Osteoarthritis year in review 2016: Mechanics

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Summary

Inappropriate biomechanics, namely wear-and-tear, has been long believed to be a main cause of osteoarthritis. However, this view is now being re-evaluated, especially when examined alongside mechanobiology and new biomechanical studies. These are multiscale experimental and computational studies focusing on cell- and tissue-level mechanobiology through to organ-and whole-body-level biomechanics, which focuses on the biomechanical and biochemical environment of the joint tissues. This review examined papers from April 2015 until April 2016, with a focus on multiscale experimental and computational biomechanical studies of osteoarthritis. Assessing the onset or progression of osteoarthritis at organ- and whole-body-levels, gait analysis, medical imaging and neuromusculoskeletal modelling revealed how the assessment of tissue damage is changing our view of inappropriate biomechanics. Traditional gait analyses studies reported that conservative treatments can alter joint biomechanics, thereby improving pain and function experienced by those with osteoarthritis. Results of animal models of osteoarthritis were consistent with these human studies, showing interactions among bone, cartilage and meniscus biomechanics and the onset and/or progression osteoarthritis. Going down size scales, experimental and computational studies probed the nanosize biomechanics of molecules, cells and extracellular matrix, and demonstrated how the interactions between biomechanics and morphology affect cartilage dynamic poroelastic behaviour and pathways to osteoarthritis. Finally, integration of multiscale experimental data and computational models were proposed to predict cartilage extracellular matrix remodelling and the development of osteoarthritis. Summarising, experimental and computational
methods provided a nuanced biomechanical understanding of the sub-cellular, cellular, tissue, organ and whole-body mechanisms involved in osteoarthritis.
**Introduction**

Inappropriate mechanical loading, namely overloading, has long been believed to be one of the main causes of osteoarthritis (OA). This belief has a scientific basis as foundational research involving animals has demonstrated that overloading, either in the form of acute large magnitude loads [14] or repetitive submaximal loads [39, 62, 73], results in degenerative changes to the articular tissues. However, other studies have noted that indirect measures of lower than normal magnitude loading to the joint, particularly following ligament transection [8, 9], are also associated with joint degeneration. Moreover, in the extreme cases of spinal cord injury [83, 84], surgical amputation [61], denervation [21], or load deprivation appear to be important factors driving articular tissue degeneration. Together, these studies have set the foundation of our modern understanding, whereby it is both over- and/or under-loading of the articular tissues are pathways to joint degeneration. Thus, research must relate to characterizing the actual structural state of the joint, i.e. the morphology, material properties, and function, and its dynamic interaction with the local biomechanical and biochemical environment (Figure 1). Moreover, the challenge for researchers is to characterize this complex system on an individual-by-individual basis, thereby understanding how therapies may promote articular tissue regeneration or attenuate disease progression, and what activities or behaviours may increase risk of disease onset and/or progression.

How we analyse and understand the role of biomechanics in articular tissue health and degeneration is now being re-evaluated and challenged, especially
when examined alongside recent findings from mechanobiology. This new perspective has been enabled through technologies that use multiscale experimental and computational methods capable of assessing the subcellular-, cell- and tissue-level through to the organ- and whole-body-level biomechanics. The rationale behind this integrative approach stems from acknowledging the wide range of biomechanical and neuromuscular factors that have the capacity to influence the loading of the articular tissues (Table 1). Specifically, it has previously been shown that gait spatiotemporal parameters [50], knee geometry and skeletal alignment [49], knee kinematics [64], external knee moments [68, 93], and muscle activation patterns [92] all influence the contact forces with the knee. Therefore, these factors may also play a role in the maintenance or degeneration of the articular tissues of the knee and other joints, and hence must be accounted for when investigating OA pathogenesis and therapies.

The stresses and strains experienced at cell-, ECM- and tissue-level are not only dependent on the applied loading, but also depend on the tissues' morphology, i.e. structure and material properties, and local biochemistry (Figure 1). In general, damaged tissues can sustain lower loads than comparable healthy tissues [5]. This must be factored into our understanding of tissue remodelling, i.e. mechanobiology, and our understanding of risk of disease onset and progression. Moreover, tissue morphology as well as biomechanical and neuromusculoskeletal features of human motor activity all interact with one another in a highly non-linear and dynamic manner. Consequently, the current standard of using linear inferential statistics may be ill-suited to model these complex and dynamic mechanisms. We suggest that
the way forward is to emphasize and promote methods that are capable of accounting for these many factors, and which fuse together sub-cellular and cell level models of mechanobiology through to tissue-, organ- and whole-body-level models. In this paper we will review a selection of last year’s publications focusing on multiscale experimental and computational studies directed to understanding the mechanobiology of articular tissues in relation to the development of OA.

Methods

A PubMed literature review was undertaken, from which recent findings are summarised. The search terms were (((biomechanics AND osteoarthritis) OR (mechanics AND osteoarthritis)) OR ((biomechanics AND cartilage) OR (mechanics AND cartilage))) AND ("2015/04/01"[Date - Publication]: "2016/04/01"[Date - Publication]) NOT (Review). The total number of manuscripts found was over 220 from which just under 140 were selected. From these papers just over 60 were included in this narrative review.

Results

Conservative OA management in modifying interrelationships between OA and biomechanics.

In the past year several publications have investigated various methods to conservatively manage knee OA, such as specialised shoe designs, wedged shoe insoles, or knee braces that act to modify the motion and/or external loading of the knee. These studies mainly assessed the joint kinematics and external moments, with additional information on pharmaceutical use and
patient-reported symptoms of pain and comfort. The central assumption was that by modifying the external joint biomechanics, the contact loading of the articular surfaces will be influenced in a predictable manner. Moreover, a further assumption was that modifying the articular contact forces may help manage the signs and symptoms of OA, or possibly mitigate the individual’s disease burden by improving joint function. However, given the weak relationship between external measures and internal loading of the articular tissues, it is understandable that these conservative management methods may only partially improve joint function and health.

Nevertheless, the results of these investigations were encouraging and indicated that certain conservative treatments were capable of modifying joint angles and moments during gait. Those who had undergone a previous ACLR and had both valgus malalignment and lateral compartment knee OA, responded to a varus unloader brace [35]. The brace improved walking gait knee kinematics, i.e. modified all three knee rotations by ~4° compared to the no brace condition, and external knee adduction (KAM), knee flexion (KFM), and external tibial rotation moments. Similarly, in medial knee OA patients, lateral-wedged insoles were effective in reducing the KAM [36, 40], and, when combined with arch support, improved immediate patient-reports of comfort [36]. Minimalist shoes were compared to wearing normal shoes in knee OA patients, and after six months wearing minimalist shoes the participants reduced their KAM, with concomitant reduction in pain and pharmaceutical use [82]. Pneumatic knee bracing was also examined in comparison to standard non-invasive therapy and was found to improve a range of gait kinematic parameters, e.g. increased knee extension at heel-strike, larger knee flexion
excursion, and greater overall gait speed, and lowered the peak KAM in those with varus knee malalignment [41].

The effect of training on walking gait biomechanics was also studied [32, 71]. A large assessor-blinded, randomized controlled trial [32] tested neuromuscular training on patients who had just undergone medial arthroscopic partial meniscectomy (APM). However, they found no differences in peak external KAM during normal walking or during sit-to-stand from pre- to post-12-weeks of training [32]. Contrary to this, Shull et al continued their work on gait re-training in knee OA patients [71] and demonstrated a training-induced toe-in gait resulted in ~20% reduction in the first peak of the walking KAM compared to normal foot progression gait. However, the toe-in gait strategy resulted in large variation in the estimated muscle forces across the different subjects, suggesting that muscle coordination patterns are highly subject-specific, particularly in individuals with painful joint diseases such as knee OA. Thus, when studying the effects of gait re-training or neuromuscular rehabilitation exercises on articular tissue loading one needs to account for subject-specific and task-specific muscle activation patterns.

Moving away from the knee, management of hip [76, 77] and metatarsophalangeal OA [56] using footwear was studied. Footwear designed to modify the medial-to-lateral centre of pressure resulted in large variations in the magnitudes and temporal patterns of hip-spanning muscle activations in females with established bilateral hip OA [77]. Importantly, when the centre of pressure was shifted medially, the consequence of these altered muscle activation patterns were to reduce the net vertical intersegmental force at the
hip joint [76] when compared to the lateral or neutral centre of pressure footwear. Finally, both foot orthoses or rocker-sole footwear were shown to reduce peak pressure under the 1st metatarsophalangeal joint in those with OA at this joint, although the effects of pain and function remain to be assessed [56].

Intrinsic factors modifying interrelationships between OA and biomechanics

This year, as in years past, the hip joint is receiving more research focus in regard to gait biomechanics. These have examined hip OA [51, 52], hip arthroplasty [25] and femoracetabular impingement [17, 42]. Asymmetrical stance times between hip OA affected and unaffected sides, i.e. shorter time on the afflicted side, during walking gait were associated with falls risk assessed by patient reported falls during the year prior to testing [52]. The authors speculated that perhaps due to increased acceleration of the trunk towards the unaffected side, combined with hip abductor weakness on the affected side, the elderly study participants may not have been able to effectively control the large mass of their truck and that may unbalance them leading to more falls.

Femoroacetabular impingement (FAI) remained an area of research focus this past year. Contrary to early work of Lamontagne and colleagues [10, 43], Diamond et al [17] showed that FAI patients walk only with reduced sagittal plane hip angles, and reported no differences in the kinematics in the other planes of motion or in any of the external hip moments. It may be that in the majority of FAI patients walking biomechanics are not substantially influenced by impingement due to the limited hip excursions required in overground gait. However, examining functional tasks that require greater hip excursions than
overground gait, such as sit-to-stand or stair climbing, may reveal important differences between FAI afflicted and normal hips. Indeed, Kapron et al [42], using a novel method that combined imaging and model-tracking to assess hip “arthrokinematics”, tested the limits of FAI hip range of motion during clinical exams. An initial computed tomography (CT)-based arthrogram was performed on the participants (3 symptomatic FAI patients and 6 asymptomatic controls) to build a three-dimensional volumetric representation of their hip joints. Then, a custom dual-fluoroscopy system was used to dynamically track and reconstruct the hip articulation during the clinical range of motion tests. At each time point through the hip motion, the static CT-based model of the hip was projected onto the digitally reconstructed radiograms, which enabled an in vivo analysis of the femoroacetabular kinematics and contact patterns. The results showed that, in both the FAI and asymptomatic hips, the patterns of contact between the femur and acetabulum/labrum were complex. Moreover, the passive forces from the muscles, ligaments, labrum and capsule were the principle restraints on hip joint motion, not hard bone-on-bone contact.

Following total hip arthroplasty (THA), many patients report substantial limitations on hip function. Foucher et al [25] examined if patient-reported hip outcomes such as pain or clinical tests (i.e. passive range of motion) were associated with pre- or post-operative gait biomechanics THA. Post-THA the primary measures of sagittal and transverse plane moments improved, but the peak hip adduction moment remained unchanged. Multivariable regression models demonstrated that pre-operative gait biomechanics and clinical assessment of hip health explained a substantial portion (~33%) of the improvements in the post-operative gait biomechanics. These results were
consistent with previous work that has also shown post-arthroplasty clinical outcomes are influenced by pre-operative gait biomechanics at the knee [3, 74, 75], reinforcing the need for gait retraining of hip and knee OA patients [72].

The interrelationships between knee injury, disease state and joint- and whole-body-level biomechanics still attract much research activity. This past year saw many papers examine the effects of meniscal damage, anterior cruciate ligament (ACL) reconstruction (ACLR), or ACLR combined with meniscal damage to understand post-traumatic OA (PTOA) [18, 20, 31-34, 64, 81, 90].

Several studies examined the effects of ACLR on post-operative knee biomechanics [31, 44, 64, 90]. Irrespective of the state of the meniscus, the individuals post-ACLR had lower KFM [44, 64, 65], lower medial and total tibiofemoral contact forces compared to controls at 2-3 years post ACLR [64, 65], and lower KAM and medial tibiofemoral contact forces compared to the unaffected joint in the first year after surgery [90].

In a similar vein, other studies investigated the influence of arthroscopic partial meniscectomy (APM) on a range of biomechanical measures and knee health outcomes [31-33]. In one study, no differences were reported in patient-evaluated knee pain between APM and intact knees, but asymmetries in the knee biomechanics during the forward lunge were found [33]. Specifically, there were reduced knee flexion angles and smaller external KFM in the APM knee compared to the unaffected contralateral knee. The forward lunge movement was an interesting choice of task, as it is a common recreational and rehabilitation movement that can often provoke anterior knee pain. The authors suggested the altered biomechanics might have been employed to lower the
compressive forces between the patella and femur. Thus, this biomechanical adaptation may potentially reduce knee pain during tasks that typically require large knee flexion angles and moments.

Further to the above work, Edd and colleagues assessed potential pathways for inflammation to influence the development of knee OA in the post-meniscal damaged knee [18], highlighting the interplay between biomechanical and biochemical effects of meniscal injury. They also demonstrated that the modifications to the knee biomechanics due to APM are activity-specific [20]. Overall, the APM knee showed more external tibial rotation and reduced knee flexion at initial foot contact compared to the intact contralateral knee. Moreover, the external tibial rotation increased as the dynamic gait tasks became more demanding, i.e. from walking, to stair ascent, to stair descent [20]. The APM knee also showed altered tibial rotations at specific points during the tasks, indicating that the effects of APM on knee kinematics are not generic, but are rather task specific. Consequently, there should be careful consideration of the effects selected rehabilitation exercises on knee kinematics and loading in the APM knee, again highlighting the interplay between biomechanical effects of meniscal injury. So after APM or ACLR surgery patients seem to unload their knees, which may have consequences for remodelling of the joint morphology, discussed later [2, 58, 66, 67, 90].

External biomechanics and electromyography relating to presence, onset and progression of knee OA

As suggested previously, a range of joint biomechanical and neuromusculoskeletal characteristics have the capacity to influence articular
tissue loading, which are summarized in Table 1. In the past year, there were numerous studies that investigated these characteristics in relation to the onset and progression of knee OA (Table 2). A larger baseline KAM was shown to be related to cartilage thinning and worsening of bone marrow lesions in those with established medial knee OA [12]. These findings were consistent with the landmark radiographic study by Miyazaki et al [57] and prospective analysis by Bennell et al [7], and added weight to current evidence that indicates higher knee loading in already diseased joints is related to progression of the OA. As well, a cross-sectional study showed that in those patients with knee OA, larger peak KAM and KAM impulse were associated with thinner medial tibial and femoral cartilage, and worsening of bone marrow lesions [55]. This relationship between KAM measurements and either current cartilage impairment or future cartilage degeneration supports the foundational cross-sectional work by Andriacchi et al [5, 45, 70].

Knee OA severity was found to influence the relationships between external KAM and KFM, and the current cartilage thickness [23]. Specifically, in more severe cases of knee OA, the KAM plus covariates of age, sex, and BMI, showed a stronger relationship to cartilage loss than in less severe cases of OA. Interestingly, in those with less severe knee OA, the KFM was significantly associated with thinner cartilage in the posterior tibial region, while the KAM was not. These results demonstrated that the relationships between KAM, KFM and the structure of the knee’s articular tissues are not static, but change with disease severity. The body of work by Andriacchi and colleagues [4, 5, 45, 47] has shown a spectrum of possible knee loading-cartilage structure relationships that are affected by the structural health of the cartilage. Healthy cartilage
appears to respond positively to the applied loading by becoming thicker, while this relationship is inverted in those with knee OA whereby larger knee loads are related to worse tissue structure. Obviously the state of tissue structure and biology alter the effects of biomechanics (Figure 1)[18, 69].

In addition to the external joint biomechanics, this year the role of muscle coordination in relation to the progression of knee OA was investigated [37]. In a prospective cohort study of individuals with established medial knee OA, the duration of medial muscle co-contraction and the duration of medial-to-lateral muscle co-contraction ratio were related to the loss of medial tibial cartilage volume. These researchers suggested that these EMG co-contraction measures indirectly indicated larger-than-normal medial tibiofemoral loading, which was associated with rapid progression of knee OA.

Longitudinal follow–up studies of APM patients examined the predictors of cartilage loss following surgery [34, 81]. Following APM patients from 3-months (baseline) to 2-years (follow-up) post-surgery, Hall et al [34] found that larger baseline peak external KAM and KFM during fast-paced walking gait were related to onset and progression of medial tibiofemoral cartilage defects and loss of patellar cartilage volume, respectively. The strength of the quadriceps, assessed via dynamometry, had negligible influence on the structural assessments of knee health. In contrast, Thorlund et al [81], using data from the MOST study, found that high knee extensor strength in women, but not men, was protective of incident radiographic knee OA in patients with existing meniscal pathology. The measure of quadriceps strength was normalized differently between Thorlund et al [81] and Hall et al [34], with unknown effects.
on the results from the statistical models. Furthermore, it is unclear why strength would be a predictor of cartilage damage or protector of the tissue, as the effect of muscle strength on the loading experienced by the articular tissues will be dependent on a many other biomechanical and neuromuscular factors, e.g. gait speed, daily activity, knee kinematics, knee moments, muscle activation pattern. Nonetheless, given the size of the MOST study (n>373 knees), it does appear that knee extensor strength likely has some statistically significant, but mechanistically unclear, role in knee OA development, and that it is worth further careful investigation. Indeed, as Thorlund and colleagues [81] themselves noted, it is particularly puzzling why knee extensor strength would appear strongly protective of women’s knee health, but have no effect for men.

In all the aforementioned studies a recurrent limitation has been the reliance on external biomechanical measures, such as joint kinematics and moments, to indirectly assess articular loading. These external measures, which do show statistical associations with the progression of tissue degeneration in cases of established OA, are surrogates for the actual loads applied to the articular tissues. Importantly, these external measures do not directly account for the action of muscles in loading the internal structures of the joint. Importantly, muscle activation patterns are known to vary between individuals [53] and different control tasks [16, 79, 80], and are influenced by joint pathology [38], and this past year were implicated in knee OA progression [37]. Moreover, the external knee loads and internal loading of the articular tissues can be decoupled, as demonstrated by instrumented knee implant studies whereby changing the KAM through a targeted gait re-training program did not guarantee concomitant changes the contact forces [88]. Thus, modelling
methods are required that can integrate these important and influential external biomechanical measures with measures of subject- and task-specific muscle activation patterns to better estimate the actual loads applied to the articular tissues. This year several studies met this challenge.

Articular contact loading following ACLR

The role of joint loading in the knee health of ACLR patients has received research focus this year [58, 64, 66, 67, 90]. Wellsandt and colleagues [90], showed that certain ACLR patients have substantial asymmetries in their knee contact forces, demonstrating lower magnitude peak medial knee contact forces in the ACLR knee compared to the intact contralateral knee. Importantly, those individuals who developed radiographic OA in the medial compartment of the ACLR knee by 5-years showed medial knee contact force asymmetries, i.e. ~0.5 BW lower in the ACLR knee, at 6-months post-ACLR during walking, despite completing post-operative physical therapy and resolving clinical symptoms. In contrast, those ACLR patients who had symmetrical medial knee contact forces at the 6-months post-ACLR did not develop radiographic medial knee OA by 5-years post-ACLR. The main limitation of this study was that the knee OA was assessed using radiography, and only at 5-years post-ACLR. Subsequently, it was unclear if those who had substantial knee contact force asymmetries post-ACLR were those with worse knee structural damage, or whether the asymmetry was a cause of the subsequent degeneration. However, other OARSI 2016 abstracts and papers published this year shed some light on this issue [58, 64, 66, 67].
Recent studies [64, 66, 67] compared ACLR patients 2-3 years following surgery and healthy controls. They revealed that in healthy individuals, larger medial tibiofemoral contact forces were related to thicker medial articular cartilages [66], consistent with previous studies that have found positive influences of the KAM on femoral articular cartilage thickness distribution [5, 45, 46]. However, ACLR patients showed a flat, non-significant relationship between contact forces and cartilage thickness [66]. Importantly, when the ACLR patients were grouped into those without and with meniscal injury different relationships between load and articular tissue pathologies emerged. In the ACLR patients without meniscal injury, larger magnitude medial tibiofemoral contact forces had reduced prevalence of medial compartment articular cartilage defects and subchondral bone marrow lesions, while in meniscal-injured ACLR’s there were no significant relationships between load and pathology. The latter suggests that compromised articular loaded sharing [29, 87] and/or altered biochemistry due to the meniscal injury dominates structural signs of OA onset post-ACLR rather than the net contact forces per se. However, Wellsandt et al, did not find meniscal injury to be more prevalent in the ACLR patients who went on to acquire OA compared to those who did not, although their sample size was too small, i.e. 22 participants, to explore this issue.

The role of meniscal damage in knee OA

In addition to the whole-body-level studies above, this year several modelling [27, 29, 54, 89, 91] and experimental [11, 27, 48, 87] studies provided new insights into meniscus biomechanics and orthopaedic treatments for articular
injures. A strong confirmation of the critical role played by the meniscus in load bearing and stabilization of the knee was provided by Walker et al [87]. In their study of cadaveric knees instrumented with pressure pads between the femur and tibia articulations, the meniscus was shown to bear >50% of applied loading throughout a range of continuous and combined physiological loading conditions, with the posterior horn sustaining most of the shear loading particularly at large knee flexion angles. The importance of posterior horn, and both the shape and size of the remaining meniscus was confirmed experimentally [48] and via modelling [54, 91]. By combining experiments with modelling, the laxity of meniscal horns was shown to substantially increase medial tibiofemoral contact force transmission to the cartilage [27]. Compared to the intact uninjured knee, in vivo cartilage strain, measured using a combination of static MRI and dynamic biplanar fluoroscopy, was also shown to be increased in those with medial meniscal tears and was associated with increased matrix metalloproteinase (MMP) activity in the synovial fluid [11]. This combination of measuring local cartilage strain with dynamic medical imaging and biomarkers of cartilage degeneration in the meniscal-injured knee, was a highly novel contribution to the literature, and further strengthens the prevailing consensus that meniscal injury plays both a biomechanical and biochemical role [19] in subsequent tissue remodelling (Figure 1) and knee OA development.

*The role of subchondral bone in OA*

This year, degenerative changes to the subchondral bone were again implicated in the onset and development of OA, which was examined in ACL
In injury studies [1, 58]. In humans, Mundermann et al [58] used pQCT to quantify volumetric bone mineral density prior to and at 3, 6, and 12 months after ACLR. The ACLR knees showed a loss of both cortical (~5-11%) and trabecular (~11-12%) bone compared to the contralateral knee at all time points, including the pre-surgery measurements in the afflicted knee. Interestingly, there was a trend towards increasing bone mineral density from 3 to 6 to 12 months post-ACLR, which paralleled the post-ACLR tibiofemoral contact force profiles seen in ACLR patients who develop knee OA in Wellsandt et al [90], suggesting an influence of unloading on bone loss. Continuing this theme, but in a mice model of PTOA, Andersen et al [1] studied the effects of ACL rupture in presence or absence of hind limb unloading. Similar to their previous research [14], their new study again revealed the “unexpected finding” of trabecular bone loss at 7-days post-ACL rupture in mice with their hind-limb loaded. However, an equivalent amount of trabecular bone loss occurred in both sham injured and ACL-injured mice with their hind-limbs unloaded [1], suggesting unloading to be a main factor in early bone loss. Nevertheless, by 14 days post-ACL injury trabecular bone was somewhat regained in the hind-limb loaded mice, while all hind-limb unloaded animals (ACL and sham injury) still had substantial bone loss. This indicated trabecular bone loss is not only explained by the lower-loading to the joint, but by a coupled interaction between the biochemical and biomechanical effects of joint injury (Figure 1).

Subcellular-, cell-, tissue-level biomechanics and OA

The role of trabecular bone loss is relevant to the health and function of the articular cartilage. In an simulation study using an finite element model (FEM)
of the knee, Venalainen et al [86] reduced the subchondral bone material strength, while applying simulated physiological loading conditions. This produced substantially reduced principle strains throughout the overlying articular cartilage, but, importantly, reduced the cartilage pore pressures from the surface layer down to the bone-cartilage interface. Pore pressure, and the associated characteristic permeability, are crucial to poroelastic, dynamic mechanical and weeping lubrication behaviour of cartilage [26, 59, 60, 95].

Cartilage permeability and pore pressure was the topic of a set of studies this year [59, 60, 95]. It was shown that pore pressure was required to adequately pressurize the articular cartilage during high-frequency mechanical loading typically applied during recreational and rehabilitation activities such as running. Furthermore, when cartilage glycosaminoglycan (GAG) content was decreased this resulted in an increase in cartilage permeability, and reduced cartilage pressurization and compressive stiffness [59, 60]. Using explant and animal models, combined with FEM analyses, nanoscale aggrecan solid-fluid interactions were shown to be the primary determinants of articular cartilage’s dynamic mechanical function and permeability, which were severely compromised with depletion of the GAG content [60, 95]. Overall, this impairs the tissue’s ability to resist strains and puts the collagen network at risk of damage.

A number of studies this past year suggested that if the normal porosity and fluid flow within cartilage were disrupted, this will alter the fluid exudation process that is essential to adequate lubrication of the articulating surfaces [26, 94, 95]. Without adequate lubrication, substantial surface wear due to
damaging tissue shear stress and strain can occur. This is essential to overall cartilage health because results of micro-strain analysis of articular cartilage subject to impact loading [6] suggested that the cartilage superficial region offers protection to the underlying cells. Indeed, the strain response of chondrocytes within the superficial zone of the articular cartilage was shown to be highly heterogeneous, showing regional patterns of strain in response to different modes of applied stress, i.e. compression and tension [30]. The loss of the superficial zone was examined using FEM and confirmed an increased permeability and strain of the remaining cartilage [28, 63]. Therefore, degeneration of the superficial zone of the articular tissues, which is a common feature of the early stage of OA, compromised the tissue and made chondrocytes vulnerable to strain-induced death.

Multiscale modelling was able to link other tissue level damage to cartilage pressure and permeability [15, 78]. Focal cartilage defects caused a loss of cartilage fluid pressure, but this was dependent on the defect depth, location and contact conditions suggesting that not all defects may lead to localized cartilage degeneration [15]. In contrast, Tanska et al [78] showed that medial meniscectomy exposes the chondrocytes to elevated levels of fluid pressure and maximum principal strains during walking possibly contributing to cell viability and OA.

Thus, from all these publications in the past year we can track a direct line between reductions in subchondral bone mineral density following ACLR or presence of cartilage defects to the lowering of pore pressures and increased principle strains in the articular cartilage, and, ultimately, to reduced cartilage
stiffness and impaired fluid exudation for lubrication leading to OA. Alternatively, meniscectomy had the opposite affect possibly leading to overloading of the chondrocytes leading to OA.

Multiscale modelling: A promising future research pathway

As with the previous year in review of mechanics [85], the promise of future breakthroughs and progress in the field of the mechanics of OA is thought to lie with multiscale modelling. This past year, Chokhandre et al [13] made publically available a multiscale data set that reported on both joint- and tissue-level anatomy as well as biomechanics for the same specimen. The characterization included joint-level MRI to assess joint-level anatomy, mechanical testing on a robotic jig to measure the net joint laxity, tissue mechanical testing to establish the material properties of the articular cartilage, menisci and ligaments, and, finally, histological analysis performed to provide insight into the composition of the above structures. The publication of these data (multiscale data set, https://simtk.org/projects/j2c/) represents an enrichment of the current publically available anatomical and mechanical data sets. Hopefully, these data will provide a wealth of information for future validation and bench marking of knee joint simulation research.

Following on this theme of multiscale models, Erdemir and colleagues [22] presented a commentary on some of the technical challenges faced by researchers when attempting to implement multiscale high-fidelity biomechanical models with a high-throughput. They acknowledged the demands imposed by in silico analysis, not only in direct computational costs and the complexity of the analysis, but also in collating the results into
manageable and interpretable forms. They identified a need for methods that rapidly, and in a user-friendly way, generate models representing the anatomy and material properties at the cell-, tissue- and organ- (joint) levels. They propose that such methods be controlled by simple and intuitive configuration files that would dramatically reduce the burden on the human operator. This would have the important benefit of enabling researchers who do not have extensive background in computational methods to use these powerful modelling tools.

Fernandez and colleagues [24] also focused on the multiscale modelling, but used population-based modelling techniques that allow the user to generate patient-specific models from sparse data sets. Such approaches reduce the costs associated with additional imaging and make it possible to leverage existing data sets to create personalized models. It was also highlighted that it is important to include individual muscle activation patterns, a feature often overlooked by pure mechanical/mathematical optimization approaches, to further our understanding of human muscle coordination in the specific context of bone remodelling. Importantly, when subject-specific muscle anatomy and activation patterns were incorporated into FEM models of hip loading, these additions realised more physiological stress distribution patterns.

Other modelling efforts have explored the development of combined biomechanical and biochemical models (Figure 1) of cartilage remodelling using a structural reliability analysis [26]. This approach focused on the integration of multiscale experimental data and computational models to predict cartilage ECM remodelling and the development of OA. Because these are
mechanistic models, they aim to provide a detailed risk assessment for structural injury to the articular tissues on a subject-specific basis. They do this by including a wide range of subject-specific factors from cell- and tissue- joint-level whole-body-levels biomechanics, as well as environmental, biochemical and genetic influences. The promise of these models was shown by modelling weight loss of 10 kg, or increasing weekly physical activity on an individual’s risk of future OA development, not in a statistical manner, by through a comprehensive understanding of how those changes in behaviour influenced the cell, tissue and organ response.

Conclusions

In summary, the past year has seen new experimental and computational methods elucidating the relationships between sub-cellular-, cell-, tissue-, organ- and whole-body-level biomechanics with the onset and progression of OA. Integration of these methods is also leading to a more nuanced understanding of the multiscale biomechanical and biochemical causes of OA, which should enable better treatments for the disease.

Contributions

Both authors searched the literature, selected the articles, summarized the results, and wrote the manuscript.

Conflict of interest

The authors have no conflict of interest.

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Figure 1: Multiscale remodelling cycle of articular tissue subject to biomechanical and biochemical environment.
Table 1: Summary of the behavioral, biomechanical, neuromusculoskeletal characteristics that have possible influence over articular tissue loading.

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<th>Characteristic</th>
<th>Possible alterations to articular loading</th>
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<td><strong>Whole-body behaviour</strong></td>
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<tr>
<td>Less moderate and high intensity physical activity</td>
<td>➔ articular surfaces loaded less often</td>
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<td><strong>Knee motion and loading affected in walking</strong></td>
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<tr>
<td>Altered knee adduction joint moments</td>
<td>➔ altered distribution of lateral versus medial articular forces</td>
</tr>
<tr>
<td>Altered flexion-extension joint moments</td>
<td>➔ altered knee extension muscle forces applied to articular surfaces</td>
</tr>
<tr>
<td>Slower walking speed</td>
<td>➔ articular surfaces loaded for longer time periods</td>
</tr>
<tr>
<td>More flexed and reduced range of motion</td>
<td>➔ load concentrated over smaller region of articular surface</td>
</tr>
<tr>
<td>More internally or externally rotated</td>
<td>➔ different region of articular surface loaded</td>
</tr>
<tr>
<td><strong>Action of knee muscles are affected</strong></td>
<td></td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>➔ smaller muscle forces applied to articular surface</td>
</tr>
<tr>
<td>Arthrogenic Muscle Inhibition</td>
<td>➔ smaller muscle forces applied to articular surface</td>
</tr>
<tr>
<td>Higher co-contraction when walking</td>
<td>➔ more muscles apply forces to articular surface</td>
</tr>
</tbody>
</table>
Table 2: Sample of studies examining biomechanical variables in gait associated with onset or progression of knee OA following either ACLR, APM, or existing OA disease.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Group</th>
<th>OA outcome measure</th>
<th>Muscle Co-act</th>
<th>Knee Joint Contact Force</th>
<th>KAM</th>
<th>KFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al. [12]</td>
<td>Medial knee OA K-L ≥ 2</td>
<td>↑ WORMS cartilage damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ WORMS bone marrow lesion</td>
<td></td>
<td></td>
<td>↑</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Tibial &amp; femoral cartilage thickness loss</td>
<td></td>
<td></td>
<td>↑↑</td>
<td>ns</td>
</tr>
<tr>
<td>Hodges et al. [37]</td>
<td>Medial knee OA K-L = 2 and 3</td>
<td>↑ Medial tibial cartilage volume loss</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hall et al. [34]</td>
<td>Arthroscopic Partial Meniscectomy Nil OA</td>
<td>↑ Medial tibial cartilage volume loss</td>
<td></td>
<td>↑</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Medial tibial cartilage defects</td>
<td></td>
<td>↑</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Patella cartilage volume loss</td>
<td></td>
<td></td>
<td>ns</td>
<td>↑</td>
</tr>
<tr>
<td>Wellsandt et al. [90]</td>
<td>ACLR Nil OA</td>
<td>Acquired radiographic OA, K-L ≥ 2</td>
<td></td>
<td></td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

KAM: Peak knee adduction moment or moment impulse, KFM: Peak Knee flexion moment, Knee Joint Contact Force: Medial Tibiofemoral contact forces, Muscle Co-act: Duration of co-activation of medial knee muscles, ns: tested but not significant.