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The Nature of In Vivo Mechanical Signals That Influence Cartilage Health and Progression to Knee Osteoarthritis

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Abstract Knee osteoarthritis is a disease that can be initiated along multiple pathways that ultimately leads to pain, loss of function and breakdown of the articular cartilage. While the various pathways have biological and structural elements, the mechanical pathways play a critical role in the development of the disease. The forces and motions occurring during ambulation provide mechanical signals sensed at the scale of the cell that are critical to healthy joint homeostasis. As such, ambulatory changes associated with aging, obesity, or joint injury that occur prior to the development of symptoms of OA can ultimately lead to clinical OA. Conversely, inter-scale signaling (e.g., pain) generated by biological changes in the early stages of OA can produce adaptive ambulatory changes that can modify the rate of OA progression. Thus, the nature of the physical and clinical response to the mechanical signals that occur during ambulation is critical to understanding the etiology of osteoarthritis.

Keywords Osteoarthritis · Ambulation · Aging · Obesity · Knee joint · Joint trauma · Neuromuscular function · Joint kinematics · Joint kinetics

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Introduction

Knee osteoarthritis (OA) has been described as a disease of mechanics where [1••] increased physical forces cause injury to joint tissues leading eventually to osteoarthritis. However, future needs for developing new treatments and prevention strategies for OA call for a better understanding of the broad scope of mechanical factors that influence the initiation and progression of the disease. While loss of articular cartilage is the hallmark of knee OA, it is often the case that the increased physical forces cause damage to joint tissue other than cartilage and the degradation of the cartilage is secondary to damage in other tissues. For example, the common non-contact injury mechanism for anterior cruciate ligament (ACL) injury typically produces greater trauma (force) to the lateral compartment of the knee, as evidenced by the greater incidence of lateral bone bruises [2]; yet, ultimately, knee OA develops in the medial compartment [3, 4]. Further, when considering aging as the primary risk factor for knee OA [5], it is difficult to isolate increased mechanical force alone as the mechanical condition leading to OA in an aging population.

Important insight into the etiology of OA can be gained from isolating the mechanical changes that are secondary to traumatic events (e.g., ACL injury) or chronic neuromuscular changes associated with aging, since these conditions present a major risk for developing knee OA. Yet, there is no evidence that these conditions increase the physical force on the articular cartilage. Given that the ultimate manifestation of OA is the breakdown of the articular cartilage over time [6••], it is useful to explore the chronic cyclic mechanical changes that occur during ambulation that lead to cartilage breakdown. There are numerous mechanical measures that can be captured during ambulation. However, it is difficult to identify which measures have the greatest impact on the etiology of knee OA without establishing an

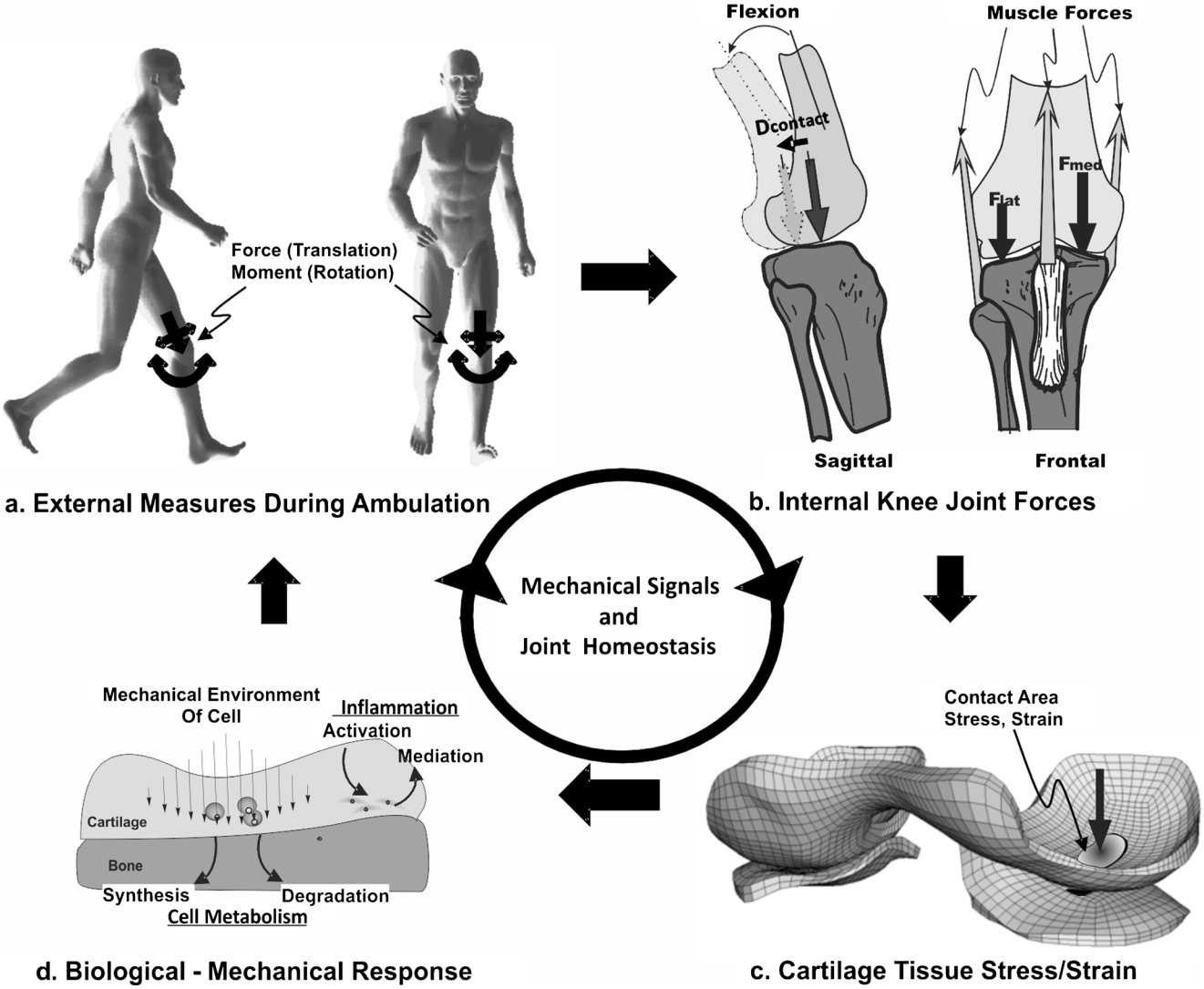

Fig. 1 Overall joint homeostasis is dependent on the interaction of biomechanical signals across scales (inter-scale signaling) ranging from full body mechanics during ambulation to the local mechanical environment of the cell. **a** The external kinematic and kinetic signals related to OA. These measures are considered to be acting on the body and can be measured in the laboratory. **b** The joint internal forces acting at the knee are the sum of the muscle forces, passive tissue forces and contact forces that balance the external forces/moments. The sagittal plane view illustrates the movement (*Dcontact*) of the joint contact with flexion and the frontal plane view illustrates the balance between medial contact force (*Fmed*) and lateral contact force (*Flat*). **c The cartilage tissue stress/strain** is determined by internal force acting over an area of contact. The stress and contact area are dependent on the curvature of the cartilage and the mechanical property of the cartilage in the contact region. **d** The biological response is related to the local mechanical environment that is determined by the local mechanical properties of the cell mediated by local metabolic and inflammatory cytokines. Note: Biological changes at this scale can produce signals that influence ambulatory changes and thus close the inter-scale signaling loop

association between the external ambulatory measures (Fig. 1a) and physical (biological, structural) changes at the joint (Fig. 1c, d). The measures in Fig. 1 can be considered "biomechanical signals", which refer to a broad scope of measures that can influence a physical response across scales. The measures summarized in Table 1 are the specific metrics identified in this review that are related to the physical condition of the joint and/or clinical status of knee OA.

Thus, this review explores the literature on the mechanical changes during ambulation that are associated with the initiation and progression of knee OA and concurrently associated with physical and/or clinical changes at the joint. While it is clear that the complex nature of all the biological, structural, and mechanical interaction that takes place across scales (Fig. 1) are not well understood, it is possible to identify specific mechanical signals generated during ambulation that are sensed across scales at a systems level [15] and, more importantly, that provide the basis for a meaningful clinical interpretation.

Table 1 A summary of the key ambulatory measures associated with a physical response and clinical outcome

Clinical status	Ambulatory measure (mechanical signal)	Phase of gait cycle	Physical outcome	Clinical outcome
ACL injury pre–osteoarthritis	Rotation offset [7] (kinematic)	Stance shase	Thickness location	Cartilage thinning
ACL reconstruction pre-osteoarthritis	Knee flexion [8] (kinematic)	Heel strike	Thickness location	Clinical thinning
Meniscus injury pre-osteoarthritis	Rotation offset [9] (kinematic)	Stance phase	Thickness location	X
Aging pre-osteoarthritis	Knee flexion [10] (kinematic)	Heel strike	Thickness location	Cartilage thinning
Aging pre-osteoarthritis	AP translation [10] (kinematics)	Heel strike	Thickness location	Cartilage thinning
Obesity preoosteoarthritis	Knee flexion [11••] (kinematics)	Stance phase	Thickness location	X
Obesity pre-osteoarthritis	Adduction moment [12] (load)	1st peak early stance	Med/lat thickness	Cartilage thinning
Medial compartment osteoarthritis	Adduction moment [13] (load)	1st peak Early stance	Med/lat thickness	Disease progression
Medial compartment osteoarthritis	Flexion moment [14] (load)	1st peak early stance	Pain	Symptoms pain

X Indicates topics that require future research

Biomechanical Signals

At the scale of the whole body, biomechanical signals are defined by measures (forces and motions) that act externally on the body during ambulation (Fig. 1a). These measures are important, since they are the most direct measure of function and can be captured in gait laboratories under conditions that do not constrain natural movement. It has been noted previously [16] that capturing unencumbered movement ("fidelity" to natural movement) is important for studies of OA, since the disease ("wear and tear") is associated with repetitive cyclic loading. If measurement methods that constrain natural movement are used, they should be considered in light of their relevance to OA.

Ambulatory Loading and OA Given that the measures captured during natural ambulation are obtained by placing sensors on the surface of the body, they introduce limits on the capacity to infer the actual internal joint force and motion that act directly on the joint. However, the external measures captured during ambulation can be used to estimate or calculate joint contact motion and/or joint contact force (Fig. 1b). The term 'estimate' is used here, since these measures cannot be measured directly in vivo at the level of the joint with the exception of introducing an instrumented joint replacement [17, 18]. Thus, for studies of knee OA, these measures of joint mechanics are typically obtained by various modeling methods, in which the external measures (Fig. 1a) are used as input to some form of a joint model that calculates the forces generated by muscles during ambulation. Muscle forces contribute the major portion of the peak forces acting at the joint and thus are critical for determining the forces acting on the articular surfaces of the joint. However, the accurate determination of muscle forces during ambulation presents a complex unsolved problem, since there are many different combinations of muscle forces that can balance the external forces and moments captured during ambulation [19]. The models often use optimization algorithms that require a spectrum of simplifying assumptions which reduce the anatomical and physiological complexity of the problem. Even with the use electromyography (EMG), there remains ambiguity in the relationship between the EMG signals and force in the muscle. The problem of predicting muscle forces during ambulation becomes more complex for OA patients whose patterns of muscle contraction can adapt to pain or instability using patient-specific strategies, notably co-contractions [20, 21]. A detailed summary [22] of the state of the art for the prediction of joint contact force using modeling suggests the need for future work on this topic.

In spite of the challenges for predicting joint forces noted above, rather simple methods [19] to predict joint forces have provided useful general insight with important clinical implication on the nature of the mechanical loading at the joint. For example, a critical finding has been the relationship between the adduction moment during walking and the greater force on the medial compartment relative to the lateral compartment [19]. These observations have provided the basis for addressing the adduction moment in terms of the pathomechanics of knee OA. For example, studies have shown the association of the maximum adduction moment during walking with treatment outcome [13], disease progression [23], and disease state [24] in patients with OA in the medial compartment of the

knee. Interestingly, the magnitude of the adduction moment is also influenced by increasing age and obesity in subjects without OA [12]. Furthermore, a positive relationship between the adduction moment and the ratio of the medial to lateral cartilage thickness has been found in young healthy subjects [25], whereas a negative relationship exists in patients with medial knee OA [26]. Recent research has shown that the positive relationship found in young healthy subjects is diminished [27] in older obese subjects without knee OA and approaches the negative relationship seen in patients with knee OA [26]. These observations suggest that there is a transition in the way cartilage responds to load that occurs prior to developing clinical knee OA, and that testing for this transition might be a useful marker for developing knee OA. Thus, the maximum adduction moment measured during walking has become an important mechanical signal that reflects clinical conditions associated with medial compartment knee OA.

The above observations have led to the selection of the adduction moment as a target for a range of interventions [28•, 29] which are designed to reduce medial compartment load during walking. However, as the understanding of the relationship between ambulation and knee OA has developed in recent years it has been recognized [30] that when an intervention is introduced the adduction moment is not the only component of load that changes and there can be changes in the patterns of muscle firing that are reflected in changes in the flexion-extension moment. Thus, an intervention that reduces the adduction moment can potentially increase the flexion moment and thus the peak force across the joint can be increased [14]. As such, care must be taken when designing new load-modifying interventions and considering the appropriate measures for evaluating their efficacy.

In addition to influencing the total load across the joint, the flexion-extension moment can be useful for assessing neuromuscular adaptations to knee OA. Specifically, the flexion-extension moment can reflect compensatory adaptations to pain, weakness, or instability [31–33, 34•] associated with knee OA. The nature of the functional adaptation can vary among patients [35] and might help to explain why some patients can cope with rather advanced stages of knee OA, while others present with symptoms of pain quite early in the development of OA [36]. It is also possible that adaptive changes occur prior to developing clinical symptoms of OA, as the literature reports substantial inter-subject variations in the patterns of muscle activation and flexion moments in older populations [37, 38]. As such, the variation in the flexion moments among populations of older healthy subjects reflects the possibility that some older subjects are adapting to the early development of OA before clinical symptoms are detected. Interestingly, in looking at the comparable age groups in patients with knee OA, the literature is more consistent with the common finding that the maximum flexion moment during mid-stance is reduced [39–42], suggesting that the pain associated with OA is driving a common neuromuscular adaptation to pain in patients with knee OA.

In light of the variability in assessing self-reported pain, the flexion moment offers a particularly attractive opportunity to develop an objective measure of pain related to knee OA. Several studies have shown [31, 43, 44] that when pain is modified through controlled administration of analgesic or anti-inflammatory medications there is a change in the magnitude of the flexion moment. Similarly, pain created in healthy subjects through injection of isotonic saline [43] is associated with a reduction in the magnitude of the flexion moment. Thus, it appears that reducing the flexion moment is a common adaptation to pain. Given the fact that the flexion moment is balanced by net quadriceps contraction, the reduced quadriceps strength [44] reported with advancing stages of knee OA is consistent with an ambulatory adaptation to pain. In general, muscle function is altered as the severity of the disease becomes worse [34•]. Hence, the last link from Fig. 1d to a suggests the potential that the biological changes in joint tissues can create signals (e.g., pain) that change the normal patterns of ambulation.

It is useful to summarize the implications of loading relative to assessing knee OA in the context of the inter-scale mechanical signaling illustrated in Fig. 1. In spite of a number of unknown factors that influence the transmission of a mechanical signal from the scale of the whole body (Fig. 1a) to the scale of the cell (Fig. 1d), there is evidence that the cartilage homeostasis in both healthy and OA joints is responsive to specific mechanical signals (e.g., adduction moment) generated during walking. It also appears that signals (Fig. 1d to a) generated at the scale of the local environment of the cell can influence adaptive ambulatory changes (e.g., reduced flexion moment) as OA develops. Thus, a better understanding of the way inter-scale mechanical signaling drives the adaptation to the state of the disease and influences progression of knee OA will be important in the development of future treatments.

Ambulatory Kinematics and OA While the loading conditions described above appear to reflect conditions associated with the progression of OA, the literature suggests that kinematic changes reflect conditions that place the system at risk for developing knee OA. Specifically, the movement and location of the tibial femoral contact can change with knee flexion (Fig. 1b, sagittal plane). This is important since the location of the thickest region of the femoral cartilage is associated with the angle of knee flexion near the heel strike phase of the gait cycle in healthy subjects [45]. As such, the cartilage thickness contours (i.e., the local variations in cartilage thickness [30]) can be considered an individual morphological "fingerprint" that is adapted to the repetitive patterns of walking, and these contours reflect a subject-specific pattern of gait. This subject-

specific morphological adaption of cartilage to gait mechanics creates substantial topological variations across the load bearing regions of the articular cartilage [46–48]. Thus, maintaining consistent patterns of gait within an envelope of healthy homeostasis [49] between external ambulatory mechanics (Fig. 1a) and cartilage metabolism (Fig. 1c) is a necessary condition to sustain cartilage health.

The nature of these topological variations places knee cartilage health at risk for kinematic changes in ambulation because kinematic changes can shift the routine loading on the articular surface to new regions of joint contact (Fig. 1b, sagittal plane). If the kinematic changes are sufficient to shift cyclic loading during ambulation to regions that cannot adapt to a change in the local mechanical environment, then normal homeostasis is disrupted in a manner that can initiate a degenerative pathway. The knee joint is particularly sensitive to kinematic changes, since there is a larger range of translational motion at the knee than in other joints, and the movement of the knee is dependent on stable ligaments, healthy menisci, and coordinated muscular function.

Joint trauma produces kinematic changes that should be considered in the context of developing knee OA. Specifically, the sensitivity of knee cartilage health to kinematic changes, taken together with a number of studies [9, 26, 50, 51] reporting kinematic changes in patients following ACL injury and meniscectomy [52] provide a kinematic basis for explaining the incidence of premature OA [3, 7] in these patient populations. Interestingly, both ACL and meniscus injury have the same type of kinematic change: a rotational offset that is sustained through the stance phase of the gait cycle. The rotational changes following ACL injury have been explained [8] by the loss of the normal contribution of the ACL to tibial external rotation with extension ("screw home movement") at the end of the swing phase. Similarly, in patients following meniscectomy [52], the rotational change is associated with loss of constraint provided by the posterior portion of the medial meniscus. Thus, the rotational changes could be explained by the loss of function of the ACL or of the meniscus. The change in cartilage thickness following ACL injury [26] has been explained by the topological variation of cartilage properties, as described above for healthy knees. Rotational changes at the knee can produce a shift in contact location to regions of cartilage not conditioned for the new regional loading.

Knee flexion is also an important consideration in the development of knee OA following ACL reconstruction. As noted above, healthy articular cartilage adapts to the cyclic patterns of knee flexion at heel strike. The importance of knee flexion is supported by studies reporting that [53•] some patients following ACL reconstruction do not reach full extension at heel strike during walking. Further, clinical studies [54] have also shown that loss of knee extension following ACL reconstruction is associated with adverse self-reported and objective outcome scores. The gait results and the clinical results taken together with the studies [45, 53•] that report a relationship between knee flexion and the location of regions of peak cartilage thickness suggest that loss of extension at heel strike following ACL reconstruction could help to explain the development of clinical OA in this population.

Aging and obesity also produce ambulatory kinematic changes prior to the development of clinical OA that are similar to the changes associated with joint trauma. Specifically, there are a number of studies [10, 55, 56] that report that the knee is less extended in older subjects at heel strike. While the literature suggests that there are differences in knee flexion–extension motion with both increasing age and OA severity, it is difficult to draw firm conclusions regarding other kinematics alterations due to the different study designs across publications. However, a recent study [11••] controlled for possible confounding factors and found several critical ambulatory changes that occur with aging. Specifically, kinematic differences were observed at heel strike with significantly less knee extension, less posterior femoral displacement, and less backward shank inclination in the older healthy population as compared to the younger population. Importantly, these differences were even more pronounced in patients with moderate and severe OA relative to the younger asymptomatic population. These findings suggest that there are kinematic changes occurring with aging and preceding the development of clinical knee OA, and that these changes increase with disease severity. It is important to note that similar kinematic changes have been reported [57] in healthy subjects with high BMI. It has also been reported that obese subjects walk more slowly than lean controls and that the reduced speed was associated with kinematic changes and reduced loads [58•]. While the reduced load might mediate the risk for developing clinical OA, the kinematic change appears to be a critical risk factor that is similar to kinematic changes reported with aging and joint trauma. Interestingly, a recent study [59••] demonstrated similar kinematic changes in patients with medial compartment knee OA to those reported in subjects with the risk factors, including aging, obesity, and joint trauma, as noted above.

The facts that aging, obesity, and joint trauma are the primary risk factors for developing knee OA, and that these conditions are associated with similar kinematic changes that precede the development of knee OA, suggest a kinematic pathway to knee OA that develops prior to clinical symptoms. While the cause of the kinematic changes is likely different for aging than for either obesity or joint injury, it appears that each of these diverse risk factors converges to a kinematic pathway that can lead to knee OA. Given that there is a substantial time interval, often greater than 10 years between the emergence of kinematic changes and development of clinical OA suggests that the combination of the repetitive cyclic loading and the number of cycles over time contribute to the development

of clinical knee OA. More importantly, during this time interval, there could be the opportunity to introduce interventions that can modify these kinematic changes. Clearly, future research in this area is needed to gain a better understanding of the cause-and-effect basis of these kinematic changes.

Conclusions

Knee osteoarthritis is a disease that can be influenced by ambulatory function. Conversely ambulatory function can be influenced by knee osteoarthritis. As such, there is a reciprocal interaction between joint health and the mechanics of ambulation. There is evidence that cartilage homeostasis in both healthy and OA subjects is responsive to specific mechanical signals generated during walking. The nature of the inter-scale signaling illustrated in Fig. 1 should be considered a fundamental component in developing a more comprehensive understanding of the etiology of knee OA that can be applied to improving treatment. One of the critical elements illustrated in Fig. 1 is the potential for inter-scale signals between the local environment of the cell and ambulatory function. These signals represent the pathway that can enable protective adaption to degenerative changes at the joint. There is evidence cited in this review that these signals occur prior to the development of OA and can also help to explain the variable rate of progression to clinical knee OA.

This review has identified several specific measures that have been associated with physical characteristics of the healthy knee joint or clinical outcome for knees with OA (Table 1). Relating these measures to physical findings is important in the sense that it is only feasible to capture these measures as they act as external influences (Fig. 1a) to the joint, yet the clinical interpretation is enhanced by understanding how these external measures produce signals that are sensed at the scale of the local environment of the cell (Fig. 1d).

The information summarized in Table 1 also provides insight into mechanical conditions that influence the rate of progression to OA, as well as conditions that precede the development of knee OA. It is interesting to note that the primary risk factors, including aging, obesity, and joint trauma, in spite of diverse causes, appear to converge on similar kinematic changes. The fact that these kinematic changes occur before the development of clinical OA suggests opportunities for developing new prevention strategies. Once clinical OA develops, the literature indicates that load modification offers the greatest opportunity to slow the rate of progression. The consolidated observations presented here can help to enhance the understanding of how the mechanical measures captured during ambulation influence cartilage health and disease, and ultimately how this understanding can be applied to the development of future treatments for knee OA.

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Compliance with Ethics Guidelines

Conflict of Interest Thomas P. Andriacchi and Julien Favre declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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