as well as 15-20% proteo- and glycosaminoglykans (GAGs). [16 25 176]

The main physiological feature of cartilage tissue is its elastic cushioning and deformability under compression load. The key factor for this behaviour is the combination of high water content, negatively charged and thus strongly water-binding macromolecules and a tensile collagen fiber network.

Histologically, articular cartilage can be divided into zones that show different characteristics, with the main difference being a distinct metabolic activity of chondrocytes:
A thin superficial zone with many flat, inactivated chondrocytes is followed by a thicker transitional zone, showing round chondrocytes with a higher metabolic activity.

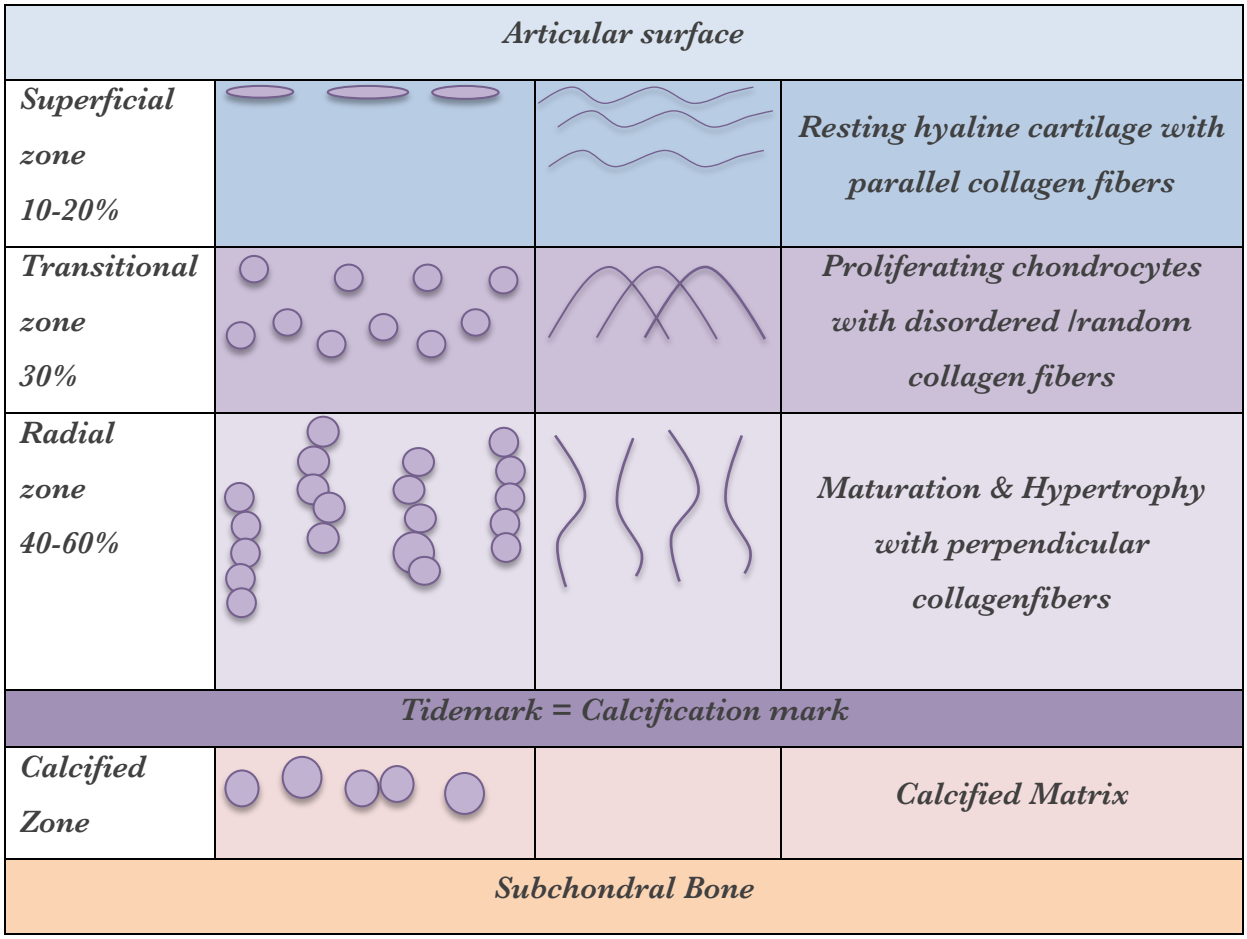

Figure 1: Histological Composition of Cartilage

Afterwards, the thickest, deep-laying radial zone follows, with the chondrocytes forming columns and showing up to 10-times more metabolic activity than chondrocytes of the superficial, joint-space-facing layer.

In this radiar zone the highest proteoglycan and collagene levels can be seen while the water content is the lowest of all zones. The last zone above the subchondral bone is the calcified zone, which is having a higher concentration of apatite, calcium and non-grouped chondrocytes with less organells, being prone to degeneration. [16 25 176]

A healthy cartilage section is presented in the upper Figure 2A, showing an intact network between the ECM and chondrocytes, which are neatly lined up in different zones without visible defects or structural inconsistency.

In contrast, Figure 2B shows a decreased integrity of the components, swollen and elongated chondrocytes and superficial fissures and ulcerations, altogether being characteristic for osteoarthritic cartilage. [16 25 176]

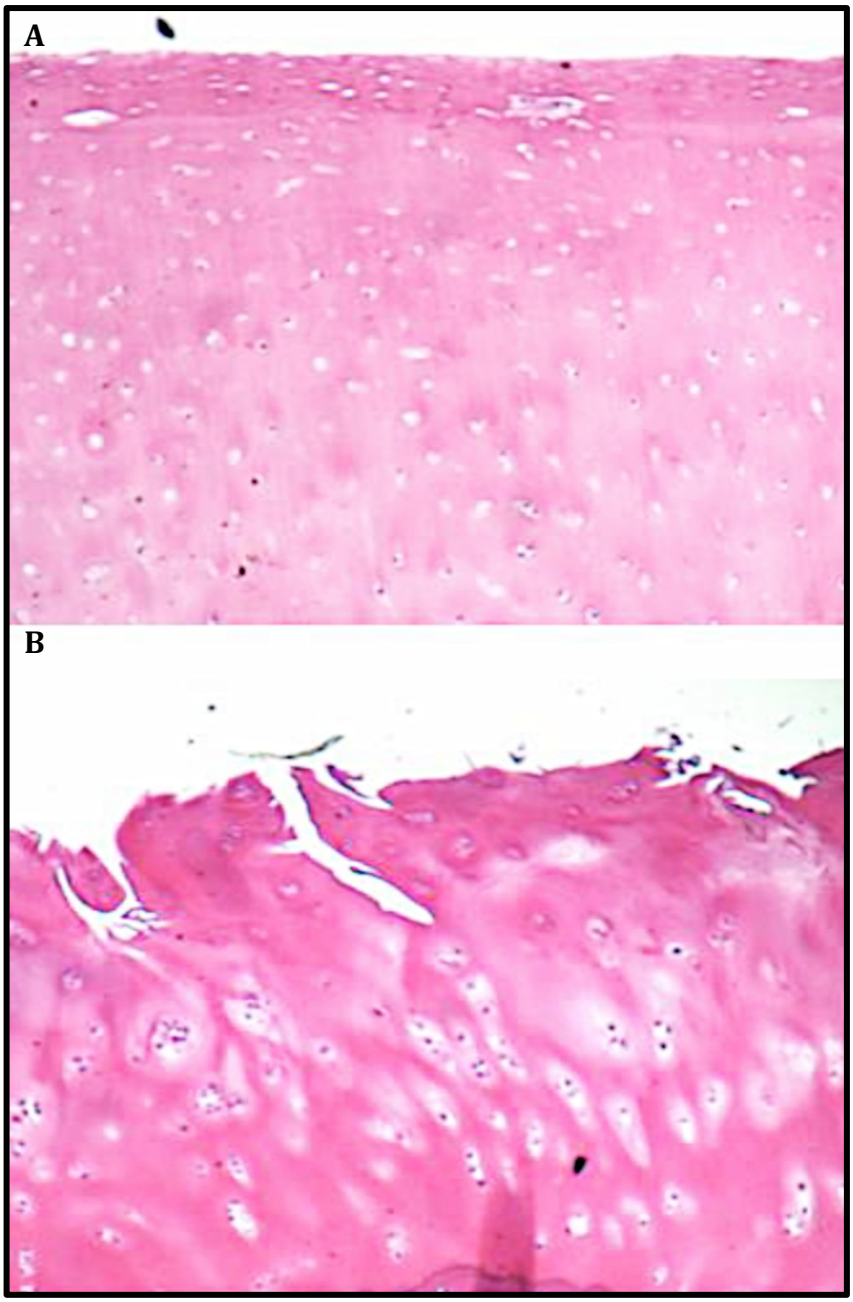

Figure 2: Light microscopy of healthy (A) and osteoarthritic (B) cartilage using hematoxylin-eosin stain; Image courtesy by The Abramson Lab; NYU School of Medicine

Before such visible damage occurs, the first signs of cartilage degeneration can be seen on a biochemical level. An altered composition, such as increase of water content, decrease of proteoglycan concentration and loosening of the tight collagene network, leads to a loss of the unique biochemical matrix features and reinforces macroscopically visible, morphological defects. [16 25 104 176]

3.5

DIAGNOSIS AND CLASSIFICATION

Generally, the combination of clinical examination and diagnostic imaging tools leads to the diagnosis of osteoarthritis, which can be classified in various systems. The diagnostic process itself is challenging for clinicians, as on the one hand OA often lacks apparent symptoms in early stage and on the other hand, is not becoming radiographically evident until irreversible damage to the joint has already occurred. [69]

Clinically, the leading symptom in the affected joint is pain. Although pain intensity and duration is heterogeneously distributed in patients, characteristical start-up pain and exacerbation during activity in early stage is described, which aggreviates during nighttime and resting periods as the disease advances. [49 69 138]

In addition to pain, a physical examination can reveal clinical symptoms such as stiffness, swelling, crepitus, bone tenderness and bone thickening. The American College of Rheumatology (ACR) describes these symptoms as diagnostic criteria for the evaluation of an osteoarthritic joint, complementing imaging results. A clinically applied questionnaire, to further evaluate the extent of symptoms and their progression is the standardized Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), primarily focussing on pain, stiffness and physical functioning in the everyday life.

In regard to imaging, plain radiographs are the current gold standard to assess the damage in a ***symptomatic*** joint. Those can be implemented easily into the clinical routine or average medical office, due to the moderate costs, as well as its fast and simple imaging technique compared to techniqually advanced but more complex and time consuming imaging techniques such as MR Imaging.[74]

The most common system used to grade radiographical findings is the Kellgren-Lawrence-score (KL), firstly published in 1957. [82] Classical pathologies such as joint space narrowing, osteophytes, subchondral sclerosis and cysts are evaluated to score the grade of OA. The higher the KL score, the more osteoarthric pathologies have been scored, which are reflecting the severeness of the disease.

Figure 3 shows a radiograph of the left knee, taken from an inhouse patient at the UCSF. The knee joint shows severe destructions, including multiple osteophytes on both sides, definite medial joint space narrowing and medial as well as lateral subchondral sclerosis, outlined in colors. Due to all occuring pathologies, a KL score of 3 can be considered.

Criticism has risen, as the radiographic imaging and the KL-classification is not being sensitive for early stage OA as soft tissue pathologies, which are strongly involved in the pathophysiological process, are not considered. Additionally, a meta-analysis uncovered an inconstistent application of KL-classification criteria throughout various studies, leading to a low comparability and disagreement for diagnostic purposes. [105] [145]

Concludingly, studies could confirm a low agreement between the above-mentioned ACR clinical criteria and radiographic knee OA, leading to bisected information about symptoms and imaging, which are difficult to objectify or interpret. [126]

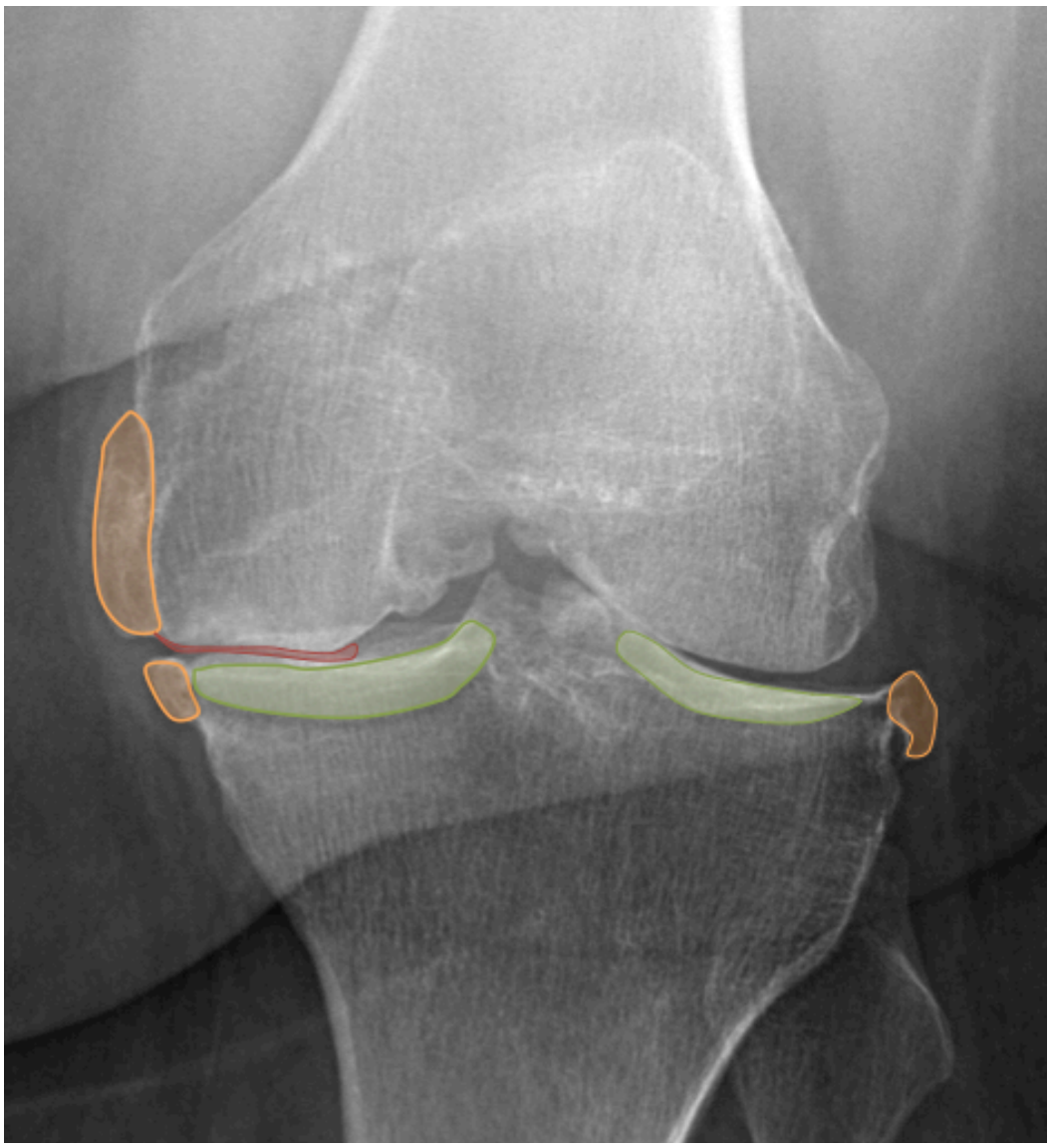

Figure 3: Radiograph of left knee with osteoarthritis signs:
osteophytes (*), joint space narrowing (*), subchondral sclerosis (*)

Therefore, some scientific publications suggest an addendum to the traditional classification in order to implement new knowledge from research and evaluate soft tissues, achieved by the complementary use of advanced imaging techniques to classify osteoarthritis.

Thus, an OA classification based on the predominant structure lesion can be considered to distinguish a chondrogenic, osteogenic, ligamentogenic, meniscogenic or synoviogenic source of OA. [105]

To evaluate soft tissue structures, the clinical use of Magnetic resonance imaging (MRI) can be added complementary to radiographs, in order to further evaluate the whole joint organ. Figure 4 shows an MR image with classic radiographicly evaluated pathologies, such as subchondral sclerosis, cysts, osteophytes and joint space narrowing. Moreover, the detection of soft tissue pathologies concerning menisci, ligaments, bone marrow and synovia can be ensured.

A widely used MRI classification is the semi-quantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS), which evaluates 14 different features, including cartilage integrity, osteophytes, effusion, cysts, menisci, ligaments, subchondral bone and bone marrow edema.

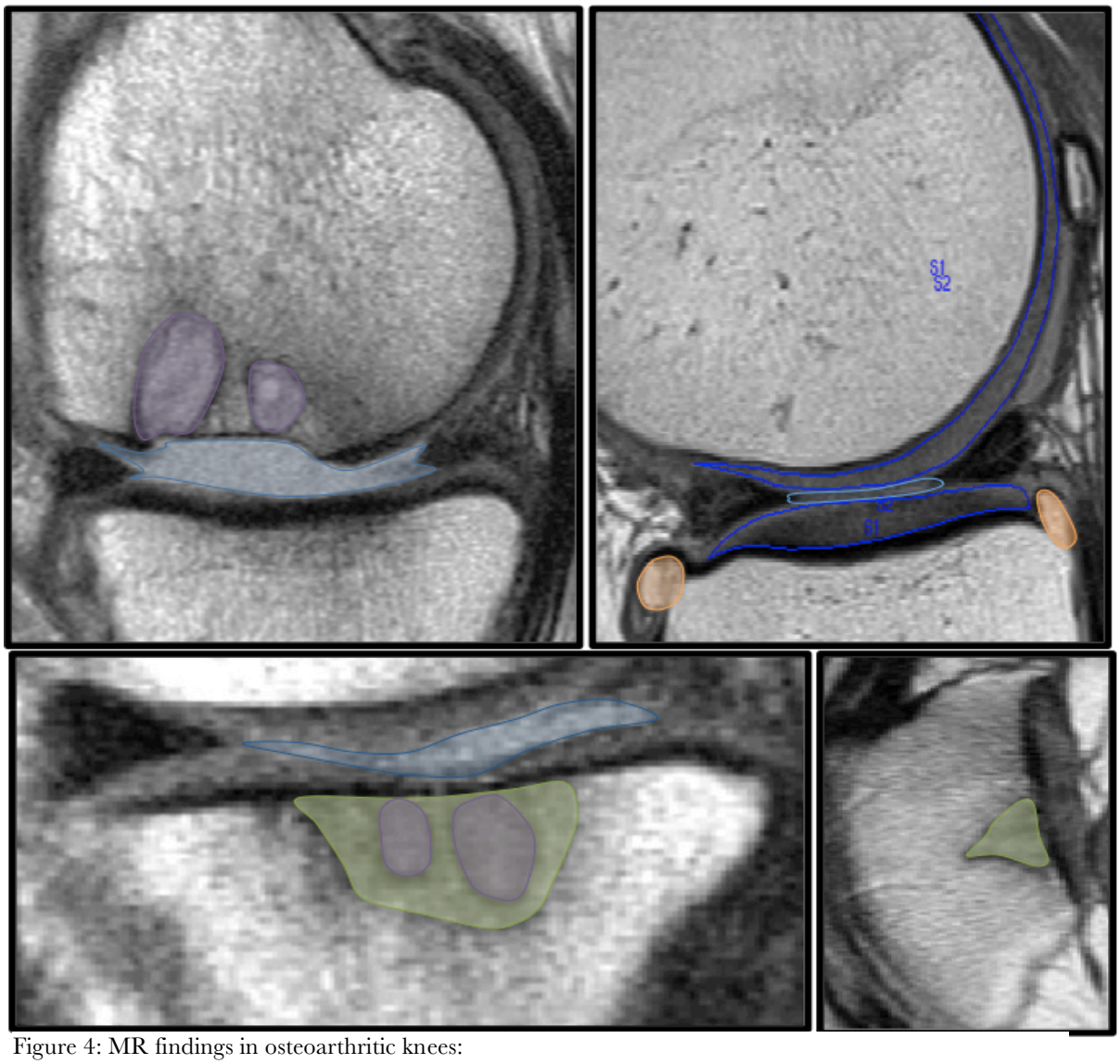

Figure 4: MR findings in osteoarthritic knees:
osteophytes (*), subchondral cysts(*) and subchondral sclerosis(*), medial fluid(*)

Lastly, a macroscopic and microscopic approach is available to evaluate the damaged cartilage and hence to conclude the severity and irreversibility of OA:
An arthroscopic intervention is an invasive method to macroscopically evaluate the cartilage morphology, menisci and ligaments in-vivo. A score developed by the International Cartilage Repair Society (ICRS) rates the quantity and depth of cartlage lesions as well as the involved underlying bone, from ICRS 0, meaning normal cartilage to ICRS 4, used to describe severely damaged cartilage. [83] The histological/histochemical grading system (HHGS) by Mankin is applied to microscopically assess cartilage damage leading to OA. Surface irregularities including clefts, fissures, cell morphology and staining characteristics are used to study matrix integrity and score the stage of degeneration. [83]

3.6

NOVEL IMAGING TECHNIQUES

Although conventional radiography remains the standard diagnostic imaging technique, no direct depiction of cartilage or other soft tissues is achievable with this method. The additional use of conventional MR imaging provides the possibility to assess the whole joint morphology with a high spatial resolution and increased soft tissue contrast. New MRI sequences are regularly developed and clinically introduced to refine the evaluation of different tissues by improving the cartilage-fluid-contrast, reducing acquisition time and artifacts, as well as increasing the resolution. [61] However, the MR technique is not sufficiently closing the diagnostic gap. Similarly to the discrepancy encountered in radiographic imaging, studies have described a mismatch between findings on MRI and clinical symptoms, not offering a satisfying approximation between imaging results and physical ailments. [97]
Novel imaging techniques aim to close this diagnostic gap with the introduction of MR-based compositional imaging markers, which aim to quantify changes in the cartilage composition and thus offer an imaging tool that targets cartilage biochemistry.
Imaging biomarkers provide a unique opportunity to detect early structural alterations non-invasively in a potentially reversible state, even before the onset of clinically evident symptoms. This is a huge progress as both routinely used imaging methods – conventional radiographic and magnetic resonance imaging – depict morphological defects, when irreversible damage to the cartilage has already occurred. [61 139]

Various compositional imaging techniques are available to quantify molecular changes in articular cartilage:

MR-based relaxation time measurements describe the time molecules need, to revert to their initial state after being excited by the magnetic field pulse.

Different parameters can be used for the analysis, such as T_2, T_{1rho} and T_2* relaxation time measures.

T_2 describes the relaxation time after transverse magnetisation and reflects the water content and collagen distribution in articular cartilage. The higher the T_2 relaxation time, the longer the molecules need to reach their state of equilibrium, reflecting a higher water content and lower collagen network integrity, altogether displaying a damaged cartilage tissue. A similar interpretation is offered by high T_2* values, which are describing the immediate decay of transverse magnetisation, which is highly influenced by magnetic susceptibility, magnetic field inhomogeneities and chemical shift, causing a faster relaxation signal than T_2. [30] Compared to T_2 measurements, T_2* is characterized by a higher speed of imaging and resolution. [42] Encountered limitations in both measurements include a structural variation and sensitivity to artifacts such as magic angle effects (T_2) or suscepitibility artifacts (T_2*). Still, an utmost high level of reproducibility and validity for T_2 and T_2* measurements as quantitative biomarkers was proven in innumerous studies over the past decade. [5] [46] [47] [48] [113] [120]

T_{1rho} reflects the relaxation time after a longitudinal magnetisation in a rotating frame and is inversely correlated with the proteoglycan content in cartilage, showing higher values when loss of proteoglycans and thus cartilage deterioration occurs. [180] Also, studies suggest that collagen distribution and changes of other macromolecules are having influence on T_{1rho} relaxation time measurements, helping to depict changes in the cartilage matrix especially in early-stage OA. [62] [94]

Another non-invasive MR-technique developed for the evaluation of cartilage integrity is the T_1-based delayed gadolinium-enhanced MRI of cartilage (dGEMRIC).

This technique makes effective use of the negatively charged glycosaminoglycans (GAGs), which are long polysaccharide side chains of proteoglycan macromolecules with strong waterbinding properties.

The application of the likewise negatively charged contrast agent gadopentetate dimeglumine ($Gd\text{-}DTPA^2$) leads to a distribution within the joint, which is inversely related to the GAG concentration. A low GAG concentration, indicating a lower negative charge density and reflecting a disrupted extracellular matrix, enables a high penetration of negatively charged contrast agent, as both identically charged molecules would normally repel each other,

hindering the contrast agent to enter the cartilage barriers.[15] As Gd-DTPA^{2} shortens T_1 relaxation time measurements, areas with a high accumulation of contrast agent and accordingly low GAG quantities will display lower values, being related to high water permeability, which is attributable to a destruction of cartilage integrity. [15 62]

Another imaging method focusing on GAG quantification is the sodium imaging technique. Inherently, sodium concentration in healthy cartilage accounts for 200-300mmol/L, which is approximately 320 times lower than water proton concentration. As GAG concentration provides a high density of negative charges, it physically attracts positively charged ions such as sodium, both reaching an equilibriate in vivo state between positively and negatively charged ions. Yet, when cartilage destruction occurs, the GAG concentration and thus fixed negative charge density descreases. Quantitative sodium MRI correlates the sodium signal intensity with charge density and GAG concentration, indicating a disruption of biochemical homeostasis and cartilage degeneration. [62 182]

Lastly, diffusion weighted imaging (DWI) offers a potential noninvasive in-vivo biomarker to assess cartilage degeneration in early stages by measuring and displaying molecular diffusion processes. This MRI technique is based on the depiction of water molecule mobility, which is naturally limited by many anatomical barriers. If the diffusivity of water molecules is altered, e.g. by an increased water content as seen in deteriorating cartilage, DWI quantifies this pathologically increased water diffusion, which correlates with the destruction of extracellular matrix.

Recapitulating, biomedical imaging markers show promising results in research, as they enable a sensitive way to longitudinally track the evolution of osteoarthritic disease. Additionally, functional markes can be applied in preventive care or for prognostic purposes in order to evaluate the effect of different therapeutical strategies such as surgical interventions, conventional pharmaceuticals or novel therapeutic targets.[61]

Although they enable an insight into deeper biochemical processes, these techniques show limitations, as they are not widely available for diagnostic purposes in clinical routine, are time-consuming, require specific training and financial expenditure for advanced technologies.

One future approach is adressing the time factor, as the completely automated analysis processes of biomedical markers in MRI is under development.

3.7

THERAPEUTIC OPTIONS

Patients suffering from OA are presenting pain as leading and most burdening symptom, which is especially occurring during early stages of the disease. [69] Therefore, pain relief is seen as the foundation of therapeutical OA management.

Analgesia is pharmacologically targeted with non-steroidal anti-inflammatory drugs (NSAID), such as ibuprofen, naproxen, celecoxib or diclofenac, which can be applied topically or orally. NSAID show a high effectiveness to relief pain and improve physical functioning in chronic and inflammatory diseases.[41] Yet, the safety profile, especially for elder patients, is concerning in regard to gastrointestinal, renal, cardio- and cerebrovascular events.

Many overviews and studies describe various adverse effects of NSAID such as gastrointestinal dyspepsia, heartburn and at worst upper gastrointestinal bleedings. Renal complications include hypertension, which is attributable to electrolyte retention, also leading to edema and weight gain. Additionally, estimates imply that 1-5% of patients using NSAIDs may develop acute or chronic renal failure. [67] In extreme cases, NSAID can increase the risk of cardio- and cerebrovascular incidents such as myocardial infarction, atrial fibrillation and thrombotic events. Also, patients utilizing NSAID are 17% more likely to develop heart failure. [122] [151]

If NSAID are not sufficiently reducing the pain intensity, the pharmacological concept can be further expanded, accordingly to the WHO analgesic ladder, by the introduction of opioid analgetics. In various studies, opioids show to have a highly pain-reliefing effect with limited effects on physical functioning, as they do not act anti-inflammatory. Still, adverse effects, especially opioid-induced constipation, sedation or sleep disturbances shall be considered. [7] Chronic opioid use commonly leads to the loss of analgesic potency due to tolerance and to physical dependance, altogether limiting the clinical use. [136]

Other conservative treatment options include physiotherapy and patient education, aiming to eliminate risk factors such as overweight and obesity, support patients in their lifestyle changes as well as management and coping strategies of their chronic disease. Additionally, the two naturally occurring cartilage constituents chondroitin sulphate and glucosamine sulphate are commonly prescribed by physicians, showing a worldwide rise in sales, which directly mirrors an increase of utilisation by patients.[171] Research concerning the effect of these oral supplements is disconcordant with some meta-analyses suggesting significant efficiency in delaying the radiological progression of knee OA, as well as clinical improvent in pain & physical functioning. [91] [137] Other meta-studies report nonexisting effects of chondroitin,

glucosamine or the combination of both supplements on joint pain and physical performance. [171] A meta-analysis conducted by Vlad et al. adresses these huge differences between trials and concludes, that industry involvement leads to a heterogeneity between trials, allegedly creating a significant bias.[170] Moreover, a patients' positive perception of nutritional supplements could be based on a significant placebo effect. [183] Ultimately, pain reduction can be also targeted by co-treatment of mental comorbidities. Lin et al. found significant reduction in pain perception and level, when intensifying treatment for depression in OA patients. [95]
If pain relief is insufficiently achieved with conservative methods, more invasive pain reduction strategies such as intraarticular injections with corticosteroids, platelet rich plasma or hyaluronic acid can be applied. Once again, research remains controversial in regard to effectiveness and superiority of these interventions, with some studies suggesting non-existent or minimal effect of intraarticular injections, while others are showing comparable effects of oral NSAID and intraarticular injections.[12] [142]
Other studies claim the superiority of intra-articular treatments, as they show significant clinical improvement in regard to pain, function and stiffness compared to oral treatments. [11]
Many authors point out the differences between the injectable agents in regard to duration of effect and safety profile, altogether recommending intraarticular injections in early stage OA and describing a high level of patient satisfaction. Concludingly, it remains unclear in the literature, whether these results are based on actual disease modification or on placebo effects. [8] [110]
If the osteoarthritic joint further degenerates, surgical interventions become another option, offering a wide range of procedures and levels of invasiveness.
As OA is a multi-structural disease, instabilities and lesions of menisci or ligaments are major risk factors for OA progression. Both structures can be targeted with minimal-invasive procedures in order to restore stability and delay OA progression. Meniscal lesions can be surgically treated through arthroscopic techniques, while ligament instabilities can be refixated with autologeous grafts. Although the routine application of arthroscopy is controversial, efforts have been made to improve the surgical techniques, as it can be combined with mesenchymal stem cell injections, microfracturing or autologous chondrocyte transplantation. Those techniques stimulate bone marrow and aim to treat focal cartilage defects. Altogether these are valid alternatives to achieve clinical improvement of symptoms, with limitation to early stage OA and heterogenous study results. [85] [86] [117] [135] [175]
Ultimately, if a complete destruction of the joint commenced, joint replacement surgery is inevitable. In the US, a drastic increase of joint replacement surgeries can be seen, which is disproportionally high, as it only partly correlates with increased population growth and

ageing. Knee replacement surgeries have risen by 134% in 11 years (1999-2008) and projections estimate, that by 2030 the number of hip replacements will increase by 174%, whereas knee replacements will increase by 673%.[87] [102] Also, revision procedures shall be counted in, as they are supposed to double for hip surgeries by 2026, whereas knee revision surgeries will estimatedly rise by 601% until 2030. [87] Approximately 54% of patients with symptomatic knee osteoarthritis are receiving knee replacement surgery, while they are averagely spending 13.3 ± 10.4 years with conventional treatment regimens beforehand.

Although being the last and potentially promising option to regain life quality, surgical interventions are accompanied by general risks, including infection, bleeding, impaired wound healing or allergic reactions to prosthesis material. Surgical advances have been made, which include the use of hypoallergenic materials like titan, decreasing the allergic potential of prothethics. Also, improvements have been made in surgical techniques, needing less traumatic surgical incisions. Additionally, navigated systems were introduced, which are intraoperatively calculating axle positions to improve the mechanical alignment and joint angles.

Nonetheless, intraoperative as well as postoperative events such as myocardial infarction, venous thrombosis, pulmonary embolism or death can occur with a rate of approximately 2.2% of all joint replacement procedures. [177]

Another important issue affects the average prosthetics survival of 15.8 ± 9.7 years. This creates a mismatch between the expected survival time of prosthetics and the patients' life expectancy, requiring a change of prosthetics in higher age groups, moreover increasing surgery-related risks. Nowadays, around 8% of the patients are in need of revision surgery. [101]

Lastly, studies show that >9% of patients receiving hip replacement surgery and about 20% of patient receiving knee replacement surgery report pain during long-term follow ups. [17]

Nonetheless, study results verify the benefits of a succesful surgery, that supposedly outweighs the risks, as the overall satisfaction, life quality and physical functioning are significantly improving after surgery.[152]

Taking everything into consideration, both, the present pharmacological and surgical treatment options are offering potential for improvement but are simultaneously accompanied by many risks, which become even greater in an ageing patient population.

Novel therapeutical perspectives are offered by pharmacological research, that precisely targets the local inflammation in the joint. Anti-inflammatory drugs, designed to reduce local inflammation and modify the immune system such as Methotrexate, TNF-alpha and IL1-antagonists are already commonly used in autoimmune disease and their application for OA

is now researched. The idea is to target the elevated macrophage activation in inflamed synovium, linked to OA, synovitis and metabolic syndrome. [159] [179]

The new concept of disease-modifying osteoarthritis drugs (or DMOADs) is constinuously extended by new research, investigating the potential of promising drugs, mostly in preliminary animal studies. Some insight into new DMOADs:

Strontium ranelate is an anti-osteoporotic drug, used in postmenopausal women to reduce bone resorpion and fractures. New studies hypothesize that the application of strontium ranelate in OA patients can potentially influence the remodelling of subchondral bone and stimulation of chondrocytes. [133]

Other targets aim at mitochondrial dysfunctions, which are naturally occuring during the ageing process, to reduce the production of reactive oxygen species to decelerate the progression of OA.[37]

When looking at other processes at molecular level, another research is also assessing the Wnt pathway, a pathway for signal transduction between protein molecules that play an essential role in cell proliferation and differentiation of osteoblasts and chondrocytes. Research is done to develop a pathway-inhibitor, which inhibits catabolic proteases and induces chondrocyte differentiation, altogether leading to an increased cartilage thickness and thus being chondroprotective. [45] [125]

Another concept, firstly published in 1990, describes the imbalance of active metalloproteases (MMP) and their inhibitors in cartilage lesions, altogether triggering cartilage degradation during inflammatory conditions. Recent research groups build upon this work to develop an orally available MMP-inhibitor, called ADAMTS-5, in order to directly decelerate cartilage degeneration by reducing the overactive MMPs. [19] [35] [127] Lastly, some research groups focus on injectable DMOADs to reduce systemic side effects and apply higher concentrations of active agent. For instance, the cytokines IL-4 and IL-10, both inhibiting macrophages and classified as anti-inflammatory cytokines, are experimentally injected into canine models. It is assumed that they unfold their anti-inflammatory potential, reduce inflammation in the joint and thus enhance chondroprotection. [70]

4

MATERIAL & METHODS

For the longterm monitoring of cartilage health, a thorough patient selection was required, in order to isolate the weight loosing effect, as this study specifically targets overweight and obese subjects with different weight developments. The access to detailled demographical patient and imaging data, were both obtained from the Osteoarthritis Initiative (OAI) . In order to perform the image analysis, a specific analysis strategy and computer-based software were used. Supplemented by the access to clinical data and questionnaires, a statistical analysis was performed to interpret the data. All of the above mentioned study features are now explained in detail as followed.

4.1

STUDY DESIGN

In this longitudinal study, we studied MRI data at 3.0 Tesla (T) of the right knee in overweight and obese subjects over 8 years.

The patients were selected in regard to a moderate (5-10%) or high (>10%) weight loss amount and matched to constantly overweight subjects. All three groups had a baseline body mass index (BMI) ≥25 kg/m^2 and risk factors or mild signs for OA.

The biochemical cartilage composition and clinical symptoms were evaluated as followed:

MR-based T_2 values, laminar and texture analysis reflect the biochemical cartilage structure, whereas additional clinical data and weight loss questionnaires study the change in quality of life, which determine the patients' contentment in their everyday life as well as possible benefits from the chosen method of weight reduction.

4.2

OAI – ROLE AND DATABASE

The Osteoarthritis Initiative, publically accessible at http://www.oai.ucsf.edu, is a longitudinal research project, publically sponsored by the U.S. National Institute of Health (NIH) and additionally receiving private funding from several phramaceutical companies*, which are managed by the Foundation for the National Institutes of Health. This prospective, multi-center, observational research study was conducted in the United States of America and has collected imaging, clinical and biospecimen data of 4796 men and women aged 45–79 in order to increase the understanding of the natural evolution, progression and potential prevention of knee and hip osteoarthritis.

The study protocol included a huge variety of parameters, which were assessed annually during the first four years of follow up, such as bilateral knee radiographs and MR imaging, blood and urine collections and clinical measures such as blood pressure, weight, height and abdominal circumference. Furthermore, clinical knee examinations and physical function performance tests (timed walking tests, balance and strength tests) were performed, as well as interview measures including gathering of information about demographics, medication, health and risk behavour. Lastly, the OAI protocol included a regular administration and distribution of symptom-, functioning- and health-realted questionnaires (see chapter 4.7 clinical questionnaires).

The participating subjects were either healthy (control cohort), showed risk factors for developing OA (incidence cohort) or suffered from symptomatic and radiographically evident knee OA (progression cohort).

At all four participating centers, the informed consent of each participant was obtained and granted by the local institutional review board. The OAI public datasets are accesible to scientists and researchers worldwide. In this study the following datasets were used:

Baseline imaging dataset 0.E.1, 48-month follow-up imaging dataset 6.E.1, 96-month follow-up imaging dataset 10.E.2.

Baseline clinical dataset 0.2.2, 48-month follow-up clinical dataset 6.2.2, 96-month follow-up clinical dataset 10.2.2, 108-month follow-up 11.2.1.

* Private funding companies: Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

4.3

PATIENT SELECTION STRATEGY

For this study, 726 subjects (age 62.9 ± 9.0; 62.3% females) were selected from the progression and incidence cohort of the Osteoarthritis Initiative database. All patients presented overweight and risk factors or radiographic evidence for mild to moderate osteoarthritis at baseline.

The OAI Database consists of 4796 patients, from which we excluded every subject with a baseline BMI < 25 kg/m^2 (N=1048), as the targeted study population were overweight and obese subjects. Besides, patients without fully available BMI data or T_2 mapping sequences at the timepoints of interest were excluded, as those were crucial data needed to perform the further analysis (N=294).

Subjects with weight gain >3% of their baseline BMI, minor weight loss of 3-5% or cyclic weight change between the time points were excluded, in order to maintain a clear and continous group categorization. Also, subjects with a KL-score >3 were excluded, as the massive loss of cartilage in end-stage OA impairs the analysis. Finally, patients diagnosed with rheumatoid arthritis during the follow up examinations were excluded.

Categorization was performed depending on the patient's longitudinal weight development. For this purpose, the difference between the BMI at baseline and 72-months-follow-up was calculated, as those have been the most recent data at the set up of the study.

Subjects, either loosing 5-10% of their initial BMI or even decreasing their BMI over 10% were grouped accordingly into a 5-10% weight loosing (WL; n=275) and >10% weight loosing (n=88) group. Patients from the WL-cohorts were frequency-matched to stable overweight controls (n=365), whose BMI changed <3% over 72 months. The matching process was performed for the parameters age, sex, baseline BMI and KL score, as these are shown to be major influence factors for the development and progression of OA.

Therefore, the matching process was significant to increase the comparability between groups, reduce the covariate bias and simulatenously isolate the weight loosing effect. [51 146 156]

In an additional subgroup analysis, a weight loss questionnaire (see chapter 4.7. clinical questionnaires) was used to categorize all weight loss patients depending on the chosen method of weight loss, while the amount of weight loss was not considered anymore.

Out of 363 weight loosing patients 185 questionnaires were available. Those patients with completed weight loss questionnaires were assigned to one of the following four groups based

on their chosen weight loss method: diet (n=40), exercise (n=32), diet and exercise combined (n=97) and bariatric surgery (n=16).

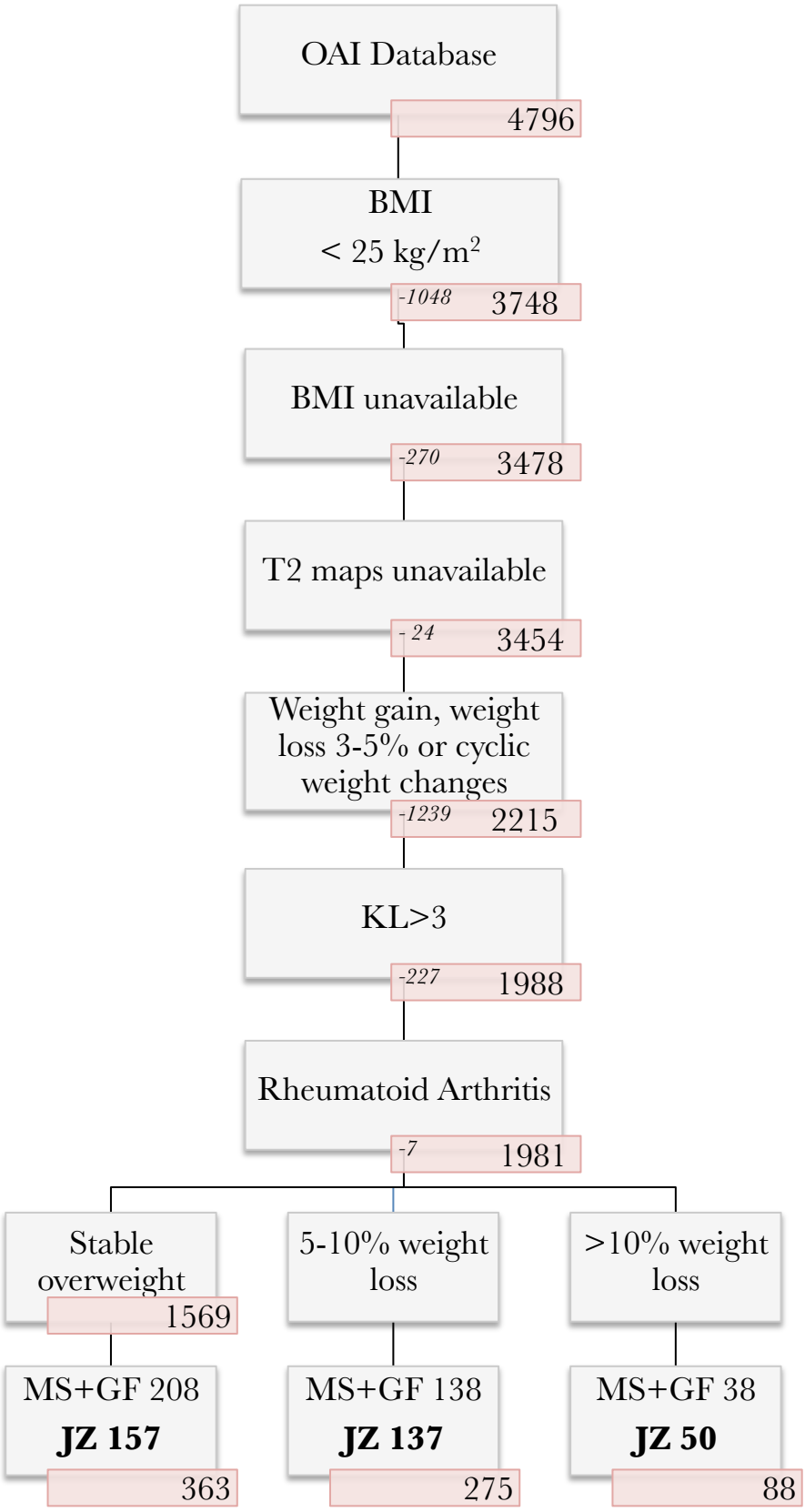

Figure 5: Flow chart illustrating patient selection process

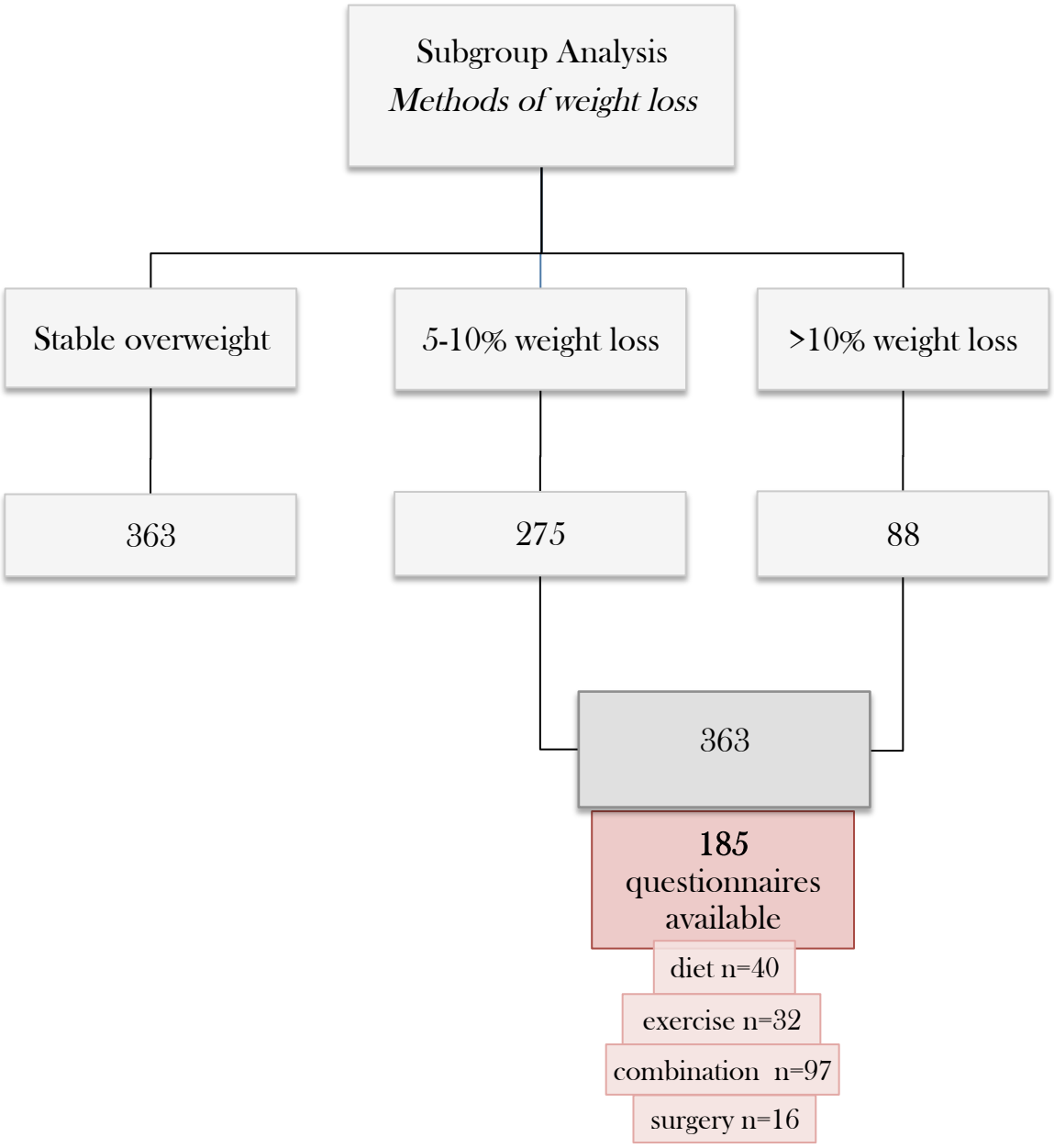

Figure 5.1: Flow chart illustrating subgroup analysis

4.4

MR IMAGING

Clinical data and imaging of both knees were obtained annually during in-clinic examinations. Imaging included radiographs and MR imaging.

The acquisition of MR images was performed at four clinical sites:

- University of Maryland/John Hopkins University, Baltimore, Maryland
- Memorial Hospital of Rhode Island / Brown University Pawtucket, Rhode Island
- Ohio State University Columbus, Ohio
- University of Pittsburgh, Pittsburgh, Pennsylvania

As the Osteaorthritis Iniative is conducted as a multicenter study, the quality assurance and standardization process was highly important for the increase of comparability and reduction of discrepancies between study centers. This was achieved by the use of identical 3.0 T scanners (Magnetom Trio; Siemens AG, Medical Solutions, Erlangen, Germany) with a monthly maintenance performed by Siemens field engineers and the use of identical quadrature transmit-receive knee coils (USA Instruments, Aurora, Ohio, USA) at each clinical site. Additional quality assurance procedures included image aquisitition and analysis of study phantoms. This was performed daily on the OAI study phantom and monthly on the ACR study phantom, both being cylindral bodys containing different chambers, that were either hollow inside or filled with contrast agent.

The OAI MR image acquisition protocol included following sequences:

No.	Scan	Duration in Minutes		
		R knee	L knee	Total
1	Localizer (3-plane)	0.5	0.5	1.0
2	COR IW 2D TSE	3.4	3.4	6.8
3	SAG 3D DESS WE	10.6	10.6	21.2
4	COR MPR SAG 3D DESS WE	0.0	0.0	0.0
5	AXIAL MPR SAG 3D DESS WE	0.0	0.0	0.0
6	SAG IW TSE FS	4.7	4.7	9.4
7	COR T_1W 3D FLASH WE	8.6	-	8.6
8	SAG T_2 MAP 120 mm FOV	10.6	-	10.6
Total		38.4	19.2	57.6

Figure 6: OAI MR protocol

Every sequence targets the optimal depiction of specific structures, shortly described as followed:

COR IW TSE

Coronal two-dimensional intermediate-weighted (IW) turbo spin-echo is ideal for the evaluation of the cartilage-bone interface and shows sensitivity for the evaluation of menisci, collateral ligaments, osteophytic and cystic changes.

SAG 3D DESS WE

Sagittal three-dimensional (3D) dual-echo at steady-state with water excitation is used for morphological cartilage measurements such as cartilage thickness and volume, as it is accurately depicting delineation of cartilage. Additionally, osteophytes, cysts, bone marrow edema and collateral ligaments can be evaluated.

As this sequence has thin slices (0.7mm), it can be reformatted to multiplanar reformation images (MPR), without further acquisition time needed:

COR MPR SAG 3D DESS WE

Coronal multi-planar reformatting of the Sagittal 3D DESS with Water Excitation Is useful to display tibial and central weight-bearing surface of the femoral cartilage.

AXIAL MPR SAG 3D DESS WE

Axial multi-planar reformatting of the Sagittal 3D DESS with Water Excitation is used to outline the trochlear and patellar cartilage.

SAG IW 2D TSE FS

Sagittal intermediate weighted two dimensional turbo spin echo sequence with fat suppression is offering good contrast and sensitivity for the evaluation of cysts, joint effusion and bone marrow edema.

COR T_1W 3D FLASH WE

Coronal 3D Fast low angle shot with Water Excitation is a sequence, that has shown to be accurate in cartilage thickness and volume measurements. Also, it can depict cartilage contours in a high resolution.

SAG T_2 Map 120mm FOV

Sagittal T_2 mapping sequence with a rather small field of view is used to evaluate the cartilage morphology and other joint structures such as menisci, crucial ligaments, cysts and improves the assessment of the osteochondral junction.

In our study, the sagittal T_2map of the right knee with an aquisition time of 10.6 minutes was used to quantify T_2 relaxation time measurements. This sagittal two-dimensional (2D) multi-

slice, multi-echo (MSME) sequence offered seven echo times (TEs; 10ms, 20ms, 30ms, 40ms, 50ms, 60ms and 70ms) and a repetition time (TR) of 2700ms. Other sequences were utilized to perform the WORMS readings and semi-quantitavely evaluate the morphology of different joint tissues.

4.5

IMAGE ANALYSIS

The segmentation process included five cartilage compartments, so-called regions of interest (ROIs): Lateral femur condyle (LF), lateral tibia (LT), medial femur condyle (MF), medial tibia (MT) and patella (PAT), highlighted in the following Figure 7.

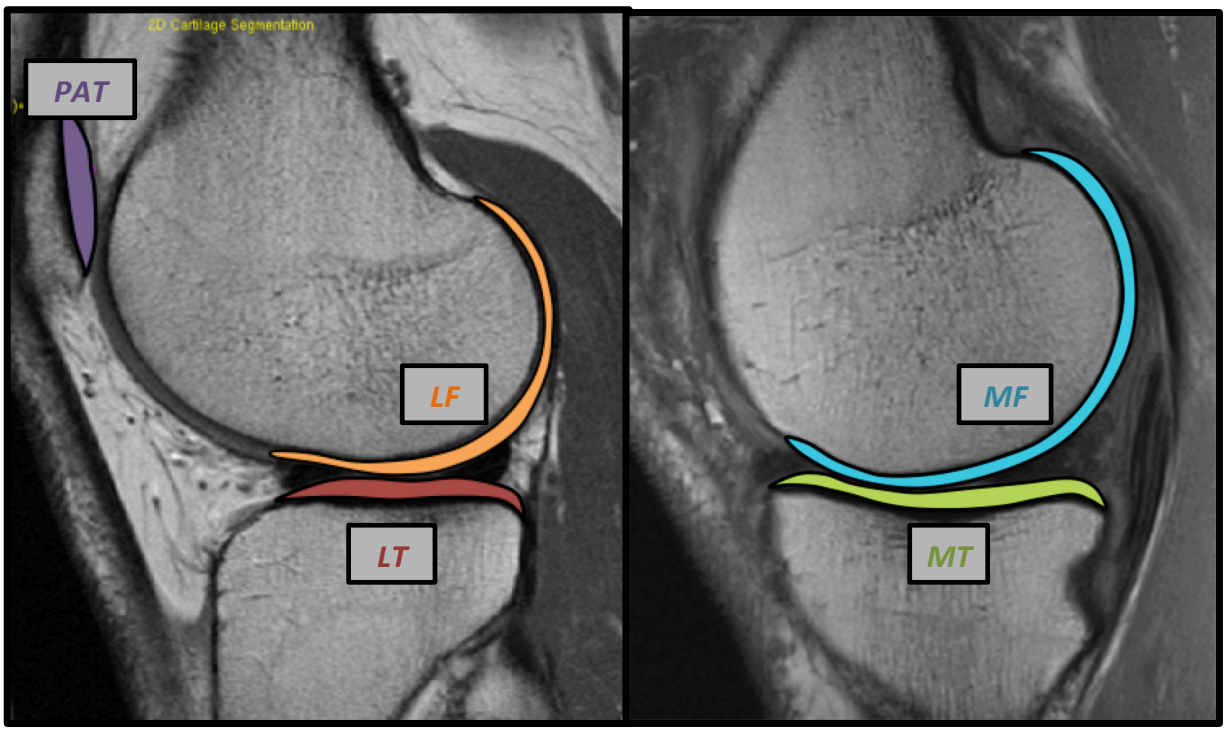

Figure 7: Five regions of interest (ROI) in right sagittal knee

The trochlea was excluded from segmentation, as previous studies have shown a higher frequency of interfering flow artifacts caused by the popliteal artery. [80]

The segmentation of each compartment and the subsequent T_2 analysis were performed separately for each region. Three trained researchers, referred to in the subject selection as "MS, GF and JZ", performed the cartilage segmentation during this project.

The segmentation process was performed on the first echo of the sagittal 2D MSME sequence, and is based on a semi-automatical, spline-oriented algorithm, which extracts T_2 values from the segmented compartments. [13]

Figure 8 displays the segmentation process in detail:

As seen in Figure 8A, firstly the manual setting of single contouring points, seen as blue crosses between the deep cartilage layer and subchrondral bone, was performed. After positioning all the marking points individually, they were automatically connected to form the deep cartilage spline, seen as blue line in Figure 8B.

Afterwards, the algorithm automatically calculated the according superficial cartilage spline, which complemented the outlining of the ROI, seen as pink line in Figure 8B1. In order to achieve a thoroughly defined ROI, appropriable for further T_2 analysis, the intermediate steps B1 and C were obligatory, as the algorithm regularly presented software bugs, which displaced the splines over the cartilage boundaries. This correction process required a manual reposition of each point individually under the supervision and corcordance of experienced radiologists (AG, TML)

The final ROIs can only be used for T_2 analysis, when a precise cartilage contouring was achived, are presented in Figure 8C*.

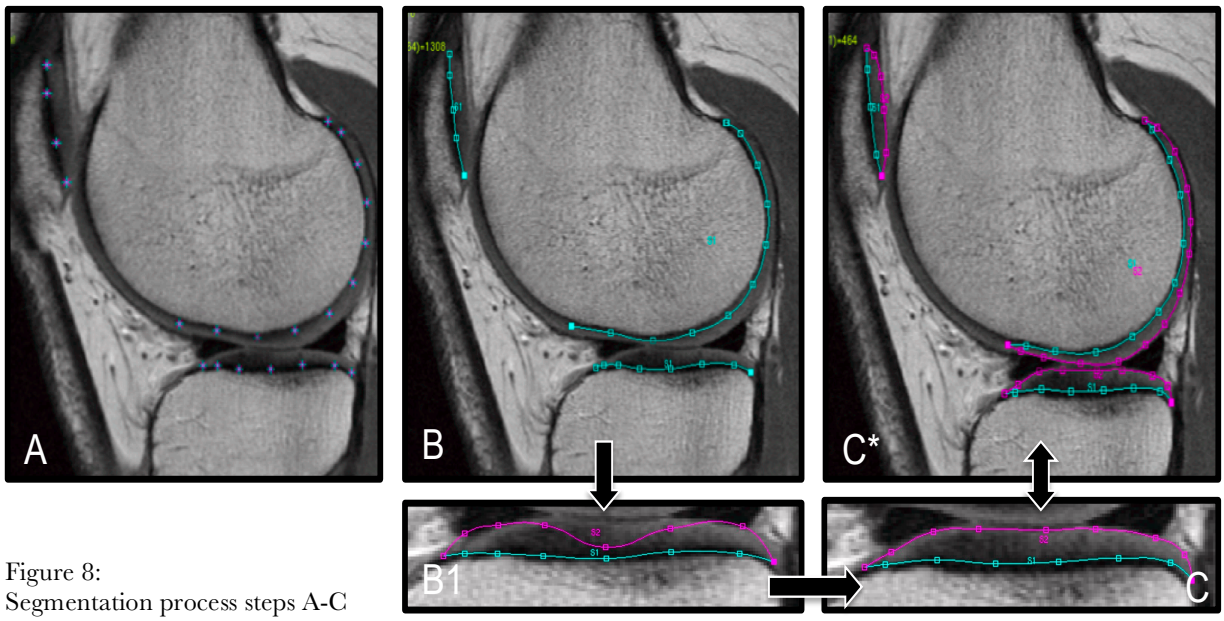

Figure 8:
Segmentation process steps A-C

If the segmented ROI would include bone, menisci or fluids, a significant alteration of analysis could be assumed, leading to a high distortion of T_2 values. Thus, the maintenance of a meticulous segmentation technique, as well as consistency in image quality was unavoidable

for a high analysis quality. Practically, this meant to include only clearly contoured cartilage boundaries into the segmentation process and dismiss artifacts which impaired image quality . Figure 9 illustrates some of the occasionally encountered artifacts, which impeded the segmentation and required a time-consuming, thorough selection as well as rejection process.

Firstly, artifacts could occur during MR acquisition itself, leading to pulsatile artifacts resulting from a popliteal flow, wrapping due to an insufficient anatomical coverage (aliasing) or susceptibility possibly arising from metallic objects or patients' motion.

This could lead to a dismission of single slices. Secondly, difficult anatomical conditions could impair the software algorithm, which then miscalculates the secondly created, superficial spline and dislocates it to other tissues. This does not demand the rejection of images but requires a significant amount of time for the manual correction process of each crosspoint individually. Lastly, an anatomical loss of cartilage, massive effusion and medial fluid, as well as very pronounced osteophytes impede the segmentation completely, requiring the rejection of all images concerning the ROI.

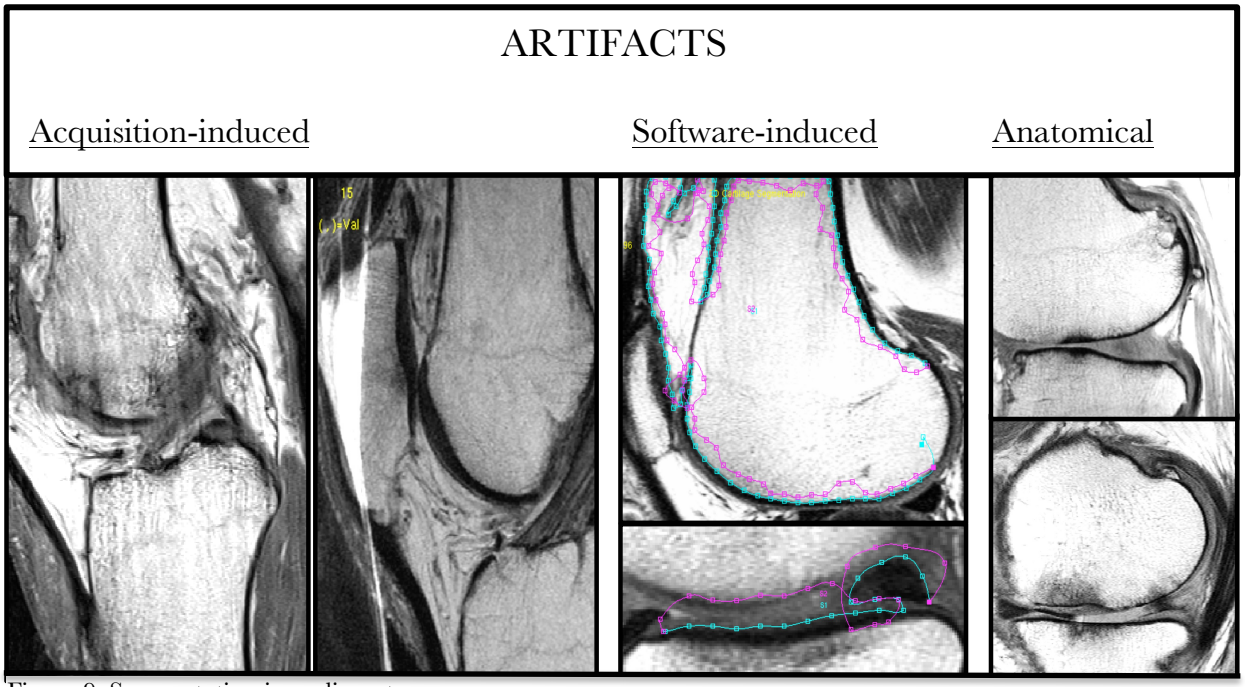

Figure 9: Segmentation impediments

After completing the segmentation of the whole dataset, the calculation of T_2relaxation time values was performed using the in-house developed software "Image processing package" (IPP), with an algorithm being based on MATLAB (MathWorks, Natick, Massachusetts). T_2 values were calculated separately for each compartment with a mono-exponential curve fitting model, using a noise-correction-algorithm that would exclude the first echo in order to

minimize errors and improve signal-to-noise ratio, compared to traditional uncorrected exponential fitting methods.

Following equation demonstrates the T_2 value calculation for each pixel creation on the MSME sequence:

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

with S being the signal intensity at a given echo time (TE), S_0 being the signal intensity at the excluded first echo time (TE: 10ms) and B being an estimated noise at a given echo time (TE). This calculation of the signal intensity was performed on a pixel-by-pixel basis, using six echo times (TE: 20ms-70ms) and the above-mentioned parameters in the model, accounting for noise, altogether increasing the accuracy of T_2 relaxation time measurements. [27] [78]

4.6 LAMINAR AND TEXTURE ANALYSIS

The previously segmented cartilage contour is used in the laminar analysis to automatically split the cartilage outline into two equally thick parts: a deep layer (blue; bone facing spline) and a superficial layer (pink; articular space facing spline), as depicted in Figure 10.

Afterwards, T_2 relaxation time values were calculated separately for both layers, to assess the differences between superficial and deep T_2 values. Histologically and biochemically, the water concentration in the deep cartilage layer is increasing from approximately 65% to around 80% in the superficial cartilage layer. [114] Additional water mobilisation is achieved through mechanical pressure on the cartilage or can be due to pathological, degenerative processes, which lead to a disruption of the collagen network and increased water contents. This cartilage property allows us to longitudinally analyse a potential disruption of the T_2 laminar organization. [27]

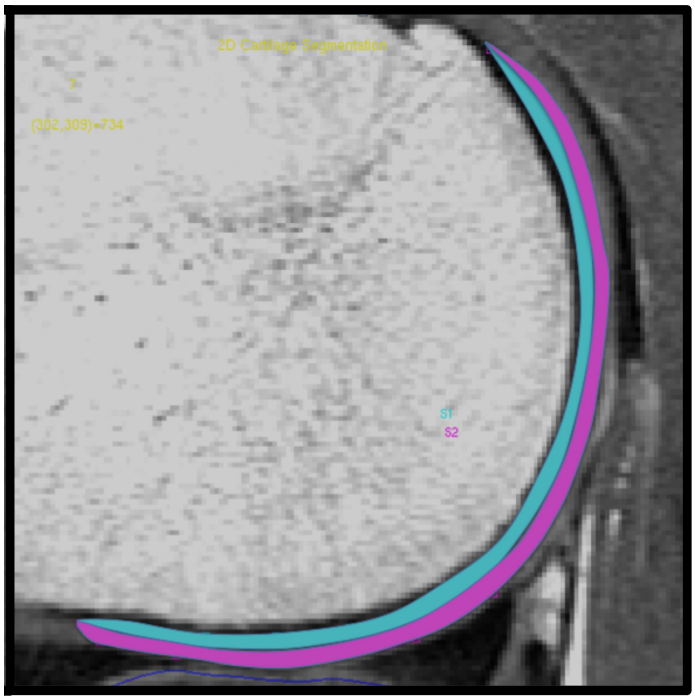

Figure 10: Illustration of Laminar Analysis
deep bone layer (blue), superficial articular layer (pink)

In 1973, Haralick et al. introduced an approach to texture analysis in order to classify images, which can be applied on our segmented cartilage compartments to understand the spatial distribution of T_2 values. [13 65]

Generally, texture is represented by different brightness or grey levels in an image. To compute a statistical texture analysis, the software treats the image pixel-by-pixel, assessing the brightness level of each pixel and subsequently embedding single pixel information into the overall texture context. In the end the spatial distribution and combination of brightness levels between neighboring pixels is statistically assessed. [1]

For this purpose, each grey value is allocated a digit, a so-called grey level digital number or GLDN, seen in Figure 11, which is used by the GLCM-software to calculate the neighboring-relationship between two pixels at a time, the so called reference-pixel and the neighbor-pixel.[64]

This relationship analysis is reflected in different texture features, divided into following groups:

The contrast group consists of the parameters contrast, dissmiliarity and homogeneity. A highly homogeneous image shows only few grey levels, whereas contrast refers to a wider variation of grey levels. [1] In the orderliness group, consisting of the parameters angular second moment (ASM), maximum probability and entropy, the disorder or regular distribution of

pixel values within an image is assessed. The parameters ASM and entropy are an example for a very uniform distributed image, if showing high values. [1] [13]

The Statistical Group, consisting of GLCM mean, variance and correlation, measures the relationship between pixels at specific positions and their grey level from a statistical point of view. [1]

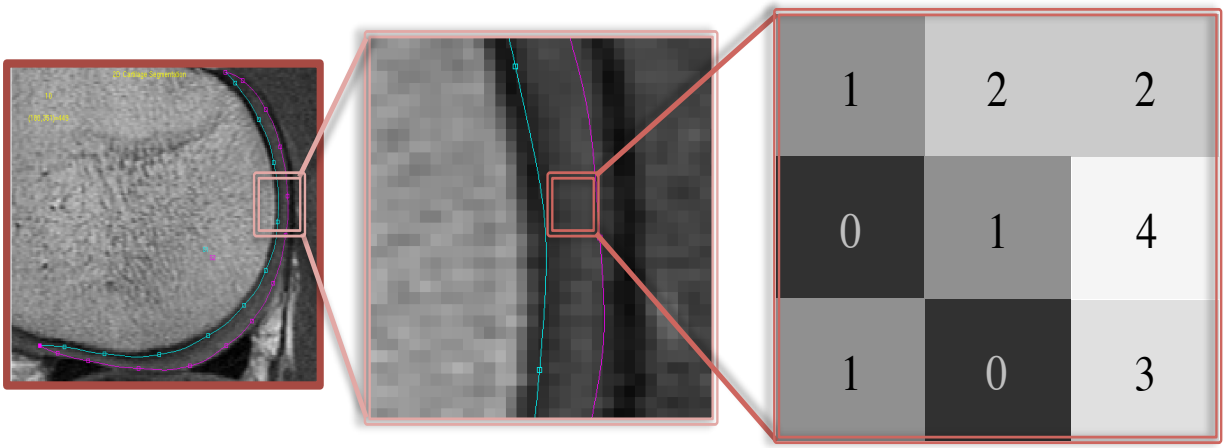

Figure 11: Illustration of Texture Analysis

As previous studies have demonstrated an elevation of contrast, entropy and variance as well as decline in homogeneity values in subjects suffering from OA, this texture analysis focuses on these four parameters. [27] [79] [130] [168]

4.7 CLINICAL QUESTIONNAIRES

The Osteoarthritis Initiative includes various questionnaires into the study protocol, such as joint pain rating scales, a modified Mini-Mental State exam, depression and late life disability rating scales and follow-ups on total joint replacement surgeries.

This study focussed on questionnaires investigating quality of life. Additionally, at the 8th year of follow-up a weight-loss questionnaire was administered, further looking into the strategies and methods of weight loss. For this study, following questionnaires were used:

The Knee Injury and Osteoarthritis Outcome Score (KOOS) consists of 42 items on five subscales, which inquire pain frequency, swelling and stiffness, difficulties during activities of daily living, difficulties during sports and recreation and lastly quality of life. The score range

for every item is 0-4, indicating more experienced symptoms the higher the score. [38] Altogether the sums are transformed to a percentage scale with zero reflecting extreme problems concerning knee symptoms and quality of life while 100 displays no encountered problems. For this analysis, the focus was places on KOOS quality of life.

The Short-Form 12 Health Survey (SF-12) is a shortened version of the SF-36 survey, which originally contains 36 items, primarly designed to assess quality of life. This questionnaire is built on eight subscales, which contain 12 items, with a total score range of 0-100: physical abilities (2 items), body pain (1 item), vitality (1 item), mental well-being (2 items), subjective health perception (1 item), social role functioning (1 item), physical and emotional role functioning (2 items, respectively). In this case, the value 100 complies with the best possible quality of life whereas 0 is the poorest outcome. [131]

The OAI take-home weight loss questionnaire was administered to patients 96 months after enrollment. It enquires into unintentional vs. deliberate weight loss and further looks into explanatory reasons such as change in diet, increased exercise, diet pills, commercial weight loss programm and other. If applicable for patients, it also investigates different types of bariatric surgery.

4.8

QUALITY ASSURANCE

For this study, five researchers (ASG, GF, JZ, MS, NC) analyzed image data of the right knee in the selected patient cohort (see Figure 5: Flow chart illustrating patient selection process).
Three researchers (MS, GF, JZ) conducted the cartilage segmentation on the previously mentioned cartilage compartments.
To assure that our segmentation process is standardized and our results will not be conflicted with intra- or interpersonal deviations, our quality assurance process included an identical trainingdataset, consisting of 10 randomly selected patients.
Each researcher performed cartilage segmentations at two different time points with a minimum of 14 days and a maximum of 30 days between the two time points.
Afterwards, an intra- and interreader reproducibility was calculated for the segmentation process by using the root mean square average of the single coefficients of variation (CV) on a percentage basis. [60] After accomplishing the trainingdataset, all researchers were blinded in regard to the patient characteristics, meaning that no information about individuals' data or

assigned group was available while performing the segmentation and reading analysis of the study population.

4.9 STATISTICAL ANALYSIS

Statistical analysis was performed with IBM SPSS Statistics 22 (released 2013. Version 22.0. Armonk, NY: IBM Corp.), using a two-sided level of significance (p=0.05).

The comparison of baseline parameters between groups (Table 2, Table 3, Table 3.1, Table 3.2, Table 3.3, Table 3.4) was performed using one-way analysis of variance (ANOVA) for parametric variables and Pearson-Chi-Square test for binary variables.

To calculate differences between groups after 8 years, a mixed model analysis adjusting for age, sex, baseline KL and baseline BMI score was used, as it considers repeated measurements on each subject over time.[149] Additionally, this model integrates missing values, e.g. missing segmentations due to artifacts, and uses fixed and random effects:

The assigned group (stable overweight, 5-10% WL, >10% WL, diet, exercise, combination, surgery) is used as fixed effect, meaning that data from all levels are considered to be of interest.

Time points (baseline, 48months, 96 months) are representing the predictor variable, also defined as covariate. Lastly, the dependant variables are allocated, including all target parameters such as T_2 values, laminar, texture and clinical performance parameters.

Altogether the multivariable regression model is well suited to interpret the huge amount of multilayered data and to study the association between weight loss and structural cartilage degeneration over eight years. This statistical analysis calculated the differences between the stable overweight group vs. the weight loosing 5-10% and >10% groups in Table 4, Table 4.1 and Table 4.2.

Additionally, differences between the stable overweight cohort and weight losing groups in dependance of their chosen regime of weight loss (diet, exercise, diet + exercise, bariatric sugery) were calculated in Table 5, Table 5.1 and Table 5.2.

5

RESULTS

5.1

REPRODUCIBILITY

To employ the quality assurance, a calculation of the coefficient of variance was performed after the researchers analysed a trainingdataset consisting of 10 cases as described in chapter 4.8. During the first segmentation of the trainingdataset, the inter-reader reproducibility ranged from 1.66% to 2.31%.

Table 1: Interreader-Reproducibility calculated from Trainingsdataset at the beginning

Researchers			
	J.Z.	G.F.	M.S.
	Coefficient of variation in %		
J.Z.	-	1.93 %	2.31%
G.F.	1.93 %	-	1.66%
M.S.	2.31%	1.66%	-

After 14-30 days, segmentation of the same dataset was repeated, and the inter-reader reproducibility was ranging from 1.45% to 2.08%. The value of the calculated intra-reader reproducibility ranged from 1.13% to 2.06%.

Table 1.1: Inter- and Intrareader-Reproducibility calculated from Trainingsdataset within 30 days

Researchers			
	J.Z.	G.F.	M.S.
	Coefficient of variation in %		
J.Z.	1.13%*	1.67%	1.45%
G.F.	1.67%	2.06%*	2.08%
M.S.	1.45%	2.08%	No data

* Intrareader Reproducibility

5.2

SUBJECT CHARACTERISTICS

When comparing demographic parameters at baseline between both weight loss cohorts and the stable overweight group, no significant differences were seen regarding age, sex, baseline BMI and baseline KL Score. This was expected due to the frequency matching process of controls and weight-loss-groups.

At baseline, our study population was averagely aged 62.9 ± 9.0 years with 62.3% of the patients being female. The overall baseline BMI of 29.9 ± 3.5 kg/m^2 can be classified as preobesity, but when looking at every study group individually, the stable overweight group with a baseline BMI of 30.0 ± 3.5 and the >10% weight loss group with a baseline BMI of 30.2 ± 3.7 would be already associated with class I obesity.[148] Approximately half of all patients (48,2%) presented with KL score 0 or 1, meaning either no or only mild signs of osteoarthritis in radiographic imaging, while the other half of all patients (51,8%) showed moderate to severe osteoarthritic changes, represented by KL score 2 or 3.

Patients with KL score >3 were excluded, as severe cartilage damage strongly hinders cartilage segmentation.

Table 2: Subject Characteristics at baseline

	Group				P-Value 5-10%*	P-Value >10*
	All	stable overweight[1]	5-10% weight loss[1]	> 10% weight loss[1]		
Mean ± SD						
n (%)	726 (100%)	363 (50.0%)	275 (38%)	88 (12%)		
Age in years	62.9 ± 9.0	62.7 ± 8.6	63.1 ± 9.3	63.3 ± 9.5	0.5■	0.6■
Sex - females n (%)	452 (62.3%)	226 (62.3%)	171 (62.2%)	55 (62.5%)	0.9◆	0.9◆
Baseline BMI (kg/m^2)	29.9 ± 3.5	30.0 ± 3.5	29.6 ± 3.5	30.2 ± 3.7	0.3■	0.6■
Baseline KL Score n (%)	726 (100%)				0.8◆	0.7◆
KL = 0	216 (29.8%)	106 (29.2%)	83 (30.0%)	27 (30.7%)		
KL = 1	134 (18.4%)	66 (18.2%)	53 (19.4%)	15 (17.3%)		
KL = 2	244 (33.6%)	127 (35.0%)	92 (33.6%)	25 (28.7%)		
KL = 3	132 (18.2%)	64 (17.6%)	47 (17.0%)	21 (23.3%)		

■Anova ◆Pearson-Chi Square

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

5.3

BASELINE PARAMETERS

To better understand the natural progression and evolution of osteoarthritis, potential confounders such as malalignment, previous knee injuries and prior surgery must be excluded, as these parameters significantly influence the progression and severeness of OA. This circumstance can potentially distort values and bias the interpretation. Appropriate data was available for 425 out of 726 study patients, corresponding to 58,5% of the study population.
In a statistical comparison of these parameters at baseline, no significant differences could be detected between the three study groups, thus excluding potential misleadings.

Table 3: Alignment & History of prior injury or surgery at baseline

	Group				P-value 5-10%*◆	P-value >10%*◆
	ALL	stable overweight [1]	5-10% weight loss[1]	> 10% weight loss[1]		
Alignment 426/726 patients (58,5%)						
Normal[2]	201	58%	22%	20%	0.7	0.2
Varus[2]	156	59%	25%	16%	0.7	0.2
Valgus[2]	68	47%	21%	32%	0.7	0.3
Knee Injury						
Yes (/100%)	37%	34%	39%	37%	0.7	0.6
Knee Surgery						
Yes (/100%)	18%	17%	18%	20%	0.9	0.6

◆Pearson-Chi Square *P-value compared to the stable overweight group

[1] Subjects machted for BMI, KL, Age and Sex

[2] Varus defined as >182°, Valgus defined as <178°, Normal defined as 178-182°

The primary research question is based on a comparison of T_2 values over 96 months between our study groups, with T_2 measurements representing the biochemical cartilage composition and thus reflecting cartilage integrity and health. To ensure that our groups are comparable, and no underlying differences subsist at baseline, an analysis of variance was conducted. The

comparison of T_2 relaxation time values showed no significant variation between weight losing patients and stable overweight patients at baseline. Therefore, we can assume a comparable degree of osteoarthritis and cartilage composition, which eliminates another possible bias.

Table 3.1: T_2 parameters at Baseline

	Group			P-value 5-10%*■	P-value >10%*■
	Stable Overweight[1]	5-10% weight loss[1]	>10% weight loss[1]		
	Mean T_2 ± SD in milliseconds (ms)				
Global T_2					
LF	35.98 ± 3.02	35.47 ± 2.83	35.60 ± 3.16	0.1	0.6
LT	27.03 ± 2.09	26.90 ± 2.36	27.05 ± 2.31	0.7	0.6
MF	39.06 ± 2.95	38.64 ± 2.90	39.12 ± 2.94	0.3	0.5
MT	28.59 ± 1.98	28.77 ± 1.81	28.77 ± 2.46	0.9	0.7
PAT	30.55 ± 2.75	30.77 ± 3.26	30.79 ± 2.38	0.7	0.3
Total	32.14 ± 1.95	31.96 ± 2.19	32.19 ± 2.06	0.4	0.5
Bone Layer T_2					
LF	33.40 ± 2.99	32.96 ± 2.87	33.06 ± 2.78	0.1	0.6
LT	23.49 ± 1.61	23.43 ± 1.75	23.48 ± 1.59	0.7	0.9
MF	28.13 ± 2.77	28.03 ± 2.90	28.15 ± 2.31	0.8	0.6
MT	26.42 ± 1.85	26.12 ± 1.53	26.16 ± 1.64	0.1	0.2
PAT	28.13 ± 2.77	28.03 ± 2.90	28.15 ± 2.31	0.8	0.6
Total	29.45 ± 1.67	29.20 ± 1.99	29.41 ± 1.68	0.2	0.8
Articular Layer T_2					
LF	38.51 ± 3.35	37.81 ± 3.12	38.08 ± 3.78	0.6	0.5
LT	30.59 ± 2.85	30.34 ± 3.34	30.59 ± 3.23	0.6	0.5
MF	41.83 ± 3.36	41.24 ± 3.58	41.68 ± 3.16	0.3	0.8
MT	31.30 ± 2.73	31.16 ± 2.65	31.26 ± 3.57	0.8	0.3
PAT	33.11 ± 3.54	32.48 ± 3.87	32.44 ± 2.88	0.6	0.3
Total	34.94 ± 2.40	34.72 ± 2.63	35.03 ± 2.59	0.5	0.5

■Anova

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

Table 3.2: Texture parameters at Baseline

	Group			P-value 5-10% *■	P-value >10% *■
	Stable Overweight[1]	5-10% weight loss[1]	>10% weight loss[1]		
	Mean ± SD				
Medial Tibia					
Entropy	5.62 ± 0.33	5.62 ± 0.3	5.63 ± 0.31	1.0	0.9
Homogeneity	0.17 ± 0.04	0.17 ± 0.03	0.17 ± 0.04	0.9	1.0
Variance	204.53 ± 61.41	191.93 ± 50.06	193.93 ± 46.78	0.1	0.2
Contrast	306.57 ± 109.95	285.25 ± 88.28	287.06 ± 81.95	0.1	0.1
Global					
Entropy	6.02 ± 0.26	6.03 ± 0.26	6.04 ± 0.23	0.9	0.5
Homogeneity	0.14 ± 0.02	0.15 ± 0.03	0.14 ± 0.02	0.6	0.6
Variance	201.36 ± 46.88	196.32 ± 42.34	196.85 ± 36.69	0.4	0.4
Contrast	280.87 ± 75.33	273.44 ± 67.84	272.78 ± 55.06	0.4	0.4

■Anova

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

Similarly, when comparing texture parameters for all compartments (global) and the medial tibia, no differences could be shown. Again, this indicates a comparable texture distribution in the cartilage tissue between all three study groups at baseline.

In the clinical data set, scores for mental health and metabolic parameters were analysed, displaying no significant differences between groups.

When categorizing blood pressure levels according to recommended guidelines, with stage1 hypertension being defined as systolic blood pressure values of 130-139 mmHg or diastolic blood pressure values of 80-89 mmHg, all three study groups present values considered as healthy, showing a mean systolic pressure of 125.8 ± 16.6 mmHg and a mean diastolic blood pressure of 75.3 ± 9.9 mmHg.[132]

Table 3.3: Clinical Data at Baseline

	Group				P-Value 5-10% group *■	P-Value >10% group *■
	All	stable overweight[1]	5-10% weight loss[1]	> 10% weight loss[1]		
	Mean ± SD					
Mental Healh						
KOOS Quality of Life	69.6 ± 20.8	70.5 ± 20.5	69.1 ± 21.4	67.6 ± 20.9	0.6	0.3
SF-12 Mental Health	54.2 ± 7.8	54.3 ± 7.5	53.6 ± 8.7	54.6 ± 7.2	0.5	0.7
Metabolic Parameters						
Blood Pressure Systolic in mmHg	125.8 ± 16.6	124.9 ± 16.7	127.2 ±16.1	126.4 ±16.7	0.2	0.5
Blood Pressure Diastolic in mmHg	75.3 ± 9.9	75.8 ± 9.9	75.4 ± 9.1	73.6 ± 10.8	0.7	0.07
Heart Rate per minute	67.1 ± 9.7	67.0 ± 9.8	68.8 ± 9.9	65.9 ± 9.3	0.2	0.4
Abdominal Circum-ference in cm	106.1 ± 10.2	106.4 ± 10.1	105.4 ±10.4	106.1 ±10.6	0.4	0.8

■Anova

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

Besides being overweight or obese according to their BMI values, study groups showed a considerable increase in the abdominal circumference, with averagely 106.1 ± 10.2 cm, while normal values are defined under <102 cm in men or <88 cm in women. This result implies an increased abdominal fat distribution and significantly raises general health risks other than obesity alone. [148]

Lastly, to ensure a comparability of the subgroup categorization depending on the chosen regime of weight loss, an analysis of T_2 values at baseline was carried out, which showed no significant differences between all five groups, seen in Table 3.5.

Questionnaires, used for the subgrouping categorization, were available for approximately half of the weight loss cohort (185/363 patients = 51%).

Table 3.4: T_2 parameters at Baseline depending on weight loss method

	Group				
	stable overweight	diet weight loss	exercise weight loss	combinate weight loss	surgical weight loss
	n= 363	n=40	n=32	n=97	n=16
	Mean T_2 ± SD in milliseconds (ms)*▪				
Global T_2					
LF	35.98 ± 3.02	35.06 ± 3.75	35.08 ± 2.94	35.73 ± 2.89	35.96 ± 2.79
P-value		0.2			
LT	27.03 ± 2.09	26.80 ± 2.61	26.47 ± 2.33	27.47 ± 2.03	26.77 ± 3.52
P-value		0.3			
MF	39.06 ± 2.95	38.34 ± 3.69	38.30 ± 2.47	38.97 ± 2.64	38.75 ± 2.97
P-value		0.2			
MT	28.59 ± 1.98	28.16 ± 2.10	27.65 ± 2.60	29.01 ± 2.01	28.78 ± 2.58
P-value		0.4			
PAT	30.55 ± 2.75	30.68 ± 2.60	30.16 ± 2.89	31.18 ± 2.77	31.79 ± 3.59
P-value		0.2			
Total	32.14 ± 1.95	31.64 ± 2.56	31.23 ± 2.17	32.43 ± 1.93	32.33 ± 2.51
P-value		0.3			
Bone Layer T_2					
Total	29.45 ± 1.67	29.12 ± 2.18	28.78 ± 1.80	28.57 ± 1.50	29.66 ± 1.83
P-value		0.1			
Articular Layer T_2					
Total	34.94 ± 2.40	34.19 ± 3.11	33.76 ± 2.64	35.35 ± 2.54	34.99 ± 3.14
P-value		0.1			

▪Anova

*P-value compared to the stable overweight group

5.4

WEIGHT LOSS OVER 96 MONTHS

When comparing T_2 relaxation time values over 8 years (Table 4), significant differences can be seen in both weight loss groups compared to the continuously overweight cohort.

The 5-10% weight loss group shows a significantly lower rise of T_2 values in the medial tibia compared to the stable overweight patients (0.60 ± 0.73 ms versus 2.35 ± 0.55 ms, p=0.001). Similarly, the >10% weight loss group shows significantly lower T_2 values (0.06 ± 0.75 ms versus 2.35 ± 0.55 ms, p=0.000). Additionally, significantly lower progression of T_2 relaxation time values can be seen for the >10% weight loss group for the lateral tibia (1.45 ± 0.86 ms versus 2.72 ± 0.63 ms, p=0.049) and patella (0.42 ± 0.69 ms versus 1.77 ± 0.50 ms, p= 0.032). When calculating a global value, the >10% weight losing cohort shows a significantly slower T_2 progression over all compartments (2.03 ± 1.00 ms versus 2.36 ± 0.74 ms, p=0.008).

The laminar analysis shows significantly lower T_2 values in the 5-10% and >10% WL group compared to the stable overweight group in the articular layer of the medial tibia (1.12 ± 1.04 ms versus 3.02 ± 0.79 ms in the moderate WL group and 0.28 ± 1.08 ms versus 3.02 ± 0.79 ms in the significant WL group). In the bone layer, several compartments of the >10% weight loss group showed a significantly decelerated T_2 progression over 8 years:

In the lateral tibia (0.09 ± 0.73 ms versus 1.40 ± 0.53 ms, p=0.013), in the medial tibia (0.44 ± 0.68 ms versus 1.47 ± 0.50 ms, p=0.021) and the global T_2 value (1.11 ± 1.00 ms versus 1.63 ± 0.73 ms, p=0.005). Altogether, the relaxation time values increased higher in the articular layer than in the bone layer, suggesting a higher water content in the superficial layer and a lower water content in the deep layer. This corresponds to the histological composition of cartilage, as the highest proteoglycan and collagene levels occur deeply, whereas the water content is the lowest compared to all zones. In view of the above results, weight losing effects were strongest in the >10% group, showing a slower rise in T_2 values over several compartments. From all compartments, the medial tibia benefits mostly from the weight losing effect, showing a slower cartilage deterioration in the two WL cohorts and in both layers of the laminar analysis in the >10% WL group.

Table 4: Mean T_2 change over 96 months

	Group			P-value 5-10%*●	P-value >10%*●
	stable overweight [1]	5-10% weight loss[1]	> 10% weight loss[1]		
	Mean T_2 change ± SD in milliseconds (ms)				
Global T_2					
LF	1.78 ± 0.76	1.22 ± 1.01	1.00 ± 1.04	.833	.563
LT	2.72 ± 0.63	2.47 ± 0.85	1.45 ± 0.86	.513	**.049**
MF	2.40 ± 0.80	1.56 ± 1.09	0.66 ± 1.11	.564	.340
MT	2.35 ± 0.55	0.60 ± 0.73	0.06 ± 0.75	**.001**	**.000**
PAT	1.77 ± 0.50	1.37 ± 0.67	0.42 ± 0.69	.286	**.032**
Total	2.36 ± 0.74	2.13 ± 0.98	2.03 ± 1.00	.189	**.008**
Bone Layer T_2					
LF	1.70 ± 0.77	1.18 ± 1.03	0.83 ± 1.06	.373	.231
LT	1.40 ± 0.53	0.93 ± 0.71	0.09 ± 0.73	.132	**.013**
MF	1.22 ± 0.73	0.80 ± 0.99	0.35 ± 1.01	.115	.098
MT	1.47 ± 0.50	1.08 ± 0.65	0.44 ± 0.68	.098	**.021**
PAT	2.44 ± 0.44	2.05 ± 0.59	0.92 ± 0.61	.295	.123
Total	1.63 ± 0.73	1.47 ± 0.98	1.11 ± 1.00	.079	**.005**
Articular Layer T_2					
LF	1.21 ± 0.91	1.80 ± 1.22	1.10 ± 1.25	.597	.818
LT	4.08 ± 0.85	4.36 ± 1.15	2.98 ± 1.17	.971	.203
MF	3.54 ± 1.02	3.27 ± 1.38	1.92 ± 1.41	.807	.779
MT	3.02 ± 0.79	1.12 ± 1.04	0.28 ± 1.08	**.002**	**.000**
PAT	3.17 ± 0.64	3.07 ± 0.85	1.57 ± 0.87	.346	**.028**
Total	3.92 ± 1.15	4.77 ± 1.13	3.67 ± 0.85	.563	**.035**

●Linear Mixed Model

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

Additionally, the analysis of texture parameters supports these findings, as homogeneity in the medial tibia is significantly higher in both WL groups compared to the stable overweight patients (5-10%WL: 0.17 ± 0.03 versus 0.16 ± 0.01, p=0.06; >10%WL: 0.18 ± 0.03 versus 0.16 ± 0.01, p=0.01) Also, the global homogeneity averaged over all compartments in the >10%-WL group was significantly higher compared to the overweight patients (0.16 ± 0.02 versus 0.14 ± 0.01, p=0.02).

Previous studies performing GLCM analysis demonstrated elevated and more heterogeneous distribution of T_2 values in subjects with OA. [79] [130] Thus a significantly lower homogeneity in stable overweight and obese subjects represents a heterogeneous spatial distribution of T2 values, reflecting degenerative changes in cartilage composition. [79]

Table 4.1: Texture Parameters over 96 months

	Group			P-value 5-10% *●	P-value >10% *●
	stable overweight [1]	5-10% weight loss[1]	> 10% weight loss[1]		
	Mean ± SD				
Medial Tibia					
Entropy	5.69 ± 0.12	5.61 ± 0.27	5.56 ± 0.29	0.3	0.1
Homogeneity	0.16 ± 0.01	0.17 ± 0.03	0.18 ± 0.03	**0.06**	**0.01**
Variance	201.15 ± 23.64	187.56 ± 52.00	186.53 ± 55.55	0.3	0.4
Contrast	296.43 ± 42.33	275.12 ± 92.41	274.55 ± 98.64	0.4	0.5
Global					
Entropy	6.01 ± 0.09	5.96 ± 0.21	5.92 ± 0.22	0.4	0.2
Homogeneity	0.14 ± 0.01	0.15 ± 0.02	0.16 ± 0.02	0.5	**0.02**
Variance	199.51 ± 18.54	189.95 ± 41.61	185.82 ± 44.14	0.4	0.3
Contrast	264.60 ± 32.62	245.42 ± 73.29	242.68 ± 77.75	0.4	0.3

●Linear Mixed Model

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

Table 4.2: Clinical Parameters over 96 months

	Group			P-value 5-10% *●	P-value >10% *●
	stable overweight [1]	5-10% weight loss[1]	> 10% weight loss[1]		
	Mean score ± SD				
Mental Health					
KOOS QOL	57.89 ± 5.75	59.59 ± 12.26	59.93 ± 12.82	0.6	0.6
SF-12 Mental Health	51.69 ± 2.88	53.98 ± 7.25	48.01 ± 7.83	0.5	0.4
Metabolic					
Blood Pressure Systolic in mmHg	136.08 ± 6.26	129.35 ± 13.83	128.42 ± 14.02	0.3	0.3
Blood Pressure Diastolic in mmHg	77.77 ± 0.91	76.92 ± 1.66	77.10 ± 1.88	0.2	0.6
Heart Rate per minute	66.40 ± 1.92	62.35 ± 1.00	62.26 ± 0.95	**0.03**	**0.01**
Abdominal Circum- ference in cm	111.41 ± 4.02	104.05 ± 3.27	100.25 ± 4.01	***0.60***	**0.035**

●Linear Mixed Model

[1] Subjects machted for BMI, KL, Age and Sex

*P-value compared to the stable overweight group

Looking at the development of clinical parameters over 96 months, significant differences could be seen in both groups concerning Heart Rate and Abdominal Circumference, as both parameters developed significantly lower compared to the stable overweight group. The abdominal circumference decreased, as both groups lost weight. The lower heartrate could be derived from an adaption to the lower weight and thus less effort compared to the stable overweight group. Interestingly, no significant differences could be detected between groups regarding quality of life and mental health (KOOS quality of life and SF-12).

5.5

WEIGHT LOSS IN DEPENDANCE OF DIFFERENT METHODS

After subcategorizing the weight-loss patients into different methods of weight reduction, T_2 relaxation time values over 8 years showed a significant ***increase*** in the solely exercising weight loss group compared to the stable overweight cohort.

Significantly higher T_2 values were detected in the LF (40.84 ± 3.52 ms versus 38.13 ± 1.26 ms, p=0.02), MT (31.60 ± 2.44 ms versus 29.67 ± 0.63 ms, p=0.04) and Total T_2 (35.75 ± 2.10 ms versus 33.53 ± 0.56 ms, p=0.005). Statistical trends, indicating higher relaxation time values in the exercise group, are seen in the LT (31.08 ± 2.59 ms versus 29.24 ± 0.69 ms, p=0.06) and MF (42.15 ± 3.16 ms versus 39.90 ± 0.82 ms, p=0.06).

As displayed in Table 5.2, the exercise cohort also showed significantly higher T_2 values in the bone layer of the LF (37.07 ± 2.97 ms versus 34.33 ± 0.81 ms, p=0.001) and articular MT (36.94 ± 3.44 ms versus 33.68 ± 0.88 ms, p= 0.001). The articular LT tends to also develop higher T_2 values (36.42 ± 3.53 ms versus 33.92 ± 0.94 ms, p=0.06), although not being statistically significant. Also, the laminar analysis showed a significant rise in T_2 values of the overall bone layer (31.48 ± 1.92 ms versus 29.84 ± 0.51 ms, p=0.02) as well as articular layer (40.16 ± 2.62 ms versus 37.38 ± 0.69 ms, p=0.005), as depicted in Table 5. Interestingly, all other weight loss strategies showed no significant differences compared to the stable overweight controls.

It has to be discussed, whether intense exercise in overweight and obese subjects, who already show a higher mechanical joint load, excessively increases biomechanical stress. [109]

Clinical parameters, seen in table 5.1, show a significantly lower heart rate in the exercise only group (77.20 ± 7.51 min^{-1} versus 81.27 ± 3.48 min^{-1}). Patients combining diet and exercise statistically also tend to have lower heart rate (78.73 ± 6.12 min^{-1} versus 81.27 ± 3.48 min^{-1}, p=0.06). When comparing trained with untrained subjects, studies show slower maximal heart rate during training as well as descreased resting heart rate in subjects performing endurance training, which would explain these results. [93] [22]

Patients, loosing weight through dietary intervention, showed a significantly higher SF12 score (118.02 ± 14.86 versus 107.32 ± 4.63, p=0.04), indicating a higher experienced life quality.

Table 5: T2 Methods of Weight loss – Mean T2 over 96 months

	Group				
	stable overweight	diet weight loss	exercise weight loss	combinate weight loss	surgical weight loss
	Mean T_2 ± SD in milliseconds (ms)●				
Global T_2					
LF	38.13 ± 1.26	38.82 ± 3.30	40.84 ± 3.52	38.56 ± 2.64	38.39 ± 4.27
P-value		0.5	**0.02**	0.5	0.9
LT	29.24 ± 0.69	28.97 ± 2.41	31.08 ± 2.59	29.60 ± 1.79	28.48 ± 3.45
P-value		0.8	***0.06***	0.5	0.6
MF	39.90 ± 0.82	41.04 ± 2.90	42.15 ± 3.16	40.02 ± 2.04	38.63 ± 3.71
P-value		0.3	***0.06***	0.9	0.4
MT	29.67 ± 0.63	28.85 ± 2.17	31.60 ± 2.44	29.46 ± 0.86	29.36 ± 2.90
P-value		0.3	**0.04**	0.7	0.8
PAT	31.92 ± 0.89	31.39 ± 3.32	33.47 ± 3.39	32.34 ± 2.26	31.56 ± 4.39
P-value		0.7	0.2	0.5	0.8
Total	33.53 ± 0.56	33.65 ± 1.93	35.75 ± 2.10	33.66 ± 1.42	33.35 ± 2.68
P-value		0.9	**0.005**	0.8	0.9
Bone layer T_2					
Total	29.84 ± 0.51	29.33 ± 1.77	31.48 ± 1.92	29.92 ± 1.30	29.79 ± 2.45
P-value		0.4	**0.02**	0.8	1.0
Articular layer T_2					
Total	37.38 ± 0.69	38.11 ± 2.42	40.16 ± 2.62	37.68 ± 1.77	36.99 ± 3.35
P-value		0.4	**0.005**	0.6	0.8

●Linear Mixed Model

All P-values compared to the stable overweight group

Table 5.1: Clinical Parameters in dependence of weight losing method

	Group				
	stable overweight	diet weight loss	exercise weight loss	combinate weight loss	surgery weight loss
	Mean score ± SD ●				
Mental Health					
SF-12	107.32 ± 4.63	118.02 ± 14.86	110.74 ± 16.01	112.83 ± 11.53	110.19 ± 22.40
P-value		**0.04**	0.6	0.1	0.8
KOOS QOL	72.18 ± 3.17	73.23 ± 4.36	72.43 ± 4.47	72.58 ± 4.05	72.08 ± 5.21
P-value		0.08	0.7	0.3	0.9
Metabolic Parameters					
Blood Pressure Systolic	132.66 ± 2.81	125.73 ± 13.49	131.48 ± 14.58	133.87 ± 10.43	130.33 ± 20.75
P-value		0.2	0.8	0.8	0.8
Blood Pressure Diastolic	76.11 ± 0.80	74.20 ± 1.47	81.18 ± 1.54	74.26 ± 1.25	75.72 ± 1.96
P-value		0.5	0.09	0.3	0.9
Heart Rate	81.27 ± 3.48	79.69 ± 7.18	77.20 ± 7.51	78.73 ± 6.12	78.27 ± 9.70
P-value		0.4	**0.05**	***0.06***	0.3
Abd. Circumf.	110.58 ± 5.12	108.47 ± 15.58	113.87 ± 21.68	109.12 ± 3.66	114.90 ± 16.84
P-value		0.7	0.7	0.7	0.5

●Linear Mixed Model

P-values compared to the stable overweight group

Table 5.2: Laminar T2 analysis over 96 months depending on regime

	Group				
	stable overweight	diet weight loss	exercise weight loss	combinate weight loss	surgical weight loss
	Mean T_2 in ms ± SD ●				
Bone layer T_2					
LF	34.33 ± 0.81	33.93 ± 2.73	37.07 ± 2.97	34.50 ± 2.03	35.17 ± 3.77
P-value		0.7	**0.001**	0.8	0.6
LT	24.65 ± 0.57	23.89 ± 2.01	25.77 ± 2.16	24.83 ± 1.49	24.29 ± 2.87
P-value		0.3	0.2	0.7	0.8
MF	36.31 ± 0.89	36.62 ± 3.12	38.49 ± 3.39	36.34 ± 2.19	35.14 ± 3.99
P-value		0.8	0.09	1.0	0.5
MT	26.15 ± 0.54	25.17 ± 1.86	26.92 ± 2.10	26.21 ± 1.34	29.15 ± 0.42
P-value		0.1	0.3	0.9	0.7
PAT	28.71 ± 0.81	27.91 ± 2.97	29.38 ± 3.02	28.74 ± 2.02	27.88 ± 3.91
P-value		0.5	0.6	1.0	0.6
Articular layer T_2					
LF	41.94 ± 0.91	43.06 ± 3.09	43.93 ± 3.36	42.08 ± 2.29	41.56 ± 4.26
P-value		0.3	0.1	0.8	0.8
LT	33.92 ± 0.94	34.00 ± 3.29	36.42 ± 3.53	34.46 ± 2.44	32.53 ± 4.70
P-value		0.9	***0.06***	0.5	0.5
MF	43.69 ± 0.97	45.63 ± 3.44	46.03 ± 3.76	44.02 ± 2.41	42.09 ± 3.44
P-value		0.1	0.1	0.7	0.4
MT	33.68 ± 0.88	33.19 ± 3.06	36.94 ± 3.44	33.37 ± 2.20	33.44 ± 4.10
P-value		0.7	**0.001**	0.7	0.9
PAT	35.17 ± 1.11	34.87 ± 4.12	37.64 ± 4.20	36.11 ± 2.81	35.25 ± 5.44
P-value		0.8	0.1	0.3	1.0

●Linear Mixed Model

P-values compared to the stable overweight group

Figure 12 shows the development of T_2 values in the subgroup analysis over all compartments. As described before, the exercise group shows higher values, represented by a steeper red curve compared to the black-dotted curve of the stable overweight group (35.75 ± 2.10 ms versus 33.53 ± 0.56 ms, p=0.005). The graphs of all other weight-loss groups are showing similar courses with no statistically significant differences.

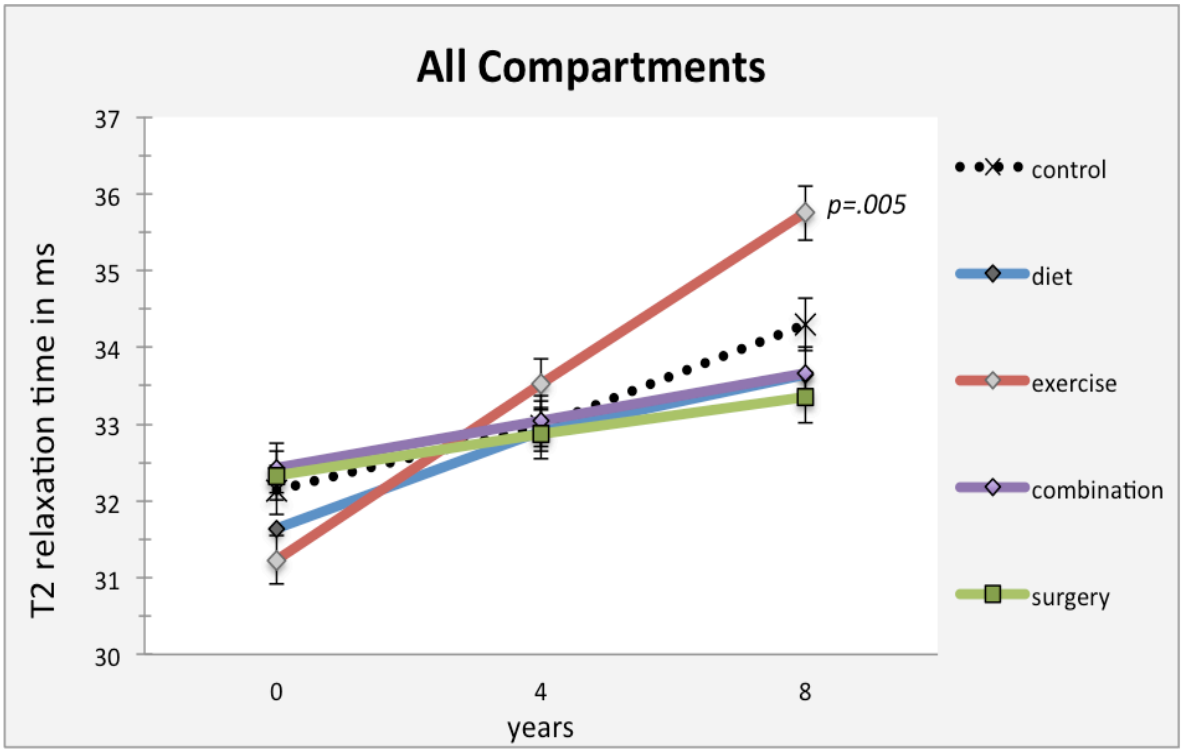

Figure 12: T_2 relaxation time values of all compartments

Figure 13 presents the T_2 values of the medial tibia, showing a significantly steeper rise of relaxation time values in the exercise only group compared to all other groups (31.60 ± 2.44 ms versus stable overweight 29.67 ± 0.63 ms, p=0.04).

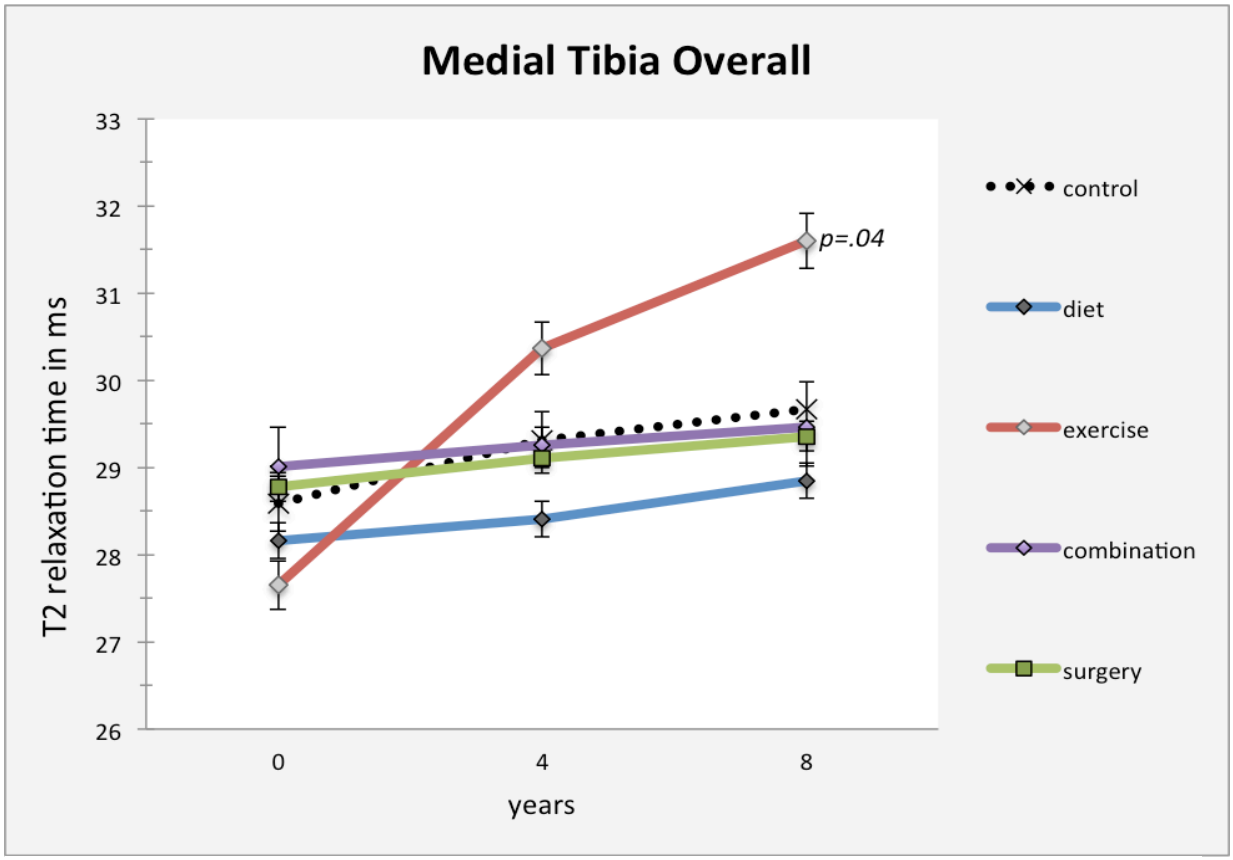

Figure 13: T_2 relaxation time values of the medial tibia

5.6

COLOR MAPS

This chapter shows representative T_2 color maps and corresponding graphs, which display the spatial distribution of T_2 relaxation time values. As previously mentioned, osteoarthritic changes are not only characterized by elevated T_2 values, but are also showing a heterogeneous distribution over the cartilage compartment. [79] [130]

The T_2 values are color-coded, with blue representing 0 ms to dark red, coding for 70 ms. Higher T_2 relaxation time values are correlated with a higher deterioration of cartilage matrix, indicated by a red-colored cartilage compartment.

The color maps show three individuals, each being a representative of one study group (stable overweight subject, 5-10% weight loss subject, >10% weight loss subject). Every column represents one time point (baseline, 4 year follow up or 8 year follow up) and every row shows the longitudinal development of one representative study subject.

The first color map, seen in Figure 14, represents the lateral cartilage compartment, consisting of lateral tibia and lateral femur. The subjects from the stable overweight control group showed a mean rise in T_2 values in the lateral tibia of 2.72 ± 0.63 ms over 8 years compared to 2.47 ± 0.85 ms in the 5-10% weight loss group and 1.45 ± 0.86 ms in the >10% weight loss group, latter being significant with $p=0.049$. Similar development, although not statistically significant, can be seen in the lateral femur, which shows rising mean T_2 values of 1.78 ± 0.76 ms in the stable overweight group compared to 1.22 ± 1.01 ms in the 5-10% weight loss group and 1.00 ± 1.04 ms in the >10% weight losing group.

Interestingly, the LT articular layer of the 5-10% weight loss group shows higher T_2 progression (4.36 ± 1.15 ms) than the control group (4.08 ± 0.85 ms), but without statistically assessable differences.

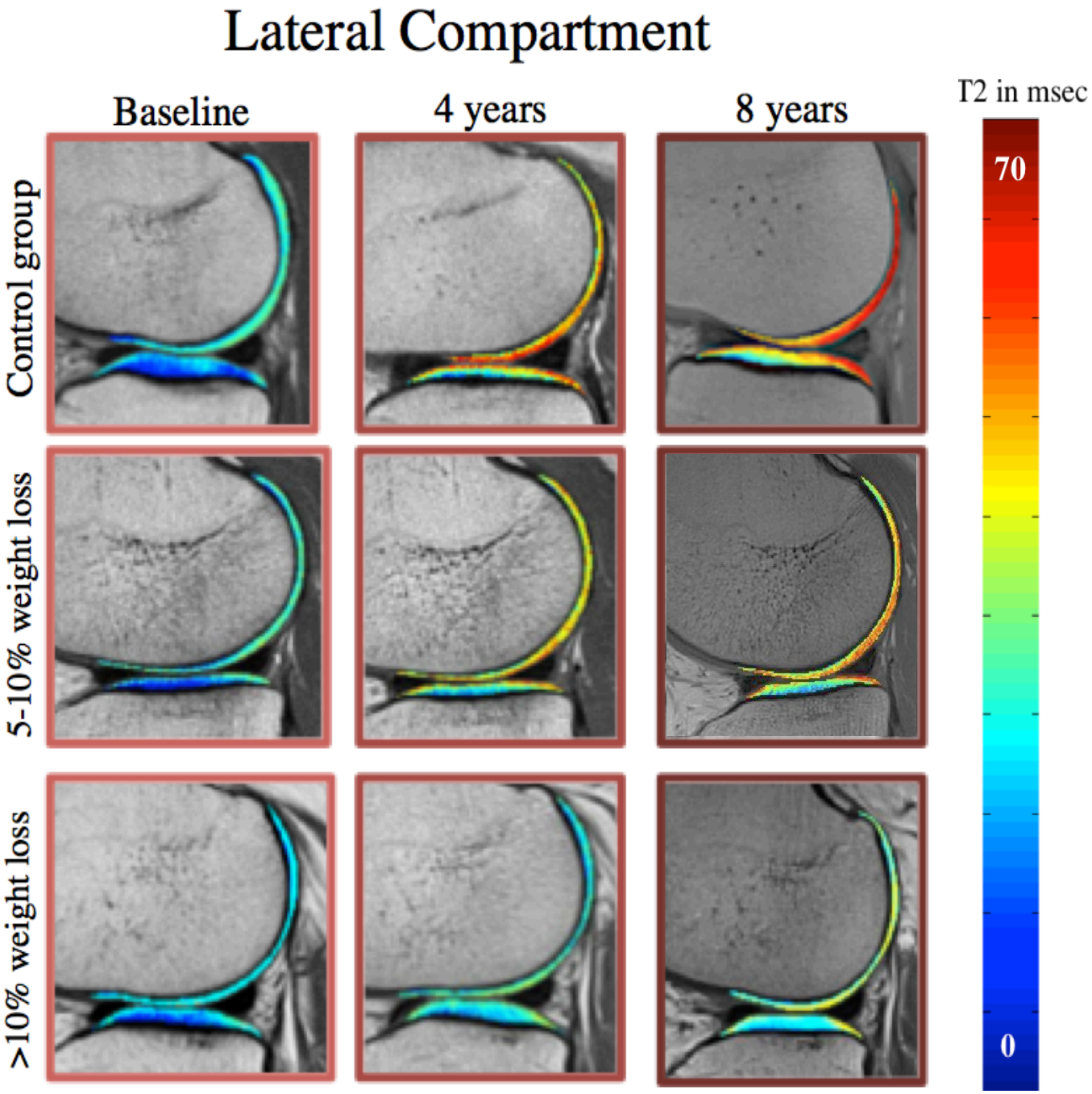

Figure 14: Color map of the lateral compartment

Figure 15 displays the T_2 progression of the lateral tibia, showing a significantly slower T_2 elevation (p=0.049) in the LT of the >10% weight loss group, seen as red line in the graph and supported by a homogeneously blue cartilage in Figure 14.

The laminar analysis shows a significantly lower T_2 progression in the bone layer of the >10% WL group compared to the stable overweight subjects, p=0.013.

The articular layer showed no significant differences in T_2 evolution between the three study groups, although the >10% weight loss group shows a flatter rise compared to the stable overweight and the 5-10% WL group.

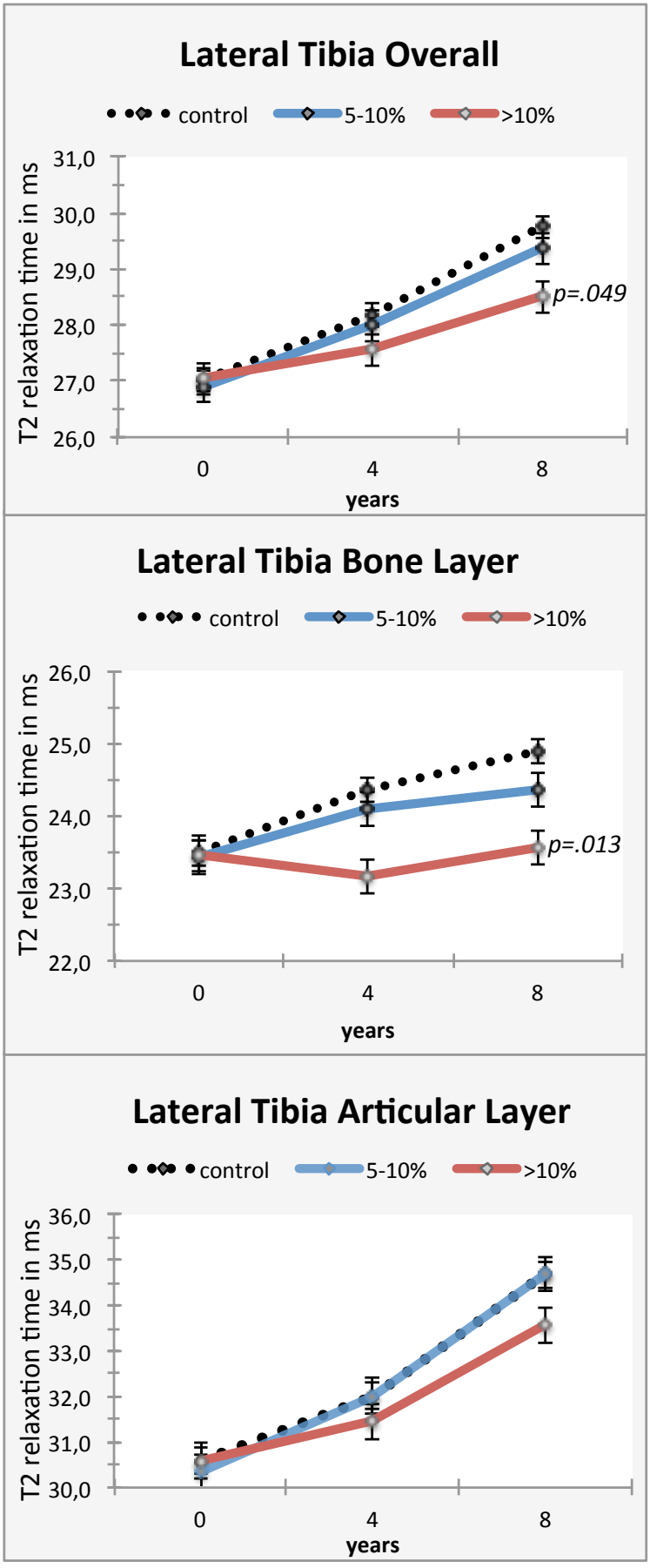

Figure 15: T_2 relaxation time values of the lateral tibia

The most significant findings in our analysis could be seen in the medial cartilage compartment. After eight years, the MT of both WL groups showed a significantly slower T_2 increase compared to the stable overweight group, with 0.60 ± 0.73 ms in the 5-10% WL group (p=0.001) and 0.06 ± 0.75 ms in the >10% WL group (p=0.000) compared to 2.35 ± 0.55 ms in the the stable overweight group.

These differences are also seen in the distribution of T_2 values in the MT, showing a significantly higher homogeneity in both weight loss groups (5-10%WL: 0.17 ±0.03, p=0.06; >10%WL: 0.18 ± 0.03, p= 0.01) compared to the stable overweight group (0.16 ± 0.01), indicating a higher cartilage integrity.

Represented in Figure 16, both weight loss subjects show a more homogeneous, green and yellow coloring, whereas the stable overweight cohort shows a heterogeneous, imposingly red-colored T_2 elevation.

While the medial femur has not shown any significant between-group differences, the color map and absolute values also indicate a higher deterioration of the MF in the overweight subjects with a T_2 rise in eight years of 2.40 ± 0.80 ms in the control cohort compared to the lower progression of 1.56 ± 1.09 ms in the 5-10% WL group and 0.66 ± 1.11 ms in the >10% weight-lossing cohort.

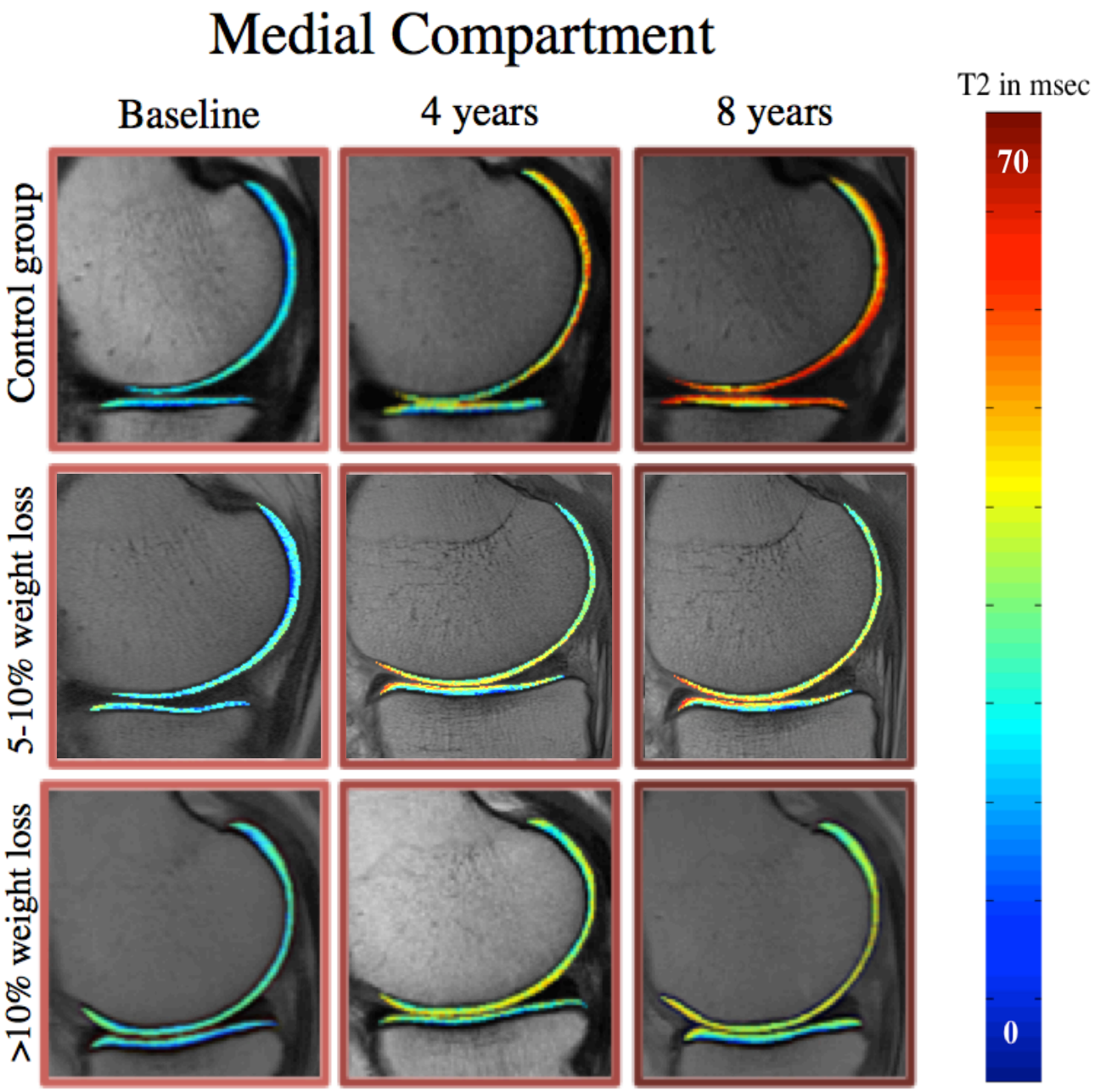

Figure 16: Color map of the medial compartment

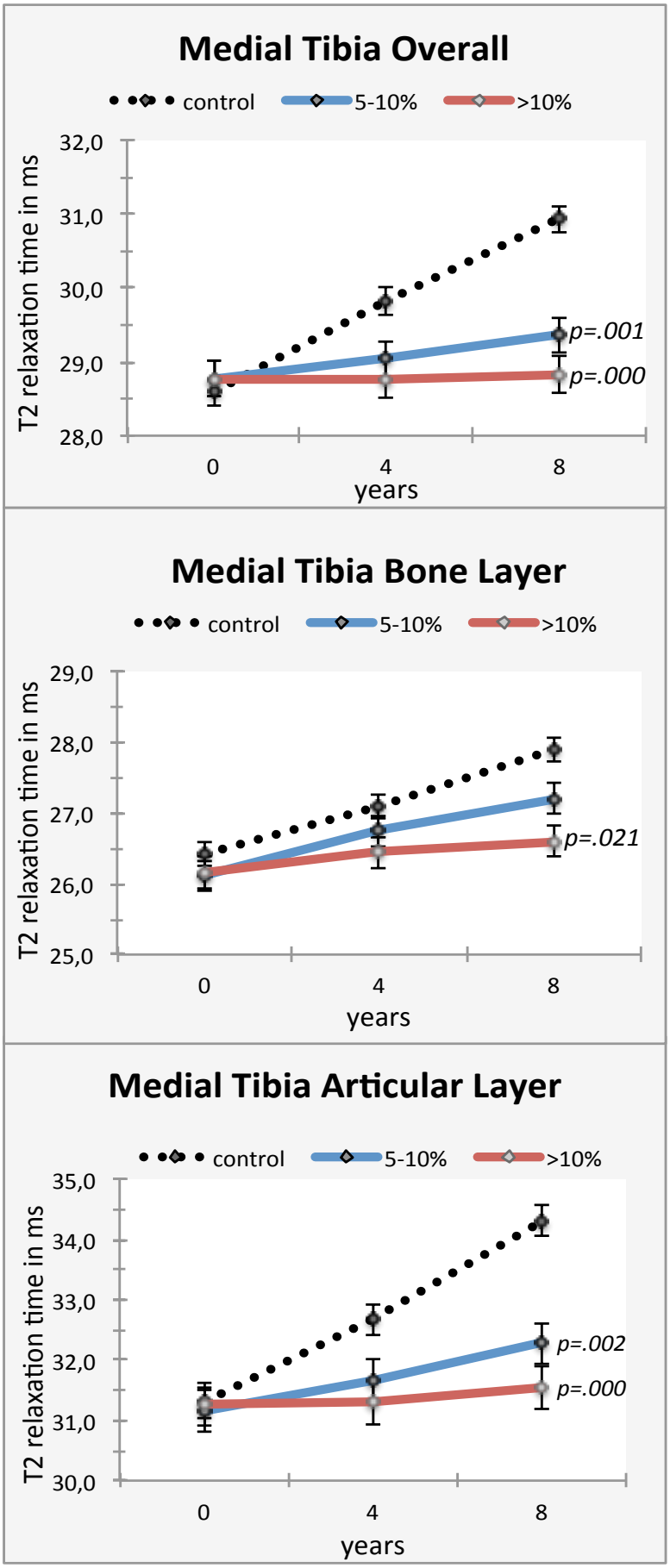

Figure 17: T_2 relaxation time values of the medial tibia

These results are illustrated in Figure 17, which shows a distinctive divergence between the stable overweight, black dotted graph and the two blue and red colored graphs of the weightloss cohorts. The overall T_2 values for the MT showed a significantly slower progression for the 5-10% WL group (p=0.001) and the >10% WL group (p=0.000) over 8 years with latter seemingly to have a plateau-like course.

Also, the laminar analysis of the MT reveals a significantly lower rise of relaxation time values in the articular layer of both weight loss groups (5-10%WL: p=0.002, >10% WL: 0.000) as well as a lower progression in the bone layer of the >10% WL group (p=0.021).

Lastly, the patella shows a significantly decelerated progression of T_2 values in the >10% WL group with 0.42 ± 0.69 ms compared to the stable overweight group with 1.77 ± 0.50 ms, p=0.032.

The laminar analysis could detect significant differences between the stable overweight cohort and the >10% weight loss group in the articular layer, showing a T_2 progression of 1.57 ± 0.87 ms in the weight losing patients compared to 3.17 ± 0.64 ms in the stable overweight subjects, p=0.028. The T_2 progression in the bone layer has not shown significant differences but showed an overall slighter increase with 0.92 ± 0.61 ms in the >10% WL group compared to 2.44 ± 0.44 ms in the overweight subjects.

Although not being statistically decisive, the overall and laminar T_2 values of the 5-10% weight loss cohort have also risen less compared to the constantly overweight patients with T_2 values progressing 1.37 ± 0.67 ms overall, 2.05 ± 0.59 ms in the bone layer and 3.07 ± 0.85 ms in the articular layer.

Figure 19 represents these results, showing a more homogeneous distribution of green and yellow colors in the >10% WL group compared to the more heterogeneous and reddish areas.

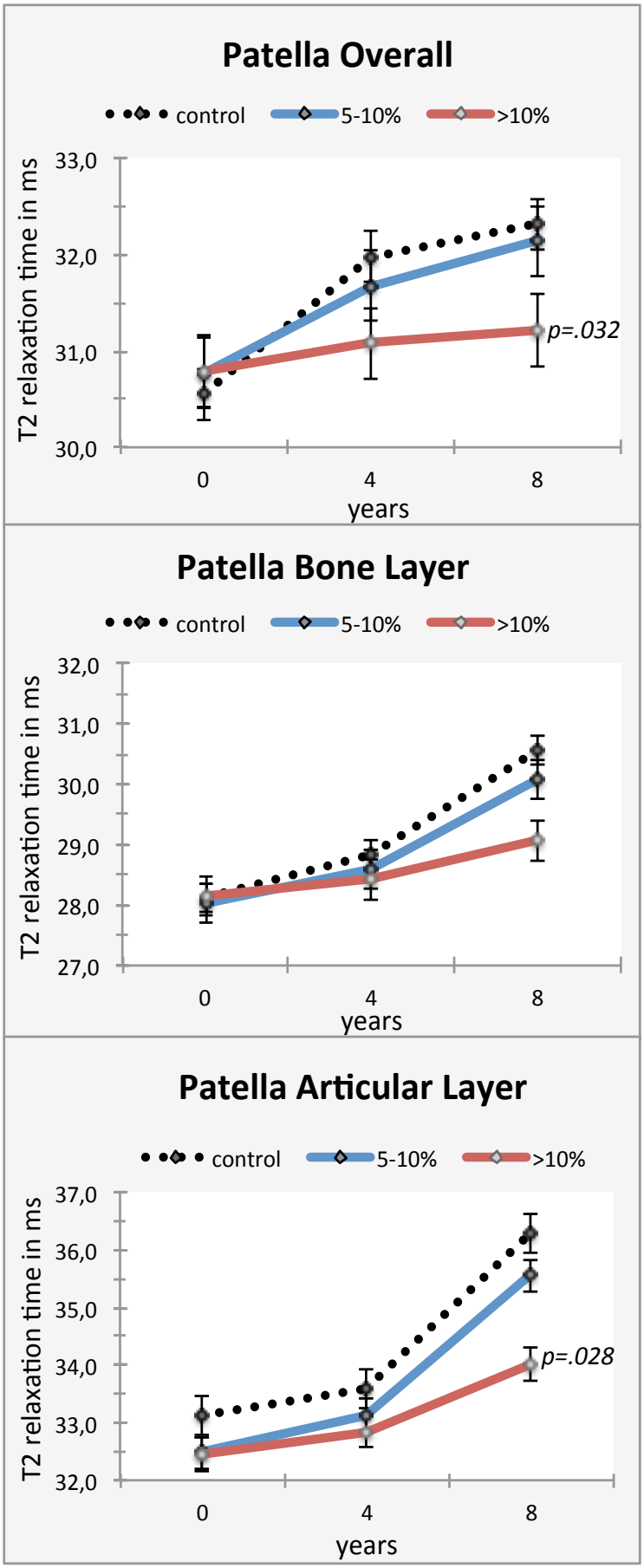

Figure 18: T_2 relaxation time values of the patella

This is also seen in Figure 18, which displays significantly less ascending T_2 values in the >10% weight loss group overall (p=0.032) and in the bone layer (p=0.028) compared to the considerablely higher T_2 progression in the non-weight losing group.

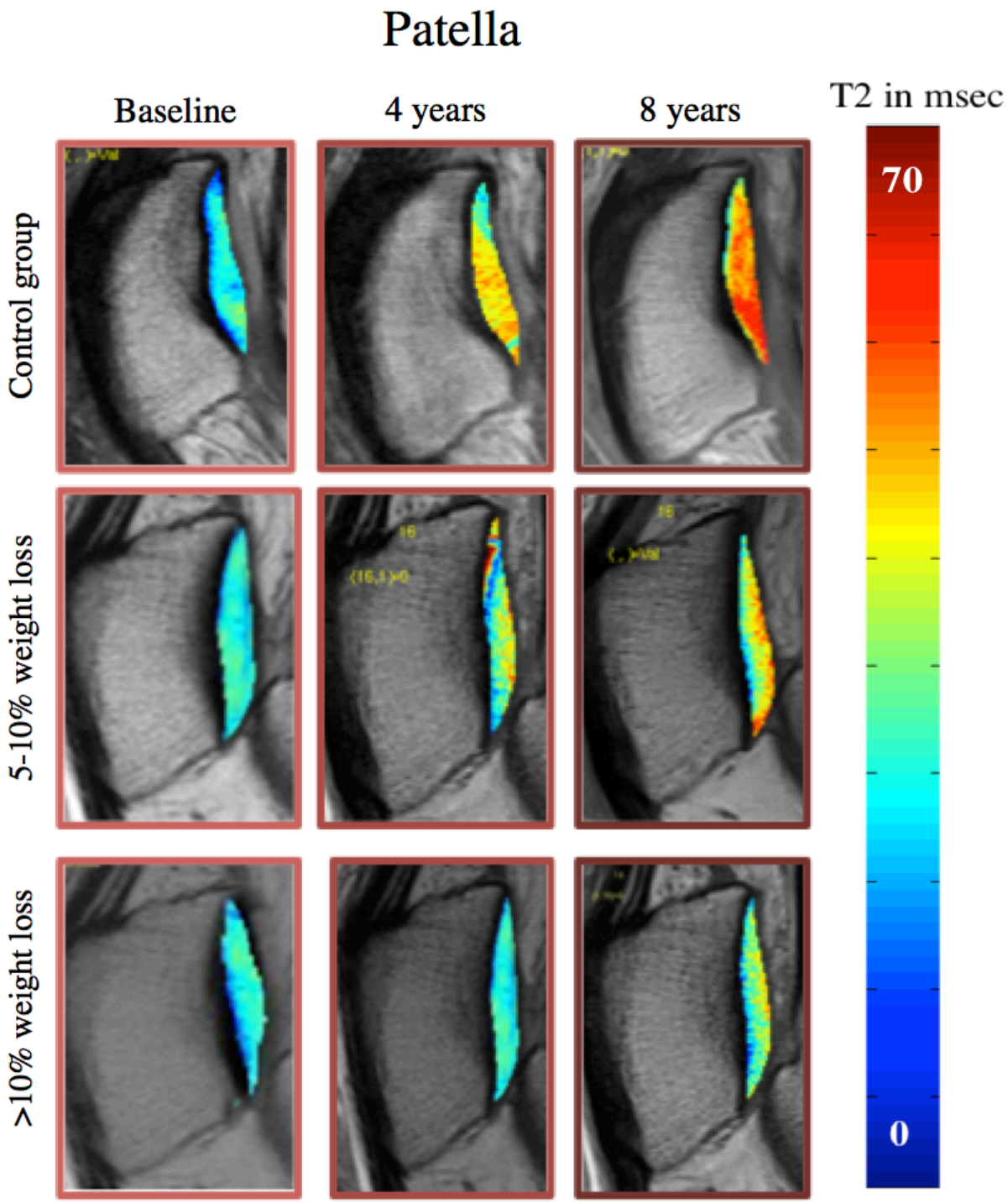

Figure 19: Color map of the patella

6

DISCUSSION

This study shows a clear link between weight loss over 8 years and cartilage health of patients with early signs of OA. Also, it reflects the effect of continuous overweight on cartilage damage. In all western countries, overweight and obesity show rising numbers, hugely influenced by the western diet and sedentary lifestyle, leading to cardio- and cerebrovascular, neurological, psychological or musculoskeletal health problems. [18] [174]

The association between overweight and advancing osteoarthritis is well-established, as excessive weight increases the joint load, alters the gait and enhances focal stress on cartilage through pre-existing malalignment, altogether accelerating osteoarthritic changes of the joint. [50] [66] [134]

6.1

OBESITY, WEIGHT LOSS AND CARTILAGE HEALTH IN LITERATURE

Aside from the association between chronic overweight and osteoarthritis, some studies focus on current weight gain, to determine its effect on the progression of osteoarthritis.

Bucknor et al. studied weight gain in a longitudinal study over 4 years on patients showing MRI signs for early knee OA. They concluded a significantly greater deterioration of cartilage, meniscal tissues and bone marrow edema in weigh gaining patients, graded with WORMS. Altogether weight gain could be correlated with a strong progression of OA compared to a weight stable group. [23]

A study conducted by Tanamas et al. chose a cohort with a wide weight spectrum, ranging from normal weighted to obese patients, who were followed-up over 2 years, in order to assess weight changes and knee symptoms using the WOMAC score. Compared to our study, considerable clinical effects could be seen: Patients losing >5% of their initial weight showed reduced clinical symptoms, while patients who gained weight presented with a clinical worsening of all three parameters (pain, stiffnesss and functional impairments). Interestingly, the association between symptom worsening and weight gain was seen in patients, who did not present any symptoms at baseline. Associations between pre-existing symptoms and weight gain were not detected. [160]

Weight gain and the influence on osteoarthritis is mostly studied in elder patients, but the huge impact on young patients with prior knee injury or surgery, is not neglectable. Analysing a huge sample of nearly 500 patients, Thoma et al. could display a greater risk of either developing radiographic knee OA or worsening of already existing, symptomatic knee OA when encountering a clinically significant weight gain >5% BMI. [165]

Older work from more than 10 years ago, showed not only the strong relationship between BMI and structural OA progression, but also between BMI and malalignment worsening. A moderate malalignment showed the highest susceptibility for progression, influenced by BMI increase. No direct effect of weight gain on neutral alignments was reported. Higher loading, due to weight gain, affected average malaligned knees, possibly by an irregular, focal distribution compared to neutrally aligned knees. [50]

Also, weight gain has been associated with cellular and molecular effects such as increased macrophage expression and infiltration with T cells in adipose tissue as well as increased levels of circulating inflammatory cytokines. [89] As weight gain has a huge influence on osteoarthritis, a possible benefit of weight loss on cartilage health can be assumed, which has been already investigated in various studies. Serebrakian et al. showed a slower progression of T_2 values in patients with weight loss while Anandacoomarasamy et al. used the dGEMRIC technique to analyse the effect of weight loss, showing a decreased cartilage thickness loss and quantitively higher dGEMRIC values. [3] [150]

Finally, a previously conducted study from our research group used a multilayered approach to show a significantly lower rise of T2 values in the MT of the >10% WL group with no effects seen in the moderate weight losers. Similar to our results, GLCM data showed a higher homogeneity in the MT of the >10% WL group, indicating a higher cartilage integrity. Moreover, the increase of T2 values was associated with clinical worsening, detected with WOMAC questionnaires. The highest effect on cartilage integrity was found, as in our study, in the >10% WL group and MT. [59] A significant benefit of weight loss has been described already in literature, opening the gates for further research in the metabolic and molecular connections between overweight or obesity, weight gain, weight loss and cartilage health.

6.2

INFLAMMATORY AND METABOLIC INFLUENCE FACTORS

Traditionally, mechanically induced cartilage deterioration was seen as a main feature of OA, but recent studies are looking closer into the relationship of overweight and osteoarthritis from a metabolic and inflammatory point of view. More and more studies are pubshlied about the central role of biochemical alterations in OA pathogenesis, which are disrupting the homeostasis of joint metabolism and leading to degeneration of various tissues.[56]

Generally, obesity is characterized by a high amount of adipose tissue, which shows strong metabolic activity. A linear association between BMI and C-reactive protein elevation was found in men and women. Compared to healthy subjects, the likelihood for a higher C-reactive protein concentration in obese patients was 2.13-fold increased in men and 6.21-fold increased in women. Unlike other studies, these findings could be confirmed when restricting to a young cohort ranging from 17-39 years, while confounding diseases, possibly increasing CRP levels, such as smoking, estrogen application and cardiovascular, metabolic or inflammatory disease were excluded concurrently. [169]

Another study demonstrated the chronic rise of circulating systemic inflammation markers such as interleucines, TNF- α and C-reactive protein in obese subjects. Concludingly, obesity can be seen as a low-grade inflammatory condition, induced by a morbid amount of hormone- and cytokine-producing adipose tissue. [6]

Various studies have described the significant interrelation between OA and metabolic syndrome, elevated blood glucose levels or ultimately type-2-diabetes, suggesting either a strong metabolic impact on the pathogenesis of OA or even a common biochemical pathway between OA and obesity, originating in the endocrine-active adipose tissue. [34 68 81 129 144]

A 2014 published study took blood samples and visceral fat samples of patients planned for bariatric surgery and detected collective involvement and strong reciprocal interaction between macrophages, circulating cytokines and T cells on adipose inflammation. [89]

In this context, Mobasheri et al. introduce the emerging field of immunometabolism, which describes a metabolic shift in cells, hugely influencing function and metabolic activity. Altogether this leads to a metabolic turnover towards proteolytic enzymes, proinflammatory mediators and increased catabolic activities, which are hypothesized to also occur in chondrocytes, bone cells and synovial tissues, promoting degeneration. [112]

Similarly, Katz et al. conclude that chondrocytes, interleukins, macrophages and

metalloproteases are undergoing cellular or biochemical changes in osteoarthritic joints and are influenced by leptin dysregulation and endothelial dysfunction.[81] Also, concentrations of inflammatory cytokines like IL-6 and increased levels of adipose-secreted hormones, so called adipokines, were detected in osteoarthritic joints. Examples for adipokines whose involvement in deteriorated joints was detected, are leptin, adiponectin, visfatin, chemerin, apelin and resistin. Especially leptin and adiponectin receptors and molecules have been detected in the synovial tissues, synovial fluid, cartilage, bone and infrapatellar fat pad and are thought to influence osteoarthritis through the promotion of local inflammation. Leptin levels correlate with cartilage damage and show catabolic and proinflammatory features as they promote MMP production. Adiponectins are believed to play a modulating effect in immunometabolic processes, as 100-fold greater concentrations are found in synovial fluid of OA patients compared to their plasma levels. [39 56 155 178]

All these findings acknowledge the major influence of metabolism and inflammation on the evolution, pathogenesis and progression of osteoarthritis. OA was historically seen as a non-inflammatory disease, but research is encountering a change of perspective, apparent in a shifted focus on inflammation and metabolism in recently published OA studies.

6.3

INFLUENCE OF DIET, EXERCISE AND BARIATRIC SURGERY

As overweight and obesity have huge influence on the onset or progression of musculoskeletal diseases such as OA, aiming for weight loss is a fundamental therapeutic strategy. Various options such as dietary or physical exercise programmes as well as bariatric surgeries exist to achieve this aim. The effect of certain weight loss strategies on cartilage and health has been studied previously.

Although this study at hand could not detect any significant benefits in regard to T_2 values or clinical symptoms depending on the chosen weight loss method, a detrimental effect on cartilage health was found in the exercise only group, who presented increased T_2 values compared to stable overweight patients and other weight loss methods. This reflects an altered biochemical composition and disrupted cartilage integrity. Exercise has an ambivalent role in the pathogenesis of OA as on the one hand heavy weight lifting, frequent knee bending activities and high-performance sports are accelerating cartilage deterioration and on the other hand, moderate training seems not to increase cartilage damage. [58 69]

Galois et al. looked at the relationship of exercise intensities and osteoarthritis severity in a rat model. They examined exercise as a treatment option in light, moderate and intense running trainings. Cartilage lesions were evaluated histologically. A decrease of histological lesions was found in the light and moderate exercise groups while the intense exercise group showed no beneficial outcome for cartilage lesions, which reached deeply into the radial zone. [58]

Galois et al. have also found an interesting relation in regard to exercise and imunohistochemical changes. Proteases from the caspase family play a big role in the induction of proteolytic and apoptotic events, leading to chondrocyte cell death. Heat shock proteins on the other hand show a protective influence on chondrocytes, reducing apoptotic events. An increased expression of heat shock proteins, indicating a protecting effect on chondrocytes, was found in the moderate and slight exercise group. A significant trend for increased heat shock proteins was strongly found in the medial compartment, which has also shown the strongest overall benefits in our study. [58]

Concludingly, chondroprotective effects were lost during intense exercise while moderate exercise reduced apoptotic events through the promotion of heat shock proteins. [58]

Adverse effects of exercise training were also described in 2014 by Henriksen et al.

192 obese patients who accomplished a 16 week weightloss programme with focus on diet or exercise were included. A follow up after 1 year showed a weight gain of 1.1 kg in the diet group and a significant greater weight gain of 6.6. kg in the exercise group, as well as significantly more bone marrow lesions in the exercise only group. [71]

Similarly, an older study from the 90s aimed to evaluate the effect of physical training on the muscular strength and symptoms and detected increased knee effusion in patients who exercised regularly.[140]

The 'Arthritis, Diet and Activity Promotion Trial' investigated the effects of diet, exercise or the combination of both in regard to knee symptoms and functioning. [108]

252 patients accomplished the study, and patients from both diet groups reported a significant improvement in functioning. Both exercise groups improved their walking distance significantly after 18 months while pain decreased significantly in the combination group. This study concluded that a combination of dietary and physical interventions is the most beneficial method for significant improvements of self-reported symptoms with the WOMAC questionnaire. [108] In a similar concept, the 'Intensive Diet and Exercise for Arthritis Trial' studied the influence of diet and exercise separately or in combination on inflammatory markers, clinical symptoms and imaging outcomes.[109] 399 patients were included and followed up for 18 months. The highest weight loss was achieved in the combination group

(10.8kg) compared to a moderately high weight loss in the diet group (8.9 kg) and a very low weight loss in the exercise group (1.8kg) who showed aditionally an unchanged fat mass. Levels of the proinflammatory cytokine Il-6 decreased in both diet groups. Also, the combination group showed less pain and the most significant effects on quality of life improvement of all groups. Altogether, the exercise only group showed less improvement of inflammation, pain, functionality and quality of life. Another study of the trial concentrated on radiographic and MRI outcome and could not detect any differences regarding joint space narrowing or MRI detected cartilage loss between all three groups. [75] [109]

The results regarding inflammatory markers could be confirmed by another study, which investigated the effects of diet, exercise or their combination on inflammatory markers, showing that dietary weight loss reduced TNF-a, Il-6 and CRP levels, with no improvement seen in the exercise only group.[119]

As weight loss through dietary measures is often denounced as unsuccessful due to weight recurrence, weight cycling and lack of compliance, Christensen et al. target this prejudice in a longitudinal study.[32] Long weight maintenance, minor weight regain and stable symptoms over 3 years have been shown in the studied diet cohort. Although no clinical improvement could be seen after weight loss and weight maintenance, researchers emphasize that symptom maintenance has the potential to prevent invasive knee replacement surgery. [32]

Literature also offers research on the outcome of bariatric surgery procedures, which are hugely invasive but offer the potential for fast and major weight loss.

Arismendi et al. studied 129 obese patients, out of whom all showed elevated inflammatory biomarkers before undergoing bariatric surgery. A significant correlation of BMI and C-reactive protein levels was found. Additionally, central adiposity was associated with higher adiponectin levels. After undergoing bariatric surgery, blood samples were collected one year afterwards showing significant improvement of leucocytes, adiponectin, leptin and C-reactive protein, leading to the assumption, that rapid weight loss achieved by BS significantly improves the inflammatory state, priorly induced by obesity.[6]

Freitas et al., who studied blood samples of patients before bariatric procedures and 6 months post-surgery, reported similar results. [57]Besides an improvement of proinflammatory cytokines such as TNF-a, adiponectin and leptin, a significant improvement of lipid metabolism (cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides) was revealed.

Although carried out on a small population of 13 obese patients with diabetes and 15 non-diabetic controls, a Nature-published study hints at significant metabolic alterations through surgically achieved major weight loss, suggesting deep metabolic changes, that might also

affect cartilage.[26] While patients underwent gastric bypass surgery, samples of omental fat, subcutaneous fat and rectus abdominis muscle were taken. One year after surgery, subcutaneous and muscular samples were taken again. Histological, immunohistochemical and blood analysis were included. Altogether a high BMI was associated with an expanding size of adipocytes, higher fatty infiltration of muscular tissue and higher IL-6 levels. After one year of extensive weight loss, histological findings in fat and muscle tissue improved, while IL-6 levels decreased.[26] In addition to the above-mentioned serochemical results, improved clinical symptoms could also be detected in regard to bariatric surgery.

A 2018 published study analysed the development of T_2 values and WOMAC pain scores in severely obese patients with a BMI >35, who experienced a rapid weight loss with either bariatric surgery or conventional medical interventions. T_2 relaxation time values as well as WOMAC pain scores decreased significantly in those, who lost >20% of their initial body weight.[77]

Another recent study found a significant clinical improvement of knee pain in patients one year after receiving lab-band surgery. The improvement was associated with the degree of weight loss, while the strongest pain relief was seen in the highest weight loss group with > 13 kg/m^2 decrease of their original BMI.[31]

After clear benefits of weight loss on osteoarthritis have been described in literature, this chapter gives an overview of various studies investigating different weight loss methods. Studies hint at significant metabolic changes and clinical improvement, achieved through a combined approach of diet and exercise as well as bariatric surgery.

It remains unclear whether the chosen regime of weight loss plays an important role, or whether the total weight reduction is the most important feature to reduce inflammatory mediators and joint degradation. Even a low weight reduction has significant effects, as a 5% loss of body weight contributes to a 2-times higher likelihood of normalization of inflammation markers.[14] Also, a loss of 1 pound of body weight reduces compressive forces on the knee joint 4-fold for every step.[107]

6.4

LIMITATIONS, PERSPECTIVE AND CONCLUSION

This study has several limitations, first to mention is the retrospective design, which cannot control for previously existing confounders. Also, it does not permit a complete analysis of all weight loss subjects regarding their chosen method of weight loss. Moreover, the participation rate for the weight loss questionnaire has been only 50%. Furthermore, the chosen kind of exercise, frequency and intensity for weight loss remains unknown, as it was not inquired. This information would be crucial to interpret the significant progression of T_2 values in the exercise only group compared to the diet and exercise group.
Additionally, group sizes for diet (N=40), exercise (N=32) and surgery (=16) were small in comparison to the diet and exercise group (N=97).
Lastly, no analysis of blood and urine specimen was included, which would be especially interesting in relation to the recent research focus on inflammatory markers and lipid metabolim in connection to osteoarthritis and obesity.

Perspectively, further research connecting metabolism and inflammation to osteoarthritis can be expected, possibly conducted in a similar long-term design as in the study at hand.
As the OAI database includes various blood and urine samples, their use for analysis will likely increase in future studies. Potential alterations of blood parameters could support or expand published studies and common knowledge in regard to the chosen regime of weight loss and weight maintenance after long periods. Also, the use of serological markers for effect control of future DMOADs, possibly targeting metabolic and inflammatory pathways, is conceivable.
Advanced imaging will possibly combine serological and compositional biomarkers of cartilage metabolism, to further increase sensitivity for discrete, early or progressive joint pathologies.
After conducting the study, it is not possible to confirm that novel biomarkers used for compositional imaging like T_2 relaxation time measurements can close or even narrow the gap between symptomatic osteoarthritis and diagnostic imaging, as no improvement of symptoms were detected although T_2 values progressed significantly slower in patient losing >10% weight. This matter of fact offers an opportunity for future techniques and research to contribute to the merger of qualitative and quantitative cartilage composition, inflammatory profile and symptomatic disease, preferably by means of automated technology.

Future studies are needed to combine serological and imaging methods to further expand our common knowledge about the onset, progression and possible maintenance or even treatment of osteoarthritis.

Although many studies investigate the longitudinal association of weight loss, cartilage health and clinical symptoms, this study design is unique as manifold complex and time-consuming research methods over a long observation period of 8 years are combined T_2 measurements were studied at three time points, supported by laminar and texture analysis, clinical measurements and questionnaires. As life-style adaptions of overweight and obese patients often seem frustrating in clinical practice[32], this study shows that even weight reduction among advanced age groups (patients were averagely 62.9 ± 9.0 years old at baseline and followed up until almost 71 years of age) show detectable benefits for knee cartilage, emphasized on the medial tibia and substantial weight loss of >10%.

Taking everything into consideration, this study enables a long-term insight into the evolution of cartilage health over eight years. T_2 relaxation time measurements are a sensible method to detect not only early or macroscopically unconspicious cartilage lesions, but also to be used as a follow-up technique. Weight reduction is associable with lower T_2 progression and a more homogenous distribution of T_2 values, suggesting higher cartilage matrix integrity and offering a valuable treatment option for patients suffering from OA.

Although no information are available concerning the patients' period of overweight or obesity, decades of excessive weight can be assumed, possibly leading to a lack of quality of life improvement due to the high average age of almost 71 years at the end of the study. Although no significant mental health or quality of life improvements were detected, striving for weight loss earlier in life and with specially selected methods, such as combined dietary and joint-gentle exercise interventions, could be hypothesized to improve quality of life, mental health, clinical symptoms and functioning altogether.

The clinical and scientific impact of this presented study can be summarised in three striking findings:

Firstly, the strongest benefits of weight loss were seen in the substantial weight loss group, who reduced >10% of their baseline weight. Compared to the moderate 5-10% weight loss group, the >10% group showed significantly lower T_2 values in the LT, PAT and global T_2 summation, as well as significantly lower T_2 values in both layers of the laminar analysis and a higher global homogeneity. Soleley the T_2 values and the homogeneity of the MT showed

significanly beneficial developments in both weight loss groups.

Magkos et al. conducted a study to demonstrate the benefit of weight loss on metabolic outcomes while differentiating between amounts of weight loss (maintenance, 5%, 11% and 16% weight loss). Although a weight loss of 5% decreased fat mass, intra-abdominal adipose tissue and some cardiometabolic parameters like glucose, insulin, triglycerides and leptin, other parameters like free fatty acides, high- and low-density lipoprotein, cholesterin and adiponectin remained unchanged. Especially adipose-tissue derived hormones and circulating inflammatory markers were not affected by a moderate weight loss. A linear relationship between amount of weight loss and decreased concentrations of above-mentioned blood parameters was described, with the highest effect seen in the 16% weight loss group. Although a 5% WL shows significant health improvements considering insulin sensitivity, progressive weight loss has not only a stronger metabolic impact, but can also influence secretion and gene expression of adipose tissue.[103]

Relating this information to our results, a substantial weight reduction has the potential to strongly influence cardiometabolic, inflammatory and adipose-tissue-derived markers. As described in chapter 6.2, metabolism and inflammation are gaining more scientific attention in the pathogenesis of OA, possibly sharing similar biochemical pathways. Thus, the highest beneficial effect could be explained with the highest achieved WL of >10%.

Secondly, the strongest effect of weight loss was seen in the medial tibia of the moderate and substantial weight loss group. T_2 values progressed slowly and cartilage heterogenity remained high. As prior studies have described similar results, a possible explanation could be a higher glycosaminoglycan concentration in the thin, weight-bearing cartilage layer of the medial tibia. This increased focal loading leads to an alteration of proteoglycan and matrix biosynthesis. [180]

Teichthal et al. followed up on obese subjects over 2 years to examine the effect of weight loss, cartilage health and knee symptoms. Again, the conclusion highlights the effect on the medial compartment, describing a strong relationship between weight gain and significant medial cartilage loss.[163] A one-year follow-up study by Anandacoomarasamy et al. found a significantly decreased cartilage thickness loss and enhanced dGEMRIC values in the medial femoral compartment. In total, an improved quantitative and qualitative cartilage outcome, emphasized on the medial compartment, was concluded.[3]

A similar study by Serebrakian et al. also emphasized the leading effect of weight loss on the medial compartment, as the results showed a significantly slower progression of T_2 values,

which are reflecting a higher cartilage matrix integrity in the medial compartment due to weight loss. [150]

Thirdly, the subgroup analysis indicates that exercise alone is not recommendable, as patients who chose exerise only as weight loss strategy show a strong progression of T_2 values.
Although these results should not be overinterpreted due to above-mentioned limitations such as the small group size and low participation rate, other research groups have come to similar results. Both trials that investigated different weight loss strategies (The 'Arthritis, Diet and Activity Promotion Trial' as well as the 'Intensive Diet and Exercise for Arthritis Trial') have shown that exercise alone has the least effect of all weight loss methods on weight loss amount, pain, function and inflammatory status. [108] [109]
It can be hypothesized, that exercise as primary weight loss method in overweight and obese subjects is not recommendable in clinical practise. As indicated by previous studies, the amount of weight loss and thus the effect on fat mass, adipose tissue, metabolic and inflammatory activity is insufficient, leading to stagnation instead of clinical and imaging improvement.
Especially high intense exercise should be avoided, as it increases joint loading and shear forces, possibly promoting cartilage abrasion and "wear and tear" of neighbouring joint structures. [58] [75]

7

SUMMARY

OBJECTIVE

To investigate the long-term effect of different amounts and methods of weight loss on knee cartilage health in overweight and obese individuals over a period of 96 months.

DESIGN

We studied clinical and imaging data in overweight and obese subjects over 96 months to evaluate the effect of weight loss on biochemical cartilage composition.
Methods used include MR-based T2 values, laminar and texture analysis and clinical questionnaires concerning quality of life and chosen weight loss method.
The participants were selected from the Osteoarthritis Initiative regarding a moderate weight loss (5-10%, n=275) or high weight loss (>10%, n=88) and were frequency matched to constantly overweight subjects (n=363). All three groups had a baseline body mass index (BMI) ≥25 kg/m^2 and risk factors or mild signs for osteoarthritis (OA) at baseline. The weight-losing cohort was additionally subgrouped into chosen methods for weight reduction: diet (n=40), exercise (n=32), diet and exercise combined (n=97) and bariatric surgery (n=16).

RESULTS

A significantly decelerated progression of T_2 values was detected in the medial tibia of both weight-loss groups compared to the stable overweight cohort (5-10%-WL: 0.60 ± 0.73 ms, p=0.001; >10%-WL: 0.06 ± 0.75 ms, p=0.000 versus stable overweight: 2.35 ± 0.55 ms, respectively). Also, a significantly higher homogeneity in both WL groups was seen in the medial tibia (5-10%-WL: 0.17 ± 0.03, p=0.06; >10%-WL: 0.18 ± 0.03 versus stable overweight 0.16 ± 0.01, p=0.01, respectively). The laminar analysis reveiled significantly lower T_2 values in both WL groups regarding the articular layer of the medial tibia (5-10%-WL: 1.12 ± 1.04 ms; >10%-WL: 0.28 ± 1.08 ms versus stable overweight: 3.02 ± 0.79 ms, respectively). After subgrouping both WL cohorts into the chosen method of weight reduction, significantly higher T_2 values were detected in the exercise only group compared to stable overweight controls in the LF (Exercise: 40.84 ± 3.52 ms versus stable overweight: 38.13 ± 1.26 ms, p=0.02), MT (Exercise: 31.60 ± 2.44 ms versus stable overweight: 29.67 ± 0.63 ms, p=0.04) and overall T_2 (Exercise: 35.75 ± 2.10 ms versus stable overweight:33.53 ± 0.56 ms, p=0.005).

CONCLUSION

This study provides evidence for a significantly decelerated T_2 progression in the MT of both WL groups over 8 years, indicating a slower deterioration of cartilage through weight loss. This chondroprotective effect was strongly seen in the >10% WL group, that reveiled significantly slower progressing T_2 values in the LT, MT, PAT and total cartilage sum. The subgroup analysis suggests an accelerated T_2 progression in the exercise only group, possibly caused by an overweight-related, attrition-promoting joint load during extensive workouts. Further research is needed to expand this knowledge.

8

LIST OF DIRECTORIES

8.1

LIST OF ABBREVIATIONS

	Acronym	Abbreviation for -
Numbers	3D	Three-dimensional
A	ACR ANOVA ASM	American College of Rheumatology Analysis of variance Angular second moment
B	BMI	Body mass index
C	COR CV	Coronar Coefficient of variance
D	DESS dGEMRIC DMOADs DNA DWI	Dual echo steady state Delayed gadolinium-enhanced MRI of cartilage Disease-modifying osteoarthritis drugs Deoxyribonucleic acid Diffusion-weighted imaging
E	ECM	Extracellular matrix
F	FOV FS	Field of view Fat-saturated
G	GAG Gd-DTPA GLCM GLDN	Glycosaminoglycan Gadolinium-diethylenetriamine penta-acetic acid Gray level co-occurrence matrix Gray level digital number
H	HHGS	Histological Histochemical Grading System
I	IBM ICCC ICRS IL(-4/-10) IPP IW	International Business Machines Corporation Intraclass correlation coefficient International Cartilage Repair Society Interleukin(-4/-10) Image processing package Intermediate-weighted

K	KL KOOS	Kellgren-Lawrence Knee Injury and Osteoarthritis Outcome Score
L	LF LT	Lateral femur Lateral tibia
M	MMP MPR MR(I) MSME MF msec MT	Matrix metalloproteinase Multiplanar reformation/reformatting Magnetic resonance (imaging) Multi-slice multi-echo Medial femur millisecond Medial tibia
N	NIH NSAID	National Institutes of Health Nonsteroidal antiinflammatory drug
O	OA OAI	Osteoarthritis Osteoarthtis Initiative
P	P-value PACS PASE PAT	Probability value Picture archiving and communication system Physical Activity Scale for the Elderly Patella
Q	QOL	Quality of life
R	ROI	Region of interest
S	SAG SD SF-12 SPSS	Sagittal Standard deviation Short form-12 Statistical Package for the Social Sciences
T	T TE TR TRO TSE	Tesla Time of excitation Time of repetition Trochlea Turbo spin echo
U	UCSF US(A)	University of San Francisco California United States (of America)

W	WE	Water excitation
	WHO	World Health Organisation
	WL	Weight loss
	WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
	WORMS	Whole-Organ Magnetic Resonance Imaging Score
J, V, X, Y, Z	-	-

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PUBLICATIONS

Title	Location/ Journal	Authors
Scientific conference contributions		
Association of diabetes mellitus and structural knee abnormalities and cartilage degeneration assessed by T2 relaxation time measurements: Data from the Osteoarthritis Initiative	International Skeletal Society 2016, Paris, France	N.Chancheck, A. Gersing, **J. Zarnowski,** L. Facchetti, B. Schwaiger, J. Guimaraes, G. Feuerriegel G, M. Nevitt, C. McCulloch, T. Link
Weight loss is associated with slower cartilage degeneration over 96 months in obese and overweight subjects: data from the Osteoarthritis Initiative	European Congress of Radiology 2016, Vienna, Austria	A. Gersing, B. Schwaiger, **J. Zarnowski**, G. Feuerriegel, J. Guimaraes, L. Facchetti, N. Chancheck, M.Nevitt, T. Link
Association of weight loss with slower cartilage degeneration over 96 months in overweight subjects: Data from the Osteoarthritis Initiative	World Congress on Osteoarthritis 2016, Amsterdam, Netherlands	A. Gersing, G. Feuerriegel, **J. Zarnowski**, B. Schwaiger, G. Joseph, J. Guimaraes, L. Facchetti, N. Chancheck, U.Heilmeier, P. Jungmann, M. Nevitt, C. McCulloch, T. Link
Degeneration der Knorpelmatrix im Kniegelenk, gemessen mit 3T MRT T2-Relaxationszeit, hängt mit Vorhandensein und Schweregrad des Diabetes mellitus Typ 2 zusammen: Daten der Osteoarthritis Initiative	98. Deutscher Röntgenkongress 2017, Leipzig, Deutschland	A. Gersing, N. Chancheck, B. Schwaiger, **J. Zarnowski,** G. Joseph, M. Nevitt, C. McCulloch, T. Link
Oral conference presentation		
Gewichtsreduktion übergewichtiger und adipöser Patienten ist mit einer verlangsamten Knorpeldegeneration assoziiert über einen Zeitraum von 96 Monaten: Verlaufsdaten aus der Osteoarthritis Initiative	97. Deutscher Röntgenkongress 2016, Leipzig, Deutschland	**J. Zarnowski**, A. Gersing, B. Schwaiger, G. Feuerriegel, J. Guimaraes, L. Facchetti, N. Chancheck, T. Link

Paper		
Weight Loss Regimen in Obese and Overweight Individuals is Associated with Cartilage Degeneration: 96-Month Data from the Osteoarthritis Initiative	Osteoarthritis and Cartilage. 2019 Feb.	A. Gersing, B.Schwaiger**,** M. Nevitt, **J. Zarnowski,** G. Joseph, G.Feuerriegel, P. Jungmann,J. Guimaraes, L. Faccetti,C. McCulloch, T. Link
Association of Diabetes Mellitus and Biochemical Knee Cartilage Composition Assessed by T2 Relaxation Time Measurements: Data from the Osteoarthritis Initiative	Journal of Magnetic Resonance Imaging 2018 Feb.	N. Chancheck, A. Gersing, B.Schwaiger**,** M. Nevitt**,** G. Joseph, N. Lane, **J. Zarnowski,** L.Facchetti, , J. Guimaraes, C. McCulloch, T. Link
Longitudinal changes in subchondral bone structure assessed with MRI and their association with functional outcome after high tibial osteotomy	Journal of ISAKOS 2018 Jul.	A. Gersing, P. Jungmann, B.Schwaiger**, J. Zarnowski,** F. Kopp, M. Schauerschnig, E. Rummeny, J. Kirschke, T. Baum
Cartilage Repair Surgery prevents Progression of Knee Degeneration in a mid-term Follow-up: a quantitative longitudinal control-matched MR Imaging Study	Knee Surgery, Sports Traumatology, Arthroscopy. 2018 Dec.	P. Jungmann, A. Gersing, F. Baumann, C. Holwein, S. Braun, J. Neumann, **J. Zarnowski**, F. Hofmann, A. Imhoff, E. Rummeny, T. Link

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