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Review Article

The role of metabolites in the progression of osteoarthritis: Mechanisms and advances in therapy

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ABSTRACT

Osteoarthritis (OA) is a progressive degenerative disease affected by many factors, and there is currently no effective treatment. In recent years, the latest progress in metabolomics in OA research has revealed several metabolic pathways and new specific metabolites involved in OA. Metabolites play significant roles in the identification and management of OA. This review looks back on the development history of metabolomics and the progress of this technology in OA as well as its potential clinical applications. It summarizes the applications of metabolites in the field of OA and future research directions. This understanding will advance the identification of metabolic treatment goals for OA.

The translational potential of this article: The development of metabolomics offers possibilities for the treatment of OA. This article reviews the relationship between metabolites associated with chondrocytes and OA. Selectively altering these three metabolic pathways and their associated metabolites may hold great potential as new focal points for OA treatment.

1. Introduction

It is estimated that by 2050, there will be 2.1 billion people over the age of 60. This will be followed by significant rises in age-related illnesses, such as Alzheimer's disease, heart disease, cancer, and Osteoarthritis (OA) [1]. OA is the most common degenerative joint disorder that affects one or several diarthrodial joints, including small joints (such as those in the hand) and large joints (such as the knee and hip joints) [2,3]. It presents as alterations in the structure of joint cartilage, subchondral bone, ligaments, the joint capsule, the synovial membrane, and the muscles surrounding the joint [4,5]. With the increasing prevalence of OA, its burden on society is increasing. However, no effective disease-modifying drugs are currently available; therefore, it is critical to develop therapeutic targets, techniques, and/or drugs that can effectively reverse or halt the disease process [6]. This review article delves into the metabolic alterations observed in the development and advancement of OA, placing special importance on amino acid metabolism, glycolysis, and lipid metabolism. It also explores the recent progress made in unraveling the significance of chondrocyte metabolism in OA. The aim is that these new findings will pave the way for innovative approaches to managing OA.

2. OA

OA is a prevalent degenerative condition distinguished by localized articular cartilage deterioration in synovial joints, alterations in subchondral bone structure, the development of bony outgrowths at the edges of joints, thickening of the joint capsule, and mild inflammation of the synovial membrane [17,18]. Among the elderly population, OA stands out as a primary culprit for joint discomfort and impaired mobility [19]. Globally, OA is reported to negatively impact the well-being of over 500 million individuals. Furthermore, it contributes

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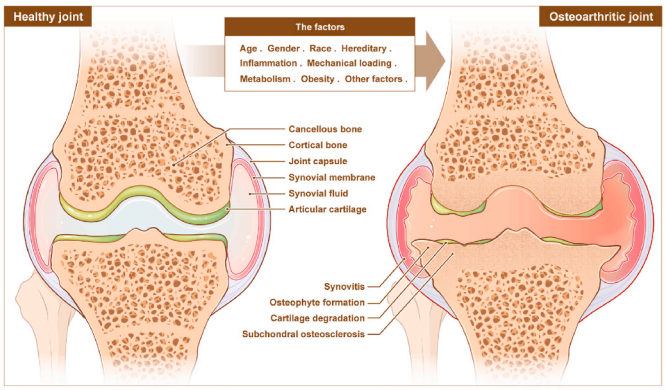

Figure 1. Schematic overview of structural changes in OA and a comparison of a normal joint and an OA joint.
Under the influence of age, sex, race, inflammation, genetics, obesity, mechanical load, metabolism and other factors, the normal knee joint gradually exhibits synovitis, cartilage degradation, subchondral bone remodeling and sclerosis, osteophyte formation and other manifestations, and ultimately progresses to advanced OA.

significantly to healthcare expenses and results in substantial socioeconomic strains [5,20]. OA can occur in multiple joints of the body, including but not limited to the knee, hip, spine, and hand [21,22]. The pathogenesis of OA is regarded as a complex process and has not been fully studied [23]. It primarily involves age, sex, race, inflammation, heredity, obesity, mechanical loading, metabolism and other factors [5,24,25]. Since 1990, global epidemiological research has revealed a steady rise in the prevalence of OA [26,27]. The pain and mobility problems caused by OA affect the quality of life of older people. Additionally, it presents a considerable challenge to societal spending and healthcare systems on a large scale [5,28,29]. In the context of aging, the slow progression of OA and the correlation between pathological changes and clinical symptoms indicate that the progression of OA is usually substantially advanced at the time of diagnosis [30] (Fig. 1).

The treatment regimen for OA typically involves a gradual approach, starting with the administration of NSAIDs and corticosteroid injections into the affected joint to alleviate pain. In cases where the condition has progressed significantly, joint replacement surgery may be recommended for patients [31]. Currently, treatments for OA can relieve symptoms but cannot control the biological process of tissue damage [32]. Given the lack of targeted pharmacological treatments to halt the onset of OA, the identification of substantial biomarkers and treatment objectives is imperative. These markers and targets should not only enhance early detection and monitor disease advancement but also facilitate the creation of novel intervention approaches [33].

As OA advances, numerous enzymes within chondrocytes undergo alterations, triggering a cascade of metabolic shifts. These changes may render specific metabolites as promising diagnostic indicators for OA. On the other hand, certain metabolic pathways or metabolites may exacerbate or prevent the progression of OA [10]. Metabolic syndrome is believed to be associated with the development and advancement of OA [34,35]. Metabolic syndrome is characterized by the presence of three or more seemingly benign and relatively prevalent conditions, including central obesity, hypertension, elevated triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, and glucose intolerance [36]. Collectively, these conditions significantly elevate the risk of developing serious chronic diseases. It is estimated that approximately one-quarter of the adult population globally is affected by metabolic syndrome, a statistic that raises concern given that individuals within this demographic are five times more likely to develop diabetes and two to three times more likely to experience heart disease, stroke, and certain types of cancer [36,37]. OA is no longer regarded merely as a condition resulting from 'wear and tear'; rather, the involvement of metabolic factors in the pathogenesis of OA contributes to the complexity of the disease [38,39].

3. Metabolites

Metabolites, as the substrates and byproducts generated during cellular biochemical processes, can be quantitatively measured in a single analysis [40,41]. They may originate from the host organism itself, microbial sources, or external factors like diet [42].

3.1. Discovery of metabolites

For the past three centuries, the discovery of metabolites has been the foundation of biochemical advancements. Urea, discovered by scientist Hermann Boerhaave in the 18th century, was the first metabolite to be identified. The discovery of urea was largely due to its ubiquitous presence. Extensive research and identification were subsequently conducted on the most abundant metabolites, such as amino acids, sugars, and lipids [59]. Metabolomics-related research can be traced back to metabolic profiling, which began in the 1970s. Metabolic profiling of this type typically employs gas chromatography–mass spectrometry (GC–MS) technology for the qualitative and quantitative analysis of metabolites present in patients' body fluids, facilitating disease screening and diagnosis. This method of using metabolic profiling in the clinical diagnosis of related diseases has been used. In 1983, van der Greef used mass spectrometry to study metabolites in rat urine samples for the first time worldwide. Following this, numerous researchers started utilizing high-performance liquid chromatography (HPLC) and nuclear magnetic resonance (NMR) techniques for analyzing metabolic spectra [60]. After the 1990s, the research targets were mainly focused on the metabolism of drugs in the body [61]. In 1997, Oliver proposed the need to assess the genetic function of yeast genes and their redundancy by quantitative analysis of as many metabolites as possible, linking the function of metabolites and biological genes for the first time [62]. The year 2000 saw Fiehn et al. from the Max Planck Institute in Germany introduce the notion of metabolomics, which they described as the comprehensive examination, both qualitatively and quantitatively, of all metabolites present in a particular biological sample while adhering to specific conditions [63].

3.2. Application of metabolites

Various studies have been performed to expand the understanding of the role of metabolites. Metabolomics is an emerging field in which small-molecule metabolites are systematically studied in a biological system. Moreover, this approach has potential for early diagnosis and therapeutic effect monitoring. In addition, these discoveries can enhance our comprehension of the etiology of illnesses [41]. Metabolites represent the ultimate outcomes of perturbations in genomics, transcriptomics, and/or proteomics. Consequently, alterations in the concentrations and/or flow of metabolites can unveil significant biological changes within the system [42]. First, metabolites play important roles in regulating epigenetic changes and maintaining the pluripotency of embryonic stem cells [64,65]. In addition, metabolites play a role in signaling through metabolite–protein interactions that initiate signaling cascades to help facilitate cellular responses [66,67]. Furthermore, metabolites have the potential to impact the surrounding environment in an indirect manner [40]. Typically, the body's homeostatic mechanisms work to offset any negative biological effects caused by this impact. Nonetheless, this regulatory balance can be disrupted by factors such as aging and illness, leading to a decrease in function and the inability to restore equilibrium [40].

3.3. Metabolites and diseases

Metabolites play a significant role in the onset and progression of

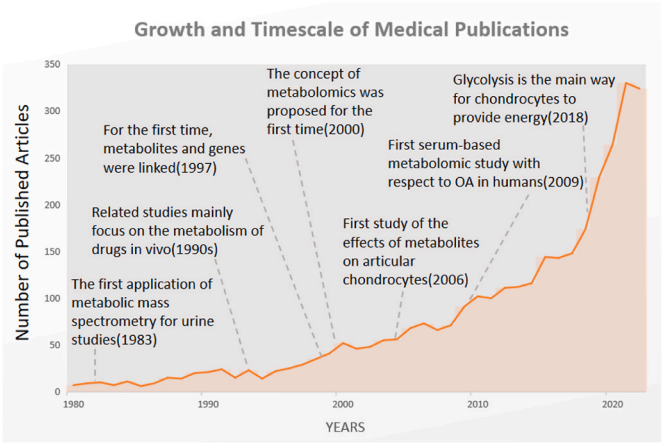

Figure 2. Modern historical landmarks regarding metabolites and OA research. The Medline database was searched for articles related to "osteoarthritis" and "metabolism" published from January 1, 1980, to December 31, 2021. In 1983, metabolic profiling was first applied to study rat urine, after which a number of scientists applied metabolic profiling technology. In the 1890s, research focused on the metabolism of drugs in the body and other aspects. In 1997, the functions of metabolites and biological genes were first linked. With further research in this area, the concept of metabolomics was first proposed in 2000. Since then, research on "osteoarthritis" and "metabolism" has increased rapidly. In the Medline/PubMed database, "osteoarthritis", "arthrosis", "degenerative arthritis", "wear-and-tear arthritis", "joint degeneration", and "osteoarthrosis" were used as the search terms, combined with "metabolism", "metabolomics", "metabolite", "metabolin", "metabolite", and "metabolic syndrome".

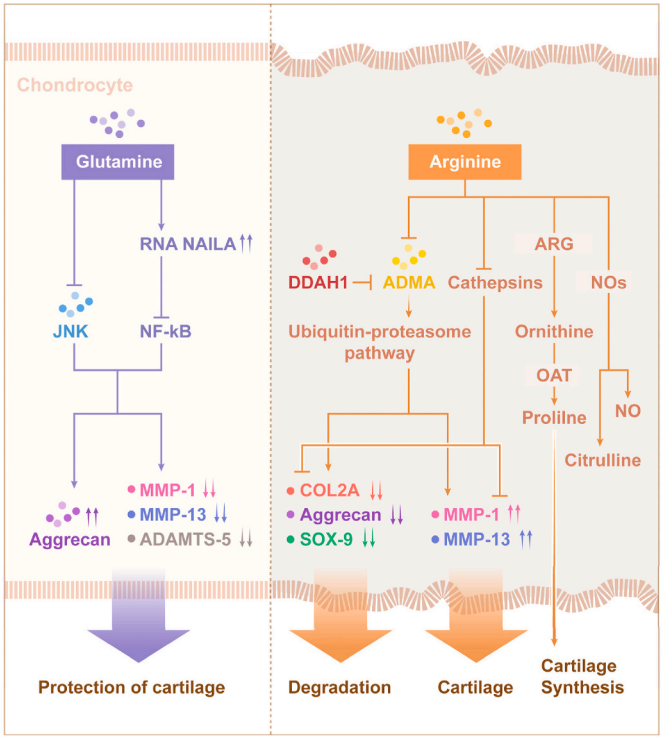

Figure 3. Amino acid metabolism in chondrocytes.
Glutamine protects OA chondrocytes by inhibiting the Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) signaling pathways to promote the expression of proteoglycans and inhibit the expression of MMP-1, MMP-13 and ADAMTS-5. ADMA affects the metabolism of chondrocytes through the ubiquitin–proteasome pathway, reducing anabolic factors (COL2A1 and aggrecan) and increasing catabolic factors (MMP3 and MMP13), inducing degeneration and senescence of chondrocytes, and reducing extracellular matrix deposition, thus accelerating the progression of OA. Downregulation of dimethylarginine dimethylaminohydrolase-1 (DDAH1) leads to increased ADMA levels in OA patients.

diseases. In contemporary society, there is a prevalence of various long-term illnesses, including obesity, diabetes, and cardiovascular diseases, in which disruption of metabolic processes significantly contributes to the development and advancement of the conditions. Over time, scientific investigations have shed light on how metabolic disturbances are emerging as a primary factor in the onset of disorders like cancer, cognitive decline, and respiratory conditions, which were traditionally not associated with metabolic issues [68]. Diabetes mellitus is a group of metabolic conditions resulting from either a lack of insulin secretion or a decrease in the responsiveness of target tissue cells to insulin, either partially or completely [69]. Disorders of the nervous system, such as Alzheimer's disease and major depression, are linked to alterations in the concentration of polyunsaturated fatty acids (PUFAs) and the signaling pathways under their control. PUFAs and their derived compounds influence mood and cognitive functions by modulating a range of mechanisms, including neurotransmission, cell viability, and neuroinflammation [70]. The microbiota in the digestive tract breaks down complex carbohydrates, like fiber from the diet, to generate essential

Table 1
Key studies investigating amino acid metabolism.

Study design	Study population	Specimen	Findings	Sample size	Ref.
Cross-sectional	Human, Canadian population	Plasma	The levels of arginine in OA patients are on average 65 % lower than in healthy controls.	256	[7]
In vitro	Human	Osteoblasts-OA cells	Supplementing L-arginine can reduce the levels of inflammatory mediators in human osteoblasts.	/	[8]
Cross-sectional	Human, Italian population	Plasma and SF	The concentration of ADMA in the synovial fluid of OA patients is significantly higher than in the plasma.	63	[9]
In vivo and in vitro	Human and mice	Chondrocytes and SF	An increase in ADMA levels can induce cartilage degeneration and aging.	12	[10]
In vivo and in vitro	Human and mice	Serum and chondrocytes	L-arginine metabolism inhibits arthritis and inflammatory bone loss	52	[11]
Cross-sectional	Human, British females	Serum	The ratio of BCAAs to histidine in OA patients is higher than in the control group.	598	[12]
In vitro	Rabbits	Chondrocytes	Treatment of chondrocytes with glutamine can protect cells from heat stress and NO-induced apoptosis.	32	[13]
In vitro and in vivo	Mice	Chondrocytes and mice	Alleviating OA by regulating glutamine metabolism in chondrocytes.	30	[14]
In vitro and in vivo	Rats	Chondrocytes and rats	L-Gln can alleviate cartilage degeneration and delay the progression of OA.	18	[15]
In vitro and in vivo	Human and mice	Chondrocytes and mice	Glutamine inhibits JNK and NF-κB signaling pathways.	10	[16]

SF, synovial fluid; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine.

compounds like short-chain fatty acids and succinate through fermentation [71]. Numerous research findings have demonstrated the positive impacts of metabolites in combating and managing conditions such as obesity [72,73], type 2 diabetes mellitus [74–76], and nonalcoholic fatty liver disease [77–79]. Different diseases and different conditions have different metabolomic changes. Therefore, regulating the concentration of metabolites can play a certain regulatory role in disease.

4. Metabolites and OA

4.1. History

In 1989, Williamson et al. first performed metabolic profiling of synovial fluid from OA patients using NMR technology [80]. Since then, a number of researchers have applied NMR technology to study chemical markers of arthritis [81–83]. Although these studies focused mainly on rheumatoid arthritis, they still provide useful biochemical information about joint synovial fluid. With the introduction of the concept of metabolomics in 2000 [63], research in this field has gradually accelerated. In vitro experiments conducted in 2006 by Tonomura examined the impact of glutamine on rabbit chondrocytes. This study is believed to be the pioneering research on the influence of metabolites on articular chondrocytes [13]. The initial serum-based metabolomics investigation of human OA occurred in 2009, revealing that the ratio between branched-chain amino acids and histidine could serve as a promising biomarker with potential clinical utility for OA [12]. The development of metabolomics provides a new direction for OA research (Fig. 2).

5. Amino acid metabolism (Table 1)

Amino acids serve as the essential components for the creation of proteins, in addition to acting as the origins of different metabolites and biologically active compounds [84]. Changes in amino acid metabolism are related to the pathogenesis, diagnosis and treatment of OA [84,85] (Fig. 3).

5.1. Arginine

Arginine is a semiessential amino acid in the human body. It is a component of the ornithine cycle and has vital physiological functions. It is the precursor of nitric oxide, polyamines, glutamate, urea, proline, citrulline, creatinine and agmatine [86]. Zhang et al. reported that, on average, 65 % lower levels of arginine were present in OA patients than in healthy control individuals [7]. In the first phase of the study, 64 individuals with knee OA and 45 without the condition participated, while in the second phase, there were 72 knee OA patients and 76 control individuals involved. Upon accounting for age, gender, and BMI, it was observed that the average plasma arginine level in knee OA patients was 69 μM lower compared to the control group [7]. Ornithine, originating from the conversion of arginine, undergoes further metabolism to generate proline, polyamines, and glutamine. In scenarios where cartilage sustains damage, there is a likelihood of the arginine–-proline metabolic pathway becoming excessively stimulated to facilitate the production of proline necessary for collagen synthesis and the repair of cartilage [33]. Moreover, arginine serves as a precursor for the production of nitric oxide (NO) [86]. NO was traditionally believed to be involved in various processes, such as apoptosis, and consequently playing a role in the development of OA [87]. Furthermore, arginine has an antimetabolic effect as a natural inhibitor of cathepsins, which are proteases that degrade cartilage [88]. A decrease in arginine due to endogenous consumption reduces the inhibitory effect of arginine on tissue proteases, leading to the destruction of cartilage [7].

In addition, arginine also directly or indirectly affects the functions of osteoblasts and osteoclasts. It has been shown that supplementation with L-arginine reduces inflammatory mediator levels in human osteoblast-OA cells [8]. The latest research indicates that L-arginine has inhibitory effects on arthritis and bone loss, and directly blocks the generation of osteoclasts induced by TNF-α in both mice and humans [11]. Their study found that L-arginine converts glycolysis into oxidative phosphorylation in inflammatory osteoclasts, resulting in increased ATP generation, elevated purine metabolism, and higher levels of adenosine and xanthine. These findings confirm that L-arginine improves arthritis and bone erosion by reprogramming and disturbing purine metabolism in osteoclasts. Therefore, despite the lack of comprehensive research on how arginine affects OA development, existing research suggests that arginine has some potential in OA treatment.

Asymmetric dimethylarginine (ADMA) is a L-arginine analog found in human plasma and urine, but they have different functions [9]. Elevated levels of ADMA have been shown to inhibit bone formation in the musculoskeletal system [89]. A cross-sectional study revealed that ADMA concentrations were significantly greater in synovial fluid than in plasma in patients with OA [9]. The involvement of ADMA in the advancement of OA has also been explored by other researchers [10]. Metabolomic data showed that ADMA levels were significantly elevated in degenerating chondrocytes. In experiments with human chondrocytes, increased ADMA levels in degenerated chondrocytes were shown to trigger cartilage degeneration and senescence. The results showed that ADMA levels had good predictive value for the diagnosis of OA with good sensitivity and specificity. ADMA, a rival endogenous antagonist of nitric oxide synthase (NOS), is capable of diminishing NOS function, leading to a decline in the levels of NO [90]. By inhibiting NOS, ADMA is involved in cardiovascular diseases, such as ventricular hypertrophy [91] and atherosclerosis [92]. NO has been shown to promote chondrocyte apoptosis by inhibiting proteoglycan and type II collagen synthesis, which activates metalloproteinases [87]. In fact, in the absence of inflammatory stimuli, basal levels of NO are quite low [10]. Thus, the anti-NOS effect of ADMA may not be evident under physiological conditions [10]. These findings indicate that ADMA has the potential to hasten the deterioration of cartilage and advance the development of OA regardless of the NOS/NO pathway. ADMA impacts the metabolic processes of chondrocytes via the ubiquitin-proteasome pathway, leading to a decrease in anabolic factors (COL2A1 and aggrecan) and an increase in catabolic factors (MMP3 and MMP13). Consequently, this triggers the wear and tear of chondrocytes and their aging, resulting in diminished extracellular matrix (ECM) deposition, thereby expediting the progression of OA. Downregulation of dimethylarginine dimethylaminohydrolase-1 (DDAH1) causes an increase in ADMA levels in OA patients [10]. Hence, triggering the activation of DDAH1 to decrease ADMA levels could serve as a promising therapeutic approach for addressing OA.

5.2. Branched chain amino acids (BCAAs)

The molecular structures of BCAAs, including leucine, isoleucine and valine, are similar [93]. BCAAs are essential amino acids for protein synthesis and make up approximately one-third of skeletal muscle in the human body. BCAAs are building blocks for all life forms [94]. An investigation involving 598 British women through targeted metabolic profiling found that the correlation between BCAAs and histidine levels could serve as a promising biomarker for OA in a clinical setting. The study observed a higher ratio of BCAAs to histidine in individuals with knee OA compared to those in the control group. Notably, this represents the inaugural human serum metabolomic study focusing on OA [12]. Later, this finding was confirmed in a cohort study in Canada. Moreover, the study population was expanded to include male patients with OA [58]. However, this longitudinal cohort study, which spanned ten years, found that this ratio could not predict the progression of OA [58]. A Korean clinical study that included 65 patients with knee OA, divided into an experimental group (n = 32) and a control group (n = 33), found that supplementation with leucine-rich protein was safe and effective in improving muscle density and quality of life [95]. These results suggest a

Table 2
Summary of studies on the association between lipid metabolism and OA.

Design	Sample	Lipid	Finding	Ref.
Cohort study	OA patients	Cholesterol	Higher cholesterol was associated with increased risk of generalized OA	[43]
Animal experiments	Mice and rats	Cholesterol	Hypercholesterolemia precipitates OA progression by mitochondrial dysfunction in chondrocytes.	[44]
Human and animal experiments	OA patientsand mice	Cholesterol	The CH25H-CYP7B1-RORα axis of cholesterol metabolism in chondrocytes is a key metabolic regulatory factor in the pathogenesis of OA.	[45]
Animal experiments	Mice	LDL	High LDL levels lead to increased synovial inflammation and accelerated ectopic bone formation	[46]
Animal experiments	Mice	cholesterol	IL-1β inhibition combined with cholesterol-lowering therapies decreases synovial lining thickness and spontaneous cartilage degeneration.	[47]
RCT	Women	HDL, LDL	The incidence of RHOA was inversely associated with HDL levels. RHOA incidence was not associated with LDL levels.	[48]
Longitudinal observational study	3026 participants	TC, LDL and HDL	Neither TC, LDL nor HDL showed a significant association with radiographic or symptomatic OA.	[49]
Case-control study	OA patients	LDL, TG and HDL	The severity of OA is related to LDL, but not TG and HDL.	[50]
Case-control study	RA, PsA, and OA patients	Lipoprotein and lipid	The levels of LDL-C and TC were higher in OA patients than in controls.	[51]
Animal experiments	Mice	LDL	Accumulation of LDL in mice leads to increased synovial activation and osteophyte formation.	[52]
Bidirectional mendelian randomization Study	UK Biobank	apolipoproteins and lipoprotein lipids	LDL had a genetic protective effect on OA.	[53]
Animal experiments	Mice	FAs	FAs are predictors of obesity leading to OA	[54]
RCT	OA patients	FAs	Dietary SFAs may promote the development of OA. PUFAs and MUFAs may be protective against OA.	[55]
Case-control study	OA patients	FAs	Modifying dietary FAs may be one way of reducing the development of knee OA.	[56]
Animal experiments	Mouse	FAs	Omega-3 PUFAs can alleviate the severity of OA.	[57]
Cross-sectional and longitudinal studies	OA patients	Plasma metabolites	The ratio of lysoPCs to PCs is a novel metabolic marker for predicting advanced knee OA.	[58]

RCT, prospective cohort study; RHOA, radiographic hand osteoarthritis; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; KOA, knee osteoarthritis. RA, rheumatoid arthritis; PSA, psoriatic arthritis; FAs, fatty acids; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; lysoPCs, lysophosphatidylcholines; PCs, phosphatidylcholines.

potential therapeutic role for BCAAs in OA. However, more and further clinical trials are needed to confirm this.

5.3. S-Adenosylmethionine (SAMe)

SAMe is an important physiologically active substance that is involved in more than 40 biochemical reactions in organisms through transmethyl, transsulfide, and transaminopropyl groups [96]. SAMe is synthesized in the body through the fusion of the indispensable amino acid methionine with adenosine triphosphate (ATP). Although research on the effects of SAMe on OA dates back to the 1980s, there is still significant controversy over whether SAMe has therapeutic effects on OA. In a series of clinical trials conducted in 1987, around 22,000 patients suffering from OA were recruited. The findings from these trials provided strong evidence regarding the effectiveness and safety of SAMe in managing OA symptoms [97]. After this, SAMe was widely promoted as a drug with protective effects on joint health and improved joint mobility and comfort. As a highly popular dietary supplement, SAMe can be purchased over the counter at pharmacies or health food stores [98]. In a meta-analysis conducted in 2002, the effectiveness and safety of SAMe in the treatment of OA were analyzed from three aspects: improvement of joint pain, relief of functional limitations, and adverse drug reactions. The findings of this study suggest that SAMe is equally efficacious to NSAIDs in alleviating pain and enhancing functional abilities in patients with OA, while avoiding the potential side effects commonly associated with NSAIDs [99]. Yet, a systematic literature review in 2009 undertaken by academics focused on the utilization of SAMe for OA. The review encompassed four trials involving 656 participants, all of which juxtaposed SAMe against a placebo. The findings from all four trials indicated that SAMe did not yield any significant pain relief benefits [98]. Due to incomplete exploration of SAMe's mechanism in treating OA and absence of long-term efficacy evaluation through randomized controlled trials, there remains insufficient evidence to endorse the clinical use of SAMe for OA treatment. It is imperative to conduct further research to verify the therapeutic benefits of SAMe on OA and delve into its mode of action.

5.4. Glutamine

Glutamine is a nonessential amino acid that is abundant in the human body and is required for many anabolic processes [100]. Glutamine has received increasing attention due to its biological properties, such as its anti-inflammatory and antioxidative effects and improved immune activity [100–102]. Glutamine is essential for various physiological processes, including cell structure, maintaining balance within the body, regulating pH levels, and facilitating the exchange of nitrogen among organs [100,103]. In addition, glutamine was confirmed to be involved in energy production and anabolic processes in mouse chondrocytes [100,104]. There is a common belief that inflammatory cytokines and reactive oxygen species (ROS) play a role in the development of OA under stressful conditions. Currently, many animal experiments have confirmed that glucosamine can delay the progression of OA. Experimental studies in rabbits have shown that treating chondrocytes with glutamine protects cells from heat stress and NO-induced apoptosis [13]. Studies in mice have shown that exosomes regulate glutamine metabolism in chondrocytes by regulating glutamine metabolic activity-related proteins, thereby alleviating OA [14]. Ma et al. explored the potential therapeutic role of glutamine in OA. In vitro, studies have shown that L-glutamine (L-Gln) boosts the survival of rat chondrocytes stimulated by IL-1β. Through the TGF-β1/SMAD2/3 signaling pathway, L-Gln controls the levels of lncRNA-NKILA to mitigate OA. Animal studies have substantiated that L-Gln effectively mitigates cartilage breakdown and slows down OA advancement in rats [15]. Matrix metalloproteinases (MMPs) and thrombospondin motifs (ADAMTSs) are major matrix-degrading enzymes that play key roles in OA progression. Aggrecan is a major component of the cartilage ECM. The research conducted by Zhong and colleagues demonstrated that glutamine plays a protective role in preventing OA in chondrocytes. This protective effect is achieved by blocking the Jun N-terminal kinase (JNK) and nuclear factor kappa-B (NF-κB) signaling pathways. Furthermore, glutamine

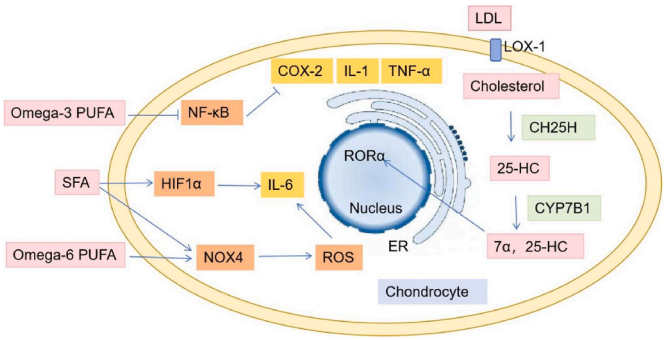

Figure 4. Schematic representation of the relationship between lipid metabolism and OA pathogenesis.
The CH25H-CYP7B1-RORα axis of cholesterol metabolism regulates OA. Omega-3 PUFAs inhibit the expression of COX-2, IL-1and TNF-α by inhibiting the NF-κB signaling pathway. SFA promotes IL-6 expression by activating the HIF1α pathway. Omega-6 PUFA regulates ROS production through the NOX-4 signaling pathway, thereby promoting IL-6 expression and exacerbating the progression of OA.

facilitates the synthesis of aggrecan while suppressing the expression of MMP-1, MMP-13, and ADAMTS-5 [16].

Furthermore, in a clinical experiment, it was discovered that consumption of L-Gln led to partial amelioration of symptoms in individuals with early-stage OA [15]. The research involved 47 patients with early-stage OA, and results indicated that after a 4-week regimen of 500 mg/d L-Gln, 34 patients exhibited a reduction in WOMAC scores while 36 patients showed improvement in Lequesne scores, both with statistical significance ($P < 0.01$). This study confirmed the positive therapeutic effect of L-Gln on OA, and further research can be conducted to explore its molecular mechanisms.

6. Lipid metabolism (Table 2)

Lipids are complex molecules with diverse types and intricate structures that are crucial in regulating cellular activities [105]. Lipids can be categorized into four main classes, including triglycerides (TG), fatty acids (FA), cholesterol, and phospholipids, based on their distinct chemical structures [106]. Lipids are important nutrients needed by the human body and can affect a variety of biological functions [107]. Lipids play a crucial role in maintaining the physiological and structural integrity of cartilage as a component of the chondrocyte membrane. Under physiological conditions, lipids serve as the main components of articular cartilage boundary lubricants and have a protective effect against cartilage surfaces. Moreover, lipids play a role in controlling bone metabolism through their impact on the activity and viability of osteoblasts and osteoclasts [108]. The disruption of lipid content or metabolism results in impaired cartilage function. There has been a growing focus on the dysregulation of lipid metabolism in individuals with OA. It has been suggested by recent research that OA may be characterized as a metabolic disorder, with changes in lipid metabolism being identified as a potential contributing factor [109]. It has previously been reported that there is significant heterogeneity in lipid metabolites in the synovial fluid of healthy individuals and OA patients [110]. A prospective cohort study conducted at multiple centers in Europe, which included 216 participants, investigated the correlation between lipid levels and the severity of OA in the knees and hands [108]. The study revealed that lipidomics accounted for some of the differences in OA severity, although the impact was relatively modest. Specifically, lipidomics demonstrated the most pronounced correlation with hand discomfort [53] (Fig. 4).

6.1. Cholesterol

Cholesterol is a prevalent constituent of mammalian cell membranes and is essential for the regulation of membrane fluidity, permeability, and microstructure. Additionally, it serves as a crucial precursor in the synthesis of bile acids and steroid hormones [111]. An excess of cholesterol can diminish membrane fluidity, disrupt membrane microdomains, modify the function of membrane proteins, and ultimately result in cellular dysfunction and apoptosis [112]. Hypercholesterolemia may be the result of abnormal intestinal cholesterol uptake and/or improper regulation of plasma cholesterol levels [113]. There is a suggestion that elevated cholesterol levels could represent a new risk factor in the onset of OA [21,43,44]. There is substantial evidence indicating that individuals with OA exhibit elevated concentrations of cholesterol and cholesterol crystals in their synovial fluid [51]. High levels of cholesterol have a significant impact on the activation of synovial cells and the formation of abnormal bone in the early stages of collagenase-induced OA in mice [46]. Mice fed a high-cholesterol Western-type diet developed hypercholesterolemia, and spontaneous OA developed while on a high-cholesterol diet [47].

Research has revealed that enhancing cholesterol synthesis in chondrocytes by disrupting *Insig1 and Insig2* led to a heightened severity of OA in mice. This suggests that the control of intracellular cholesterol levels plays a crucial role in the development of OA [114]. There are also studies that have found that lysosomes are involved in the metabolism and distribution of cholesterol. Abnormal cholesterol metabolism leads to the accumulation of cholesterol in cells, which promotes the occurrence of OA [115]. A recent investigation has additionally validated the significance of the CH25H-CYP7B1-RORα axis in chondrocytes' cholesterol metabolism as a crucial metabolic regulatory element influencing the development of OA [45]. As a result of elevated consumption, heightened expression of cholesterol hydroxylases (CH25H and CYP7B1), and augmented generation of oxysterol metabolites, the cholesterol concentrations within chondrocytes elevate, subsequently inducing experimental OA in mice. The pathogenesis of OA can be eliminated by adenovirus knockdown or downregulation of CH25H or CYP7B1. The findings from this study provide evidence in favor of the theory that OA is connected to metabolic irregularities. Additionally, they propose that a potential treatment strategy for OA could involve focusing on the CH25H-CYP7B1-RORα pathway in cholesterol metabolism [45]. A prospective, non-randomized, controlled clinical trial enrolled 38 patients with OA who were treated with pentosan sulfate for dyslipidemia [116]. They found significant reductions in cholesterol and LDL levels, and significant improvements in knee pain.

To sum up, a correlation between cholesterol levels and OA has been demonstrated in a variety of animal experiments and human epidemiological studies [48,117,118]. Therefore, the use of statins to lower cholesterol levels is considered a potential treatment for OA [119]. In some studies, the use of statins has been proven to be associated with a reduction in the incidence and progression of knee OA [113,120], but significant associations were not found in other studies [119,121,122]. Given that OA is a result of multiple factors, it may be difficult to completely reverse the onset and progression of OA by merely changing cholesterol levels.

6.2. High-density lipoprotein (HDL)

HDL, comprised of both proteins and lipids, is the most diminutive lipoprotein found in circulation and is ubiquitous in nearly all cells [123]. Apart from its role as a carrier of cholesterol, HDL exhibits various other functional attributes, such as the ability to facilitate cholesterol removal, as well as possessing antioxidant, anti-inflammatory, and immune-modulating properties [124]. In the past, the relationship of HDL cholesterol with vascular diseases has received increased attention [125]. The role of HDL in OA progression has also been studied in several ways. In a population-based cohort

study, after 11 years of follow-up, the incidence of radiographic hand OA (RHOA) decreased with increasing HDL-c levels, but there was no relationship with total cholesterol or low-density lipoprotein (LDL) cholesterol [48]. This implies that higher levels of HDL seem to be able to prevent RHOA. However, in another multi-center OA study (MOST) cohort study that included 337 cases of incidental symptomatic OA and 283 cases of incidental imaging OA, no significant association was found between total cholesterol, low-density lipoprotein, or HDL levels and imaging manifestations or symptomatic OA. Moreover, the presence of these lipids did not correlate with cartilage degradation, exacerbation of synovitis, or increased knee discomfort [49]. In a similar fashion, a research study involving 55 patients with OA and 55 individuals without the condition revealed no significant statistical variance in the levels of TG and HDL between the two cohorts [50]. The causal relationship between HDL and OA is not yet clear. Up to now, there have been limited clinical studies examining the correlation between HDL and OA, with small sample sizes and varying results.

6.3. LDL

LDL is a group of heterogeneous lipoproteins [126]. LDL, one of the five main lipid-transporting plasma lipoproteins found in the human bloodstream, is responsible for carrying lipids to cells in peripheral tissues [127]. LDL is the main cholesterol carrier in human circulation [128]. Numerous researchers have explored the connection between LDL and OA, and discovered that there is an increase in LDL levels among patients with OA [51,129]. In a controlled study that included 28 OA patients and 36 healthy participants, it was observed that the levels of LDL in the OA patients were elevated compared to those in the control group [129]. The same result was found in another control study involving 16 OA patients and 33 healthy participants [51]. A control study by Tootsi and colleagues, which included 55 OA patients and 55 healthy participants, showed that the severity of OA is related to the levels of LDL-c and oxidized low-density lipoprotein (oxLDL) after eliminating potential confounding factors (BMI, age, and gender) and multiple tests [50]. LDL particles are easily affected by ROS, leading to an increase in the formation of oxLDL particles. OxLDL cholesterol fully exhibits its pro-inflammatory properties after oxidation. OxLDL particles are absorbed through scavenger receptors, such as lectin-type oxLDL receptor 1 (LOX-1), leading to the activation and secretion of various proteases and inflammatory mediators, and ultimately promoting the occurrence and progression of OA [117]. Apart from the clinical trials mentioned earlier, corresponding animal studies have validated the significant function of LDL in the development of OA. In particular, certain studies involved the administration of a high-fat diet to mice lacking the low-density lipoprotein receptor ($LDLr^{-/-}$) for 120 days, followed by the induction of experimental OA through intra-articular collagenase injection in the 12th week. The results found that in experimental OA, the accumulation of LDL in synovial lining cells leads to synovial activation and increased osteophyte formation [52].

Nevertheless, conflicting findings have emerged from other research studies on the association between LDL and the occurrence of OA. In an analysis based on bidirectional Mendelian randomization (MR), which included 39,427 OA patients and 378,169 healthy individuals from the UK Biobank, the study found that an increase in LDL would reduce the risk of OA in the knee or hip [53]. Moreover, in a longitudinal cohort study that directly assessed the relationship between LDL and the incidence of OA, 3026 participants were included [49]. After a follow-up of up to 7 years, there were 337 cases of incidental symptomatic OA and 283 cases of incidental imaging OA. The results showed that total cholesterol, LDL, and HDL were not significantly related to imaging or symptomatic OA [49]. In another longitudinal cohort study with a follow-up of 11 years, it was also found that there was no correlation between LDL and the incidence of OA [48]. These research findings offer fresh perspectives on the correlation between lipids and the susceptibility to OA, shedding light on the underlying factors contributing to OA development.

6.3.1. Fatty acids (FAs)

FAs are organic compounds categorized into short-chain (up to 6 carbons), medium-chain (6–12 carbons), long-chain (14–20 carbons), or very long-chain FAs (more than 22 carbons) based on their carbon atom count. FAs can be classified into saturated FAs (SFAs) and unsaturated FAs (UFAs) based on their saturation levels. Within UFAs, there are monounsaturated FAs (MUFAs) and polyunsaturated FAs (PUFAs) distinguished by the quantity of double bonds present [130]. FAs have different lengths and degrees of saturation, which determine their different biological effects. FAs can exist in the body independently or can be bonded with glycerol, resulting in the formation of TG, diacylglycerol (DAG), or monoacylglycerol (MAG) [131]. As individual FAs and their derivatives have proinflammatory or dual anti-inflammatory and proresolving properties, they may affect the health of joint tissues [132,133].

Being overweight or obese is considered a risk factor for OA. Studies have shown that overweight and obese adults tend to have higher levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in their plasma [134]. These elevated levels of TNF-α, IL-6, and IL-1 are believed to play a crucial role in the degradation of cartilage in individuals with OA [135,136]. There is evidence that the FA composition of synovial fluid and serum is a predictor of OA resulting from obesity [54]. Obesity causes cellular stress, induces lipolysis of adipocytes, and increases the level of circulating free FAs [57,137].

Chondrocytes, the sole cellular constituents of cartilage, are derived from mesenchymal progenitor cells and are responsible for the synthesis of an extracellular matrix predominantly composed of proteoglycans and collagen [138]. PUFAs are critical for maintaining chondrocyte and cartilage homeostasis. In vitro investigations have demonstrated the influence of various PUFAs on the secretion and expression of inflammatory cytokines, prostaglandins, and enzymes implicated in cartilage degradation. FAs, primarily in the forms of triglycerides and phosphatidylcholine, are incorporated into chondrocytes and facilitate signaling pathways. Both in vitro and in vivo studies indicate that distinct FAs exert varying effects on OA. Specifically, SFAs and n-6 PUFAs are associated with an upregulation of pro-inflammatory and pro-apoptotic markers, whereas n-3 PUFAs correlate with a reduction in inflammatory and degradative markers in chondrocytes and synovial cells [57,139]. Omega-3 PUFAs are considered a potential treatment option for patients with OA [140]. Fatty fish and seafood, grain products, seeds, nuts, and vegetables contain considerable amounts of omega-3 PUFAs [131,141]. In an OA model of injury-induced obesity in mice, omega-3 PUFAs also played a role in alleviating OA [57]. Some in vitro studies investigated the effects of supplementing UFAs on animal-derived chondrocytes [142–145]. Omega-3 PUFAs like eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA) were employed in these research experiments for chondrocyte cultivation. The results showed that under the influence of Omega-3 PUFAs, markers such as ADAMTS-4, ADAMTS-5, cyclooxygenase (COX)-2, MMP-3, IL-1α, IL-1β, and TNF-α all decreased [143]. Omega-3 PUFA can be oxidized into specialized pro-resolving mediators and oxylipins with strong anti-inflammatory properties [146]. These specialized pro-resolving mediators can reduce inflammation by inhibiting inflammatory lipid mediators and cytokines [147]. Krill oil is a dietary component that is high in anti-inflammatory long-chain Omega-3 PUFA. A research study examining the impact of krill oil supplementation on pain and functionality in individuals with mild to moderate knee OA involved 235 participants over a 6-month period in a randomized, double-blind, controlled trial. The findings indicated that krill oil notably alleviated knee pain and stiffness in the patients [148]. A randomized, double-blind, multicenter trial of 202 patients with knee OA also found that supplementation with omega-3 PUFA-rich fish oil improved patients' condition [149]. In canines diagnosed with OA, the administration of fish oil supplements has been shown to decrease various

indicators of oxidative stress [150]. However, a US study of 1398 patients followed for an average of 5.3 years found that supplementation with Omega-3 PUFA did not improve symptoms in patients with knee OA [151].

In contrast, Omega-6 PUFAs have pro-inflammatory properties. It has been reported that linoleic acid, a PUFA, can induce human chondrocytes to secrete IL-6 [152]. Arachidonic acid (AA), also a PUFA, is one of the most critical lipid metabolites [153]. The presence of AA in the OA synovium is associated with enhanced synovitis and acceleration of OA progression through modulation of adaptive/innate immune cell infiltration, activation of inflammatory mediators, which in turn leads to heightened cartilage degradation and inflammatory responses [154,155]. In their research, Tu and colleagues carried out an extensive examination on the impacts of genes related to AA metabolism on OA synovitis. They pinpointed seven key genes within the AA metabolism pathway (LTC4S, PTGS2, PTGS1, MAPKAPK2, CBR1, PTGDS, and CYP2U1) that have the potential to serve as novel diagnostic indicators for individuals with OA [153]. Omega-6 PUFA regulates the generation of ROS and the apoptosis of chondrocytes via the NADPH oxidase 4 (NOX-4) signaling pathway. Additionally, it undergoes further metabolism to form bioactive molecules, including proinflammatory prostaglandins and leukotrienes, which are pivotal in driving joint inflammation, degradation of cartilage matrix, and bone resorption in OA [156,157]. Similarly, SFA is also known to be a pro-inflammatory lipid. Stearic acid, an SFA, induces the production of pro-inflammatory cytokines by activating Hypoxia Inducible Factor 1α (HIF1α) in chondrocytes [142]. Palmitic acid has also been shown to be a pro-inflammatory and catabolic factor in the pathogenesis of OA, which can up-regulate the expression of IL-6 and COX-2 in chondrocytes [158]. The NOX-4 signaling pathway is implicated in the mediation of ROS production and chondrocyte apoptosis in articular cartilage, as influenced by elevated concentrations of palmitic acid and oleic acid [159].

In conclusion, FAs exert their effects through various pathways in chondrocytes. Therefore, a more comprehensive understanding of the mechanisms by which FAs operate is essential for assessing and endorsing their application in the treatment of OA and associated joint disorders.

6.4. *Lysophosphatidylcholines (lysoPCs) and phosphatidylcholines (PCs)*

PC is a typical eukaryotic membrane phospholipid that can be synthesized by the methylation pathway or CDP-choline pathway [160,161]. In addition to its structural role in the cell membrane, PC can act as a modulator of a variety of cellular functions [162,163]. LysoPCs are a group of biologically active lipids that are metabolites of PCs. LysoPCs and PCs have also received some attention in different diseases. Research has indicated that the proportion of lysoPCs to PCs in the cerebrospinal fluid of individuals with Alzheimer's disease is reduced compared to that of individuals in the control group [164]. Other research has found that the increase in the ratio of lysoPCs to PCs in human sperm and red blood cells is associated with a decrease in fertility [165]. In addition, one study also suggested that the ratio of PCs to lysoPCs in human plasma can be used as an indicator of early RA [166]. These research findings suggest that the proportion of lysoPCs to PCs has the potential to serve as an indicator for the advancement of specific illnesses.

A new metabolic marker for late-stage knee OA was identified in a cohort study of 415 participants, where the ratio of lysoPCs to PCs was found to be indicative [58]. Following adjustments for age, gender, and body mass index, the research categorized the subjects into two cohorts using the designated threshold of 0.09 for the lysoPCs to PCs ratio. The analysis revealed that individuals exceeding the 0.09 threshold were associated with a 2.3-fold increase in the probability of requiring total knee replacement (TKR) for advanced knee OA within a decade of monitoring. These findings indicate that the lysoPCs to PCs ratio has the potential to serve as a novel metabolic indicator for anticipating late-stage knee OA [58]. LysoPCs can be generated from PCs in the presence of phospholipase A2 (PLA2) [167]. Alternatively, lysoPCs may also be produced from PCs in reaction to ROS released by neutrophils [166,168]. LysoPCs play an important role in human lipid metabolism [169,170]. An increase in lysoPCs causes the death of both apoptotic and nonapoptotic cells [171]. PCs contribute to the boundary lubrication provided by synovial fluid (SF). A lack of PCs may lead to increased friction, potentially causing damage to the articular cartilage [172,173]. Further investigation is needed to determine if this ratio can accurately forecast early changes in OA. Moreover, whether the progression of OA can be intervened by regulating the related metabolism of lysoPCs and PCs seems to be an attractive research direction.

Table 3
The key regulatory enzymes of glycolysis implicated in the pathogenesis of OA.

Enzyme	Function	Role in OA pathogenesis
GLUT1	Transports glucose from the outside of the cell	Loss of GLUT1 results in decreased glucose metabolism. The increased expression of GLUT1 will produce excessive AGEs, leading to cartilage degradation and increasing the risk of OA
HK2	Catalyzes the phosphorylation of glucose to glucose-6-phosphate	HK2 promotes the conversion of glucose metabolism from oxidative phosphorylation to aerobic glycolysis. Excessive HK2 resulted in elevated expression of IL-6, IL-8, and MMPs in OA FLS
PFKFB3	A key stimulator of glycolysis	PFKFB3 enhance the survival of OA cartilage and chondrocytes, inhibits caspase 3 activation and enhances ECM synthesis
PKM2	Catalyzes phosphoenolpyruvate acid to pyruvate acid and ATP	PKM2 can regulate glycolysis and ECM production. PKM2 knockdown inhibits glycolysis, inhibits the proliferation, promoted the apoptosis, inhibits ECM production
LDHA	Converts pyruvate to lactate	LDHA promotes the spread of reactive oxygen species, leading to changes in catabolism and mediating OA. Specific inhibition of LDHA increased the secretion of hyaluronic acid.

ECM, extracellular matrix; AGEs, advanced glycation end products.

7. Glucose metabolism (Table 3)

Glucose metabolism includes glycolysis, the tricarboxylic acid (TCA) cycle and the pentose phosphate pathway (PPP) [174]. In normal oxygen conditions, glucose undergoes enzymatic conversion to pyruvate, which then participates in the TCA cycle to generate energy through oxidative phosphorylation (OXPHOS). Conversely, in hypoxic environments, the predominant metabolic pathway is the highly active glycolysis in the cytoplasm facilitated by lactate dehydrogenase A (LDHA). Glycolysis yields 2 mol of ATP per mole of glucose, while OXPHOS produces 36 mol of ATP [175,176]. Glucose produces ATP, which serves as the main source of energy for numerous cellular activities [177]. ATP, functioning as an energy substrate, significantly contributes to the proliferation, differentiation, and functional upkeep of chondrocytes [178]. Under physiological conditions, chondrocyte energy is derived from the combination of glycolysis and OXPHOS. The low energy production determined by OXPHOS is a consequence of the hypoxic conditions that chondrocytes inhabit [179]. Therefore, chondrocytes rely heavily on glycolysis in vivo. Glycolysis, which is independent of oxygen, quickly but inefficiently produces ATP, whereas energy production via OXPHOS is extremely efficient when oxygen is available [180].

More focus is being placed on exploring the link between metabolism and OA, yet there is a limited number of studies investigating the

pathogenesis of OA in terms of glucose metabolism at present [174]. Glycolysis is a ubiquitous glucose degradation pathway in all living organisms. Glycolysis is a tightly regulated process, and various enzymes, such as hexokinase (HK), pyruvate kinase (PK), phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) and lactate dehydrogenase A (LDHA), participate in this process [181,182]. After entering the cell, glucose undergoes phosphorylation to form glucose-6-phosphate (G-6-P) through the enzymatic action of HK. Subsequently, G-6-P is integrated into the glycolytic pathway, resulting in the production of pyruvate, along with the generation of two molecules of nicotinamide adenine dinucleotide (NAD^+) and two ATP. Pyruvate can either be converted to lactate, thereby facilitating the regeneration of NAD^+ to complete the glycolytic process, or it can be transported to the mitochondria, where it is transformed into acetyl-CoA for participation in the TCA cycle [24]. Several in vivo studies have also shown a significant increase in the content of metabolites related to glycolysis in OA, which illustrates the link between glycolysis and OA [183,184]. In contrast to many other types of tissues, articular cartilage primarily consists of ECM and chondrocytes, lacking blood vessels, nerves, or lymphatic vessels [185]. The ECM is primarily composed of water, collagen, proteins, glycoproteins, and proteoglycans [186,187]. The pathogenesis of OA is attributed to the diminished survival of chondrocytes and a decrease in ECM content caused by various risk factors [188]. Research has indicated that glycolysis serves as the primary energy source for chondrocytes [189]. Issues in glycolytic metabolism can result in the enlargement of chondrocytes and the breakdown of the ECM, consequently contributing to the development of OA [190]. Physiologically, the majority of ATP in chondrocytes is produced by glycolysis [191]. In addition, a small amount of ATP is produced by oxidative phosphorylation of mitochondria in chondrocytes [192]. Therefore, cartilage chondrocytes exhibit higher susceptibility to glycolytic dysregulation. Increasing evidence indicates that heightened glycolysis allows cells to generate extra energy, vital for triggering immune responses and inflammatory pathways in OA [193]. Hence, regulating the activities of glucose transporters and key enzymes that control glycolytic metabolic reprogramming may present a major advancement in the treatment of OA.

7.1. NAD^+

NAD^+ serves as a crucial metabolite and indispensable cofactor in the processes of cellular energy metabolism. The regulation of intracellular NAD^+ levels is vital for the preservation of tissue homeostasis [194]. NAD^+ has the capacity to influence various essential cellular functions, either directly or indirectly. These functions encompass metabolic pathways, DNA repair mechanisms, chromatin remodeling processes, cellular aging, and the functionality of immune cells [195]. These cellular processes and functions are essential for maintaining tissue and metabolic balance and for healthy aging. Importantly, research conducted on various model organisms, such as rodents and humans, indicates that the aging process is associated with a progressive reduction in NAD^+ levels within tissues and cells. This decline in NAD^+ has been causally associated with several age-related diseases, including cognitive decline, cancer, metabolic disorders, sarcopenia, OA, and frailty [196]. Restoration of NAD^+ levels have the potential to decelerate or even reverse various age-related diseases. Consequently, the modulation of NAD^+ metabolism has been identified as a promising therapeutic strategy for the enhancement of conditions associated with aging. Research indicates that CD38 levels rise with advancing age, and CD38 is considered the primary enzyme responsible for the consumption of NAD^+, which subsequently leads to a decline in NAD^+ levels as individuals age [197,198]. Recent research indicates that the expression of CD38 is significantly increased in the cartilage of individuals with knee OA and in chondrocytes exposed to the pro-inflammatory cytokine IL-1β. This upregulation leads to a reduction in intracellular levels of NAD^+/NADH. Furthermore, the inhibition of CD38 has been shown to mitigate the decline in these intracellular NAD^+/NADH levels and to diminish the catabolic effects of IL-1β on chondrocytes and cartilage, thereby potentially slowing the progression of OA [199]. In summary, the inhibition of NAD^+ degrading enzymes using small molecule inhibitors, as well as the restoration of NAD^+ levels through dietary precursors, represent two promising approaches for enhancing NAD^+ concentrations in the treatment of OA.

7.2. Acetyl-CoA

Acetyl-CoA is a critical metabolite that plays a vital role in numerous cellular physiological processes. Its functions can be classified into several categories, including energy production, biosynthesis, regulatory mechanisms, and the acetylation of both macromolecules and small molecules. This compound is indispensable for the oxidative metabolism of glucose, fatty acids, the majority of amino acids, ethanol, and free acetic acid, which can be produced through endogenous metabolic pathways or by gut microbiota [200]. After glucose is converted to pyruvate, the pyruvate is converted either to lactate or to acetyl-CoA in the mitochondria [201]. Research indicates that acetyl-CoA is crucial for the preservation of cartilage homeostasis. The buildup of acetyl-CoA promotes *de novo* lipogenesis and may trigger inflammatory responses, ultimately resulting in the deterioration of the cartilage matrix [202,203]. Based on this, studies have been conducted to inhibit cartilage destruction by capturing acetyl-CoA through injectable bioactive nanoparticles [204].

7.3. Lactate

Lactate, as the end product of glycolysis, was originally considered a metabolic waste product [205]. As research advances, lactate is increasingly recognized as a significant regulator of systemic metabolism [206]. The lactate shuttle hypothesis posits that lactate functions as a pivotal signaling molecule, facilitating the coordination of signal transduction among various cells, organs, and tissues [207]. Lactate and pyruvate act as circulating redox buffers, balancing the NADH/NAD^+ ratio between cells and tissues [208]. The accumulation of lactate can lead to a significant influx of monocarboxylic acids into the mitochondria, which subsequently results in an increase in acetyl-CoA levels [209]. Lactate enhances the expression of NOX4 by modifying glucose metabolism and activating the PI3K/Akt signaling pathway. This process leads to an increase in ROS production, which triggers an oxidative stress response in chondrocytes. Consequently, there is an upregulation of catabolic enzymes and inflammatory factors, thereby facilitating the progression of OA [210]. In a mouse model of arthritis, lactate has been shown to enhance the expression of its transporter, SLC5A12. This transporter facilitates the uptake of lactate into $CD4^+$ T cells, subsequently promoting the production of IL-17 through the PKM2/STAT3 signaling pathway. This process contributes to the progression of arthritis [211]. In conclusion, lactate is involved in the OA process as a metabolic factor, and controlling the level of lactate can be a potential metabolic treatment for OA in the future.

LDHA is involved in the conversion of pyruvate to lactate and NAD^+. One study focused on LDHA expression levels and metabolite profiles in synovial fibroblasts (SFs) from patients with temporomandibular joint OA (TMJOA) [212]. LDHA is highly expressed in the synovial tissue of patients with TMJOA. Treatment of TMJOA SFs with the LDHA-specific inhibitor GSK2837808A suppressed glycolytic activity, inhibited the secretion of lactate and promoted the expression of hyaluronic acid synthetase 2 (HAS2), thereby increasing the secretion of hyaluronic acid (HA). These results offer fresh perspectives on the crucial involvement of LDHA in the development of TMJOA. Separately, research revealed a notable rise in both the activity and presence of LDHA in primary chondrocytes upon exposure to IL-1β. Inflammation and metabolism can interact to regulate cartilage degradation. Additionally, animal trials also demonstrated a marked decrease in the intensity of OA in mice that

Table 4
The clinical outcomes of drug interventions corresponding to metabolic substances and pathway targets for OA.

Drug	Sample	Target	Function	Clinical outcome	Ref.
Leucine	65 OA patients	BCAAs	Improving muscle density	Improve symptoms	[95]
SAMe	22000 OA patients	SAMe	Anti-inflammatory, analgesic, promote proteoglycan synthesis	Pain relief	[97]
SAMe	656 OA patients	SAMe	No significant improvement in pain or function	No significant improvement in pain or function	[98]
L-Glutamine	47 OA patients	L-Glutamine	Up-regulating TGF-β1/SMAD2/3 pathway	Relieve pain and improve function	[15]
Statin	2921 people	Lipid metabolism	Decreased the progression of knee OA, but not hip OA	Decreased the progression of knee OA, but not hip OA	[120]
Pentosan sulfate	38 OA patients	Dyslipidemia	Lower cholesterol and LDL levels	Pain relief	[116]
Krill oil	235 OA patients	Omega-3 PUFA	Supplement with Omega-3 PUFA	Improved knee pain and knee stiffness	[148]
Fish oil	202 OA patients	Omega-3 PUFA	Supplement with Omega-3 PUFA	Improve symptoms	[149]
Marine Omega −3 PUFA	1398 OA patients	Omega-3 PUFA	Supplement with Omega-3 PUFA	Have no effect	[151]
AGEs inhibitor	30 OA patients	AGEs	AGEs inhibitor	Reduced pain and inflammation and increased daily activity and mobility	[219]

BCAAs, Branched chain amino acids; AGEs, advanced glycation end products. PUFA, polyunsaturated fatty acid.

lacked LDHA [213]. LDHA binds NADH and promotes the propagation of ROS, which induces catabolic changes through IκB-ζ and mediates the occurrence of OA. LDHA inhibition reduced the catabolic activity of the IκB-ζ protein, resulting in a protective effect against OA [213]. In conclusion, LDHA is considered a potential target for OA treatment.

7.4. Advanced glycation end products (AGEs)

AGEs are heterogeneous molecules that arise from non-enzymatic interactions between glucose or other sugar derivatives and proteins or lipids [214]. Various forms of AGEs have been recognized as biomarkers for assessing aging and disease status. The formation of AGEs is an irreversible process, and their accumulation within neuro-musculoskeletal tissues results in alterations in charge and cross-linking, which negatively impacts biomechanical properties and leads to tissue damage. Additionally, AGEs bind to receptors such as the receptor for AGEs (RAGE) and induce inflammation through intracellular signaling. These mechanisms are implicated in a range of conditions associated with aging and diabetes, such as osteoporosis, OA, muscle wasting, tendon disorders, and neuropathies [215]. In addition, AGEs can bind to RAGE on macrophages, promote M1 polarization of macrophages, and increase TNF and IL-1β transcription through NF-κB [216]. Research indicates that the accumulation of AGEs within chondrocytes enhances their sensitivity to cytokines and chemokines. This process stimulates the expression of inflammatory mediators, including MMPs, which contributes to cartilage degradation and compromises the integrity of the collagen network in articular cartilage. Consequently, this phenomenon elevates the risk of OA [217]. Furthermore, it has been established that the accumulation of AGEs diminishes the signaling pathways involving AMPKα/SIRT1/PGC-1α in chondrocytes. This reduction contributes to oxidative stress, inflammation, and heightened apoptosis, which in turn results in mitochondrial dysfunction and ultimately accelerates the progression of OA [218]. A randomized, double-blind, placebo-controlled study of 30 patients with OA found that AGEs inhibitor reduced pain and inflammation and increased daily activity and mobility in OA patients [219]. In conclusion, AGEs in combination with RAGE can trigger a series of signaling events, promote inflammation, and affect chondrocyte homeostasis.

8. Conclusion and perspective

This review of the literature presents evidence indicating that metabolic alterations in chondrocytes are intricately linked to the development and advancement of OA. As a common disabling disease, OA lacks effective radical treatment. Nevertheless, the emergence of metabolomics opens up new potential avenues for managing OA. L-arginine supplementation reduced inflammatory mediator levels in human osteoblast-OA cells. ADMA levels have good predictive value for the diagnosis of OA with good sensitivity and specificity. An elevated concentration of BCAAs can be used as a diagnostic index for OA. Glutamine can alleviate the progression of OA through the NF-κB/TGF-β1/SMAD2/3 signaling pathway. Elevated levels of cholesterol in the blood can induce oxidative stress in mitochondria and degradation of chondrocytes, ultimately contributing to the development and advancement of OA. Patients with high HDL levels have a low risk of OA, and the opposite is true for LDL. FAs of different saturations have distinct effects on OA. The process of glycolysis serves as the primary energy provider for chondrocytes and is significantly involved in the progression of OA. Enzymes such as GLUT1, HK2, PKM2, LDHA, and PFKFB3 play crucial roles in glycolysis and may serve as promising targets for the treatment of OA. Targeted modification of these three metabolic pathways and their corresponding metabolites may be a promising avenue to develop new therapies for OA. We reviewed clinical trials of drug intervention in these metabolites or metabolic pathways (Table 4). Although there are many basic studies on the treatment of OA with drugs, and many of them have significant therapeutic effects, there is still a long way to go before these drugs are translated into clinical use. Basic research is usually conducted under laboratory conditions, and the results of preclinical research may not be replicated in a clinical setting, affecting the reliability and usefulness of research results. There are certain difficulties and obstacles in translating basic research results into applications that can be used in clinical practice, including challenges in technology transformation, regulatory requirements, and market demand. Drugs need to go through rigorous clinical trials to prove their safety and effectiveness. The establishment of multi-center and large sample clinical trials to ensure scientific and reasonable research design is conducive to improving the reliability and clinical application of the results.

Credit author statement

X.L., and J.G., drafted and conceived the initial manuscript. H.L., J. Z., and C.Z. provided the essential assistant for our final manuscript. X. L., J.G., and H.L. drew the figures and arranged tables. Y.Z., J.Z., and C. Z. revised the manuscript. All authors have read and approved the article.

Declaration of competing interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript in the Journal of Advanced Research.

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