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INTRODUCTION

Obesity is a well-recognized global epidemic and its relationship with knee osteoarthritis (OA) is well documented (1, 2). The association between obesity and hip OA has shown more inconsistent results (3); however, a meta-analysis reported that body mass index (BMI) is positively associated with hip OA risk (4).

The mechanisms by which obesity affects OA appear to be multifactorial. A systematic review concluded that structural loading and altered biomechanics induced by obesity may be related to the initiation of OA in the weight-bearing joints (5). Further, adipose tissue releases many factors, including adipokines which may be present and unregulated in tissues that undergo OA changes (6).

Multiple imaging techniques have been applied to explore potential effects of weight loss on structural OA pathologies. An RCT compared the effects of diet-induced weight loss with or without exercise to exercise alone on 3T magnetic resonance imaging (MRI), measuring pathologies like synovitis and bone marrow lesions (BMLs) in patients with knee OA. Despite reported benefits of weight loss on symptoms, there was no difference between the groups on the rate of structural progression (7). In contrast, another study showed that weight loss of more than 10% was associated with a slower progression of cartilage matrix loss (using T2 values) in people at risk of knee OA, suggesting a beneficial impact of weight loss on cartilage degradation in early stages of the disease (8). It has further been reported that weight gain over a 4-year period in people with obesity and knee OA was strongly associated with increased progression in cartilage damage (9). Another recent study reported that weight loss reduced medial cartilage volume loss and improved knee symptoms, while weight gain seemed to increase the medial cartilage volume loss and worsen knee-symptoms (10).

Overall these sometime discrepant findings suggest that weight changes in individuals who are overweight or obese may have the potential to induce both structural and symptom-modifying effects. One explanation for the conflicting results may be the choice of different outcome measurement instruments (OMIs).

According to the recent OMERACT (Outcome Measures in Rheumatology) core domain set, joint structure as assessment is mandatory in trials investigating structure-modifying interventions for all hip and/or knee OA clinical trials (11). In light of this, the aim of this systematic review was to evaluate the structural effects of weight loss on hip and/or knee OA in people who are overweight or obese.

METHODS

Protocol

A prespecified protocol following the guidelines from the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 statement (12) was registered online (PROSPERO: CRD42017065263) and made available on www.parkerinst.dk.

The systematic review aimed at answering the following questions:

1. What is the effect of weight loss on imaging outcomes in OA of the hip or knee in people who are overweight or obese?
2. Which structural joint pathologies have been examined in OA weight loss studies?
3. Which OMIs have been used in the assessment of structural OA changes, and what were the reported performance metrics?

Information sources:

We searched three bibliographic databases on June 8th, 2018; MEDLINE via OVID (1946-present), EMBASE via OVID (1974-present) and Web of Science via Web of Knowledge (1900-present). The search was updated April 30th, 2019. We also screened the reference lists of relevant retrieved articles. The search strategy included the following areas: weight loss, imaging modalities and osteoarthritis in hip and/or knee, all combined with AND (For search strategy see appendix A).

Eligibility criteria and selection process:

Anticipating a limited number of randomized controlled trials (RCTs), both clinical trials and observational studies, which quantitatively estimated the effect of weight loss in people with overweight/obesity and OA, were considered eligible (according to the protocol). We included studies examining participants of any age. All or part of the cohort had to be diagnosed with OA of the hip and/or knee according to the criteria given by American College of Rheumatology (ACR) (13-15) or similar clinical criteria. All interventions resulting in weight loss were included; e.g. diet interventions, exercise programs, weight loss medications, surgical interventions, or a combination of these. There were no limitations regarding the duration of interventions and length of follow-up. All imaging modalities evaluating change in joints with OA were applied in the search strategy, including X-rays, MRI, computed tomography (CT), dual energy X-ray absorptiometry (DXA), and ultrasound. Datasets using the same modality and acquisition had to be available at both baseline and follow-up. Two review authors (CLD and SH) performed the selection process independently using the online software Covidence (16). Disagreements were resolved by discussion or a consensus meeting with a third author, regarding clinical matters (HB and HG) and imaging (MB).

Data extraction and management:

We developed a customized data extraction sheet. Two reviewers (CLD and SH) separately extracted the data. Extracted information included characteristics of participants and type of intervention. Outcome measures included weight loss induced changes in joint structures affected by OA. We also included comparing changes in imaging with the clinical domains: pain and physical function. Disagreements were resolved by discussion between the two reviewers.

Assessment of risk of bias in included studies

Risk of bias assessment was performed at study level using both the Cochrane risk of bias tool for randomized trials (RoB 2) (17) and the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I)(18). Important confounders of interest were specified prior to the risk of bias assessment with ROBINS-I (appendix B).

RESULTS

Study selection

The search strategy identified 1625 records after removal of duplicates (**Figure 1**). 1496 records were excluded based on title or abstract. The subsequent full-text assessment resulted in 14 records eligible for the systematic review (7, 19-31). During the study selection, authors of two studies were contacted, and their response provided additional information resulting in exclusion of both records (32, 33).

Figure 1

Study characteristics

Of the 14 included studies 12 were results from 4 cohorts: ADAPT (RCT) (24, 25), CAROT

(non-randomized study (NRS)) (23, 27), IDEA (RCT) (7, 20, 26) and OAI (NRS) (21, 22, 28, 29, 31) (Table 1). The IDEA studies (n=3) included only participants with radiographic OA (Kellgren-Lawrence grading (KLG)≥2); the rest of the studies (n=11) are based on participants with and without OA ranging from 19-53% with KLG ≥2. One study provided data on the hip (20), the rest of the studies examined the knee joint(s). The duration of the intervention and follow-up ranged from 16 weeks to 96 months. The eligible studies included between 19 and 760 patients, including between 61% and 100% women. The average age ranged from 49 to 69 years, and BMI ranged from 27.9 to 42.3 kg/m^2. Interventions included weight loss induced by either diet or exercise, a combination of these or surgery (e.g. gastric banding). Eleven studies used MRI (1.5 and 3T) (7, 19, 21-23, 26-31), one study used DXA (20), and three studies used x-ray (7, 24, 25). One study used both MRI and x-ray (7).

Table 1

Effect of weight loss

The studies assessed structural changes in the joint focusing on different pathologies (**Table 2**). Three studies also looked at changes in clinical symptoms in relation to structural pathologies (22, 23, 30). Because the pathologies assessed and OMIs varied markedly, we focused on describing the studies with qualitative synthesis of their results rather than performing a quantitative synthesis. Reported reliability-scores are shown in **Table 2**. Most intra-observer and inter-observer reliability of the applied OMIs were excellent with intraclass correlation coefficients >0.85 and root mean square coefficients of variation ≤2%.

Table 2

Joint Space Width

Three studies evaluated joint space width (JSW) using x-ray (7, 24, 25). None of the studies found any significant changes between groups.

Articular cartilage:

Using MRI (n=7) cartilage was evaluated using several different OMIs. Using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (34), one study (21) from the OAI reported at 48-months follow-up that adjusted mean increase of cartilage WORMS was significantly smaller in the weight loss group compared to the stable weight group, and also percentage of weight change was significantly associated with increase in cartilage WORMS (β =0.2; 95% CI: 0.02, 0.4; p= 0.007). Another study (28) based on the OAI found at 96-months follow-up no significant differences in WORMS sum score between groups in the rate of change of global knee cartilage score or cartilage score for each compartment. One study (30) assessed cartilage using the MRI Osteoarthritis Knee Score (MOAKS) (35) and found no significant change between groups.

Based on the OAI-cohort, two studies (22, 28) assessed cartilage composition with 3T MRI and T2–relaxation time mapping (visualization of the collagen matrix and tissue hydration in cartilage; increased values are associated with disease progression) at 48- and 96-months follow-up respectively. The first study (22) showed for the > 10% weight loss group that T2 relaxation times decreased -0.3ms (95%CI:-0.9, 0.4; p<0.001) in the medial tibia indicating decreased degenerative changes in comparison to controls. No change was observed in the lateral tibia. It should be noted that 81 % of the participants in this study did not have radiographic OA at baseline. The second study (28) showed the rate of increase over 96

months of global (averaged over all compartments) cartilage T2 was smaller in the weight loss group compared to the stable group: 0.24ms/year (95%CI: 0.20, 0.41; $p < 0.001$).

Two studies used delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC; quantification of relevant macromolecules in cartilage such as glycosaminoglycans; a compositional assessment where increased values are associated with healthier articular cartilage). One study (27) reported improvement/increase of the dGEMRIC index as surrogate measure of cartilage quality in the lateral compartment in early stage knee OA (KLG 1) but not in KLG2 knees following weight loss using 1.5T MRI. The other study using dGEMRIC (19) reported that weight loss was associated with an increase in dGEMRIC in multiple regression analysis ($\beta=3.9$, $R^2=0.26$; $p=0.008$) in the medial compartment using 3T MRI.

Cartilage segmentation was used to analyze cartilage thickness in two studies. One study (19) found that higher percentage weight loss was associated with reduced loss of cartilage thickness in the medial femoral compartment ($\beta=0.006$, $R^2=0.19$, $p=0.029$) using 3T MRI. The other study (7) found no significant difference in MRI cartilage loss between groups.

Bone

Five studies reported on BMLs using MRI (7, 21, 23, 28, 30). None of the studies found any association between weight loss and change in BMLs. Two studies (7, 23) used the Boston Leeds Osteoarthritis Knee Score (BLOKS) (36) as OMI. Two studies (21, 28) assessed BMLs using WORMS and one study (30) used MOAKS as an OMI. Using DXA, one study (20) evaluated the effects on bone mineral density (BMD) in the hip and found that BMD in the hip and femoral neck correlated positively with changes in body weight ($r = 0.21$ and 0.54 respectively, both $p \leq 0.01$).

Infrapatellar fat pad (IPFP)

Using 1.5T MRI, one study (26) found a significant reduction in IPFP volume in all weight loss intervention groups with a maximum of -5.2% reduction (95% CI -3.5, -7.5%). Assessed with 3T MRI, another study (31) found that >10% weight loss was correlated with a significant reduction in IPFP volume of -2.2% (SRM = 0.38).

Synovitis

Two studies have evaluated synovitis (7, 30). Both studies found no significant difference between groups. One study (7) used BLOKS and the other study (30) used MOAKS as an OMI.

Meniscus

Three studies (21, 28, 29) assessed meniscus using WORMS at 48- (n=2) and 96-months follow-up. One study (21) reported at 48-months a beneficial effect of >10 % weight loss with significant lower odds of worsening of meniscal pathologic abnormality compared to the stable weight group (odds ratio, 0.42 (95% CI: 0.22, 0.83; p=0.007). However, the adjusted mean change in WORMS grades over 48 months did not reach statistical significance between groups. Another study (29) including only participants with meniscal degeneration (WORMS=1) found no significant association between the weight loss group (>3%) and the stable weight group. In the study with a follow-up period of 96-months (28) the weight loss group (>5%) showed significantly lower rates of progression of both menisci together and the medial meniscus. Adjusted mean differences of rate of change/year between stable group and weight loss group: WORMS meniscus lesions sum, 0.08 (95% CI: 0.02, 0.21, p= 0.021) and WORMS medial meniscus lesions sum, 0.06 (95% CI: 0.02, 0.09, p=0.005).

Relationship of structural change to pain, disability and physical function:

Three studies compared structural changes from imaging to change in symptoms. One study

(23) failed to relate changes in BML response to clinical improvements assessed with the knee injury and osteoarthritis outcome score (KOOS) and OMERACT-OARSI (Osteoarthritis Research Society International classification) Responder Criteria following weight loss. Another study (30) found no significant correlation between change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain and change in BML, synovitis and cartilage assessed with MOAKS or cartilage thickness score. The last study (22) compared WOMAC scores with changes in cartilage T2-values and found increase of T2-values in the medial tibia was significantly associated with increase in WOMAC pain (β 0.5ms, 95% CI 0.2 to 0.6, P=0.02) and disability (β 0.03ms, 95% CI 0.003 to 0.05, P=0.03)(22).

Risk of bias assessment

The most common risk of bias in the NRS was 'Bias due to confounding' with four studies rated serious (19, 23, 30, 31) and one rated critical (27). Four studies were rated moderate (21, 22, 28, 29) and one were rated critical (27) in 'Overall bias' (**Table 3**). The most common risk of bias in the RCTs was 'Bias in selection of the reported result' were all five studies showed 'some concern' (7, 20, 24-26). None of these studies were rated with 'high risk of bias' (**Table 4**).

DISCUSSION

This systematic review found that the current evidence is not sufficient to determine specific structural effects of weight loss on imaging outcomes in people with overweight or obesity and OA in the hip or knee joint. Although there are indications that pathophysiological manifestations like cartilage compositional measures (such as T2 maps) or cartilage thickness measures may be positively influenced during weight loss in early knee OA.

X-ray is a widely used OMI in the healthcare system when assessing OA. However, the findings in the included studies (n=76–454, RCT=3, follow-up: 18 months), of which one had excellent interrater reliability score (7) strongly indicate that JSW is not a suitable outcome measure for detecting changes induced by weight loss. Several factors could be the cause of this: repositioning measurement errors which mean very large study numbers are usually required to reliably detect change, not being able to distinguish between cartilage and meniscus (37, 38), and the weight loss actually not inducing visible structural changes.

Cartilage represents the most studied structural area of the knee with a total of seven studies included in the review (n=19–760, RCT=1, NRS=6, follow-up: 16 weeks to 96 months). However, results were conflicting. Cartilage segmentation and thickness measurements were applied in three studies with somewhat contradictory results. One study (19) reported a minor beneficial effect of weight loss which is based on a non-randomized design with 78 participants out of whom only 32% had clinical knee OA. The study by Jafarzadeh et al. (30) is very similar in set-up but did not find any change in cartilage thickness. The same results were reported by Hunter et al. (7) in an RCT only including participants with OA. None of the studies reported specific reliability scores for the cartilage segmentation. Follow-up time ranged 12–18 months which may be part of the overall lack of change.

Two studies (19, 27) used dGEMRIC as an OMI and found that weight loss improved cartilage quality although in different compartments. The dGEMRIC method differed in the two studies (intra-venous vs. intra-articular gadolinium injection). This may explain the different results combined with the limited number of participants in both studies (n=14 (OA-subgroup) and n=19) making the statistical evidence limited, suggesting that larger studies are needed to

confirm the results. Although promising, the dGEMRIC method is technically difficult to set up and can usually only be performed at a single center. It is also time consuming due to the need of 90–120 minutes waiting time after injection of contrast to allow it to distribute into the joint (27).

Using cartilage T2 measurements two studies based on the OAI (22, 28) reported beneficial effect of weight loss in the medial tibia and one of the studies also reported significant global effect. Similar results were reported by another weight loss study by Serebrakian et al. (8) not included in this review as persons with OA were excluded at baseline. These results are promising, but a limitation of this method is that T2 values do not correlate well with the radiographic degree of OA. Studies have found only small difference between patients with mild and severe radiographic OA, but found a significant increase in T2 values between healthy people and people with OA (39-42), suggesting that T2 is a valuable assessment parameter with the largest potential of the method in the pre-OA and early-OA stages (43) where MRI-visible cartilage is relative preserved. The clinical meaning of the changes seen in compositional MRI is not fully understood and warrants further research (44).

Assessing cartilage degeneration with WORMS the two studies by Gersing et al. (21, 28) reported conflicting findings at 48-months and 96-months follow-up. Only the 48-months follow-up reported significantly lower cartilage degeneration. In the study (28) with an 8-years follow-up time no change was detected using WORMS which indicate this method is not suited as an OMI for detecting changes induced by weight loss. It should be noted that both studies are based on participants from the OAI which is a NRS and only 51% of the cohort had OA (KLG ≥2) at baseline making the results difficult to interpret.

Another MRI feature, BML, was evaluated in five studies (7, 21, 23, 28, 30) (n=75–760, RCT=1, NRS=6, follow-up: 16 weeks to 96 months) using MOAKS, BLOKS and WORMS. None of the studies found a statistical association between mean change in BMLs and weight loss. Although BML changes can show both progression and regression over time (45), it has not been possible to link BML changes to weight loss. In other studies, BMLs have been reported to correlate with symptoms, though the strength of such associations is weak, (45-48) and to be a prognostic marker for cartilage degradation and OA structural progression (49). Reasons for lack of structural BML change associated with weight loss could be related to the relatively insensitivity of semi-quantitative BMLs scoring systems (23), and BML detection might need several different MRI sequences to distinguish sub-types (50).

Another important pathology for joint congruity is the menisci. Three studies based on the OAI cohort (21, 28, 29) assessed the menisci with WORMS (n=487–760, NRS=3, follow-up: 48–96 months). All three studies reported beneficial effects of weight loss although only one study (28) showed statistically significant lower rates of progression in WORMS sum score in the weight loss group. Additionally, one of the studies (29) reported that weight gain >10% is associated with a significant 21-fold increase in the odds of progression of a meniscal intrasubstance degeneration (WORMS meniscus score = 1) to a meniscal tear or maceration (WORMS meniscus score: 2-4) compared to the stable weight group. The same study also showed that during 48 months none of the menisci showed regression to a normal meniscus signal. These results suggest that the menisci are influenced by weight change and should be explored further.

Synovitis, effusion and the IPFP are infrequently evaluated in relation to weight loss (n=72–105), RCT=1, NRS=2, follow-up: 12–24 months). The role of inflammation in the progression

of OA is still unclear but there is a growing interest in the area. In two large OA RCTs, Messier et al. (51) and Nicklas et al. (52) have reported that weight loss reduced inflammation by lowering circulating concentrations of IL-6. When assessing the IPFP, both Murillo et al. (26) and Steidle-Kloc et al. (31) found that weight loss is associated with a significant size reduction. A cross-sectional study by Ballegaard et al. (53) examining people with overweight and knee OA using dynamic contrast-enhanced MRI found that severe perfusion/inflammation in the IPFP was associated with more severe pain in knee OA using the KOOS. These findings combined makes the IPFP an interesting construct for further studies as there seem to be a correlation between the effects of weight loss, inflammation and pain. This effect was although not captured by Jafarzadeh et al.(30) using MOAKS to evaluate synovitis or Hunter et al. (7) using BLOKS to evaluate synovitis and effusion, none of whom demonstrated a significant difference between groups.

Weight loss is known to be associated with clinical improvement in knee OA and is widely recommended as core treatment in OA (if overweight/obese) (54, 55). Nevertheless, comparing the structural changes on imaging induced by weight loss to pain and physical function is less studied. Gersing et al. (22) found that weight change was significantly associated with T2-value change in cartilage in the medial tibia and in WOMAC subscales for pain and disability (56), while Gudbergsen et al.(23) failed to connect a change in BML response to clinical improvements following weight loss. Despite a substantial weight loss and a marked reduction in knee pain Jafarzadeh et al. (30) also found no correlation between structural changes (cartilage, BML and synovitis) and clinical symptoms.

289 This review identified only one weight loss study investigating the hip. As BMI is associated
290 with increased risk of hip OA (4) and the reported prevalence of symptomatic hip OA in North
291 America is 1.91% overall (57), this area warrants further research.

292 The main limitations of this review are the small number of studies available for inclusion and
293 the limited number of datasets available. The varying percentage of weight loss is another
294 cause of concern. Most likely a certain percentage of weight loss is required to stimulate
295 change in different structures, as there appears to be a threshold of >10% weight loss to
296 induce corresponding changes in pain and function (58). Another important limitation is that
297 patient populations and follow-up periods are not the same across studies. In 5 out of 6
298 cohorts the population consists of participants both with- and without radiographic OA.
299 Including studies with limited OA participants is not ideal. However, we felt obliged to include
300 all the studies, since we did not specify a lower threshold for the acceptable percentage of OA
301 participants in the protocol. The choice of pathologies and especially types of OMIs also differ
302 extensively. Therefor a meta-analysis was not possible to perform, due to insufficient
303 comparable analyses. Similarly, publication bias could not be assessed due to insufficient data.

304 **Perspectives**

305 A major issue is that the reporting across existing studies is inconsistent with respect to
306 choice of pathology and OMI, making the results difficult to compare. There is a need among
307 the OARSI and OMERACT Community members to achieve consensus regarding which
308 structural pathologies and measurements to apply. A possible study set-up could be a
309 longitudinal study with long follow-up time points, comparing a large sample of patients
310 (either at risk of OA or with OA) with stable weight, and patients who lose preferably ≥10%
311 bodyweight (51, 58) and patients who gain weight, which could provide further information

on which outcome measures are most sensitive to structural changes relative to changes in body weight.

Conclusion

Overall the choice of OMIs varied extensively making comparison difficult and many results are conflicting. Out of the 8 studies, which provided significant group differences related to weight loss, 6 studies were based on cohorts including participants with- and without radiographic OA (OA ranging from 19–52%) making the results even more complex to interpret.

In summary, the data in this systematic review did not find sufficient evidence to determine any effect of weight loss on OA structures in people who are overweight or obese. However, there are indications that pathophysiological manifestations like cartilage compositional measures are positively influenced during weight loss in early knee OA.

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Contributions

All authors critically revised the manuscript and approved the final version to be submitted. All authors participated in study conception and design, acquisition and interpretation of data. CLD drafted the manuscript with comments from all. The last author (MB) takes responsibility for the integrity of the work as a whole, from inception to finished article.

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Competing interests

CLD, SH, EMB, HG, HB, ME and PGC have no conflict of interest. MB is a shareholder and consultant for Image Analysis Group LTD, London UK. RC is a member of the OMERACT TAG; that might be perceived as a COI to some individuals. RC declares having no disclosures of interest in regard to the specific manuscript.

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