

Perspective

Lipid Networks in Osteoarthritis: Context-Dependent Drivers, Hallmarks of Aging, and Clinical Translation

Nijiao Qin^{1,2#}, Xiwei Fan^{3,4,5#}, Yaxin Tan^{1,2}, Miao He^{3,4}, Indira Prasad^{6,7}, Antonia Rujia Sun^{6,7}, Xiaoxin Wu^{3,4}, Ross Crawford^{6,7,8}, Yanping Wang⁹, Qichen Long^{1,5*}, Guozhi Xiao^{10*}, Xinzhan Mao^{3,4,5*}

¹Department of Laboratory Medicine, the Second Xiangya Hospital of Central South University, Changsha, China. ²Centre for Clinical Molecular Diagnostics, the Second Xiangya Hospital, Central South University, Changsha, China. ³Department of Orthopaedic Surgery, The Second Xiangya Hospital of Central South University, Changsha, China. ⁴Traumatic Orthopaedic Research Lab, The Second Xiangya Hospital of Central South University, Changsha, China. ⁵National Clinical Research Centre for Metabolic Diseases, Department of Metabolism and Endocrinology, The Second Xiangya Hospital of Central South University, Changsha, China. ⁶Centre for Biomedical Technologies, Queensland University of Technology, Brisbane, Australia. ⁷School of Mechanical Medical & Process Engineering, Queensland University of Technology, Brisbane, Australia. ⁸The Prince Charles Hospital, Brisbane, Australia. ⁹Health Management Centre, Xiangya Hospital, Central South University, Changsha, China. ¹⁰Department of Biochemistry, Homeostatic Medicine Institute, School of Medicine, Shenzhen Key Laboratory of Cell Microenvironment, Guangdong Provincial Key Laboratory of Cell Microenvironment and Disease Research, Southern University of Science and Technology, Shenzhen, China.

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ABSTRACT: Osteoarthritis (OA) is an age-related condition affecting the entire joint. Abnormal lipid regulation may act as a trigger for disease onset, or result from inflammation or mechanical injury; alternatively, it may merely manifest as a detectable signal without any direct mechanistic significance. Given that causality cannot be determined based on abundance alone, we propose a compartment-cell temporal framework: pathogenic effects may arise when lipid composition, flux or localisation exceed the tissue's adaptive capacity. Experimental evidence plays a causal role for certain cholesterol and fatty acid pathways, whilst human lipid research remains at the stage of exploring associations. Lipid stress, through dysregulation of organelles such as the endoplasmic reticulum and mitochondria, converges with common features of joint ageing—including cellular senescence, mitochondrial dysfunction, imbalances in autophagy and proteostasis, inflammation, and alterations in signalling—and may reconcile previous conflicting findings in areas such as apolipoprotein E and fatty acid oxidation. At the translational level, weight loss and metabolic management are feasible short-term strategies, and the prospects for lipid stratification are promising; however, testing has not yet met clinical diagnostic standards, and lipid nanoparticles have not yet been established as a therapeutic method. At present, they should be regarded as delivery vehicles; challenges such as joint preservation, deep tissue delivery, and safety still need to be overcome, and validation in human tissue is required. In summary, lipid research contributes to the classification and treatment of OA, but a strict distinction must be made between the maturity of causal evidence and mere correlation.

Keywords: Lipid homeostasis; Osteoarthritis; Ageing; Organelle stress; Spatiotemporal analysis; Lipid nanoparticles.

*Correspondence should be addressed to: Prof. Xinzhan Mao (Email: xinzhan.mao@csu.edu.cn), The Second Xiangya Hospital of Central South University, Changsha, China; Dr. Guozhi Xiao (Email: xiaogz@sustech.edu.cn), Homeostatic Medicine Institute, School of Medicine, Southern University of Science and Technology, Shenzhen, China; and Dr. Qichen Long (Email: qclong@csu.edu.cn), The Second Xiangya Hospital of Central South University, Changsha, China. #These authors contributed equally to this work. *Qichen Long, Guozhi Xiao, and Xinzhan Mao contributed equally as co-corresponding authors.

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Introduction

Osteoarthritis (OA) affects the entire synovial joint and is a major cause of pain and disability in later life [1, 2]. Its clinical and biological heterogeneity cannot be explained by cartilage wear alone. Mechanical injury, ageing, obesity, systemic metabolic disease, low-grade inflammation and tissue maladaptation interact over years, generating phenotypes in which the dominant drivers differ among patients and disease stages [3]. Lipid metabolism is relevant to this heterogeneity because lipids provide energy, define membrane structure and act as signalling molecules that regulate inflammation, redox balance, cell fate and extracellular-matrix turnover [4].

The conceptual difficulty is that the phrase "lipid dyshomeostasis" encompasses fundamentally different observations. A lipid alteration may be upstream and causal, as supported when genetic or pharmacological perturbation changes OA severity in an appropriate model. It may instead be a compensatory or injurious response to cytokines, altered loading, obesity, or cellular senescence. A third category comprises lipid signatures that discriminate clinical groups but are not themselves mediators. A fourth category comprises experimentally tractable targets whose therapeutic maturity may range from proof-of-concept to clinical practice. Conflating these categories overstates mechanism and translation.

This Perspective therefore advances a narrower proposition. Lipid dyshomeostasis is not a universal initiating cause of OA; rather, it is a context-dependent network that can integrate systemic metabolic exposure with local tissue stress and amplify failure of the ageing joint. Pathogenicity depends on five variables: molecular species, concentration or flux, anatomical compartment, responding cell type and disease time point. When lipid handling exceeds tissue-specific adaptive capacity, organelle stress, senescence and inflammatory signalling become mutually reinforcing. This compartment-cell-time framework provides a basis for interpreting apparently contradictory findings and for separating causal biology from biomarker discovery and therapeutic speculation.

Evidence acquisition and interpretive framework

This is a narrative Perspective rather than a systematic review. The literature base was updated and re-screened using targeted searches in PubMed/MEDLINE together with backward and forward citation tracking, covering studies published between January 2000 and 31 July 2026. Search combinations included "osteoarthritis" with "lipid metabolism", "lipidomics", "cholesterol", "fatty acid oxidation", "organelle", "senescence", "autophagy",

"mitochondria", "biomarker", "nanoparticle" and "intra-articular delivery". Evidence was weighed according to the question being addressed: OA-specific perturbation and rescue studies were prioritised for causal inference; prospective and interventional human studies for clinical translation; validated human cohorts for biomarker evaluation; and spatial or multi-omics studies with orthogonal validation for localisation and pathway nomination. Literature outside the OA field was included only where it defined a conserved organelle or delivery principle and is identified as extrapolative. No pooled effect estimates were calculated, and no formal risk-of-bias assessment was performed.

Throughout the article, four evidence categories are distinguished. "Causal driver" denotes an alteration for which direct perturbation changes OA-relevant pathology. "Secondary or adaptive response" denotes a lipid change induced by another process without proof that it initiates disease. "Discovery biomarker" denotes an association that requires independent validation and assessment of incremental clinical utility. "Therapeutic target" is reserved for a mechanism with intervention data, with its maturity specified as clinical, repurposing-stage or preclinical.

Context-dependent lipid pathogenicity

Lipid alterations do not in themselves directly equate to the pathogenic mechanism of OA; their pathological significance is determined by five contextual variables: lipid type, flux/concentration, distribution within the joint cavity, type of responsive cells, and disease stage. These variables collectively form the so-called compartment-cell-time analytical framework (Fig. 1). Existing research suggests that systemic lipid dysregulation may induce local joint lesions; however, evidence regarding whether local lipid alterations exert a regulatory effect on systemic metabolic homeostasis is currently insufficient, and no definitive conclusion can be drawn. The direction of the interaction between the two, as well as the specific causal relationship, remains to be further verified.

Resident cells in cartilage, the synovium, subchondral bone and the infrapatellar fat pad (IFP) can autonomously regulate lipid metabolism, often independently of fasting plasma lipid concentrations. The clinically relevant question is therefore not whether "lipids are high", but which lipid species accumulate, where they accumulate, which cell processes they perturb, and whether the change precedes structural deterioration. Studies on interventions targeting OA-specific pathways corroborate this logic: the absence of the peroxisome proliferator-activated receptor- α (PPAR α)-acyl-CoA thioesterase 12 (ACOT12) axis in chondrocytes enhances lipid de novo synthesis and matrix catabolic activity, whilst modulating the cholesterol 25-

hydroxylase (CH25H)–cytochrome P450 7B1 (CYP7B1)–retinoic acid-related orphan receptor α (ROR α) axis can alter the severity of experimental OA [5, 6]. Excess cholesterol can promote cartilage degeneration via the low-density lipoprotein receptor-related protein 3–syndecan-4 (LRP3–SDC4) signalling pathway, and human cartilage lipidomics suggests that OA is closely associated with impaired α -oxidation caused by defects in 2-hydroxyacyl-coenzyme A lyase 1 (HACL1), a finding

that has been validated by in vitro gene silencing experiments [7, 8]. However, inhibition of the mucosa-associated lymphoid tissue lymphoma translocation protein 1–lysophosphatidylcholine acyltransferase 3 (MALT1–LPCAT3) axis exerts a chondroprotective effect, supporting that phospholipid remodelling has functional significance rather than being a purely descriptive phenomenon [9].

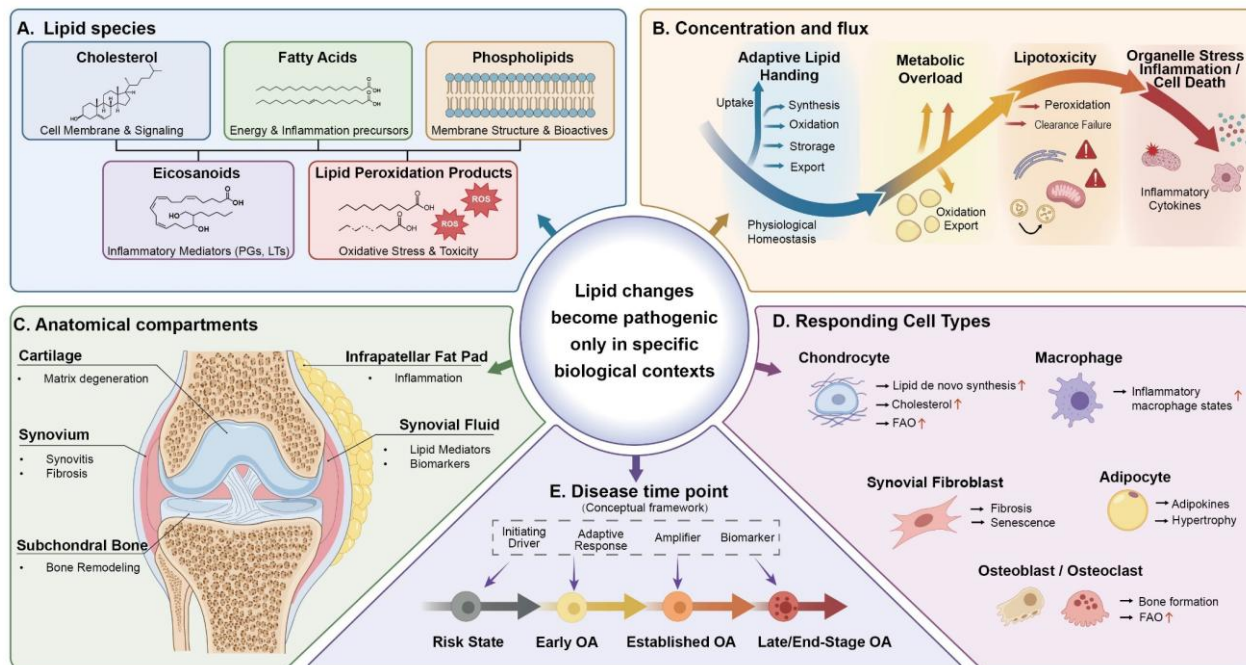


Figure 1. Context-dependent lipid dyshomeostasis across the osteoarthritis course. Lipid disturbances in OA may act as initiating drivers, amplifiers, downstream consequences or non-causal biomarkers. Their pathogenic significance depends on lipid species, concentration or flux, anatomical compartment, responding cell type and disease stage. This framework separates causal mechanisms from adaptive responses, disease correlates and discovery-stage lipid signatures. FAO: Fatty Acid Oxidation; OA: Osteoarthritis; ROS: Reactive Oxygen Species.

Fatty acid metabolism illustrates the decisive role of cell type and disease context in lipid pathogenicity. Excessive fatty acid oxidation (FAO) in chondrocytes accelerates the degradation of the SRY-box transcription factor 9 (SOX9) and catabolic reprogramming [10]. In subchondral bone, in contrast to chondrocytes, where enhanced FAO exacerbates cartilage degradation, osteoblasts in mice exhibit a protective role: upregulated FAO alleviates high-fat diet-induced impairment of bone function [11]. This beneficial effect is counterbalanced by a concurrent outcome: FAO enhancement elevates reactive oxygen species (ROS) levels, thereby promoting osteoclast production [12]. Thus, a pathway such as FAO cannot be classified as protective or pathogenic without specifying the cell type, substrate load, and redox consequences.

The synovium and IFP further demonstrate this compartmental logic. Mass spectrometry imaging shows spatially restricted phospholipid abnormalities in OA synovium that co-localise with inflammatory and vascular features [13]. Human single-cell analysis identifies apolipoprotein E (ApoE)-high stromal populations in the IFP and synovium, while experimental hypercholesterolaemia promotes synovial inflammation and ectopic bone formation [14, 15]. Yet isolated IFP dysfunction does not necessarily initiate cartilage damage; it can amplify disease when combined with systemic metabolic stress [16]. These observations support the IFP as a context-dependent lipid and cytokine hub rather than an autonomous cause of OA. At different stages of OA, whether lipid alterations are driving factors, adaptive responses, disease-amplifying factors or

correlative signals require evidence from time-course studies and interventions to distinguish between them.

Obesity and metabolic disorders alter the levels of fatty acids, lipoproteins, adipokines, gut-derived metabolites and systemic inflammation in the circulation; however, the epidemiological association between systemic lipid markers and OA is often confounded by body weight, mechanical load and comorbidities. Consequently, systemic lipid pathways represent key modulatory factors capable of raising or lowering the threshold for joint dysfunction, rather than invariable primary causes. Inter-organ signals should be interpreted with the same caution. Liver-dependent cholesterol transport and gut-barrier dysfunction can plausibly alter joint exposure, but much of the evidence remains indirect or model-specific [17, 18]. The gut-joint pathway involving intestinal farnesoid X receptor (FXR) and glucagon-like peptide-1 (GLP-1) is supported by recent experimental intervention, but its generalisability across human OA phenotypes is not established [19].

Accordingly, systemic lipid pathways are best viewed as modifiers that may lower or raise the threshold for local joint failure rather than as a single liver-gut-bone causal axis.

Lipid-organelle stress and hallmarks of joint ageing

Ageing is not a background variable in OA; it changes the capacity of joint cells to buffer metabolic and mechanical stress. Canonical hallmarks of ageing include loss of proteostasis, impaired autophagy, mitochondrial dysfunction, cellular senescence, chronic inflammation, altered intercellular communication, and stem or progenitor cell dysfunction [20]. Lipid dyshomeostasis intersects with each of these processes, although direct evidence linking lipid abnormalities to stem or progenitor cell dysfunction in OA remains limited. Nevertheless, the direction of causality is often bidirectional (Fig. 2).

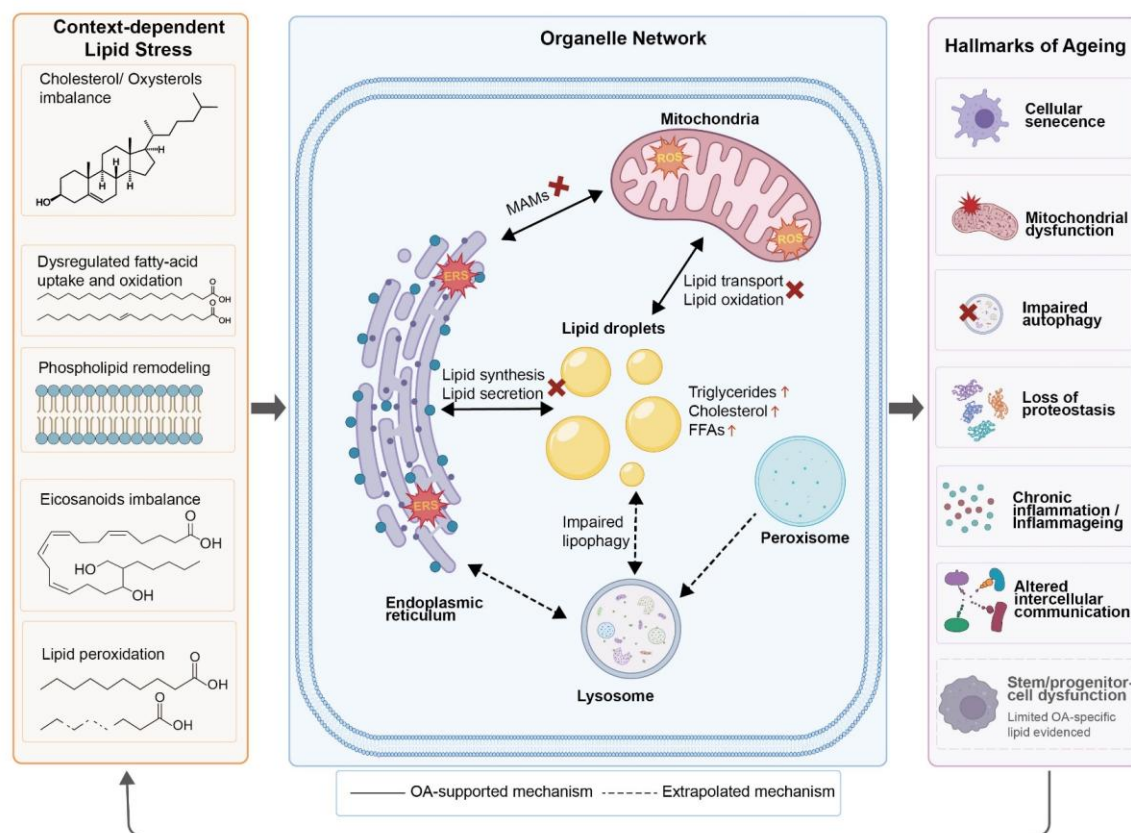


Figure 2. Lipid–organelle crosstalk converges on hallmarks of joint ageing. Lipid stress disrupts coordinated functions of mitochondria, endoplasmic reticulum, lysosomes, lipid droplets and peroxisomes. These organelle-level disturbances promote mitochondrial dysfunction, impaired autophagy, loss of proteostasis, senescence, chronic inflammation and altered intercellular communication, thereby linking lipid dyshomeostasis to ageing-related failure of the osteoarthritic joint. Solid lines indicate interactions supported by OA-specific evidence, whereas dashed lines denote extrapolated or proposed mechanisms requiring further validation. ERS: Endoplasmic Reticulum Stress; FAO: Fatty Acid Oxidation; OA: Osteoarthritis; FFAs: Free Fatty Acids; MAMs: Mitochondria-Associated Membranes; ROS: Reactive Oxygen Species.

The endoplasmic reticulum (ER) is a first convergence point because it coordinates protein folding, membrane-lipid synthesis and calcium homeostasis. Saturated fatty acids and disturbed phospholipid composition can activate the unfolded protein response. In OA chondrocytes, persistent ER stress is associated with impaired autophagy, apoptosis and matrix imbalance, whereas an initially adaptive response may become destructive when stress is sustained [21]. This distinction matters: ER stress markers are not automatically evidence that lipid change initiated disease. Stronger inference requires showing that lipid manipulation precedes ER dysfunction and that restoring lipid handling rescues the OA phenotype.

Mitochondria provide a second convergence point. Chondrocyte mitochondrial dysfunction can disrupt FAO and cholesterol handling, while lipid peroxidation can collapse the membrane potential and amplify ROS production. The reciprocal relationship between mitochondrial redox state and lipid peroxidation has been demonstrated in chondrocytes, and sterol carrier protein 2 (SCP2)-mediated transport of lipid hydroperoxides to mitochondria promotes ferroptotic injury [22, 23]. These findings support a lipid-mitochondrial feedback loop, but they do not establish that all mitochondrial abnormalities in human OA are lipid-initiated.

Lysosomal and autophagic decline represents a third intersection with ageing. Lysosomal destabilisation contributes to chondrocyte injury, and altered cholesterol partitioning can couple lysosomal dysfunction to senescence and inflammation [24, 25]. In obesity-associated OA, defective autophagy can also enhance stimulator of interferon genes 1 (STING1)-mediated inflammatory signalling [26]. Peroxisomal failure offers a complementary route: reduced ATP-binding cassette subfamily D member 2 (ABCD2) expression is associated with fatty-acid accumulation and matrix catabolism in OA chondrocytes [27]. Although some mechanistic details derive from broader cell biology, the OA-specific evidence collectively indicates that lipid clearance, organelle quality control and redox buffering deteriorate together.

The abnormal accumulation of lipid droplets, as the fourth convergence point of lipid imbalance, is consistent with the characteristics of cellular ageing. Mouse and cellular models have shown that the accumulation of 25-hydroxycholesterol (a cholesterol metabolite) synergistically upregulates the synthesis and uptake of cholesterol, fatty acids and triglycerides, promoting the formation of large numbers of lipid droplets within chondrocytes. These changes induce cellular hypertrophy and the release of catabolic enzymes; whilst these phenotypes overlap with chondrocyte ageing, they are not unique to cellular ageing [28]. Consequently, as

emphasised below, a reliable determination of cellular ageing requires multidimensional evidence that goes beyond a single biomarker.

Organelles such as mitochondria, the endoplasmic reticulum, lipid droplets and lysosomes do not exist in isolation; rather, they form a dynamic interactive network via membrane contact sites (MCS), precisely regulating lipid metabolism, redox balance and protein homeostasis. In OA, lipid imbalance leads to structural and functional abnormalities in this network. The disruption of the structural integrity of mitochondria-associated ER membranes (MAMs) leads to dysregulated calcium signalling and the sustained activation of ER stress, a burst of ROS, and an imbalance in mitochondrial dynamics [29, 30]. Concurrently, the dissociation of the lipid droplet-mitochondrial contact interface impedes the directed transport and oxidation of fatty acids, exacerbating lipid accumulation and creating a vicious cycle [31]. Lysosomal dysfunction and the blockage of the lipophagy pathway result in the inability to effectively clear damaged organelles and toxic lipids, leading to a further accumulation of cellular damage [32]. In summary, organelle crosstalk may serve as a key hub integrating lipid imbalance with ageing-related cellular responses, constituting a potential critical link in the pathogenesis of OA. However, it should be noted that some of the evidence currently supporting this mechanism stems from OA-specific studies, whilst other evidence still relies on extrapolation from the broader field of cell biology.

Cellular senescence is both a consequence and a source of lipid disturbance. Fatty acid synthase (FASN)-dependent lipid reprogramming can reinforce a senescent chondrocyte phenotype [33]. Senescent synovial fibroblasts can, in turn, release lipid-rich mediators that induce chondrocyte senescence and matrix degradation, creating a local feed-forward circuit [34]. This links lipid metabolism to chronic inflammation and altered intercellular communication rather than treating these hallmarks as separate pathways.

It is worth noting that, based on the recently proposed ‘senotype’ research framework, defining cellular senescence solely on the basis of a single ageing feature is highly prone to conceptual confusion, as these features are also observed in states such as immune activation, stress responses and terminal differentiation [35]. Consequently, future research into the ageing of joint cells must be systematically analysed across five dimensions: cellular identity and biological context; the context in which ageing is induced; the temporal dimension; multimodal molecular and structural characteristics; and functional outcomes.

Spatiotemporal heterogeneity explains apparent contradictions

Several apparent contradictions in the literature become coherent when compartment, cell type, dose, time and species are considered together. ApoE is a clear example. Systemically, ApoE-dependent lipoprotein clearance can limit cholesterol exposure; locally, ApoE-high IFP or synovial stromal populations may participate in fibrotic and inflammatory programmes. These findings are not mutually exclusive because circulating lipoprotein transport and tissue-specific stromal signalling are different biological functions [14, 15]. Isoform, concentration and disease stage may add further variation.

Lysophosphatidylcholine (LPC) may reflect the distinction between concentration and flux. Reduced LPC in OA synovium can coexist with a higher plasma LPC-to-phosphatidylcholine (PC) ratio associated with progression because tissue pools reflect local enzymatic conversion, uptake and oxidation, whereas plasma ratios reflect systemic transport and metabolism [13, 36]. Neither measure alone identifies the operative enzyme or establishes causality. Similarly, reduced sphingomyelin in equine synovial extracellular vesicles (EVs) and increased sphingomyelin species in human synovial fluid may reflect differences in species, extracellular compartment, disease induction and platform coverage rather than a true biological reversal [37, 38].

FAO is likewise cell-specific. Excessive FAO can be catabolic in chondrocytes, but the same pathway cannot be assumed to have identical consequences in osteoblasts, osteoclasts or stromal cells. The relevant variable is therefore not FAO activity in isolation but the balance between ATP demand, substrate load, antioxidant capacity and cell function [10]. A similar dose principle applies to free fatty acids: storage in lipid droplets may buffer transient exposure, whereas persistent overload can become lipotoxic.

Conventional bulk lipidomics averages across these dimensions. Spatiotemporal analysis adds information that abundance alone cannot provide: the anatomical origin of a lipid signal; the cell population or organelle in which it occurs; whether it precedes, accompanies, or follows structural damage; and whether the same species has different effects across disease stages. Mass spectrometry imaging can localise lipid species within cartilage, synovium and IFP; single-cell and spatial transcriptomics can identify the cells expressing relevant enzymes and transporters; isotope tracing and metabolic flux analysis can test pathway directionality; and serial sampling can establish temporal order [39–41]. These technologies should be integrated rather than treated as independent catalogues. The critical experiment links

spatial localisation and temporal flux to a perturbable mechanism and an OA-relevant functional outcome.

Clinical implications

Biomarkers: discovery signals are not yet clinical tests

Lipidomic studies have identified serum, plasma, synovial-fluid and tissue signatures associated with OA presence, grade or pain. Reported values for the area under the receiver operating characteristic curve (AUC) can be high, including combinations of phosphatidylcholines, sphingomyelins and related lipids [42]. These studies demonstrate biological signal, but most remain discovery-stage.

Several features limit clinical readiness. Cohorts are commonly small, single-centre and cross-sectional; control groups may differ in age or disease context; joint site and structural stage vary; and external validation is uncommon. Pre-analytical variables include fasting state, collection tube, processing delay, freeze-thaw exposure and storage. Clinical confounders include adiposity, diabetes, diet, sex, age, medication use and lipid-lowering therapy. Analytical variation arises from extraction method, chromatography, mass-spectrometry platform, internal standards, lipid nomenclature and batch correction. Importantly, associations between lipoprotein subclasses and incident OA may attenuate after adjustment for body mass and related metabolic factors [43, 44], and sex-specific metabolic patterns further complicate universal thresholds [45].

A candidate should therefore not be described as an "early diagnostic biomarker" solely because it separates cases from controls in a discovery dataset. Clinical actionability requires prospective sampling before radiographic or symptomatic progression, independent multi-centre validation, prespecified thresholds, calibration, comparison with age, body mass, symptoms and imaging, and evidence that the test changes a management decision. The same standard applies to machine-learning signatures: internal cross-validation cannot substitute for external validation, and high-dimensional feature selection can inflate apparent accuracy.

Pain-related lipids may have a nearer-term role in phenotyping than in diagnosis. Hydroxylated arachidonic-acid metabolites have shown longitudinal associations with knee pain progression, and broader lipid profiles explain some variability in pain that is not captured by structural imaging [46, 47]. These findings justify mechanistic and prognostic research, but a clinically useful pain panel would still need to outperform simple

clinical predictors and demonstrate reproducibility across analgesic use, metabolic status and joint sites. Table 1 therefore classifies current lipid-centred applications by evidence maturity rather than by headline AUC.

Table 1. Evidence maturity of lipid-centred clinical applications in OA

Clinical application	Representative evidence in OA	Key limitations	Evidence maturity	Current interpretation
Development of biomarkers	Discovery cohorts and longitudinal associations across serum, plasma and synovial fluid [42-47].	Small or heterogeneous cohorts, pre-analytical variation and limited independent validation.	Discovery-stage	Not clinically actionable until prospective, multi-centre validation demonstrates incremental utility.
Metabolic phenotype management	Randomised trial evidence for improved pain and function with semaglutide in people with obesity and knee OA [48].	Benefit does not establish direct lipid-pathway or structural modification.	Clinically actionable for an indicated phenotype	Manage obesity and metabolic risk; do not present as a lipid-specific disease-modifying OA therapy.
Nutritional lipid supplementation	Fish-oil trial data suggest possible symptomatic benefit [49].	Inconsistent dose-response and limited structural end points.	Adjunctive; uncertain	May be considered selectively, but is not an established disease-modifying treatment.
Lipid-lowering or metabolic drug repurposing	Mendelian-randomisation evidence for statin-related pathways [50].	Residual confounding and absence of OA-specific efficacy trials.	Repurposing-stage	Investigational; routine use should follow cardiovascular or metabolic indications.
Lipid nanoparticle delivery	OA animal studies support cartilage retention and delivery of RNA or small-molecule cargo [52-56].	Synovial clearance, cartilage penetration, immunogenicity, repeated dosing and lack of human OA validation.	Preclinical	Treat LNPs as delivery vehicles; specify cargo, target, pharmacodynamics and safety.

LNP: Lipid nanoparticle; OA: Osteoarthritis.

Treatment should be stratified by evidence maturity

The main impact of the Lipid Centre Framework on clinical practice at present is to promote phenotype-based management of obesity and cardiometabolic risk; however, further evidence is required to support lipid-specific diagnostic testing or disease-modifying therapies. Weight reduction and management of obesity-related risk can improve pain and function and may reduce systemic inflammatory and mechanical load. In a large randomised trial, once-weekly semaglutide improved outcomes in people with obesity and knee OA, supporting metabolic treatment in an appropriate phenotype [48]. This does not establish semaglutide as a direct lipid-targeted disease-modifying OA drug; much of the benefit may arise from weight loss and systemic metabolic improvement.

Nutritional lipid interventions require more restrained interpretation. Trials of fish-oil supplementation suggest possible symptom benefit, but dose-response findings are inconsistent and evidence for structural modification is insufficient [49]. Omega-3 supplementation may be

considered an adjunct in selected patients, not an established disease-modifying treatment. Therefore, omega-3 should not currently be described as an established disease-modifying intervention for OA; even when used for symptom management, it should only be regarded as an adjunctive strategy. Statins and other lipid-lowering agents are biologically plausible repurposing candidates, yet Mendelian-randomisation results do not establish an OA indication [50]. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition, peroxisome proliferator-activated receptor- γ modulation, bile-acid signalling and transient receptor potential vanilloid 1 (TRPV1)-directed approaches remain investigational for OA unless supported by direct OA trials.

Local biologic procedures should also be separated from lipid-targeting claims. Micro-fragmented adipose tissue (MFAT) contains stromal and immune components and has shown symptomatic improvement in clinical studies, but it is not a therapy that specifically corrects lipid dyshomeostasis, and product heterogeneity complicates interpretation [51]. It is therefore best

considered an adjacent intra-articular biologic strategy rather than evidence that lipid modulation itself is clinically established.

LNPs are delivery vehicles, not intrinsically lipid-modifying therapies

The term LNP can obscure two distinct concepts. A lipid-modifying therapy changes a pathogenic lipid pathway. An LNP is primarily a carrier whose lipid composition enables delivery of a cargo. The cargo may be messenger RNA (mRNA), small interfering RNA (siRNA), microRNA, a small molecule, protein, anti-inflammatory agent or, in future, a gene-editing component. Any claim of therapeutic effect must therefore identify both the vehicle and the cargo-mediated mechanism.

OA-specific preclinical studies provide proof-of-concept. Cartilage-retentive lipid formulations, mRNA-LNP delivery of fibroblast growth factor 18 (FGF18), and hydrogel-distributed nanoparticles targeting cholesterol metabolism have reduced cartilage degeneration or promoted repair in animal models [52-54]. pH-responsive carriers and cartilage-targeting ligands offer additional control over release and localisation [55, 56]. These are encouraging engineering advances, but there is little evidence from human OA tissues and no established clinical LNP therapy for OA.

Translation is constrained by joint-specific barriers. Synovial fluid dilutes injected material; lymphatic and synovial clearance shorten residence time; the dense, negatively charged cartilage matrix restricts penetration; diseased cartilage is spatially heterogeneous; and uptake by synovium or macrophages may divert cargo from chondrocytes. Repeated dosing raises questions about innate immune activation, complement responses, local toxicity, persistence of ionisable lipids and anti-polymer antibodies. Manufacturing variables, particle-size distribution, cargo integrity, sterilisation, storage and batch release must also be controlled [57, 58]. An OA-oriented development programme should therefore report retention, depth of cartilage penetration, cell-type uptake, pharmacodynamic target engagement, pain and function, structural outcomes, biodistribution, immunogenicity and repeat-dose safety. Organelle-targeting should remain a preclinical hypothesis until these foundational requirements are met.

Priorities for the field

Five priorities would move the field from descriptive lipidomics towards clinically useful mechanism. First, causal inference should combine human genetic or longitudinal evidence with cell-specific perturbation and

rescue experiments. Second, studies should sample matched plasma, synovial fluid and joint tissues to distinguish systemic exposure from local production, and should report sex, age, obesity, diabetes, fasting status and lipid-lowering medication. Third, ageing biology should be built into experimental design through aged animals, senescent-cell states and measurements of autophagy, proteostasis and mitochondrial reserve rather than inferred from chronological age alone. Fourth, biomarker studies should use prospective, multi-centre validation and test incremental value over clinical and imaging models. Fifth, delivery studies should prioritise OA-specific human tissue penetration, repeat-dose safety and manufacturability before increasingly elaborate organelle-targeting claims.

These priorities also define how advanced technologies should be used. Spatial omics should nominate the compartment and cell population; flux analysis should establish direction; perturbation should test necessity or sufficiency; and longitudinal clinical sampling should determine whether the signal precedes progression. Artificial intelligence may assist integration and formulation optimisation, but it cannot compensate for biased cohorts, unstandardised assays or absent external validation [59, 60].

Conclusion

Lipid dyshomeostasis is best understood as a context-dependent contributor to OA rather than a singular upstream cause. Selected cholesterol-handling, phospholipid-remodelling and fatty-acid pathways have causal support in OA models, whereas many human lipid signatures remain consequences, correlates or discovery biomarkers. The unifying biological insight is that lipid stress and the hallmarks of joint ageing converge at organelles and intercellular communication networks, creating feedback among proteostatic failure, mitochondrial dysfunction, impaired autophagy, senescence and chronic inflammation. The clinical consequence is an evidence hierarchy: metabolic risk management is actionable; lipidomic tests and repurposed lipid drugs require prospective validation; and LNPs are promising delivery platforms whose OA translation remains preclinical. Explicitly separating mechanism, biomarker status and therapeutic maturity should make lipid-centred OA research more reproducible, more interpretable and more clinically relevant. The most realistic opportunities at present lie in utilising lipid-related subtyping to support mechanistic research, patient stratification and clinical trial enrichment; routine lipidomic testing and OA-specific lipid-targeted prescriptions are still premature at this stage.

Authors' contributions

All authors contributed to the conception and design of this Perspective, acquisition and interpretation of the literature, and drafting or critical revision of the manuscript. Nijiao Qin and Xiwei Fan prepared the initial draft. Qichen Long, Guozhi Xiao and Xinzhan Mao supervised the work and coordinated the revision. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Declaration of Generative AI in Scientific Writing

During preparation of this manuscript, the authors used DeepSeek and ChatGPT (OpenAI) solely for language editing. The authors subsequently reviewed and revised all output, verified the scientific content and references, and take full responsibility for the final manuscript.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this submission. All

authors have reviewed this declaration and confirm its accuracy.

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