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Loading the joint to protect it: Exercise effects on knee articular cartilage

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Abstract

Articular cartilage was long viewed as an inert, wear-prone bearing surface whose lifespan is spent by mechanical use. Contemporary evidence characterises articular cartilage as a mechanically regulated tissue in which physiological loading contributes to matrix homeostasis and suggests that osteoarthritis is better understood as a multifactorial disorder involving developmental, metabolic, and mechanotransductive dysregulation rather than simply as a consequence of mechanical wear. This narrative review synthesises converging strands of evidence on how exercise, physical activity, and mechanical loading affect knee articular cartilage, using the hip as a comparator. We outline the mechanobiology of the chondrocyte, in which mechanosensitive channels and downstream pathways translate load magnitude, mode, and duration into context-dependent biological responses, and we propose, as an integrative hypothesis rather than an established quantitative relationship, a physiological loading window that is multidimensional rather than a single dose axis. We review how compositional magnetic resonance imaging and molecular biomarkers make cartilage responses measurable *in vivo*, and we distinguish transient acute responses from chronic adaptation. We argue that load distribution matters as much as load magnitude, drawing on post-traumatic osteoarthritis. We appraise the clinical evidence in people at risk of, or with, knee osteoarthritis, where exercise is a first-line treatment that does not appear to harm cartilage, and we examine whether population-level running epidemiology, which is observational and susceptible to injury-related confounding and healthy-runner selection, is compatible with this model. Finally, we connect exercise mechanobiology to cartilage tissue engineering, where bioreactor conditioning and post-operative loading pose the same dose problem. We identify priority gaps: empirical testing of the loading-window hypothesis, a common metric of mechanical dose, the clinical translation of compositional imaging, and the under-representation of the hip.

Keywords: Articular cartilage; Exercise; Mechanotransduction; Osteoarthritis; Magnetic resonance imaging; Tissue engineering

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1. Introduction

For most of the twentieth century, articular cartilage was conceptualised as a passive bearing surface that degrades through cumulative mechanical wear. Within this

framework, physical activity was intuitively suspect: if cartilage wears with use, then loading the joint should accelerate its loss. This intuition persists among patients and some clinicians, yet it is increasingly difficult to reconcile with the biology of the tissue and with the clinical evidence base.

A more accurate contemporary account holds that articular cartilage is a mechanically regulated tissue. Chondrocytes continuously sense mechanical signals and adjust the synthesis and degradation of the extracellular matrix accordingly; physiological loading is not merely tolerated but is required to maintain matrix composition and mechanical competence.[1,2] From this vantage point, osteoarthritis (OA) is better understood not as the inevitable end-point of use, but as a disorder of regulatory failure spanning developmental, metabolic, and mechanotransductive programmes.[3] The corollary, which we develop in this review as an integrative hypothesis rather than as an established quantitative relationship, is a dose–response relationship shaped like a window: absence of load (unloading, sedentary behaviour) and aberrant overload are both deleterious, whereas moderate, intermittent loading is homeostatic and potentially reparative.[1,2]

This reframing has direct clinical weight. Exercise is a core, first-line treatment for knee and hip OA across major clinical practice guidelines.[4,5] If exercise damaged cartilage, this recommendation would sit in tension with the goal of preserving joint structure. Resolving that apparent tension requires integrating evidence at levels that are seldom considered together: the molecular mechanobiology of the chondrocyte; the *in vivo* behaviour of cartilage as captured by compositional imaging and biomarkers; the clinical outcomes of exercise in healthy, at-risk, and osteoarthritic joints; and the population-level epidemiology of habitual loading.

This narrative review synthesises those strands. We focus primarily on the knee, the most extensively studied and most frequently affected weight-bearing joint, and we use the hip as a comparator to highlight where evidence is thinner and where extrapolation is unwarranted. Our aims are to (i) summarise how mechanical loading regulates cartilage biology, including the often-neglected role of loading mode; (ii) clarify how acute transient responses differ from chronic adaptation; (iii) argue that the spatial distribution of load deserves parity with its magnitude; (iv) appraise the clinical and epidemiological evidence on exercise and cartilage; (v) connect this literature to the mechanical conditioning of engineered and repairing cartilage; and (vi) propose an integrative conceptual model of the loading–cartilage relationship, framed as a testable hypothesis, and a research agenda.

Consistent with the narrative format, this is an interpretive synthesis rather than a systematic review. We searched PubMed, Scopus, and Web of Science for literature published from database inception to September 2026, combining terms for cartilage, mechanotransduction, exercise, physical activity, loading, OA, magnetic resonance imaging (MRI) and tissue engineering, and we prioritised randomised trials, systematic reviews, and recent authoritative syntheses, supplemented by seminal primary studies identified through citation tracking. No quantitative pooling was attempted, and the selection of evidence reflects the interpretive aims stated above rather than an exhaustive protocol-driven search.

Evidence was considered eligible if it was published in English in a peer-reviewed journal (or, for clinical guidance, issued by a national or international professional body) and addressed the effect of mechanical loading, exercise, or physical activity on articular cartilage biology, structure, or composition, or on the occurrence or progression of OA, in cell, explant, animal, or human models. Within these criteria, sources were selected according to a pragmatic hierarchy: for clinical and epidemiological questions, systematic reviews with meta-analysis and randomised controlled trials were preferred to observational studies, and observational studies to case series; for mechanistic questions, primary experimental studies and recent authoritative reviews were preferred; and where several sources addressed the same question, the most recent and methodologically robust were retained. Conference abstracts, non-peer-reviewed preprints, and opinion pieces were not used to support empirical claims. Because study selection in a narrative review is not protocol-driven, it remains susceptible to selection and publication bias; we have therefore sought to report null and unfavourable findings alongside favourable ones and to indicate the design and certainty of the evidence underpinning each conclusion. Publication bias was not formally assessed because this narrative review did not involve quantitative evidence synthesis. We sought to limit its influence by giving precedence, where available, to meta-analyses that had themselves examined small-study effects or rated the certainty of evidence; by identifying additional studies through citation tracking rather than relying on database retrieval alone; and by deliberately including null or unfavourable findings. Nonetheless, potential publication bias should be considered when interpreting the evidence on mechanical loading and articular cartilage, particularly with respect to findings from mechanistic *in vitro* and animal studies.

2. The mechanobiology of articular cartilage

2.1. A load-bearing tissue built for regulation

Articular cartilage is an avascular, aneural, and alymphatic tissue composed of a sparse population of chondrocytes embedded in a dense extracellular matrix of type II collagen and proteoglycans, the latter rich in glycosaminoglycans (GAGs).[6] The collagen network confers tensile strength and constrains the highly hydrated, negatively charged proteoglycan aggregates, which generate the osmotic swelling pressure responsible for compressive stiffness and load distribution.[7] Because the tissue is avascular, chondrocytes depend on load-driven fluid movement for nutrient exchange and metabolic signalling, which makes mechanical loading not incidental but constitutive of cartilage health.[1,8]

The chondrocyte is therefore best understood as a mechanosensor. It converts compressive, tensile, shear, and hydrostatic stimuli into biochemical signals that regulate matrix turnover, a process termed mechanotransduction.[2] The direction of this response is not fixed; it depends on the magnitude, frequency, mode, and duration of the mechanical input, and on the biological context in which it is received (for example, the inflammatory milieu and the integrity of the matrix), which is the biological basis for the loading-window hypothesis introduced above.

2.2. Mechanosensitive machinery: Piezo1, TRPV4, and downstream pathways

Among the best-characterised molecular sensors are the mechanically gated ion channels Piezo-type mechanosensitive ion channel component 1 (Piezo1) and transient receptor potential vanilloid 4 (TRPV4), which transduce membrane deformation and osmotic change into intracellular calcium signalling and, in turn, into matrix-regulating gene expression.[9] Their roles, however, are neither interchangeable nor fixed. TRPV4 appears to mediate much of the anabolic response of chondrocytes to physiological dynamic loading, whereas Piezo1 and Piezo2 respond preferentially to high, potentially injurious strains.[10,11] Even this distinction is conditional: inflammatory signalling sensitises Piezo1-mediated mechanotransduction, so that loads tolerated by healthy chondrocytes may become harmful in an inflamed joint.[12] The transcriptional coactivators Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), sensitive to cytoskeletal tension and matrix stiffness, further couple the mechanical state of the tissue to chondrocyte survival and phenotype.[2,3] Their effects are likewise context-dependent: in osteoarthritic cartilage, the activity of YAP and TAZ restrains nuclear factor κB (NF-κB)-mediated matrix degradation, illustrating that the same node can be protective or permissive depending on the inflammatory and mechanical setting.[13] Recent syntheses converge on the view that these mechanotransductive nodes are not merely markers of load but are candidate therapeutic targets whose modulation can shift chondrocytes towards survival and matrix synthesis.[3] The direction of any such shift, however, is likely to depend on dose, timing, and disease stage.

Downstream, the response integrates through canonical signalling pathways—chiefly mitogen-activated protein kinase (MAPK) cascades (extracellular signal-regulated kinase [ERK], p38, c-Jun N-terminal kinase [JNK]), NF-κB, and Wnt/β-catenin—whose net effect on the matrix depends on the mechanical, inflammatory, and developmental context rather than being intrinsically anabolic or catabolic. As a broad tendency, moderate dynamic loading has been associated with ERK and β-catenin activity that supports matrix synthesis, lubricin production, and a balanced inflammatory tone, whereas high or aberrant loading has been associated with sustained p38/JNK, and NF-κB activity, inflammatory mediators and matrix loss.[2] These associations should not be read as a fixed classification. Wnt/β-catenin signalling illustrates the point: both excessive activation and excessive suppression are detrimental to articular cartilage, so that its effect depends on the level and duration of signalling rather than on its presence or absence.[14] By analogy, the consequences of NF-κB and MAPK activation are likely to differ according to whether activation is transient or sustained. The same tissue, exposed to different mechanical doses and in different biological contexts, thus can produce opposite biological outcomes.

2.3. The loading window: Too little and too much are both harmful

Two boundaries define the window. At the lower boundary, insufficient loading is damaging: sustained unloading is associated with cartilage thinning and matrix deterioration—in humans, for example, after spinal cord injury and after only seven weeks of partial weight-bearing—reflecting the tissue's dependence on mechanical signalling for maintenance.[15,16] At the upper boundary, supraphysiological loading is injurious: *in vitro* models show that whereas modest dynamic compressive strain supports matrix formation, high-magnitude strain suppresses matrix synthesis and drives chondrocyte senescence, a cellular signature of degeneration.[2] Between these extremes lies a regime of moderate, intermittent loading that is homeostatic and, as reviewed below, capable of improving cartilage composition *in vivo* (Figure 1). We

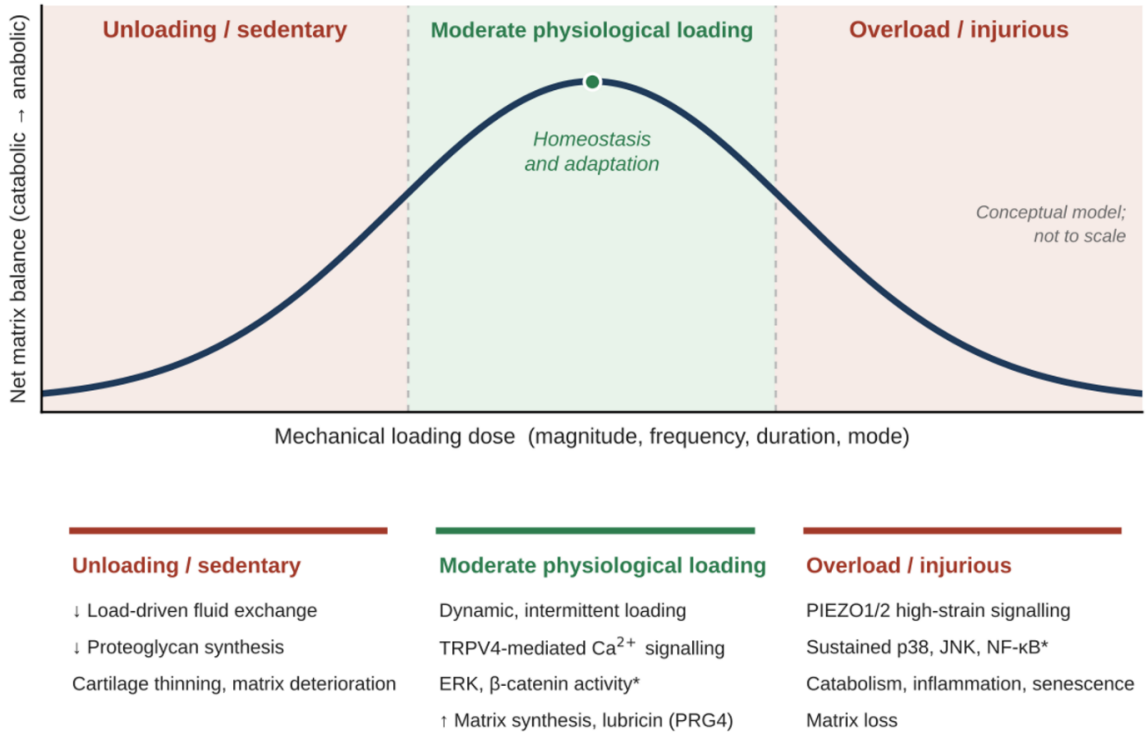


Figure 1. The mechanobiological loading window of articular cartilage: a conceptual (hypothesised) model

Note: *Pathway roles are context-dependent (mechanical, inflammatory, and developmental setting); assignments indicate predominant associations, not fixed anabolic or catabolic roles.

Abbreviations: ERK: Extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; NF-κB: Nuclear factor κB; Piezo1/2: Piezo-type mechanosensitive ion channel components 1 and 2; PRG4: Proteoglycan 4; TRPV4: Transient receptor potential vanilloid 4.

emphasise that this inverted-U-shaped relationship is an integrative, conceptual model: its general shape is inferred from convergent mechanistic, imaging, and clinical observations, but its boundaries have not been quantified in humans, and it should not be read as an established quantitative dose–response relationship.

In this model, cartilage matrix homeostasis follows an inverted-U-shaped relationship with mechanical load. Both insufficient loading (unloading/sedentary behaviour) and supraphysiological overload shift the chondrocyte towards catabolism and matrix loss, whereas moderate physiological loading engages mechanosensitive machinery (notably TRPV4) and signalling (e.g., ERK, β-catenin) associated with matrix maintenance and adaptation. Pathway assignments indicate predominant associations in each loading regime, not fixed anabolic or catabolic roles; Piezo1/2 signalling is shown in the overload regime because these channels respond preferentially to high strains. The curve is conceptual and not to scale; its shape is inferred from convergent but largely indirect evidence, and its boundaries have not been quantified in humans.

Framing exercise as a mechanobiological stimulus, rather than as generic "wear", dissolves the paradox that opened this review. The clinically relevant question is not whether to load the joint, but how much, how often and in what manner—that is, where a given activity falls within the window.

2.4. Beyond magnitude: motion, shear and the lubrication axis

The window is conventionally drawn along a single axis of magnitude, but magnitude alone is an incomplete description of a mechanical stimulus. Cartilage is also sensitive to the mode and the temporal structure of loading, and nowhere is this clearer than in the regulation of boundary lubrication.

Lubricin—the mucinous glycoprotein encoded by proteoglycan 4 (PRG4), also termed superficial zone protein—is secreted by superficial-zone chondrocytes and synovial fibroblasts and is the principal boundary lubricant of the articular surface.[17] Its role extends beyond friction: PRG4 contributes to chondrocyte metabolic homeostasis and to the suppression of inflammatory signalling, and

its production falls in OA.[18] The mechanical regulation of PRG4 is instructive. In bovine cartilage explants, dynamic shear superimposed on static compression increased PRG4 secretion to three to four times that of unloaded controls and of statically compressed samples; static compression alone did not.[19] The stimulus that upregulates the joint's own lubricant is therefore movement under load, not load as such.

The same principle holds at the whole-joint level: continuous passive motion (CPM) applied to intact joints stimulates chondrocyte PRG4 biosynthesis.[20] This observation has an immediate clinical echo—CPM is standard in the early phase after cartilage repair surgery—to which we return in Section 10.

Two implications follow for prescription. First, static or sustained postural loading is a poor substitute for dynamic activity: in cartilage explants, static compression suppresses matrix biosynthesis whereas dynamic compression stimulates it,[21] and, by extension, prolonged standing is likely to deliver magnitude without the oscillatory shear that drives lubricant synthesis and load-driven fluid exchange.[19] Second, the window is better conceived as multidimensional—magnitude, frequency, duration, mode (compression, shear, hydrostatic), and rest interval—than as a single dose axis. Activities with similar peak magnitudes but different temporal structures may fall on different sides of its boundary. This multidimensionality is one reason the curve has proved so resistant to quantification, a point we develop in Section 11.

3. Making cartilage responses measurable *in vivo*

Translating mechanobiology to humans requires tools that can quantify cartilage structure and composition non-invasively. Two complementary approaches dominate: quantitative and compositional MRI, and circulating molecular biomarkers of cartilage turnover.

3.1. Morphometric and compositional magnetic resonance imaging

Morphometric MRI quantifies cartilage volume and thickness and is well suited to detecting structural change over time. Compositional MRI goes further, probing the biochemical state of the matrix before macroscopic structural change occurs. The principal techniques are transverse relaxation time (T2) mapping, sensitive to collagen network integrity and water content; T1-rho relaxation time (T1ρ) mapping, sensitive to proteoglycan/GAG concentration; delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), which estimates GAG content through the distribution of a negatively charged contrast agent; and T2* mapping, a rapid technique related to collagen organisation and water.[8] Elevated T2 and T1ρ values generally indicate matrix disorganisation and are observed in early OA, whereas dGEMRIC indices fall as GAG is depleted.[8]

These techniques have transformed research on cartilage adaptation, but an important caveat frames their clinical use: despite three decades of development, compositional MRI remains predominantly a research tool, limited by technical demands, acquisition and post-processing complexity, and incomplete standardisation across scanners and centres.[8] Bridging this translational gap—so that compositional imaging can inform individual exercise prescription—is one of the field's open challenges. Several obstacles currently prevent its routine use in exercise prescription. Practically, compositional sequences require high-field scanners, dedicated acquisition protocols, longer scan times, and expert segmentation and post-processing, which limits availability and increases cost; dGEMRIC additionally requires intravenous gadolinium and a delay between injection and imaging.[8] Methodologically, relaxation times differ between vendors, field strengths, and analysis pipelines; reference values and minimal detectable changes are not established for clinical populations, and measurements are sensitive to the timing of the last loading bout, because activity itself transiently alters T2 and T1ρ (Section 4).[8,22,23] Clinically, there is as yet no evidence that adjusting an exercise programme on the basis of compositional imaging improves patient outcomes. Until these issues are resolved, compositional MRI is best regarded as a research and trial end-point rather than a tool for individual prescription.

3.2. Molecular biomarkers of cartilage turnover

Serum and urinary biomarkers offer a second, more accessible window on cartilage metabolism.[24] Cartilage oligomeric matrix protein (COMP) is a mechanosensitive marker of cartilage turnover; C-telopeptide of type II collagen (CTX-II) reflects collagen degradation; and the *N*-propeptide of type IIA collagen is a proposed marker of type II collagen synthesis.[25] Their responsiveness to acute and chronic loading makes them useful adjuncts, although their specificity and the influence of confounders (diurnal variation, clearance, whole-body cartilage contributions) require careful interpretation.[22] These confounders are substantial relative to the effects being measured. Serum COMP, for example, rises by approximately 10% immediately after 30 min of walking and shows a second rise several hours later,[26] and in people with knee OA several serum markers, including COMP, increase within an hour of rising from bed, whereas urinary CTX-II follows a different diurnal pattern; sampling at a standardised

time later in the day has therefore been recommended.[27] Unless sampling time and prior activity are standardised and urinary marker concentrations are corrected for creatinine, such fluctuations can be as large as the training-induced changes under study. Because the markers are systemic, they also integrate contributions from all joints and from other tissues—COMP is not cartilage-specific, being expressed also in tendon, ligament, meniscus, and synovium—so that a change cannot be attributed to the knee being trained. Inter-individual variability, renal clearance, and differences between assays further limit interpretation in the individual. At present, these biomarkers are therefore more useful for comparing groups under standardised protocols than for monitoring cartilage adaptation in a single patient.

4. Acute responses: transient loading, transient change

A recurring source of confusion is the conflation of the immediate response of cartilage to a single bout of activity with its long-term adaptation to training. The two are biologically distinct and must be interpreted differently.

Immediately after loading, cartilage deforms, and its compositional MRI signals shift. After 30 min of running, for example, T1ρ and T2 relaxation times decrease across knee cartilage regions, with the largest reductions in the patellofemoral compartment, consistent with transient fluid exudation and matrix compaction rather than damage (Figure 2A).[23] Crucially, in healthy adults these immediate changes are largely transient and recover within hours: a systematic review and meta-analysis of joint-loading activities—including walking, cycling, squatting, and hopping—concluded that such bouts do not appear to adversely affect cartilage health in the short term, and that the immediate changes observed in healthy joints are mostly reversible.[22]

The clinical implication drawn by that synthesis is explicit and patient-facing: for people with knee OA, the physical, mental, and general-health benefits of these activities are likely to outweigh any short-term risk to cartilage.[22] A transient dip in a relaxation-time value after exercise is a physiological response, not evidence of harm.

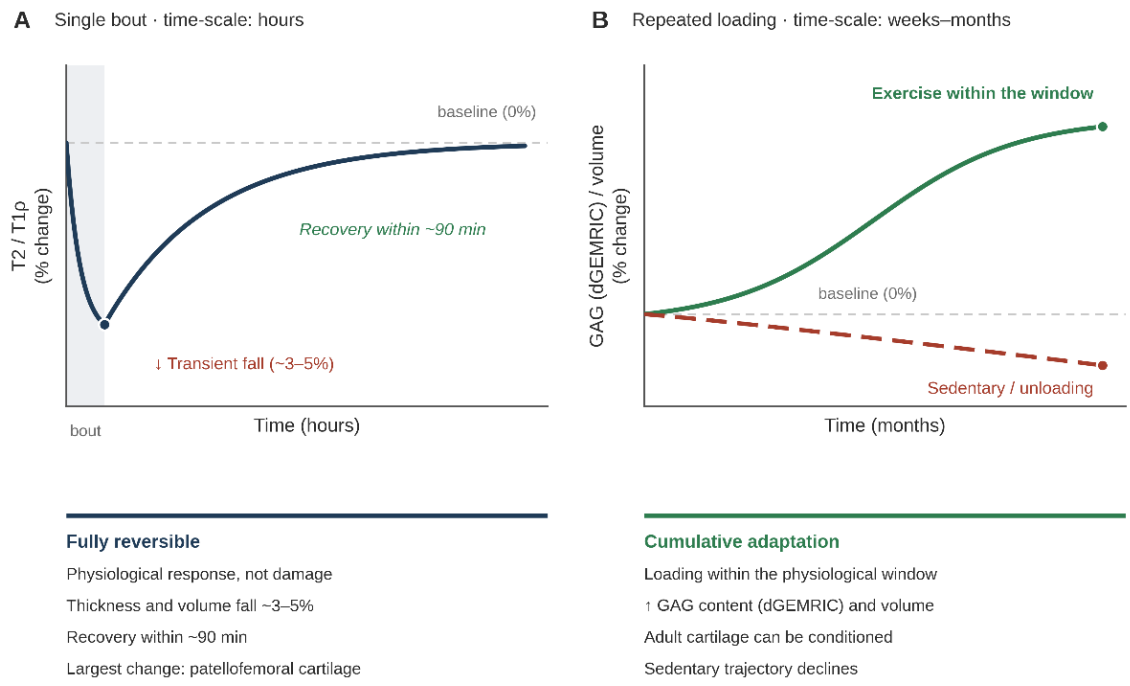


Figure 2. Acute transient response versus chronic cumulative adaptation of cartilage to loading. (A) After a single bout of activity, compositional magnetic resonance imaging signals (T2, T1ρ) decrease transiently owing to fluid exudation and matrix compaction, recovering to baseline within hours; the change is greatest in patellofemoral cartilage. (B) With repeated loading within the physiological window over weeks to months, cartilage GAG content (dGEMRIC) and volume increase relative to a sedentary trajectory, reflecting genuine adaptation. Note the differing time-scales between panels. Trajectories are conceptual and not to scale.

Abbreviations: dGEMRIC: Delayed gadolinium-enhanced magnetic resonance imaging of cartilage; GAG: Glycosaminoglycan; T1ρ: Spin-lattice relaxation time in the rotating frame; T2: Transverse relaxation time.

5. Chronic adaptation: cartilage as an adaptable tissue

If acute responses are transient, does repeated loading produce lasting adaptation? The landmark evidence that it can comes from a four-month randomised controlled trial in individuals at high risk of knee OA (following partial meniscectomy). Supervised exercise three times weekly increased the GAG content of knee cartilage, measured by dGEMRIC, relative to non-exercising controls—demonstrating, for the first time in humans, that adult articular cartilage has the potential to adapt its composition in response to a change in loading (Figure 2B).[1] This finding reframed cartilage from a static tissue that can only be spent to a responsive tissue that can, within limits, be conditioned.

Observational data are consistent with this interpretation. In cross-sectional imaging comparisons, long-term recreational runners exhibit greater cartilage volume and thickness in several knee regions than matched sedentary controls, suggesting a functional adaptation of the tissue to habitual mechanical stress rather than progressive erosion.[28] Compositional findings in that study were, however, mixed—T2* values were lower than in controls in some regions but higher in others—so the morphological differences cannot be assumed to reflect a uniformly healthier matrix. The pattern is regionally specific and should not be over-generalised: adaptation appears to occur in the weight-bearing regions most exposed to physiological load, and the cross-sectional design cannot exclude selection effects (those with resilient cartilage may self-select into running).

The adaptive capacity of cartilage is nonetheless bounded. It is slower and more limited than that of muscle or bone, and it does not license unlimited loading; the same window that permits adaptation is exceeded by supraphysiological or injurious loads.[29] The evidence supports a measured claim: appropriate, progressive loading can maintain and modestly improve cartilage composition, but adaptation is neither guaranteed nor unlimited, and it depends on staying within the physiological window.[1,28]

6. Load distribution, not only load magnitude

The evidence reviewed so far treats load as a scalar quantity. Yet much of the clinical damage attributed to "overload" arises not from excessive magnitude but from load applied to regions of cartilage unaccustomed to bearing it. Cartilage is regionally specialised: thickness, GAG content, and collagen architecture vary systematically across the joint surface, tuned over years of habitual use to a characteristic contact pattern. A change in kinematics shifts contact towards cartilage that has not been conditioned for it, and the tissue registers that shift as aberrant loading even when total joint load is unchanged or reduced.[30]

The clearest natural experiment is anterior cruciate ligament (ACL) injury: traumatic knee injury, including ACL rupture, is associated with a four- to six-fold increase in the risk of subsequent knee OA.[31] Reconstruction restores gross stability but does not reliably normalise kinematics. A systematic review of MRI studies after ACL reconstruction found compositional abnormalities to be common and persistent—most consistently elevated T2 and T1ρ values relative to contralateral or control knees—localised preferentially to weight-bearing medial tibiofemoral regions and more evident at longer follow-up, with altered biomechanics and meniscal pathology repeatedly associated with less favourable cartilage outcomes.[32] Notably, people after ACL reconstruction are typically less physically active than uninjured peers,[33] so this degeneration is unlikely to be explained by a surfeit of loading. It is more plausibly explained by a redistribution of load onto unaccustomed cartilage, compounded by persistent quadriceps dysfunction, which reduces the muscular attenuation of joint loads.[30,34]

In ACL-injured knees, load magnitude and load distribution should nonetheless be distinguished, because they can change in opposite directions and their effects are not simple. Magnitude refers to how much load the joint transmits overall—typically indexed by vertical ground reaction force, external knee moments, or estimated contact force—and after reconstruction it is often reduced in the involved limb, reflecting quadriceps weakness, pain, and protective gait. Such underloading is not benign: six months after reconstruction, lower vertical ground reaction forces and knee moments during walking were associated with T1ρ values indicating lower proteoglycan density in the reconstructed limb than in the uninjured limb.[35] Yet in another cohort, higher knee flexion moments, flexion angles, and vertical ground reaction forces at six months were associated with greater subsequent deterioration of medial tibiofemoral cartilage,[36] indicating that the relationship between magnitude and cartilage health after injury is neither monotonic nor independent of time since surgery. Distribution refers to where within the joint load is applied: persistent changes in tibial rotation and anterior translation shift tibiofemoral contact towards regions whose matrix has not been conditioned for it,[30,37] so that a normal or even reduced total load may be locally excessive. The two interact: global underloading may deprive habitually loaded regions of their maintenance stimulus while kinematic shifts concentrate load on unconditioned

regions. Rehabilitation should therefore aim to restore both a sufficient overall loading dose and a normal contact pattern, rather than simply reducing or increasing load.

Partial meniscectomy illustrates the same principle from another direction: removing meniscal tissue concentrates contact stress over a smaller area, so identical activity delivers higher local stress.[38] Frontal-plane malalignment does likewise, biasing load towards the medial or lateral compartment.[39] In each case the pathological variable is where the load goes, not how much of it there is.

This reframing has therapeutic consequences. If aberrant distribution rather than magnitude dominates in these populations, the target is not load reduction but load redistribution and reconditioning: restoring kinematics and neuromuscular control, addressing quadriceps deficit, and progressing exposure slowly enough for regional adaptation to keep pace.[34] It may also help to reconcile an apparent inconsistency in the literature—that both sedentary behaviour and injury history are associated with OA while habitual moderate loading is not. The window has a spatial dimension as well as a magnitude dimension: cartilage tolerates the load for which it has been prepared.

7. Exercise in populations at risk of, or with, knee osteoarthritis

7.1. Structural safety of therapeutic exercise

The clinical question that matters most to physiotherapy is whether therapeutic exercise—prescribed to people who already have, or are at risk of, knee OA—harms or protects their cartilage. Here the evidence is reassuring and now reasonably consistent.

A systematic review of randomised controlled trials examining the impact of knee-joint-loading exercise on MRI-assessed cartilage in people at increased risk of, or with, knee OA found that such exercise does not appear to be harmful to articular cartilage.[40] Across trials, most comparisons showed no adverse effect on cartilage thickness, volume, or defects, and some showed favourable effects on GAG or collagen outcomes; the authors appropriately cautioned that the overall quality of evidence was low and that some interventions studied fell outside a therapeutic loading spectrum. The signal, taken together with the acute-response and adaptation literature, is that therapeutic exercise is at worst neutral and at best beneficial for cartilage structure and quality.

This evidence directly addresses a persistent clinical myth—that exercise "wears down" the joint. Contemporary syntheses aimed at clinicians conclude that exercise therapy does not appear to damage cartilage structure or quality in people at risk of, or with, knee OA, and recommend that clinicians proactively pre-empt this misconception when prescribing exercise.[40] Reframing loading as a mechanobiological stimulus, and separating transient acute responses from long-term outcomes, gives clinicians the vocabulary to do so.

These structural findings sit within a broader consensus on symptoms and function. Exercise is endorsed as a core, first-line treatment for knee OA by major guidelines, including Osteoarthritis Research Society International (OARSI) and the National Institute for Health and Care Excellence (NICE), on the strength of consistent benefits for pain and physical function.[4,5] Regarding dose, an umbrella review of systematic reviews, based largely on observational data, found no evidence of accelerated OA progression with physical activity below roughly 10,000 steps per day, supporting the safety of moderate physical activity for the osteoarthritic joint.[41]

7.2. Is more load better? Intensity, dose, and the ceiling of benefit

If moderate loading is beneficial, does higher-intensity loading confer proportionally greater benefit? The Strength Training for Arthritis Trial (START) addressed this directly, randomising 377 adults with symptomatic radiographic knee OA to high-intensity strength training, low-intensity strength training, or attention control over 18 months.[42] High-intensity training produced no significant advantage over low-intensity training or control for knee pain or for knee joint compressive forces; both training arms increased strength, and neither exacerbated joint space narrowing.

The trial is usually read as a negative result, but for the present argument it is doubly informative. On structural safety, it is reassuring and concordant with the systematic review evidence: strength training, including at high intensity, did not accelerate structural progression (joint space narrowing).[40,42,43] On dose, it argues against a naively monotonic reading of the window in which more load within the tolerable range yields more benefit. Within the therapeutic range of resistance exercise, the additional mechanical stimulus of high-intensity training did not translate into additional symptomatic gain. If the window has an optimum, clinically deliverable resistance training may already sit near its plateau—at least for the outcomes measured over 18 months.

That inference should be held loosely. START measured compressive force and pain rather than cartilage composition, and it remains possible that compositional outcomes would discriminate between arms where pain did not. The practical corollary is nonetheless defensible: intensity can be individualised to tolerance and preference,

without a presumed structural penalty for going higher or a presumed structural cost to staying lower. This is a considerable clinical freedom, and it is compatible with the window hypothesis rather than contradicting it—a plateau is what the top of an inverted U would look like when sampled within its safe range, although a plateau is equally compatible with other dose–response shapes, such as a saturating curve.

8. Epidemiological evidence: the running paradox

If the mechanobiological window reflects a real property of human cartilage, it might be expected to leave a footprint at population scale, although observational data can test this expectation only indirectly. Running is the natural test case: it is the most common high-magnitude, high-repetition loading activity in the general population; it is widely believed to damage knees—in one survey, nearly 40% of the general public either perceived regular running as detrimental to the knee or were uncertain, as did a minority of healthcare practitioners[44]—and it has been studied extensively.

The epidemiology does not support this belief, although its observational nature limits the strength of that conclusion. A systematic review and meta-analysis of running and hip/knee OA reported an OA prevalence of 3.5% among recreational runners, compared with 10.2% among sedentary controls and 13.3% among competitive runners.[45] In pooled odds-ratio (OR) terms, competitive running trended towards higher odds relative to controls (OR 1.34, 95% confidence interval [CI]: 0.97, 1.86) and recreational running towards lower odds (OR 0.86, 95% CI: 0.69, 1.07); neither estimate excluded the null individually, but the difference between the two runner groups was significant ($p < 0.001$). Exposure to running for fewer than 15 years was associated with lower odds of OA than controls (OR 0.60, 95% CI: 0.49, 0.73).

More recent studies that examined running volume directly do not show a clear increase in knee OA prevalence with higher weekly volumes. A systematic review and meta-analysis of nine case–control studies (12,273 participants) found no difference in knee OA prevalence between runners and controls (OR 0.97, 95% CI: 0.56, 1.68) and no elevated prevalence in any volume stratum, including runners covering more than 48 km per week; the authors nonetheless concluded that the association between running volume and knee OA remains uncertain and called for large prospective studies.[46] In a survey of 3,804 marathon runners, the prevalence of hip or knee arthritis was 7.3% and was associated with age, body mass index, previous injury, or surgery and family history, but not with weekly mileage, cumulative years of running, number of marathons completed, or running pace.[47] More broadly, an individual participant-level meta-analysis of six community-based cohorts (5,065 participants) found no association between recreational physical activity and incident knee OA.[48] These data do not demonstrate an inverted-U-shaped relationship with respect to running volume; rather, they suggest that, among people who run, volume per se is a weaker determinant of OA than injury history, age, and body mass.

The prevalence pattern in the earlier meta-analysis, in which the sedentary and the competitive groups both sit above the recreational group, is compatible with the inverted U-shaped pattern inferred from cell and explant studies (Figure 1). It should not, however, be read as a population-level dose–response curve: the exposure categories are coarse and heterogeneously defined, the comparisons are largely cross-sectional, the estimate for competitive runners does not exclude the null, and the volume-stratified data summarised above show no clear increase in prevalence at higher weekly volumes.[45-47] The epidemiology is therefore best regarded as consistent with, rather than confirmatory of, the loading-window hypothesis (Table 1).

Imaging evidence in runners aligns with this. Meta-analysis of MRI studies before and after running found small immediate decreases in knee cartilage thickness and volume—of the order of 3%–5%, including a 3.3% (95% CI: 2.6%, 4.1%) decline in weight-bearing femoral cartilage volume—that resolve rapidly, with relaxation times returning towards baseline within approximately 90 min; the certainty of evidence was rated very low, and no hip data were available.[49] Independent syntheses reach compatible conclusions: running does not appear to generate new cartilage lesions or accelerate progression at recreational volumes.[50,51]

Three caveats are essential. First, these data are overwhelmingly cross-sectional or short-term, so causality is not established, and healthy-runner selection effects are plausible: people whose knees hurt stop running, which biases prevalence downwards among those who continue. This healthy-runner effect has two consequences for the model: it may exaggerate the apparent benefit of recreational running, and, because people who develop symptoms leave the running population, it may also mask harm associated with higher volumes. Prior injury, body mass, and occupational loading are further confounders that most studies have measured incompletely or not at all. Selection can also act on the comparison group: former runners who stopped because of knee symptoms may be classified as non-runners, which would inflate OA

prevalence in the sedentary group and thereby accentuate the left-hand limb of the curve. Taken together, these biases could, in principle, generate an apparent inverted-U-shaped relationship even if the true relation between running and OA were flat. Longitudinal cohorts in which exposure is measured before symptom onset, and in which running cessation and its reasons are recorded, are required to distinguish these possibilities. Second, the elevated prevalence among competitive runners is likely to be confounded by injury history, which is far more common at that level and is itself a potent OA risk factor;[31] consistent with Section 6, the competitive limb of the curve may reflect aberrant post-injury loading rather than cumulative volume as such. Third, almost all of this evidence concerns people with healthy knees. The safety of running in established OA is comparatively unstudied—although observational data from the Osteoarthritis Initiative found no association between self-selected running and worsening knee pain or radiographic progression in people with knee OA[52]—and should not be inferred from the healthy-knee literature.

With those caveats registered, the epidemiological signal is compatible with the mechanistic and imaging evidence rather than in tension with it. Such coherence across independent methodologies lends plausibility to the loading-window model, but it is indirect and largely observational: it supports the model as an integrative hypothesis and does not establish a quantitative dose–response relationship in humans.

9. The hip as comparator: An evidence gap

Although the knee and hip are often managed under a shared OA paradigm, the evidence on exercise and cartilage is markedly asymmetric between them. Studies specifically examining physical activity and hip cartilage are comparatively scarce, and much of the mechanistic and imaging literature reviewed above is knee-derived.[22] The asymmetry is stark enough that a meta-analysis of running and cartilage, having screened the field, could locate no hip data at all and reported on 446 knees only.[49] Where knee and hip have been examined together, the immediate effects of loading on healthy cartilage appear broadly similar and largely transient, but the smaller hip evidence base limits confidence.[22]

Table 1. Convergent evidence linking mechanical loading to articular cartilage outcomes across levels of enquiry

Level of enquiry	Representative evidence	Loading exposure	Principal cartilage outcome	Interpretation
Cell and explant (*in vitro*)	Nugent *et al.*[19]; Anderson & Johnstone[53]	Dynamic shear or dynamic compression *versus* static compression or free-swelling	PRG4 secretion increased 3–4-fold by dynamic shear, unchanged by static compression; matrix synthesis suppressed at high strain	Response depends on mode and magnitude, not on load per se
Acute human (*in vivo* imaging)	Chen *et al.*[23]; Coburn *et al.*[22,49]	Single bout (30 min running; walking, cycling, squatting, hopping)	T2/T1ρ fall; thickness and volume fall ~3%–5%; recovery within ~90 min	Transient deformation and fluid exudation, not damage
Chronic human (interventional)	Roos & Dahlberg[1]	4 months supervised exercise, 3× weekly, in at-risk knees	dGEMRIC index (GAG content) increased *versus* controls	Adult cartilage can adapt its composition
Chronic human (observational)	Zhang *et al.*[28]	Long-term recreational running	Greater cartilage volume and thickness in weight-bearing regions	Adaptation, with unresolved selection bias
Clinical (at-risk and OA populations)	Bricca *et al.*[40]; Messier *et al.*[42]	Therapeutic exercise; high- *versus* low-intensity strength training	No adverse effect on thickness, volume, or defects; no accelerated joint space narrowing	Therapeutic exercise is structurally safe; benefit plateaus with intensity
Epidemiological	Alentorn-Geli *et al.*[45]; Burfield *et al.*[46]; Hartwell *et al.*[47]	Recreational *versus* competitive *versus* sedentary exposure; weekly running volume	OA prevalence 3.5% *versus* 13.3% *versus* 10.2%; no clear increase with higher weekly volume	Pattern compatible with, but not confirmatory of, the window; observational and confounded by injury history and healthy-runner selection

Notes: Rows are ordered by level of enquiry rather than chronologically. Outcomes are summarised qualitatively; readers are referred to the primary sources for effect estimates and precision. The interpretation column indicates consistency with the loading-window hypothesis, not confirmation of a quantitative dose–response relationship.

Abbreviations: dGEMRIC: Delayed gadolinium-enhanced magnetic resonance imaging of cartilage; GAG: Glycosaminoglycan; OA: Osteoarthritis; PRG4: Proteoglycan 4 (lubricin); T1ρ: T1-rho relaxation time; T2: Transverse relaxation time.

Two features caution against simple extrapolation from knee to hip. First, the hip's deep ball-and-socket congruence distributes load differently from the knee's more incongruent, meniscus-dependent geometry, so activity-specific stress patterns differ. Second, morphological variants such as femoroacetabular impingement and acetabular dysplasia alter the local mechanical environment and interact with loading in ways with no direct knee equivalent—and, following the argument of Section 6, they do so principally by redistributing contact stress rather than by increasing its total. Clinically, aquatic exercise has some support for hip OA and is a recommended option in guidelines, plausibly because it permits movement and conditioning while attenuating peak joint load.[4,22] The hip therefore represents both a caution and an opportunity: a comparator that reveals how much of our confidence rests on knee-specific data, and a clear priority for future investigation.

Caution is therefore warranted when extrapolating knee-derived recommendations to hip OA, although the appropriate degree of caution depends on the level of the recommendation. At the level of principle, extrapolation is reasonable: exercise is recommended as a core treatment for hip as well as knee OA,[4,5] and randomised evidence shows that it improves pain and physical function in hip OA, albeit with small effects and from fewer trials than for the knee.[54] At the level of structure, extrapolation is not warranted: there is little direct evidence on how exercise affects hip cartilage composition, so the reassurance that therapeutic exercise does not harm cartilage (Section 7) rests largely on knee data. At the level of dose and exercise selection, specific prescriptions developed for the knee—particularly those involving high-impact or end-range loading—should not be transferred without considering hip morphology, because positions of deep flexion and internal rotation may concentrate contact stress at the acetabular rim in hips with impingement or dysplasia.[55] In practice, the general case for exercise in hip OA is sound, but its type, range, and progression should be individualised.

10. From exercise mechanobiology to cartilage tissue engineering

The mechanobiology reviewed here is customarily framed as a rationale for exercise prescription. It has a second application, directly relevant to the readership of this journal: the mechanical conditioning of engineered and repairing cartilage. The two are the same problem at different scales—how to deliver a mechanical dose that drives chondrocytes towards matrix synthesis rather than catabolism.

In vitro, the parallel is close to exact. Bioreactor studies of chondrocyte-laden constructs show that dynamic compression applied with physiological parameters upregulates biochemical synthesis and improves the biomechanical properties of the engineered tissue, and that the loading regime determines the outcome: short intermittent stimulation enhances chondrogenesis, whereas continuous dynamic stimulation confers no benefit or is frankly adverse.[53] Loading is necessary, but rest is part of the dose—precisely the intermittency that characterises the *in vivo* window. A critical review of this literature nonetheless cautions that results have been inconsistent, particularly for collagen content and construct stiffness, and that heterogeneity in species, cell source, scaffold, and loading regime has prevented consensus; the field needs standardised systems and analyses.[53] The parallel with the unquantified human dose–response curve (Section 11) is close, and probably not coincidental: both fields lack an agreed metric of mechanical dose.

Clinically, the same logic already governs rehabilitation after cartilage repair, although it is seldom articulated in mechanobiological terms. Protocols following third-generation autologous chondrocyte implantation, such as matrix-induced autologous chondrocyte implantation (MACI), typically initiate CPM within 24 h and permit immediate partial weight-bearing with progression to full weight-bearing by around 12 weeks—a staged reintroduction of mechanical stimulus timed to graft maturation, albeit with considerable variation between protocols.[56] The rationale is not merely protective: CPM applied to whole joints stimulates chondrocyte PRG4 biosynthesis (Section 2.4),[20] and controlled dynamic loading is thought to guide developing repair tissue towards a hyaline-like structure-function relationship.[57] Consistent with this, randomised comparison of accelerated against traditional weight-bearing progression after MACI found that the accelerated approach did not jeopardise the graft and offered clinical and biomechanical advantages.[58] Loading the repair earlier, in other words, was not a risk to be tolerated but a stimulus to be exploited.

Several gaps nonetheless prevent bioreactor loading protocols from being translated directly into post-operative rehabilitation. First, there is no validated mapping between the two dosimetries: bioreactors specify strain amplitude, frequency, and duty cycle at the construct, whereas rehabilitation is prescribed in terms of weight-bearing, range of motion, and repetitions, and the strains that a given exercise imposes on a graft depend on defect location, joint kinematics, and the stiffness of the surrounding cartilage, and subchondral bone. Second, the constructs differ: most bioreactor studies use immature,

often animal-derived constructs of defined geometry under confined or unconfined compression, whereas clinical grafts must integrate into a heterogeneous defect and withstand shear and fixation demands.[53] Third, the biological environment differs: after surgery, the graft is exposed to synovial fluid and to an inflammatory milieu that can alter chondrocyte mechanosensitivity, as illustrated by inflammatory sensitisation of Piezo1 signalling.[12] Fourth, outcomes are slow and difficult to measure: graft maturation unfolds over months to years and is monitored mainly by imaging, so few randomised trials have compared loading progressions, and these have rarely used compositional end-points.[56,58] Closing these gaps will require computational models that estimate graft strains during specific rehabilitation exercises, wearable sensors that quantify the load actually delivered, and trials that compare loading progressions using compositional MRI as an outcome.

Three points of exchange between the two literatures deserve emphasis. First, the outcome measures are convergent: compositional MRI (Section 3.1) is used both to track adaptation in exercising joints and to assess maturation of repair tissue, so progress in standardising it would pay dividends in both. Second, the mechanotransductive targets are shared: Piezo1, TRPV4, and YAP/TAZ are simultaneously candidate levers for engineering constructs and candidate explanations for why an exercise dose works.[59] Third, and most practically, rehabilitation is the delivery mechanism for the mechanical dose that engineered tissue requires; an implanted construct that is not appropriately loaded is unlikely to mature into functional tissue.[60] The surgical, bioengineering, and rehabilitative literatures are rarely read together. The loading window is a concept that spans all three, and treating post-operative loading as a biological intervention rather than a precaution would be a productive reframing for each.

11. Toward an integrative conceptual model and a research agenda

Synthesising across levels, a coherent conceptual model emerges, which we offer as an integrative hypothesis rather than as an established quantitative relationship. At the cellular level, mechanosensitive machinery (Piezo1, TRPV4, and YAP/TAZ) and downstream pathways (MAPK, NF-κB, and Wnt/β-catenin), whose effects are context-dependent, convert load into net anabolic or catabolic outcomes, consistent with a physiological window whose axes include mode and intermittency as well as magnitude.[2,10,14,19] At the tissue level, compositional imaging and biomarkers reveal that loading elicits transient responses acutely and, with repetition within the window, measurable compositional adaptation—including increased GAG content—over months.[1,23,28] At the joint and patient level, therapeutic exercise does not appear to harm cartilage and is a first-line treatment that improves symptoms and function in OA, with benefit that plateaus rather than scaling with intensity.[4,5,40,42] At population level, observational data on running are compatible with, though not confirmatory of, this pattern, and do not show a clear increase in OA prevalence with higher running volume.[45-47] The molecule, the matrix, the joint, and the population tell a consistent, if not yet quantified, story: physiological loading maintains and can improve cartilage, provided it stays within the window—and provided it reaches the cartilage that is prepared for it.

Why can existing human data, despite this convergence, not yet define clinical thresholds for safe loading? Several obstacles combine. First, the mechanical dose experienced by cartilage cannot be measured directly *in vivo*: tissue stresses and strains must be inferred from external kinetics, musculoskeletal models, or imaging of cartilage deformation, each with appreciable error, and the exposure proxies used in clinical and epidemiological studies—steps per day, running volume, external load—capture neither the magnitude nor the mode of loading at tissue level. Second, the window is multidimensional (Section 2.4) and spatial (Section 6), so a threshold defined for one parameter is unlikely to hold when frequency, rest interval, contact location, or alignment differ. Third, the position of the window appears to vary between and within individuals with age, body mass, meniscal status, injury history, prior conditioning, and the inflammatory state of the joint,[12,31] so that any population-level threshold would be imprecise for a given person. Fourth, structural outcomes change slowly, whereas the compositional and molecular surrogates that respond quickly lack validated cut-offs that predict clinical OA (Section 3). Finally, it would be unethical to randomise people to loads expected to be injurious, so the upper boundary can be approached only through observational data, which are vulnerable to the confounding discussed in Section 8. For these reasons, current evidence supports qualitative guidance—moderate, dynamic, intermittent, and progressively increased loading—but not numerical thresholds.

Several priority gaps follow directly from this model:

(i) Testing and quantifying the dose–response hypothesis: The window is qualitatively supported but quantitatively undefined, and the hypothesised inverted-U-shaped dose–response relationship has not been directly demonstrated in humans. Prospective cohorts with objective, repeated measures

of loading exposure and injury history, and trials that randomise loading dose, are needed to test it. The field needs thresholds—of magnitude, frequency, mode, and cumulative dose—that separate homeostatic from injurious loading for specific activities and populations, ideally linking *in vivo* ambulatory load to mechanosensitive cartilage biomarkers.

(ii) Agreeing on a common metric of mechanical dose: Exercise science, imaging, and tissue engineering each quantify loading differently—steps per day, peak compressive force, strain amplitude, duty cycle—which prevents findings from being pooled or translated across scales.[53] A shared dosimetry would be the single most useful methodological advance available to this field.

(iii) Translating compositional MRI: Compositional imaging remains a research tool.[8] Standardisation and validation that connect imaging biomarkers to clinical decisions would allow exercise prescription to be individualised and monitored rather than generic, in rehabilitation and after cartilage repair alike.

(iv) Characterising distribution, not only dose: Methods that quantify where load falls—contact-stress mapping, kinematic phenotyping—should be integrated with dose measures, since Section 6 suggests distribution may be the dominant variable in post-traumatic and post-meniscectomy knees.

(v) Redressing the hip gap: The hip is markedly under-studied relative to the knee.[22,49] Dedicated imaging and interventional studies, accounting for morphology, are needed before knee-derived confidence is transferred.

(vi) Testing loading in established disease and in repair: The running literature concerns healthy knees, and the strongest adaptation trial concerns at-risk knees. Whether higher-magnitude loading is safe in established OA, and how loading should be dosed to mature a cartilage graft, remain open and clinically consequential questions.[56,58]

(vii) Long-term outcomes and special populations: Most cartilage evidence is short- to medium-term. Longer follow-up and studies in younger and athletic populations, including adolescent athletes, would clarify whether early loading confers lasting protective adaptation.

12. Conclusion

The image of cartilage as a bearing surface that is inevitably spent by use is no longer tenable. Articular cartilage is a mechanically regulated tissue whose homeostasis depends on physiological loading, and OA is better construed as regulatory failure than as simple wear. Across mechanobiology, *in vivo* imaging, clinical trials, and population epidemiology, a consistent picture is compatible with a dose–response window in which moderate, intermittent loading maintains and can modestly improve cartilage, while both unloading and overload are harmful. We present this window as an integrative hypothesis, supported by convergent but largely indirect and observational human evidence, rather than as an established quantitative dose–response relationship. Two refinements deserve to survive this review: the window is multidimensional, so that motion and intermittency matter alongside magnitude; and it is spatial, so that where load falls may matter as much as how much of it there is. For the knee, therapeutic exercise does not appear to damage cartilage and is a first-line treatment; for the hip, the same principles are plausible, but the evidence is thinner. The same dose problem confronts anyone attempting to grow or repair cartilage, which makes this literature the common ground of rehabilitation and tissue engineering. Advancing the field now depends less on asking whether to load the joint than on defining how to load it—testing and quantifying the window, agreeing how to measure the dose, translating the imaging tools that track it, and extending the evidence to the joints and populations that current data neglect.

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