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REVIEW ARTICLE

Pathogenesis and clinical management of obesity-related knee osteoarthritis: Impact of mechanical loading

Lianzhi Chen [a], Jessica Jun Yi Zheng [b], Guangyi Li [c], Jun Yuan [a,d], Jay R. Ebert [e], Hengyuan Li [f], John Papadimitriou [a,g], Qingwen Wang [h], David Wood [a], Christopher W. Jones [i,j,**], Minghao Zheng [a,d,*]

[a] Centre for Orthopaedic Research, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia
[b] Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
[c] Department of Orthopaedic Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China
[d] Perron Institute for Neurological and Translational Science, Perth, Western Australia, Australia
[e] School of Human Sciences (Exercise and Sport Science), University of Western Australia, Perth, Western Australia, Australia
[f] Department of Orthopedics, Second Affiliated Hospital of Zhejiang University, School of Medicine, Zhejiang, China
[g] Pathwest Laboratories, Perth, Western Australia, Australia
[h] Department of Rheumatism and Immunology, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China
[i] Fiona Stanley Hospital Group, Perth, Western Australia, Australia
[j] Curtin University Medical School, Perth, Western Australia, Australia

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SUMMARY

Obesity-related osteoarthritis (OA) is a complex, multifactorial condition that can cause significant impact on patients' quality of life. Whilst chronic inflammation, adipocytokines and metabolic factors are considered to be important pathogenic factors in obesity related OA, there has been limited investigation into the biomechanical impact of obesity on OA development. This review aims to demonstrate that mechanical factors are the major pathological cause of obesity-related OA. The effect of obesity on pathological changes to the osteochondral unit and surrounding connective tissues in OA is summarized, as well as the impact of obesity-related excessive and abnormal joint loading, concomitant joint malalignment and muscle weakness. An integrated therapeutic strategy based on this multi-factorial presentation is presented, to assist in the management of obesity related OA.

The translational potential of this article: Despite the high prevalence of obesity-related OA, there is no specific guideline available for obesity-related OA management. In this review, we demonstrated the pathological changes of obesity-related OA and summarized the impact of biomechanical factors by proposing a hypothetical model of obesity-related OA change. Therapeutic strategies based on adjusting abnormal mechanical effects are presented to assist in the management of obesity-related OA.

Introduction

Obesity-related osteoarthritis (OA) is a complex biopsychosocial condition that contributes to increased patient morbidity and mortality, as well as increased financial burden on the health care economy [1]. Two out of every three obese individuals have OA and the incidence of OA increases with increased body mass index (BMI) [2]. It has been reported that over 50% of patients required total knee replacement (TKR) for end-stage OA are obese [3].

Despite the high prevalence of obesity-related OA, clarity is still needed in understanding the pathogenesis of this condition. Obesity-induced inflammation is believed to be significant in the pathogenesis of OA, which is evidenced by the occurrence of impaired metabolism and OA. However, there is insufficient evidence demonstrating that metabolic disorders in obese patients is the trigger of OA, and the efficiency of correcting chronic inflammation in OA patients is relatively limited. Previous clinical trials of anti-inflammatory, intra-articular corticosteroid injections have consistently found to provide only short-term relief

* Corresponding author. Centre for Orthopaedic Research, Faculty of Health and Medical Sciences, University of Western Australia, 35 Stirling Highway, Perth, 6009, Australia.
** Corresponding author. Fiona Stanley Hospital Group, Perth, 6009, Australia.
E-mail addresses: chriswjones@health.wa.gov.au (C.W. Jones), minghao.zheng@uwa.edu.au (M. Zheng).

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[4–6]. A study that examined the effect of mechanical stress and obesity-related systemic factors on knee and hand OA showed that obesity-related mechanical stress was the most important risk factor for knee OA [7,8]. Causation can be difficult to prove in a noninfectious disease, however, there is increasing evidence showing that OA is a disease primarily of mechanics, whereas the inflammation in OA is more so a secondary consequence of this [9,10]. In this review, we focused on discussing the effect of obesity-related biomechanical factors on OA development, and the management of obesity-related OA based on adjusting the abnormal biomechanics. Currently, there is no specific guideline available for obesity-related OA treatment [11]. For this reason, we conducted a literature search on PubMed in English from 1972 to 2019 using the keywords obesity, osteoarthritis, mechanical factors, biomechanics and pathology.

Impact of obesity on joint pathology

Obesity contributes to initiate the osteoarthritic joint process, via excessive mechanical loading of the joint. The isolated (and combined) effect on the osteochondral unit and surrounding connective tissues is outlined below and further summarized in Table 1, with changes in these tissues contributing to acceleration of the disease [12].

Articular cartilage

Hyaline cartilage is an avascular, aneural structure with a low friction coefficient, which allows for compressibility and gliding [20]. In the early stages of OA, cartilage surface fibrillation and swelling are associated with chondrocyte clustering, increased chondrocyte proliferation and increased production of specific extracellular matrix (ECM) proteins [20,21]. With disease progression, cartilage damage extends to the deeper layers, resulting in delamination of hyaline cartilage and exposure of underlying calcified cartilage and subchondral bone [22].

Cartilage defects have shown to be associated with increased BMI [23]. A cross-sectional study demonstrated that obesity and BMI were consistently associated with increased knee cartilage defect severity, as well as tibial bone enlargement [24]. Widmyer et al. reported that high BMI individuals had thicker cartilage on the patella and femoral groove, and thinner cartilage on the medial tibia, compared to normal BMI individuals [25]. Furthermore, expression of Matrix Metalloproteinase-12, which mediates hyaline cartilage degeneration, was positively associated with BMI [26].

Table 1
Structural changes of joints in obesity-related OA.

Structure	Obesity-related change	Reference
Cartilage	Early lesions of knee cartilage	Widhalm et al. [13]
	Increased knee cartilage defects	Anandacoomarasamy et al. [14]
	Less cartilage degradation from superficial zone	Chen et al. [10]
Osteochondral interface	Increased incidence of horizontal fissuring	Chen et al. [10]
	Increased length, increased area of fissuring	
Subchondral bone	Increased bone volume fraction, more plate-like trabecular bone, increased trabecular space, increased trabecular number	Reina et al. [15]
	Increased bone marrow lesions	Muratovic et al. [16]
	Increased osteoid formation, decreased bone mineral density and bone volume	Chen et al. [10]
Osteophyte	Higher incidence of knee osteophytes	Hart et al. [17]
Synovium	Marked fibrosis	Harasymowicz et al. [18]
	Increased macrophage infiltration	
	Higher level of Toll-like receptor 4 expression, higher level of adiponectin and adipose-related markers peroxisome proliferator-activated receptor γ (PPARγ)	
	Increased hematopoietic cells, M2-type macrophages	
Meniscus	Increased incident of meniscal extrusion	Englund et al. [19]
Infrapatellar fat pad	Larger adipocytes	Harasymowicz *et al.* [18]
	Increased PPARγ	
	Increased hematopoietic cells, M2-type macrophages	

Osteochondral interface

The osteochondral interface is a gradient tissue between stiff bone tissue and the softer, viscoelastic articular cartilage in the osteochondral units [27]. Calcified cartilage is separated by histological defined tidemarks and cement line from hyaline cartilage and subchondral bone. The osteochondral interface plays a significant role in maintaining the integrity of the osteochondral units by transmitting mechanical force and preventing the movement of large molecules [28]. However, osteochondral interface is believed to be a region of weakness, as no collagen fibers are continuous between the calcified cartilage and subchondral bone, and an abrupt change of mineral collagen orientation is observed between the hyaline and calcified cartilage [29,30]. Mechanically, articular cartilage has a soft structure with a higher Poisson's ratio, while the underlying mineralized structure is a stiff structure with low Poisson's ratio. Under high compression, articular cartilage can experience a larger deformation, compared to its attached underlying calcified bed [23,24]. Our recent study showed that mechanical overload in patients with obesity can cause horizontal fissuring at the osteochondral interface in OA. The novel pathological findings of horizontal fissuring, characterized by irregular erosion, free bone/cartilage debris, fibro-granulation tissue and the rupture of microcapillaries at the osteochondral interface, is the key pathological feature in patients with obesity-related OA. The unique feature of horizontal fissuring in obese patients with OA suggested that mechanical factors play a key role in the pathogenesis of obesity-related OA [10].

Subchondral bone

BMI plays a significant role in the pathological changes of subchondral bone during OA development [15,31]. Subchondral bone, including the subchondral bone plate and subchondral trabecular bone, exerts a stress-absorbing function and supports the metabolism of healthy joints [1]. In the early stages of OA, an increased rate of bone remodeling leads to a thinner subchondral bone plate and decreased bone volume in trabecular bone. Increased bone remodeling may be associated with the accumulation of microcracks [32]. However, in end stage OA, fewer microcracks have been reported, which can be explained by thicker trabeculae and the strengthened architecture of the subchondral trabecular bone [33].

Our recent study showed that BMI was positively associated with increased osteoid formation, but negatively associated with total bone volume and bone mineral density in the predominant compartment of knee OA [10]. While low bone volume and mineral density may be due to the high prevalence of vitamin D insufficiency or deficiency in the obese individual [34], Reina et al. showed that BMI was positively associated with bone volume fraction, trabecular spaces, trabecular number, and increased numbers of plate-like changes in subchondral trabecular bone [15]. Currently the impact of obesity on SCB is still controversial.

Bone marrow lesions (BMLs), such as bone marrow edema or bone bruises, have also been observed in individuals with OA, and are strongly associated with joint pain and cartilage degeneration [35,36]. It has been reported that the presence of BMLs was associated with increased BMI and body weight [31]. A systematic review demonstrated that high compartmental loads together with increased body weight, increased the

presence of BMLs [37]. An in vivo study by Matheny et al. reiterated this finding; epiphyseal cancellous bone of rabbits that received cyclic loading for a period of two weeks had an increased number of BMLs and higher bone resorption, when compared to controls [38].

Synovium

Since adult articular cartilage is an avascular and aneural structure, the pathological changes of synovium has drawn a concern as a major cause of pain in OA [39]. Under normal condition, synovium consists of a thin layer of synovial lining cells with features of macrophages and fibroblasts. Lubricin and hyaluronic acid, the main molecules produced by synovial lining cells, play an important role on protecting the integrity of cartilage by reducing friction, providing nutrients and removing products of cartilage metabolism and turnover [40]. During OA development, low level synovitis is associated with joint pain, cartilage degradation and subchondral bone resorption [41]. An over 2.5 years follow-up study shown that a weight gain in overweight/obese women resulted in a greater risk of progression of synovitis, compared to those with steady weight [42]. It has been reported that the synovial fluid of obese OA patients showed more inflammation than that of normal weight OA patients, as indicated by elevated levels of Interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF-α). Synovial fibroblasts isolated from obese OA patients secreted more IL-6, IL-8 and TNF-α than those from normal weight controls [43].

Menisci

The menisci are two fibrocartilaginous discs located in the tibiofemoral joint, which play an important role in dispersing body weight and reducing shock and friction during joint mobilization. Meniscal pathology, including tears, destruction and extrusions, are strong risk factors for OA development [44]. Meniscal damage affects weight-bearing capacity of the joint, leading to abnormal loading and friction on cartilage and subchondral bone, ultimately resulting in OA [44]. Several studies have demonstrated that obesity is a significant risk factor for meniscal extrusion and tears [19,45,46]. One explanation is that increased load generated by obesity is transmitted to the menisci, which may lead to meniscal pathological damage. Additionally, the levels of APLN, which may play a catabolic role in meniscal homeostasis, are negatively associated with BMI in menisci gene expression [47]. This suggests that obesity may have a negative biological impact on the menisci, through altered gene expression. Thus, meniscus pathology may be an important event in mediating the development of obesity-related OA.

Mechanical stress as a key pathological factor in obesity-related OA

Abnormal excessive joint loading

Moderate dynamic mechanical loading is one of the most important mechanical factors for maintaining joint homeostasis. The integrity of articular cartilage is maintained under moderate loading conditions during routine daily activities. However, when receiving abnormal excessive mechanical loading, disruption of cartilage homeostasis and deformation of normal joint morphology occurs, further inducing and accelerating the progression of OA. In vivo and ex vivo studies exploring the impact of biomechanical stimulation on joint structure and cellular changes demonstrated that pure mechanical factors can directly result in structural damage, abnormal cell activities, and lead to synovitis (Table 2).

Increased dynamic mechanical loading during walking or other physical activities, generated by high body weight in obese individuals, appears to play a key role in OA progression. Generally, high BMI correlates with increased absolute mechanical stress during gait, regardless of the presence or absence of OA [58]. Excessive peak compressive loads of over 1.2×10^6 N, and excessive peak shear stress of over 206,000 N per mile walking was generated by patients with a BMI between 35 and 41.3, compared to patients with a BMI between 27 and 29.9 [59]. External knee adduction moment (KAM) during the stance phase of gait, a surrogate measure of tibiofemoral knee joint loading of medial compartment of the knee, was reported to be strongly associated with excessive body weight [60]. Previously, a study showed a strong association between the high risks of OA progression and increased KAM. For every one unit increase in peak KAM, there was a 6.5-fold increase in risk of progression in osteoarthritic radiological findings of the medial tibiofemoral compartment [61]. Increased peak KAM was also associated with increased number of BMLs in the subchondral bone [62]. Interestingly, higher peak KAM displayed a thinner medial meniscus and higher bone volume, however there was little difference in cartilage thickness [63].

Considering articular cartilage and subchondral bone is subject to variation in frequency of loading, which may affect its integrity, measurement representing repetitive loading also provides insight into the effect of mechanical loading on the progression of OA. Robbins et al. reported that an increased external KAM impulse, which was used to measure patients' self-selected speeds, was positively associated with pain in patients with knee OA [64]. A twelve-year study of patients with early stage OA of the knee reported that a high KAM impulse was independently associated with greater cartilage loss [65]. These results suggested that higher knee loading and KAM impulse, although not necessarily peak KAM, is a significant risk factor in loss of medial tibial cartilage volume; given knee load is a modifiable factor, loading frequency and load-modifying treatments, should be considered when investigating the incidence, progression and management of OA.

Knee joint malalignment

Joint malalignment affects load distribution on the articular cartilage surface [66]. Increased body weight affects weight-bearing joints differently, depending on their anatomical configuration. The knee joint is a hinge joint, and surrounding tissues counteract large shearing, compressive and axial loading forces. Any dysfunction in these surrounding tissues may cause increased stress on the joint, and further propagate underlying arthritic disease. While compared to the knee, the hip joint is a ball-and-socket joint, which provides excellent stability and has less reliance on the surrounding capsule, ligaments and muscles for this stability [67]. As a result, obesity has a greater impact on the induction and progression of OA in the knee compared to the hip joint [68].

Obese patients commonly have an increased thigh girth, forcing greater hip abduction, circumferential swing phase and varus alignment, to avoid thigh contact whilst walking, which in turn reduces the effective loading area on the knee joint, and transfers this area medially [69]. Varus malalignment is associated with a greater peak external KAM during the stance phase of gait, independent of BMI [59]. It results in an increased stress across a focal area on the medial compartment of the joint, which may lead to structural damage and OA [70]. However, whilst elevated BMI may induce varus malalignment and OA progression, the correlation between BMI and risk of OA progression does not extend to those with neutral alignment [71]. Moreover, BMI was shown to be associated with knee OA severity in patients with varus malalignment, but not in those with valgus malalignment [67]. Therefore, varus malalignment intensifies the effect of obesity on disease progression, particularly in the medial tibiofemoral joint, suggesting that malalignment correction may be a therapeutic target for the prevention of obesity-related OA.

Muscle weakness

Muscles play a shock-absorbing role during joint function to help maintaining joint stability [72]. Muscle weakness affects joint stability by reducing shock absorption, dissipating joint loading and inducing high articular contact stress [73]. Nakagawa et al. observed that decreased

Table 2
Impact of mechanical factors on OA pathological changes.

Ref.	Mechanical factor	Study Model	Study design	Main Finding
Roemhildt et al. [48]	Chronic compression	In vivo	A varus compression device on tibiofemoral joint of mature rats for 20 weeks.	Decrease in cartilage aggregate modulus, cartilage thickness and cellularity; Increased histological degeneration; Increased subchondral bone thickness
Coleman et al. [49]	Cyclic axial compression	Ex vivo	7 days consecutive days of cyclic axial compression (0.25 or 1.0 MPa, 0.5Hz, 3 h) on bovine osteochondral explants.	After 7 days loading, repeated overloading (1.0 MPa) leads to chondrocyte mitochondrial dysfunction with increased proton leakage and decreases in mitochondrial membrane potential, and increased reactive oxygen species formation.
Kaplan et al. [50]	Unconfined, uniaxial compression test	Ex vivo	Cyclic, unconfined compression test under a range of loading magnitudes and frequency approximated daily activities were applied on the extracted specimen from load-bearing regions within the lateral femoral condyles of health donors.	Cyclic loading up to 36,000 cycles damages the collagen network. A number of cycles without sufficient recovery may cause permanent damage in cartilage depending on the magnitude of the force applied by the activity.
Ko et al. [51]	Repetitive cyclic compression	Ex vivo	Cyclic compression of 4.5 and 9.0N peak loads to the left tibia via the knee joint of adult mice for 6 weeks.	Increased damage severity dependent upon the duration of loading. Articular cartilage thickness decreased, and subchondral cortical bone thickness increased in the tibia plateaus. Osteophyte developed in 9.0N peak loading but not in 4.5N peak loading
Ko et al. [52]	Single cyclic compression	In vivo	A single 5-min session to the left tibia of adult mice of 9.0N for 1200 cycles for 2 weeks	Compared to baseline, cartilage pathology demonstrated by localized thinning, proteoglycan loss, bone loss was evident at 1 week, with increased osteoclast numbers, but reversed to baseline levels at 2 weeks. Fibrous and cartilaginous tissues at the margins at 2 weeks.
Matheny et al. [38]	Cyclic loading	In vivo	0.2–2.0 MPa in compression for 10,000 cycles at 2 Hz for 2 weeks	By MR, loaded limbs displayed BMLs, increased tissue microdamage and bone resorption as compared to controls
Santos et al. [53]	Impact & cyclic compression	Ex vivo	76 full-thickness, cylindrical osteochondral plugs were assigned to low-energy impact groups (none, low, high), and thereafter three cyclic compression groups (none, low, high)	Microcracks in cartilage collagen network initiate and propagate under mechanical treatments. The length and width of microcracks increased by impact and cyclic compression.
Wu et al. [54]	Single cyclic compression	In vivo	8-week old mice were placed in a hyperflexed position and subjected to compressive joint loading at 3,6, or 9N peak forces for 60 cycles	Acute joint pathology was associated with increased injured loads. Loading regimens induced chondrocyte apoptosis, cartilage matrix degradation, disruption of cartilage collagen fibril arrangement and increased serum COMP. 6N induced mild synovitis and 9N induced anterior cruciate ligament and severe synovitis and ectopic cartilage formation.
Wilson et al. [55]	Shear strain Tensile strain	Ex vivo	Full-thickness cartilage plugs from tibial plateaus of 8-month-old calves were loaded five times with 25N. Comparison of locations of maximum shear and tensile strains using antibodies directly against type II collagen.	The maximum tensile strain increased almost linearly with decreasing cartilage thickness. The maximum shear strain along the direction of collagen fibrils increased more rapidly for thinner samples.
Arno et al. [56]	Compression, shear and torque	Ex vivo	10 cadaveric knees were tested in a rig with 500N compression, 100N shear and 2.5Nm Torque, and the knee flexed from −5 to 135°.	A horizontal cleavage lesion was created in cartilage arthroscopically. And the horizontal cleavage lesion will result in small but statistically significant changes in tibiofemoral contact mechanics.
Radin et al. [57]	Repetitive impulsive loads	In vivo	Rabbit legs were applied load with ankle flexion.	Loading induced increased bone formation and decreased in porosity, which is associated with relative stiffening of bone. Horizontal splitting and deep fibrillation of the overlying articular cartilage followed by early bone changes.

knee flexor muscle strength was associated with joint malalignment [74]. Quadriceps weakness was also associated with significantly higher levels of joint loading during gait, as well as pain [75,76].

Additionally, obesity is associated with relative muscle dysfunction [77]. A six-year cohort study in Italy demonstrated that obesity was associated with low muscle strength, and increased the risk of developing mobility problems [78]. A prospective study has shown a strong negative correlation between knee extensor strength (quadriceps) and body weight in obese women with OA, suggesting reduced quadriceps strength relative to body weight is a risk factor for knee OA [79]. Hilton et al. confirmed this finding and suggested the cause may be due to excess adipose tissue infiltration of muscle in obese individuals [80]. It is worthwhile to note the risk of combined obesity and muscle dysfunction is increased in the elderly, who are already at a higher risk of OA [81]. Sarcopenic obesity, which is characterized by the combination of obesity and sarcopenia (age-related muscle loss and physical dysfunction), is associated with a higher risk of radiographic knee OA, relative to individuals in the non-sarcopenia obesity group, demonstrated in a cross-sectional study based on 2893 individuals [82]. Interestingly, a recent longitudinal study based on 1653 patients showed an association between sarcopenic obese women and increased risk of radiographic knee OA, however this was not seen in men, suggesting that the effect of muscle dysfunction on obesity-related OA development may be related to gender [83].

Therapeutic strategies for obesity-related OA

Weight loss strategies

As previously outlined, mechanical overload has a significant impact on obesity-related OA, therefore reduced joint loading through weight loss should be a core therapeutic target, which has been recommended in the updated European League Against Rheumatism (EULAR) for knee OA management [84]. Biomechanically, an absolute weight reduction reduces compressive and resultant forces within the knee, whilst also decreasing the KAM during gait. It has been reported that an absolute weight loss of 1 kg (9.8N) led to reductions of 40.6N and 38.7N in compressive and resultant forces, respectively, and was associated with a 1.4% reduction in the KAM [85]. In addition to this, weight reduction in obese patients with OA, can downregulate systemic inflammatory markers including adipocytokines such as leptin, and proinflammatory cytokines, such as IL-6, CRP, corosomucoid and fibrinogen [86].

Weight loss strategies are an effective way to prevent the onset of OA in obese individuals and those who are at an increased risk of developing OA. A study on the prevention of knee OA in overweight females showed that a decrease of 5 kg or more, or a 5% decrease in body mass, over 30

months decreased the incidence of structurally defined OA from 20% to 15% [87]. However, weight loss strategies are also a crucial treatment to reduce disease progression in patients with established obesity-related OA. A one-year randomized controlled trial (RCT) showed significant pain reduction and symptom improvement in a group of obese knee OA patients who were on a low-calorie diet, compared to a control group of obese knee OA patients without a low-calorie diet [88]. Structural changes in the knee joint have also been observed in patients undergoing various weight-loss treatments. Anandacoomarasamy et al. reported an association between weight loss and a reduced loss of cartilage thickness and increased cartilage proteoglycan content [14]. Richette et al. reported that weight loss caused increased levels of N-terminal propeptide of type IIA collagen, a marker of cartilage synthesis, and decreased the level of cartilage oligomeric matrix protein (COMP), a marker of cartilage degradation in the serum [86].

A range of surgical strategies have been employed for weight loss, including sleeve gastrectomy, gastric bypass and gastric banding, while non-surgical strategies, such as weight loss diet and exercise have been advocated [Table 3]. Weight loss by gastric surgery can result in a 20% decrease in BMI, and offers symptom improvement in a short period of time [86]. For less invasive weight loss strategies, a weight reduction of at least 5% within a period of 20 weeks is required to obtain clinically symptomatic relief for OA patients with obesity [98]. Reduced dietary fat and salt, increased fruit and vegetable intake, exercising for more than 30 min per day, motivational interviewing and specific weight-reduction targets are recommended for obese and overweight patients [99].

The combined interventions of diet and exercise seems to be the most effective non-surgical weight-loss strategy in treating obesity-related OA, with greater symptom relief and functional improvement when compared to diet or exercise alone [100]. However, neither surgery nor non-surgical weight reduction strategies, offer disease-modifying effects that can be achieved in under 2 years [91,101], although their effect is more promising after this initial period [95,97]. This emphasizes the importance of clinician driven patient education and continuity of care over an extended period of time.

Physical therapy

In clinical practice, most international guidelines suggest muscle strengthening exercises for non-surgical management of OA [102]. Paradoxically, a side effect of weight-loss for obese OA patients can be increased muscle weakness [103]. Therefore, muscle strength training is essential for obese patients who engage in both surgical and/or non-surgical weight loss strategies [104]. In obese patients, muscle strength training is also effective for symptomatic relief, with an RCT of 289 participants who completed a knee strengthening program over two years demonstrating a significant reduction in knee pain, compared to those who did not exercise [94].

Another systematic study demonstrated that resistance training improved muscle strength, reduced pain severity and increased physical function in over 50–70% of OA patients with obesity. Improvement of postural control, proprioception, muscle activation, coordination and strength were the targets for this neuromuscular training program [105], including various forms of isometric and dynamic exercise. Isometric exercise is characterized by exercising at discrete joint angles. Dynamic exercise, including isokinetic and isotonic training, uses resistance training for muscle strengthening. Both dynamic and isometric resistance training can result in improvement in joint functionality and reduced pain in obese OA patients [106].

However, whether muscle training reduces the incidence or progression of OA is still controversial. A cohort study over 30 months demonstrated that muscle strength training exhibited only a slightly decreased rate of joint-space narrowing, compared to a program focused on range-of-motion exercises, which do not strengthen muscle [107]. Another prospective longitudinal cohort study reported that greater quadriceps strength was associated with an increased likelihood of OA progression in patients with malaligned or lax knees [108]. The inconclusive effect of muscle strength training on OA progression may be explained by the challenge of long-term patient compliance with training exercises. Further research with larger sample sizes and improved patient compliance is required to identify the role of muscle strength in the incidence and progression of OA in obese individuals.

Joint realignment

Varus malalignment leads to aberrant loading of the knee joint and intensifies the effect of obesity on OA. Therefore, correction of malalignment may be considered an important adjunct intervention in obesity-related OA. Early studies showed that normalizing mechanical abnormalities improved symptoms and slowed down knee OA progression [109]. Currently, non-surgical mechanical interventions, including the use of joint unloader bracing, and orthotic devices, such as wedged insoles or orthotics in footwear, are generally recommended. A surgical procedure, high tibial osteotomy (HTO), is also widely practiced by clinicians for the purpose of correcting varus deformities [110,111].

Unloader bracing

Valgus unloading braces are used to reduce the KAM, and have been undertaken in patients with varus malalignment [112]. A RCT of patients with patellofemoral OA who wore leg braces for 6 weeks showed decreased pain severity and reduced bone marrow lesion volume, compared to patients who did not wear braces [109,112]. It was suggested by Ramsey et al. that greater efficiency was achieved by bracing in neutral alignment, compared to 4° valgus [113]. In OA patients with varus alignment, the application of valgus bracing (which lessens varus alignment and reduces medial compartment loading) contributed to improve joint function and reduced pain [114]. However, the unloading braces may not be recommended in subjects with normally aligned knees. A recent study demonstrated that valgus bracing product produced an increased KAM in participants without malaligned knees [115]. Joint unloader bracing improves the biomechanical factors that affect obesity-related OA, however the efficiency on obesity-related OA is limited. Study done by Dennis et al. demonstrated that off-loading braces achieved least effectiveness in obese patients, in which has a difficulty in optimal brace fixation [116]. Furthermore, the use of unloader bracing was shown less patients adherence in obese patients due to irritating, uncomfortable or inconvenient for patients to wear [117,118]. Currently, few studies on effect of using unloading braces on obesity-related OA patients, therefore, further studies into both short-term and long-term effects are still required.

Orthotic devices

Orthotic devices are often used in a broader setting for correcting lower limb alignment, and thus, also be used to treat obesity-related varus malalignment. A systematic review showed that foot orthotics were effective in decreasing pain, knee stiffness and drug dosage of analgesic medications [119]. In patients with medial compartment OA, lateral-wedged insoles reduced KAM and KAM impulse, compared to those without insoles [120]. Application of medial-wedge insoles on knee OA patients with valgus-deformity has demonstrated an effective reduction in in knee pain and improvement in functionality [121].

Knee joint distraction (KJD) has also been used to slow down OA progression and delay knee replacement in younger patients, particularly those with age <60 years old. The principle of the KJD is to adjust the extent of two joint surface and reduce the loading by using an external fixation frame for a limited period of time [122]. Clinically, the application of KJD was reported to effectively achieve clinical and structural improvement for at least 2 years [123,124]. Intema F et al. showed that clinical benefit with tissue structure modification was induced by joint distraction, evidenced by radiography and WOMAC index. In this study, patients with obesity were not excluded, suggesting that obesity is not a contraindication for KJR [125]. Although KJD may cause some potential

Table 3
Effect of weight loss strategies on knee OA symptoms and structural changes in patients with obesity (Evidenced by RCTs over I-year follow-up from 2010).

Duration (Study)	Interventions	Completed participants (Adherence); BMI	Effect on mean weight loss	Effect on symptoms	Effect on structural changes
12 months [88] (Bliddal et al.)	LED program vs control (dietary consultations only)		−10.9 kg (11%) vs −3.6 kg (4%)	Pain reduction in both groups Slightly reduction of WOMAC index in LED group (p-0.066)	N/A
12 months [89] (Christensen et al.)	Diary regimen followed by 3 maintenance programs: D: Dietary support; E: knee exercise support; C: control	N = 192 BMI≥30.0 kg/m^2	D vs E vs C: 11 kg vs 6.2 kg vs 8.2 kg	Significant pain reduction in all groups No significant different between groups.	N/A
12 months [90] (Henriksen et al.)	An intensive 16 week weight loss program, followed by three treatment group: D, E, control (no-attention group)	N = 196 BMI≥30.0 kg/m^2	D: gained 1.1 kg E: gained 6.6 kg C: gained 4.8 group	N/A	No significant changes in cartilage loss, synovitis and effusion between groups. Increased number of medial tibiofemoral BMLs in the E group compared to the D, C groups.
12 months [91] (Jafarzadeh et al.)<	Bariatric surgery/medical weight management and 1-year follow-up. A: large amount weight loss; B: Moderate weight loss	N = 75 BMI ≥35 kg/m^2	A: with ≥20% weight loss; B: with <20% weight loss	N/A	No significant changes of BML, synovitis, cartilage damage between groups.
18 months [92] (Messier et al.)	D, E, D + E	N_1 = 134 (89%) N_2 = 129 (85%) N_3 = 136 (89%) 27 ≤ BMI<41 kg/m^2	E: −1.8 kg D: −8.9 kg D + E: −10.6 kg Significant more weight loss in diet plus exercise and diet groups compared to the exercise only group ($p < 0.05$)	Those in diet and exercise group and diet only group had greater pain relief and functional improvement than those in the exercise group	Significantly lower levels of serum IL-6 in the diet group than those in the exercise only group Significantly lower levels of serum IL-6 in the diet and exercise group those in the in the exercise only group
18 months [93] (Hunter et al.)	D; D + E; E	N_D: 152; N_{D+E} = 152; N_E = 150; BMI = 27–41 kg/m^2	D: −8.9 kg; D + E: −9.7 kg E: −1.7 kg Significant more weight loss in diet plus exercise and diet groups compared to the exercise only group ($p < 0.05$)	N/A	No significant difference between groups in joint space width; No significant difference in MRI cartilage loss between groups.
24 months [94] (Jenkinson et al.)	Dietary plus quadriceps strengthening training Dietary intervention Quadriceps strengthening training Advice leaflet only (control group)	N_1 = 86 (79%) N_2 = 104 (85%) N_3 = 61 (74%) N_4 = 65 (86%) BMI≥28.0 kg/m^2	Dietary vs non-dietary groups: 2.95 kg weight loss (1.44–4.46; p = 0.000) Quadriceps strengthening training vs non-training groups: 0.43 kg weight loss (−0.82 to 1.68; p = 0.501) Knee strengthening training was not associated with moderate weight loss	WOMAC pain score Control: 7.04 ± 4.21 Diet only: 6.96 ± 4.33 Strength training only: 5.70 ± 3.96 Diet plus strength training: 6.39 ± 4.15 Significant knee pain reduction and function improvement in the exercise groups, compared to the non-exercises groups The difference in weight loss was not associated with improvement in knee pain or function	N/A
48 months [95] (Gersing et al.)	Moderate weight loss; Large amount weight loss; Control (stable weight)	N1 = 180 N2 = 78 N3 = 258 BMI≥25 kg/m^2	Moderate weight loss: 5–10% weight loss; Large weight loss: >10% weight loss Control: <3%	Amount of weight loss is associated with less pain, stiffness and disability.	Amount of weight loss is significantly associated with change of cartilage;
48 months [96] (Gersing et al.)	A: large amount weight loss; B: Moderate weight loss; C: stable weight	N_A = 82; N_B = 238; N_C = 320 BMI≥25 kg/m^2	N_A = with 10% weight loss N_B = with 5–10% weight loss N_C = stable weight	N/A	The increase of cartilage Whole-Organ Magnetic Resonance Imaging Score (WORMS) is smaller is A and B, compared to C. Percentage of weight change is significantly associated with increase in cartilage WORMS
96 months [97] (Gersing et al.)	Weight loss (diet and exercise, diet only, exercise only) vs control (stable weight)	N_1 = 380 N_2 = 380 BMI≥25 kg/m^2	Weight loss group: weight loss >5%	N/A	Weight loss group slowed cartilage degeneration (significantly slower increase in global cartilage T2 in MRI), compared to control group; Slower cartilage degeneration in diet only and diet plus exercise group, but not in the exercise only group.

D: Diet only, E: Exercise only, D + E: Diet plus Exercise; WORMS: Whole-Organ Magnetic Resonance Imaging Score;

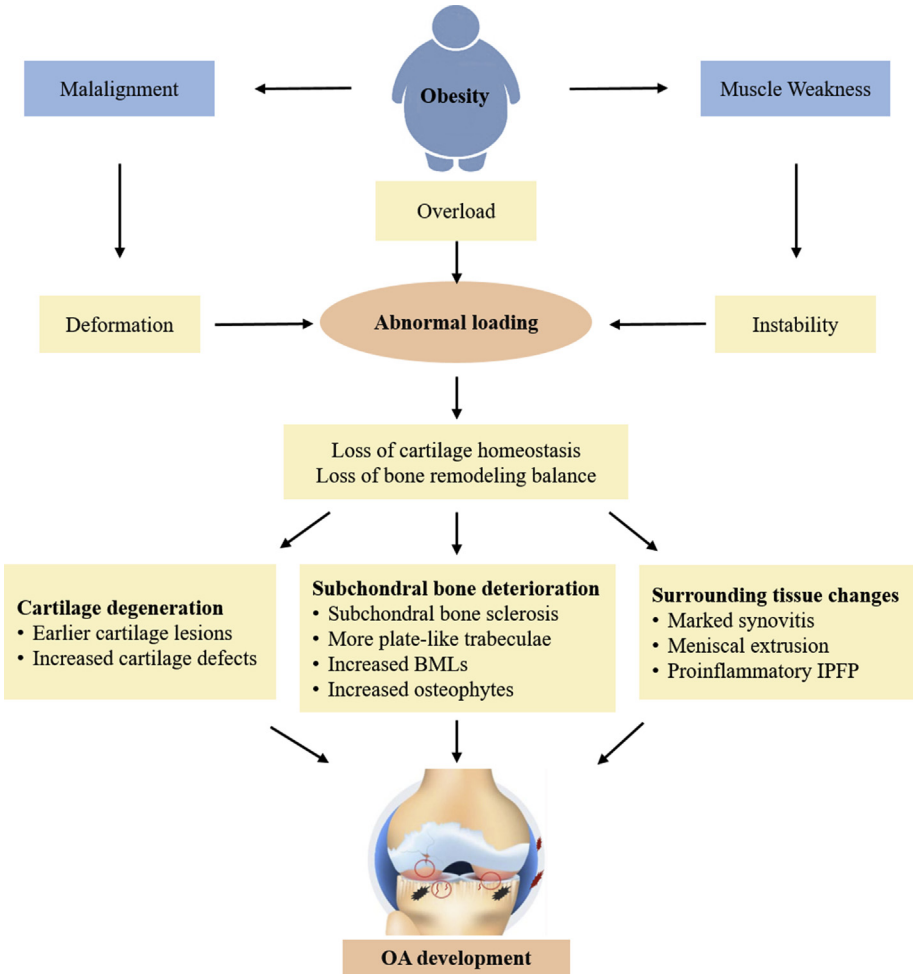

Fig. 1. A model of obesity-related OA. Abnormal loading, which is induced by over-weight loading, muscle weakness and joint malalignment, plays a central role in the biomechanics of the obesity-related OA. Malalignment induces joint deformation, amplifying the effect of overloading in obese patients. Muscle weakness leads to joint instability, increasing the effect of abnormal loading on joints. Abnormal loading leads to the loss of cartilage homeostasis and bone remodeling imbalance. Early and fast development of cartilage and subchondral bone damage occurs. Inflammatory cytokines are released into the joint space, leading to secondary chronic inflammation in surrounding tissue, and further accelerating OA development in the obese. Abbreviation: BMLs: bone marrow lesions; IPFP: Infrapatellar fat pad; OA: osteoarthritis.

risk such as pin track infection, its benefits on correcting abnormal loading and postponing TKR may take into consideration for managing OA patients with obesity. However, longer and larger trials to address the effect of obesity on KJD are warranted.

High tibial osteotomy (HTO)

HTO is frequently used for unicompartmental knee OA, particularly in young patients with medial compartment OA. HTO was shown to be superior to non-surgical treatment in patients with varus malalignment, with better pain reduction and functional improvement [110]. HTO redistributes weight loading on the knee by correcting the mechanical axis of the knee, in order to relieve pain, slow disease progression and delay or prevent knee replacement [126]. From a pathological perspective, partial or even fibrocartilage regrowth has been observed on second look arthroscopic evaluation, 18 months following HTO on knees with medial compartment OA [127]. In a longer term study, 455 patients assessed over 15 years demonstrated that 85% of patients were satisfied with their outcome; however, normal BMI, as well as age less than 50 and ACL deficiency, was an independent factor associated with improved HTO outcome [126]. This may be related to the HTO also improving the stability of knee joints with ACL deficiency.

The effectiveness of HTO in obesity-related OA remains controversial, as obesity is a risk factor for poor outcomes [128]. Even so, HTO presents as an option, particularly in the treatment of young obese patients with OA, as the life span of prosthetic implants is limited. A follow-up study over two years showed that 44.4% of obese participants had satisfactory outcomes following HTO. Higher satisfaction levels were associated with a lower post-operative BMI [111]. The poorer outcome in the obese may be due to excess loading, which suggests a combined regime of weight loss strategies and HTO for more effective treatment.

Total knee replacement (TKR)

TKR presents as an effective surgical procedure for the treatment of end stage knee OA, often achieving long-term functional improvement. However, there are still many challenges in TKR for obese patients with OA, with obesity being one of the main predictors for poor TKR outcomes [129]. A meta-analysis showed that obese patients had increased post-surgical knee pain, and functional disability in both short-term and long-term follow-up. Cushnaghan et al. showed that obese patients undergoing TKR experienced less improvement in physical function compared to non-obese patients [129]. Patients with obesity are also at higher risk of developing post-surgical complications, including deep vein thrombosis, dislocation and infection, which may compromise implant survival and outcome [130].

Obese patients with TKR also have higher rates of knee revision. Culliford et al. reported a 43.9% increase in the revision rates in obese patients compared to normal weight patients [131]. Increased loading and altered kinematics of joints in obese patients caused higher incidence of aseptic loosening and medial collapse [132]. To avoid early revisions, it was recommended that cemented stemmed tibial implants can be considered in the morbidly obese patients [132,133], however, studies on the efficacy of this technique are limited.

Despite the challenges that obese patients undergoing TKR may present, there are still many benefits of TKR in improving physical function and providing symptom relief; this procedure is still

recommended in OA patients with obesity when other management options are unsuccessful [129].

Conclusions

Obesity induces a number of pathological changes to the whole knee joint structure, including abnormal loading on the joint, joint malalignment and muscle weakness. Based on the current published research in human, animal and in vitro study, a hypothetical model for obesity-related OA change can be proposed (Fig. 1). Abnormal loading plays a central role, whilst joint malalignment and muscle weakness are in dynamic interplay, influencing each other and contributing to the abnormal loading seen in obese individuals. Muscle weakness in obese individuals results in joint disability, which then contributes to joint malalignment. The combination of these three mechanical factors affects the joint structure, stimulating the onset and progression of obesity-related OA. The significant biomechanical burden of obesity on the pathogenesis of OA indicates the need for clearer, evidenced-based management strategies. By correcting excessive or aberrant loading of joints, symptom and disease progression may be reduced.

Combined diet and exercise strategies, dynamic muscle strength training and joint realignment through non-surgical and surgical techniques, such as unloader braces and high tibial osteotomy, have been shown to be effective in readjusting joint loading and improving symptoms of obesity-related OA. However, further investigation is needed with larger sample sizes and improved patient compliance to review the efficacy of these techniques for long-term alleviation of symptoms and functional improvement, especially in those with obesity-induced knee OA.

Conflict of Interest

The authors have no conflicts of interest to disclose in relation to this article.

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