Methods for evaluating effects of unloader knee braces on joint health: a review

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Abstract

The paper aims to provide a state-of-the-art review of methods for evaluating the effectiveness and effect of unloader knee braces on the knee joint and discuss their limitations and future directions. Unloader braces are prescribed as a non-pharmacological conservative treatment option for patients with medial knee osteoarthritis to provide relief in terms of pain reduction, returning to regular physical activities, and enhancing the quality of life. Methods used to evaluate and monitor the effectiveness of these devices on patients' health are categorized into three broad categories (perception-, biochemical-, and morphology-based), depending upon the process and tools used. The main focus of these methods is on the short-term clinical outcome (pain or unloading efficiency). There is a significant technical, research, and clinical literature gap in understanding the short- and long-term consequences of these braces on the tissues in the knee joint, including the cartilage and ligaments. Future research directions may complement existing methods with advanced quantitative imaging (morphological, biochemical, and molecular) and numerical simulation are discussed as they offer potential in assessing long-term and post-bracing effects on the knee joint.

Keywords Unloader knee brace · Knee osteoarthritis · Quantitative imaging · Finite element modelling · Post-bracing effects

Abbreviations

OA Osteoarthritis
 JSN Joint space narrowing
 KAM Knee adduction moment

ECM Extracellular matrix
 EMG Electromyograms
 VAS Visual Analogue Scale
 KOOS Knee Osteoarthritis Outcome Score
 QOLS Quality of Life Scale
 WOMAC Western Ontario and McMaster Universities' Arthritis Index
 IPAQ International Physical Activity Questionnaire
 IKDC International Knee Documentation Committee
 JSW Joint space width
 MJSW Minimum JSW
 K–L Kellgren–Lawrence
 WORMS Whole-Organ Magnetic Resonance Imaging Score
 BLOKS Boston Leeds Osteoarthritis Knee Score
 MOAK Osteoarthritis Knee Score
 MOCART Magnetic resonance observation of the cartilage repair tissue
 dGEMRIC Delayed gadolinium enhanced MRI of cartilage

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1 Background

Osteoarthritis (OA) is one of the leading causes of physical disability in the world, affecting a growing portion of the elderly and has no cure. The healthcare costs associated with this disability are rising at an exponential rate, especially in the ageing community, and has become a significant public health issue [1, 2]. While there is no consensus on where, when, and how OA begins in the knee, it is understood that it involves soft tissues (articular and meniscal cartilage and cruciate and collateral ligaments), hard tissues (femur and tibia bones), loading characteristics, and stability of the joint [3]. The complex interplay of structural and biochemical changes in the knee joint results in common complaints of joint pain and instability in addition to other clinical symptoms of joint space narrowing (JSN), joint stiffness, and limited range of motion [4]. Biomechanical studies have shown that OA leads to approximately 60–80% of the total knee load passes through the medial compartment due to the loss of mechanical capabilities of the cartilage [5]. It also alters gait characteristics by decreasing external knee extension moments in terminal stance [6], and increases external knee adduction moments (KAM) in stance phase [7, 8]. This leads to a sedentary lifestyle, which starts a process of deterioration of these tissues.

Only biomechanical interventions or surgical replacement of the knee joint can reduce or control the pain, improve function, enhance the quality of life, and in turn, stops or slows down the cycle. Clinicians do not recommend surgical replacement or realignment of the joint as the primary treatment option for young and physically active persons and patients with significant confounding clinical factors. These factors are high blood pressure, diabetics, excessive body weight, heart disease, cartilage damage due to trauma, and documented treatment failures, including nonsteroidal anti-inflammatory medications, steroid injections, and viscoelastic supplementation. There are several non-surgical and biomechanical intervention treatment options available to improve the function of the knee and physical mobility, as well as reduce pain by unloading the affected knee compartment, while avoiding negative effects of them.

Researchers have used various techniques to shift the weight away from the diseased knee compartment, such as, altered gait kinematics, adopting novel gait patterns through gait retraining [9, 10], employing assistive and gait altering devices [11–13], and reducing body mass at the external knee adduction moment [14]. Unloader knee braces, wedge shoes, insoles, and joint strengthening physical exercises are the most often prescribed methods by clinicians as conservative treatment options for such

patients [9, 13, 14]. Among these treatments, unloader braces are the most often studied and effective treatment option for patients with medial OA, since they offer a reasonable alternative to surgical realignment or replacement procedures [15–17].

The unloader braces reduce the KAM by applying an opposing external valgus moment about the knee joint based on the three-point loading principle (shown in Fig. 1c), which improves the distribution of the compressive load and corrects alignment [18–20]. Clinicians and researchers have employed several methods to measure the effectiveness of the unloader braces. These methods are designed in terms of reduced pain, improved function, and indirectly quantifying the amount of unloading that happens due to bracing by quantifying the counteracting valgus moment and monitoring treatment in clinical settings. These methods can be broadly classified into three main categories, namely: (1) morphology-based, (2) biomechanics-based, and (3) perception-based methods.

Several systematic reviews have been published on quantifying the effectiveness of the unloader braces in improving clinical outcomes and mechanical leverage. However, to the best of our knowledge, there is no reported research, which surveyed and categorized evaluation methods for quantifying the long-term effects of unloader braces on the health of the knee joint tissues. In this paper, a state-of-the-art review of the current evaluation methods is presented, as well as potential techniques to develop new evaluation methods and quantitative measures, and directions for future research.

2 Change in joint loading characteristics: mechanobiological perspective

Normal physiological loading is essential for facilitating and maintaining the health of the soft tissues and bones [24]. The soft tissues are the primary load-bearing zone of the knee joint during gait that allows smooth joint movement and distributes the forces across the tibio-femoral joint. They contain cells (chondrocytes) and extracellular matrix (ECM) with water, collagen fibers, and protein molecules [21, 22]. Normal physiological loading creates dynamic compression in the musculoskeletal system, cartilage, and meniscus. The loading at the foot, transmitted via knee joint cartilage. This loading transfer mechanism involves sliding and rigid-body displacement of the cartilage at the tibio-femoral interface. There is also a constrained and unconstrained movements of the cartilage in the direction and opposite direction of the load transfer, respectively [23]. This loading generates compression strain along the loading direction and shear strain in the anterior-posterior plane of the femur and tibia. Subsequently, it leads to complex mechanical and chemical compositional changes within the cartilage tissue (matrix

Fig. 1 Effect of OA on Knee Joint. **a** Healthy knee joint; **b** narrow joint space along the medial; **c** force acting by the unloader brace using three-point loading mechanism

and cell deformation, hydrostatic and osmotic pressure, fluid flow, altered water content, ion concentration, and fixed charge density). These changes are detected by mechanoreceptors, which initiate intracellular signaling, leading to the tissue remodeling process, and restoring its original shape upon load removal [24].

The coarse and circumferential Type I collagen fiber bundles of the meniscus provide compressive strength and dynamic shear modulus that are one-half and one-fourth to one-sixth times greater than the compressive strength and dynamic shear modulus of articular cartilage, respectively [25]. Authors have reported that the posterior horn of the medial meniscus had the least movement due to its attachment to the tibial plateau by the menisci-tibial portion of the posterior oblique ligament, and the anterior horn of the lateral meniscus had the most significant movement [26, 27]. During daily physical activity, the menisci experience high levels of axial tibio-femoral forces that compress the menisci at the articulating surface of the joint. The horn attachments and wedge shape of the meniscus convert the vertical compressive forces to horizontal hoop stresses along the circumferential collagen fibers of the meniscus [22]. As a result, the meniscus deforms radially and the generated shear forces between

the collagen fibers changes the morphology of the collagen. This change in morphology of collagen fibers transduces the applied compressive and shear forces into tensile hoop forces [28]. However, the firm attachments by the anterior and posterior ligaments prevent the meniscus from extruding peripherally during loading [29].

Osteoarthritis alters the biomechanical characteristics and bio-chemical composition of the knee joint. These changes are cyclic in nature and progressively damages the joint with day-to-day physical activities. Apart from soft tissues, OA also affects the structural, biochemical, and load-bearing ability of the subchondral bone [30]. During the initial stages of OA, elevated bone remodeling and subchondral bone loss were observed due to microdamage in the subchondral region [30]. These damages induce porosity in the subchondral region and gradually decrease the thickness of the subchondral plate. In the late stage of OA, loading and cartilage thinning increases bone density, bone volume, thickens the subchondral bone plate, increases trabecular thickness and thickness of the calcified region, and decreases trabecular separation and bone marrow spacing [31, 32]. The meniscal damages also lead to pathological changes in subchondral bone (increased bone mineral density, bone cysts, and bone marrow lesions) [33, 34].

3 Current qualitative and quantitative measures

This section outlines the categorization of existing methods, measurable variables, techniques, tools, and survey instruments to diagnose knee health during post-bracing condition. The most often used surrogate biomarkers to study the efficacy of the braces are (i) semi-quantitative measures, including knee pain, joint function, and quality of life based on self-reported questionnaires, and (ii) quantitative measures, including morphological changes and biomechanical loading effects in the tibio-femoral joint. Choice of these measures primarily depends upon the purpose of the evaluation, which can be either treatment monitoring, functional performance, mechanical effectiveness, or energy expenditure, such as, clinical symptoms, strength, and gait, as shown in Table 1.

3.1 Perception-based evaluation methods

The perception-based evaluation methods are mainly self-reported outcomes based on different types of survey questionnaires and visual scales to define the state of disease progression at the point of monitoring the treatment. The most frequently used questionnaires in assessing the effectiveness of valgus unloader braces in clinical settings are the Visual Analogue Scale (VAS), Knee Osteoarthritis Outcome Score (KOOS), Knee Society Score (KSS), Quality of Life Scale (QOLS), Western Ontario and McMaster Universities' Arthritis Index (WOMAC), and the International Physical Activity Questionnaire (IPAQ).

The WOMAC score has been used extensively in both observational and treatment monitoring studies to examine the changes due to bracing treatment during walking and stair-climbing tests [35–40]. The authors found that a positive relationship existed between brace wear usage and

activity level, and improvements in WOMAC pain, stiffness, and function. Rezaeian et al. [41] studied the unloading effect of a valgus brace by comparing the patients' pain and function from WOMAC scores with the alignment angle and reported that the WOMAC scores (pain and function) were better biomarkers than the alignment angle.

Kirane et al. (2010) used KOOS scores to study the effectiveness of the unloader brace on knee pain, structure, and function in medial various knee OA and observed a significant reduction in knee pain and functional improvement [11–13]. The VAS, has been used to measure the efficacy of the unloader braces in subjects with medial knee OA and reported a significant reduction of pain throughout the day and improvement in engaging in various activities as well (stair ascending and descending, and comfortable while speed walking) [11, 13, 38]. Thoumie et al. [42] assessed the effect of unloading knee brace after 6-week treatment in terms of 24 h-pain relief (100-mm VAS) as the primary outcome at 6 weeks, the secondary outcomes including pain on motion (100-mm VAS), function (Lequesne index), safety and observance. Hjartarson et al. [43] studied the effect of the unloader braces by using two different scores (KSS and KOSS) and reported that there was a significant improvement in both scores over 52 weeks of the bracing treatment.

There are a few of other instruments, including the IPAQ [44], multi-item physical activity questionnaires [University of California at Los Angeles (UCLA) activity rating scale] [45, 46], and the International Knee Documentation Committee (IKDC). All are used to study knee health and monitor the level of the physical activity [47, 48]. However, these self-reported evaluation methods based on physical activity have not been implemented in evaluating knee health during bracing treatment and can be potential biomarkers to assess the duration and doses of the bracing treatment and monitor the knee health during the post-bracing condition based on the level of physical activity.

Table 1 Qualitative and quantitative measures to evaluate the effectiveness of braces on overall knee health

Symptoms	Measures outcomes	Evaluation methods and instruments
Clinical symptoms	Knee pain, joint stiffness and function, quality of life, physical activity	VAS, WOMAC, QoL, KOOS-QoL, IPAQ, UCLA Scale, IKDC
Functional effects	Knee proprioception, stability, posture control	KOOS, KSS, IPAQ, VAS, Lequesne index, Safety and observance
Morphological effect	JSW, JSN, tibio-femoral Angle, hip–knee–ankle angle, condylar separation, angle condylar separation distance	Weight-bearing lower limb radiographs, ultrasound, fluoroscopy, gait analysis, loaded MRI, morphological MRI, WORMS, BLOCKS grading
Gait effects	Frontal plane kinematics, sagittal plane kinematics, lower limb malalignment, knee adduction flexion angles, knee forces and moments	3D motion analysis, dynamic simulations, gait analysis
Muscle strength	Muscle co-contraction, medial/lateral, flexors/extensors co-contraction ratios	Electromyograms (EMG), muscle MRI

All of these perception-based methods assess pain, function, and quality of life, which are the qualitative biomarkers of the disease progression. The quality of these studies entirely depends on the disease condition, mood, sleep, and physical activities, and the score provided by the patients. Even though these methods are well accepted by clinicians, they are unable to quantify the morphological, biochemical, and biomechanical changes in the soft tissue regions, are not sensitive enough to capture the improvement of the knee health during the bracing treatment in patients with mild OA, and are incapable of predicting the long- and short-term effects on the overall physical activity of the subject.

3.2 Morphology-based evaluation methods

The metabolic process of OA initiates with the thinning of the superficial layer of the articular cartilage that gradually disrupts the calcified cartilage and leads to secondary changes in the subchondral bone region [49, 50]. This degradation process affects the morphological changes (osteophytes, subchondral sclerosis, cysts, bone plate thinning, and narrowing down of the joint space) of the bone [51], thickness, surface area, and volume of the weight-bearing region of the articular and meniscal cartilage. Currently, several imaging modalities, including the standard standing radiography, MRI, CT scans, and ultrasound have been used to capture the morphological changes mentioned in Table 1. As per the complexity and computational requirement of the imaging techniques, these methods are broadly classified into semi-quantitative and quantitative morphological measurement.

Direct morphological measurements help in diagnosing the disease concerning one dimensional measure. The standing weight-bearing antero-posterior lower limb radiograph is the most traditional method to capture measures, including JSN angle, joint space width (JSW), minimum JSW (MJSW), hip–knee–ankle angle, condylar separation distance, and condylar separation angle [52]. The standing radiographs also capture the structural changes (osteophytes, subchondral sclerosis, cyst) during the later stages of OA. The Kellgren–Lawrence (K–L) grading method from the standard radiographic images of the lower limb is another way to differentiate the stages of OA [53]. Studies based on radiography and fluoroscopy-based gait analysis quantify the morphological change in the knee joint in terms of the tibio-femoral angle, joint space, K–L grade, compartmental separation, and condylar separation angle. Studies concluded that the unloader braces significantly correct these morphological changes [11, 54–56]. While direct radiographic measures are the less expensive way to measure OA progression with fewer measurement steps [57], they fail to visualize the morphological feature of the soft tissues [58]. Its accuracy and precision depend on the reproducibility of radiographic

images and adequate positioning of the knee [59]. Due to the lack of references in the radiographic images, clinicians face difficulties validating MJSW with other imaging modalities. As the medial and lateral tibio-femoral joint compartments are physically connected, the narrowing of one compartment can result in the widening of the other, adding further complications to appropriate interpretation [60].

Due to advanced image processing techniques, MR-based semi-quantitative morphological imaging techniques, including Whole-Organ Magnetic Resonance Imaging Score (WORMS), Boston Leeds Osteoarthritis Knee Score (BLOKS), and MRI Osteoarthritis Knee Score (MOAK) examine morphological abnormalities at various anatomical sub-region locations of soft tissue and bones [61–65]. The magnetic resonance observation of the cartilage repair tissue (MOCART) scoring system is very popular in studying the health of articular cartilage and the surrounding structures during graft repair, chondrocyte transplantation, and autologous matrix-induced chondrogenesis [66–69].

The semi-quantitative scoring methods, WORM and BLOKS, provide an indirect regional and sub-regional assessment of cartilage, meniscal morphology, and subchondral plate degeneration in tibio-femoral joint MR-based measurements and are sensitive enough to capture the degenerative changes in soft tissues and other compartments, capable of determining the spatial distribution of femorotibial cartilage loss. In early OA, cartilage swelling is visible under the unloaded MRI image, but it is in a compressed state in radiographs [70]. The JSN obtained from the MR was more sensitive than the fixed-flexion radiographs, and the location-specific measures of JSW obtained from the MR show greater responsiveness than minimum JSW obtained from radiographs [71].

3.3 Biomechanics-based evaluation methods

Mechanical loading plays a key role in the progression of OA, and the medial tibio-femoral compartment of the knee undergoes 60 to 80 percentage of the total knee load resulting in higher KAM and various deformity [8, 72]. For equilibrium and stability of the knee during gait, this external KAM must be balanced by the contact force between the tibia and femur along the medial compartment and the magnitude of the KAM has been used as a measure of loading distribution [73, 74]. Several studies have reported that due to the increased load and accelerated cartilage damage in the medial compartment of the knee, subjects with OA have greater muscle co-contraction [75–77]. Therefore, the strength and co-contraction of the muscles around the knee joint and the lower limb are recently considered the indirect measure of the loading in the medial compartment. To study the efficacy of the unloader knee brace, biomechanical methods, including 3-D motion analysis, force plate experiments,

and electromyographic patterns have become popular in research settings. Therefore, the strength and co-contraction of the muscles around the knee joint and the lower limb are recently considered the indirect measure of the loading in the medial compartment. To study the efficacy of the unloader knee brace, biomechanical methods, including 3-D motion analysis, force plate experiments, and electromyographic patterns have become popular in research settings.

3.4 Three-dimensional motion analysis

Gait analysis uses a motion capture systems and force plates to estimate the kinematics and kinetics of the patient during bracing treatment. Several studies reported the positive effect of braces on the frontal and sagittal plane kinetics [78–81], medial compartment load in vivo condition [82, 83], tibio-femoral contact force, and lower limb alignment [84–88]. Kutzner et al. investigated the effect of three-point loading exerted by valgus braces on the medial compartment load in vivo by using strain gauges and reported that the medial load reduces during walking and stair ascension/descension [83, 89]. The unloader braces with different valgus adjustments have a significant effect on the first and second peaks of KAM, the knee adduction angular impulse, improvement in knee pain and joint function [81, 85–87, 90, 91], and the knee adduction and flexion angle [87, 88]. However, this method is not promising in the study of the kinematic and kinetic of the lower limb for various physical activities with high-flexion, such as squatting and kneeling, due to the limitations of the available measuring devices, and it fails to detect the contact pressure and internal stress distribution in the soft tissues and bone region.

3.5 Strength measurement tests

Electromyogram is another assessment technique used to diagnose knee OA by measuring the electrical activity of the lower limb muscles to show whether the pain is due to injury of a nerve or muscle tissue and locate the damaged nerve [92]. Studies have reported that OA subjects showed high KAM, reduced knee flexion, quadriceps weakness, and knee stiffening during weight-bearing [93, 94]. These in turn increase the co-contraction of muscles [95, 96] and joint contact pressures around the knee [97], and accelerate the cartilage damage [98]. Hence, the lost strength of the quadriceps and hamstring and co-contraction ratios of the quadriceps/hamstring and quadriceps/gastrocnemius, represent the indirect measure of the mediolateral distribution of load across the knee, and are useful in studying the effectiveness of the braces [18, 99–102].

Pagani et al. reported a significant decrease in muscle activity and co-contraction level with valgus knee bracing treatment [84, 103]. The authors studied the response for

valgus unloader brace on the strength of hamstrings [39], quadriceps maximum voluntary contraction, and arthrogenous muscle [104] and reported that only arthrogenous muscle had significant changes. Electromyography (EMG) technique lacks precise control in large muscles, such as quadriceps and those engaged during knee movement, due to the interweaving arrangement of muscle and difficulties in distinguishing between the neural and muscular contributions to force generation during various physical activities.

3.6 Emerging and potential evaluation methods

Even though existing methods are routinely used by clinicians and researchers in studying knee joint health during OA progression, clinicians face challenges in quantifying the effects of the braces on soft and hard tissues, especially in long-term uses. The long-term effects of the biomechanical and physiological changes on the tissues in terms of the shift in contact pressure, contact area, loading characteristics, and response to changes in physiological loading has not yet been studied. Therefore, there is a need for new evaluation methods that can address the consequences of braces on soft and hard tissues during the post-bracing phase of the treatment. Based on these measures, the clinicians would determine the optimal dose, duration, and frequency of brace usage as per the patient's knee condition to avoid worsening knee health.

Recent advances in imaging techniques, equipment, wearable technologies, computing resources, and computational methods offer several non-ionizing radiation image-based measures, such as T1rho, T2, dGEMRIC, and Sodium Magnetic resonance imaging, which can assess the soft tissue's health in vivo conditions. The MR-based T1rho and T2 relaxation times describe the changes in the amount of proteoglycan and the water content in the extracellular matrix of the soft tissues and have been used as potential measures to assess early OA [105].

Luke et al. studied the health of meniscus and articular cartilages in marathon runners and showed that long-distance running significantly affects both cartilages biochemically (measured with T1rho and T2), but with no significant morphological changes [106, 107]. Moreover, the results showed that after 48–72 h of the competition, runners had significantly higher water content and depleted proteoglycans. Water content came back to pre-competition level, while the ratio of proteoglycan to water content did not, which indicates more persistent changes in the ECM after a marathon. Souza et al. [108] evaluated the effects of mechanical loading on the knee, using T1rho and T2 relaxation times in patients with and without OA and observed that acute loading significantly decreases T1rho relaxation times in both medial and lateral compartments. Calixto et al. [109] showed that an acute loading affects relaxation

times of the menisci in individuals with and without knee OA in a non-uniform manner from the inner periphery to the outer periphery of the tissue.

Subburaj et al. studied the effect of running and acute loading on articular cartilage and meniscus in healthy subjects, using T1rho and T2 as surrogate biomarkers [110, 111]. After 30 min of running exercise, there was a significant reduction in the relaxation times in the weight-bearing region of the articular cartilage and anterior and posterior horns of the medial meniscus due to structural and compositional changes of the collagen matrix and water content. Even though these advanced quantitative techniques have been used in research settings to capture the biochemical and morphological changes in healthy and OA subjects, there still has not been any attempt to apply these techniques to study, understand, and evaluate the effects of unloader braces on the overall health of the knee joint tissues.

The delayed gadolinium enhanced MRI of cartilage (dGEMRIC) is an indirect non-invasive technique for quantifying the cartilage structural composition (glycosaminoglycans (GAGs)) from T1rho because there is an inverse relationship between the negatively charged contrast agent and the GAGs [112, 113]. The authors reported that proteoglycan content in menisci with meniscal tears increased during meniscal degeneration [22] and identified pre-radiographic degenerative changes in the meniscus [114, 115]. In addition, sodium MRI measures the fixed charged density, which is directly related to the sodium concentration in the cartilage, and have been established to be a sensitive marker for estimating proteoglycan loss and cartilage degeneration [116].

Newbould et al. [117] compared subjects with OA and healthy ones using sodium MRI and observed that T1-weighted sodium MRI relaxation time for OA subjects was significantly different from healthy subjects. They reported stability and reproducibility of the sodium signal in both healthy and diseased cartilage using T1rho. These techniques capture the complex degradation process in the cellular and macromolecular level. MR-based quantitative and molecular imaging modalities have been popular to analyze the morphology (shape, structure, and spatial distribution) and biochemical composition of soft tissue during OA progression. While these advanced imaging modalities offer additional measures (morphological and biochemical) to study the knee, they have not yet been systematically studied or explored in clinical settings to evaluate the efficacy of the braces on the knee joint during OA.

One of the new promising behavioral adaptational methods is Gait Retraining [10]. This approach is directly addresses the patient's underlying motor pattern through real-time feedback. Cheung et al. [10] evaluated the effectiveness gait retraining in patients with early knee osteoarthritis by measuring WOMAC score, KAM and KFM,

during pre-training, post-training, after six-month follow-up. WOMAC score and KAM were found to be significantly lower than the pre-training and the effect was maintained during 6-month follow-up. However, there was no significant changes in KFM during the walking cycle which indicates gait retraining could be useful in reducing knee pain in patients with early knee osteoarthritis [10]. The Biomechanical study shows that Ankle-foot orthosis (AFO) and wedged shoes are equally effective in unloading the medial compartment compared to the unloader brace [16]. The author examined the unloading effects of AFO, knee brace and wedged shoes in subjects with KOA and reported that all devices significantly decrease the first peak of KAM. Therefore, both gait retraining and other orthosis devices could be combined with the bracing treatment to enhance the effectiveness of the unloader braces.

4 Future directions

The global knee brace market growth is driven by an increasingly ageing population, the number of patients with primary OA, orthopedic knee surgeries, and a rising number of leg injuries in athletics that has led to secondary OA. With the increase in awareness about preventive care for knee health during OA and managing the disease without surgery or joint replacement, there is growing demand for unloader braces among the ageing population and young generations affected by secondary knee OA.

Unloader braces are more effective at reducing pain as compared to other braces (neutral braces or neoprene sleeves) [118]. They are effective treatment for improving pain secondary to medial compartment knee osteoarthritis. Majority of clinical studies on unloader braces reported improvement in pain outcomes using unloader braces. However, variable results were reported as to whether unloader braces significantly improved functional outcomes and stiffness. The clinical community is still unclear about the functional and stiffness effects of the valgus unloader braces even though they still prescribe [118]. As of now, clinicians determine the optimal dose, duration, and frequency of brace usage as per the patient's knee condition. When there is a deviation from the protocol, the overall knee health may worsen and lead to irreversible changes to the tissues. The optimal dose of the bracing treatment depends on the complete assessment of joint health and day-to-day physical activities.

Unloader braces act directly on the joint space of the tibio-femoral joint during medial OA and also affect the hip joint [81]. Studies have shown that the gait of knee OA patients with and without bracing affects the involved and contralateral lower limbs [81]. Decreased external KAM of the affected joint and altered ipsilateral hip kinematics and

kinetics and contralateral knee and hip kinetics during the gait were observed in patients with braces. Even though the changes in these joints have a minimal clinical impact, they may cause degenerative point stress due to the change in the gait pattern with bracing during routine day-to-day activities [81, 119, 120].

Studies have demonstrated that patients with severe knee OA have an increased hip abduction angle and lean their trunks during the stance phase to reduce the external KAM. This suggests that this compensation would positively affect the progression of the ipsilateral hip OA [121]. These findings also suggest that patients with medial knee OA suffer varying degrees of adverse effects on other joints by wearing unloading braces, as shown in Fig. 2. Therefore, it is necessary to consider not only the involved knee but also the kinematics and kinetics of the contralateral hip and ankle joints, and the health of the soft and hard tissues as additional measures during the evaluation of the bracing effect [122].

Although mechanical loading is important for cartilage health [24], altered cyclic loading due to malalignment and joint injury can directly damage the cartilage and

subchondral bone. Any abnormal loading (over- or under-loading) of the joint increases the contact stresses and contact kinematics in the weight-bearing regions of the cartilage [123, 124] and in turn modifies the gait by altering the KAM and rotational kinematics of the joint. As a result, both tibio-femoral cartilages fail to adapt the loading during physical activities [125, 126]. The increase in the number of loading cycles and frequency greatly affects the stiffness and thickness and recovery time of the cartilage [118, 127].

During the bracing treatment, the change in the knee alignment and physical activity gradually introduce additional complex dynamic loading along the lateral compartments [122]. Cusin et al., incorporated a measuring device into the brace, measured the horizontal forces at the leg-orthosis interface in the frontal plane and the resulting valgus moment based on the kinematic data. The author estimated the valgus moment produced during the stance phase of gait and proposed that the unloader knee brace must be designed to apply dynamic force (no moment during swing phase of gait) [128].

Several MR studies reported that the altered physiological loading experienced by the cartilage changes the content and

Fig. 2 Knee physiology. Effects of unloader braces on knee health

orientation of the collagen network, hydration level, content, and distribution of proteoglycan in the long-term [129]. It also alters the quantitative imbalance between anabolic and catabolic activity, resulting in depletion of ECM components [21, 24, 130]. This depletion affects the outer surface and causes substantial damage to the collagen networks, reducing the proteoglycan level over time, resulting in permanent loss of the mechanical function of the cartilage that, in turn, affects the overall knee function.

Similarly, the bone remodeling process is sensitive to the magnitude of the mechanical loading. Animal studies showed that running enhances bone remodeling in subchondral bone regions, resulting in a thicker subchondral bone plate and higher trabecular volume [131]. Stress exercise increases bone formation and bone density and thereby increases the strength of the subchondral bone [132]. Unloading during bed rest and weightlessness in spaceflight significantly reduces its mass and strength [133, 134]. Significant joint unloading disturbs the delicate balance of the homeostasis of weight-bearing bone by uncoupling the bone resorption (osteocytes) cells from bone formation (osteoblast) cells, which leads to decreased bone formation and bone mass [133]. This cyclic pattern of loading and unloading happens spatially and temporally between the medial and lateral compartments, which specifically worsens the health of the cartilages (articular and meniscal) and subchondral bone. Therefore, the biochemical, biomechanical, and structural changes of these tissues during the bracing treatment could be used as potential biomarkers to assess the effectiveness of the braces.

Currently, there is no reported quantitative evidence in the literature on the effectiveness of bracing treatment (i.e., Is it suppressing the disease, progressing the disease in other compartments, or affecting the ligaments, cartilages, and bones? And how does it affect these tissues in the short- and long-term?). Based on the literature, it is speculated that the change in physiological loading due to the braces adversely affect the degree of irreversibility associated with the morphological and biochemical characteristics of the soft tissues, bones, and muscles. If the post-treatment effects associated with the bracing treatment are not entirely reversible, then the efficacy and duration of the treatment should be questioned and regularly monitored. Moreover, prolonged usage of the brace may trigger the lower limb muscles, increasing the intramuscular pressure beneath the brace, reducing the muscle blood flow, and subsequently induce premature muscle fatigue and cause biochemical changes in the cartilages of the tibio-femoral and patella-femoral compartments.

During bracing treatment, clinicians must consider the morphological and biochemical characteristics of soft- and hard tissues while evaluating the short- and long-term effects of the knee braces. The effect of the braces on the

other joints must be evaluated by studying several parameters, including morphological changes to the tissues in the joint, contact pressure, the contact area of various tissues, structural misalignment of the tibio-femoral and patella-femoral joints, and the amount of reduction in joint pain. In the literature, all the reported studies on bracing treatment have focused either on the clinical outcomes in terms of pain, function, and quality of life, or effectiveness of joint unloading in terms of quantitative biomechanics, yet, have neglected the quantifying parameters affecting the tissues in the joint in both the short- and long-term.

There is no systematic study on the effect of braces on biochemical and morphological characteristics of the soft tissues, the degree of reversibility of these physiological characteristics associated with unloading and misalignment, the biomechanical effect on other joints and compartments in the joint itself, and the necessity for the advanced quantitative biomarkers for evaluating the bracing treatment. The internal joint contact stress and distribution of forces in the knee joint are directly related to its functional activities, which can help in better diagnosing the disease and health of the soft tissue during the bracing treatment. Therefore, there is a need for developing a detailed assessment of the effectiveness of the bracing treatment. Thus, it is recommended that additional research and clinical studies further investigate the short- and long-term consequences of the braces on the cartilages and bones. These studies may help in improving patient health, understanding the effect of braces, and setting up comprehensive evaluation strategies of the braces that physicians can follow in evaluating the knee joint health at the post-bracing period of knee OA. Controversy still exists as to whether the brace has a real effect on tibiofemoral joint space in the medial compartment during functional activity in OA patients. Previous studies have determined the effect of OA unloader braces using techniques including force sensors, torque analysis, and two-dimensional fluoroscopy with mixed results regarding the effect on knee joint space. These results are limited by a lack of dynamic in vivo quantitative data for joint space because of the difficulty of performing in vivo analysis during movement.

Assessment of the effectiveness of the bracing treatment demand three independent aspects: (i) establishment of additional independent measures, (ii) developing diagnostic techniques to assess these measures, and (iii) studying the short- and long-term effects of the braces on the joint degeneration process. These measures must capture the patient's perception of pain reduction, changes in knee alignment, improved knee function, changes in muscle activation, and a morphological and biomechanical assessment of the soft and hard tissues. Due consideration of both short- and long-term structural, biomechanical, and biochemical consequences of using these braces must be given when prescribing bracing

treatment. There is a need to develop an integrated methodology to assess the short-term and long-term effects of bracing on soft and hard tissues, as well as design, develop, and validate clinically obtainable quantitative measures and establish evaluation techniques and tools to measure patient compliance.

5 An integrated assessment methodology

In order to evaluate the effectiveness of the braces on knee joint health, this study proposes an integrated methodology, combining very distinct but advanced quantitative techniques: quantitative magnetic resonance imaging (qMRI) and patient-specific finite element analysis of 3D anatomical models reconstructed from MR images (Fig. 3). In addition to the existing pain-score and other functional measures, qMRI techniques, including T1rho and T2 MR relaxation times, sodium, dGEMRIC, and bone measures would capture the biochemical and morphological health of the tissues, (i) during pre- and post-treatment periods to assess the lasting effect of a brace, and (ii) during the bracing treatment to assess and monitor the acute effect of a brace. Patient-specific finite element analysis of 3D anatomical models reconstructed from MR images and other computational

models can provide the duration of bracing treatment, the health of tissues, and knee kinematics under low- and high-flexion angles and under strenuous activities and become an efficient tool for the analysis of the knee brace design. This methodology can also be a mechanism to study the dosage required to alleviate pain and to avoid damage to the lateral compartment in the process of unloading the medial compartment during medial knee OA.

Quantitative imaging should be included in routine clinical monitoring protocol and capture the images from the patients over the bracing treatment, study the quantitative features of soft tissues (estimation of cartilage volume and thickness and relaxation times) along the longitudinal and transverse directions, and analyze the computational models. As of now, these advanced quantitative imaging techniques have only been used in research settings to capture the biomolecular and structural health of the soft tissues. While evaluating the efficacy of the bracing treatment, clinicians could use T1rho and T2 measures, sodium, and dGEMRIC measures in addition to existing measures. These measures may help in predicting the biomolecular and structural degradation of articular cartilages and meniscus. As discussed, abnormal mechanical loading affects the peri-articular bone and bone health influences OA progression by altering the bone mineral density (BMD) [135, 136] that cannot be

Fig. 3 Evaluation methodology. Schematic representation clinical procedures to measure the effectiveness of unloader braces on the joint

predicted by radiographs. However, CT imaging modules are very popular in measuring bone mineral density and the functionality of muscle-bone interaction. A dual-energy x-ray absorptiometry (DXA) is typically used to evaluate bone mineral density. High-resolution peripheral quantitative computed tomography (HR-pQCT) and peripheral quantitative computed tomography (PQCT) provide bone mineral density, geometrical parameters (marrow and cross-sectional cortical area, cortical thickness, biomechanical parameters, cross-sectional and moment of inertia, and interaction between muscle and bone morphology) [137–139]. These measures associated with bones have not yet been utilized for studying the effect of bracing treatment. The computational models can address the duration of bracing treatment, the health of tissues, and knee kinematics under low- and high-flexion angles and under strenuous activities and become an efficient tool for the analysis of the knee brace design. The commercial software, such as OpenSim [140, 141], SimTK [142], and AnyBody [143] also provide a platform to develop, analyze, and visualize models of the musculoskeletal system. These software offer numerous inbuilt experimentations tools, such as inverse kinematics, inverse dynamics, static optimization, forward dynamics, computed muscle control. These tools help in analyzing the knee joint function under various loading conditions, studying the effects of musculoskeletal geometry, joint kinematics, and muscle-tendon properties on the muscle, electromyogram-driven neuromusculoskeletal models. The patient-specific models of the knee can be reconstructed from MR images and a dynamic simulation of the knee joint during weight-bearing conditions can be performed. A significant advantage lies in investigating the contact pressure distribution across the knee joint, stresses in the limbs, the amount of unloading needed during bracing by simulating movements (flexion during squatting, kneeling), which are difficult to visualize in real-life experiments due to the limitations of obtaining ethical clearance on such measurements. Therefore, the computational models based on the images provide a better approach to study the knee joint model and predict the internal stress, force transmission, and joint contact stress distribution under dynamic conditions.

6 Conclusions

In summary, knee OA significantly affects the tissues in the joint, the braces affect the gait and loading patterns in the affected and contralateral compartments of the knee and also the distant hip joint to cause degeneration in these joints. The existing assessment methods in clinical and research settings are limited to study the efficacy of knee braces with respect to the temporal changes in the morphology of bones and joint spaces, kinematics and kinetics of

the affected limb, and muscle activity that focuses only on the effects of bracing and after-effects of OA. This review recommends that, (1) in addition to the clinical outcomes, a holistic understanding of the effects of braces to assess the complex interplay of change in loading characteristics is needed, (2) short- and long-term effects of braces on the biochemical and biomechanical behaviors of these soft and hard tissues during this reorganized physiological loading must be understood and studied to improve the efficacy of the bracing treatment, and (3) holistic understanding needed an integrated assessment methodology that combines existing and evolving methods that use advanced techniques to provide a direction for further research and clinical trials in the domain.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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