

# Regulating Lipid Metabolism in Gout: A New Perspective with Therapeutic Potential

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**Abstract:** Gout is a metabolic disease characterized by inflammatory arthritis caused by abnormal uric acid metabolism. It is often complicated with cardio-renal damage and vascular lesions. In recent years, the relationship between lipid metabolism and gout has attracted increasing attention. Changes in blood lipids in gout patients are often clinically detectable and closely related to uric acid metabolism and inflammatory response in gout. With the development of lipidomics, the changes in small lipid molecules and their metabolic pathways have been gradually discovered, yielding a greater understanding of the lipid metabolism changes in gout patients and their potential role in gout development. Through searching the literature on lipid metabolism in gout since 2000 in PubMed and Web of Science, this article reviewed lipid metabolism changes in gout patients and their role in the risk of gout, uric acid metabolism, inflammatory response, and comorbidities. Additionally, the strategies to regulate the abnormal lipid metabolism in gout have also been summarized from the aspects of drugs, diet, and exercise. These will provide a new perspective for understanding gout pathogenesis and its treatment and management.

**Keywords:** gout, lipid metabolism, treatment, management

## Introduction

Gout, as one of the most common forms of inflammatory arthritis, is characterized by joint pain caused by purine/uric acid metabolism disorders. Patients with long-term recurrent gout are also vulnerable to extraarticular cardio-renal damage and vascular lesions, which can decrease the quality of life and even cause death.<sup>1</sup> As of 2016, the global prevalence of gout has reached 1–6.8%, and the annual incidence has risen to 0.58–2.89 per 1000 people, bringing a huge burden on patients and healthcare management systems.<sup>2</sup> Although the etiology and pathogenesis of gout remain unclear, it is well-recognized that various factors such as diet, environment, genetics, and drugs are tightly implicated in its pathogenesis. Among these factors, hyperuricemia caused by purine/uric acid metabolism disorders is considered to be the most important biochemical basis of gout.<sup>3</sup> Moreover, in addition to the above generally recognized factors, lipid metabolism is increasingly recognized to play an important role in gout development.<sup>4,5</sup>

Lipids, the most abundant metabolites in the body, participate in energy storage and oxidation and play crucial roles in biofilm construction, signal transmission, hormone synthesis, and immune response.<sup>6</sup> Lipid metabolism consists of many biological processes (such as digestion, absorption, transport, transformation, and storage of lipids) and involves multiple compounds (such as lipid, fatty acid, lipoprotein, adipokine, and lipase). Under normal circumstances, there is a dynamic balance between exogenous lipid intake and endogenous lipid synthesis and decomposition, and they jointly maintain the biological functions of the body, while the imbalance of this dynamic balance can cause opposite results and become the basis of various diseases.<sup>7–9</sup> Recent studies have shown that there is abnormal lipid metabolism in gout, and abnormal lipid metabolites affect the progression of gout.<sup>10</sup> Additionally, interventions targeting lipid metabolism can also affect the levels of uric acid and key inflammatory factors in gout, thus contributing to a favorable outcome.<sup>11</sup>

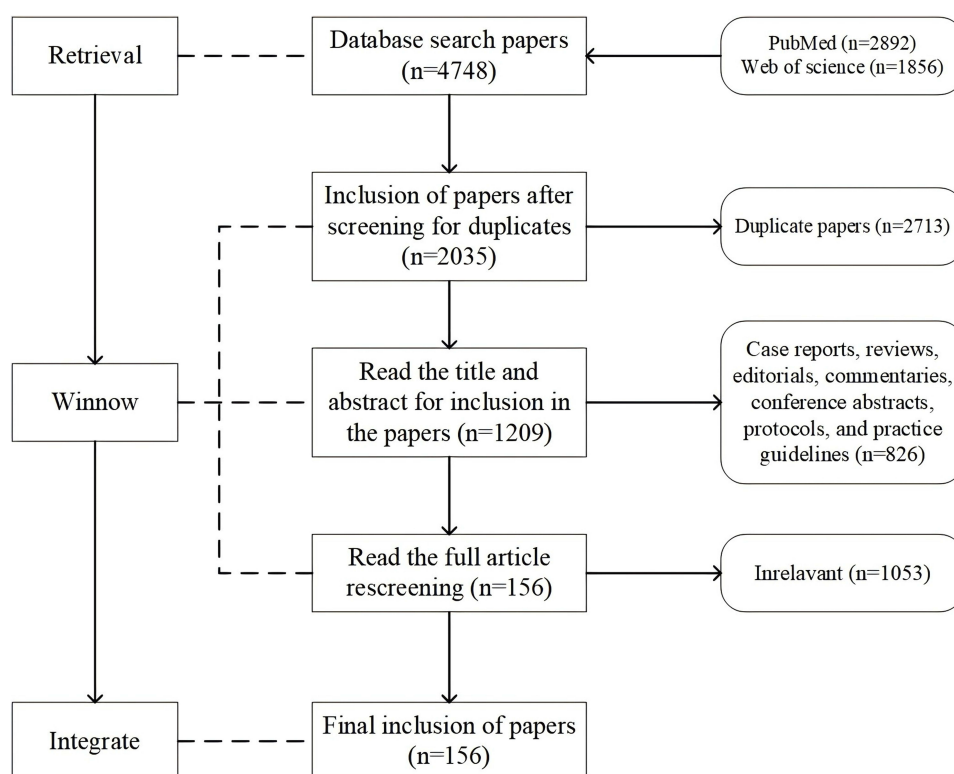
Therefore, considering the complex lipid metabolic processes and disease characteristics of gout, lipid metabolism changes in gout and their role in the risk of gout, uric acid metabolism, inflammatory response, and comorbidities were explored. Additionally, the strategies to regulate the abnormal lipid metabolism in gout were also summarized from the aspects of drugs, diet, and exercise. These results will provide a new perspective for a more comprehensive understanding of gout pathogenesis and its treatment and management.

## Search and Select Strategy

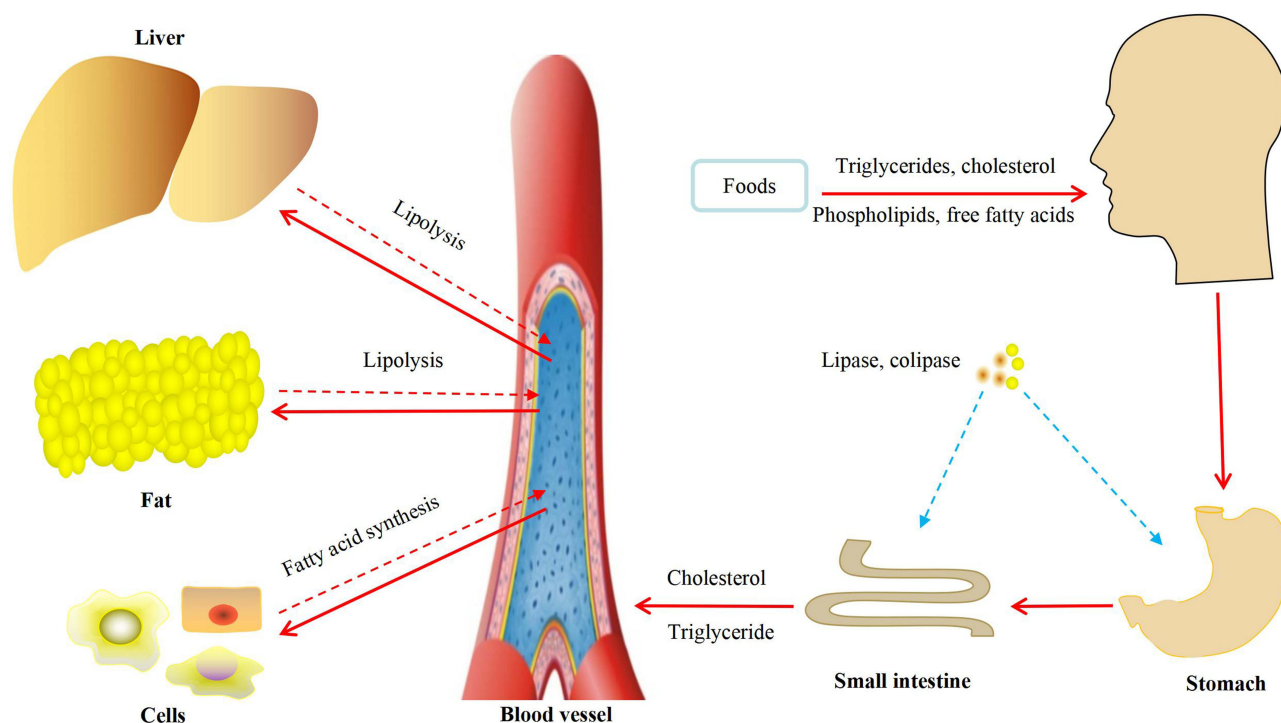
A systematic search was conducted in PubMed and Web of Science using the following search strategy: TS = (“hyperlipemia” OR “fat” OR “lipid” OR “lipid metabolism” OR “blood fat” OR “blood lipid” OR “cholesterol” OR “triglyceride” OR “adipokine” OR “adiponectin” OR “resistin” OR “leptin” OR “visfatin” OR “lipoprotein” OR “apoprotein” OR “fatty acid”) AND TI = (“gout” OR “gouty arthritis” OR “gouty nephropathy” OR “hyperuricemia” OR “Uric acid”). The search period was from January 1, 2000, to September 10, 2024. A total of 4748 articles were preliminarily obtained. After removing duplicates, 2035 articles remained; 826 documents (such as case reports, reviews, editorials, commentaries, conference abstracts, protocols, and practice guidelines) were then removed after reading the abstracts and titles. After further perusal of the full text, 1209 articles not related to the topic were removed. Finally, 156 papers were retained. All literature were processed by two researchers (Xianheng Zhang and Jian Liu) and the final selection decision was made. [Figure 1](#) shows the flowchart of the study screening process.

## Overview of Lipid Metabolism

Lipids [including triglycerides (TGs), phospholipids, cholesterol, lipoproteins, and fatty acids) play a key role in oxidation and energy supply and various biological processes. Lipid metabolism refers to the lipid synthesis and decomposition process in living organisms, involving various molecular compounds in the chain-like network of lipid synthesis raw materials to lipid storage.<sup>12</sup> The normal human body takes in lipids (including TGs, phospholipids, cholesterol, and free fatty acids) from food every day; these lipids are eventually digested and absorbed in the small



**Figure 1** Thesis screening flow chart.



**Figure 2** Metabolic pathways of lipid synthesis and lipolysis.

intestine under the action of lipase and colipase, and then enter the blood circulation by the lymphatic system in the form of lipoprotein. Some lipids are transformed by the liver and stored in liver tissues or adipose tissues, or free in the blood. The other part of lipids are used by cells or enter the mitochondria for energy oxidation, or reprogram the membrane through lipid reconstruction, affecting membrane fluidity, membrane rafts formation, and transmission of inflammatory signal cascades.<sup>13</sup> Regarding the decomposition of endogenous lipids, stored fats are hydrolyzed to fatty acids and glycerol after fat mobilization under the action of lipase. After activation and transmembrane transport, fatty acids undergo  $\beta$  oxidation to supply energy. Additionally, phospholipids enter the mitochondria directly for oxidation under the cleavage of phospholipase, while the accompanied glycerol and phosphoric acid participate in the process of glucose metabolism.<sup>14</sup> Regarding the synthesis of endogenous lipids, acetoacetyl coenzyme A, nicotinamide adenine dinucleotide phosphate, and bicarbonate ion are raw materials for *de novo* synthesis; they conduct fatty acid synthesis under the action of multi-enzyme system fatty acid synthase and then enter the network pathway of lipid metabolism (Figure 2).<sup>15</sup> Importantly, fatty acids, as precursors and substrates of other substances, mediate the synthesis of hormones and play a role in multiple biological processes (such as inflammation resolution and immune response). Abnormal lipid metabolism refers to the abnormal quality and quantity of lipids and their metabolites in the blood, tissues, and organs. Affected by genetic, neurohumoral, hormone, enzyme, disease, and other factors, lipids and their metabolites in the normal lipid metabolic network may change, which can result in abnormal physiological function. Moreover, abnormal lipid metabolism has been found in various diseases (such as tumors, rheumatoid arthritis, and diverse elderly diseases), which greatly contribute to disease development.<sup>7,16,17</sup>

## Changes in Lipid Metabolism in Gout

As one of the routine test items, blood lipids [total cholesterol (TC), TGs, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein] are important parameters for clinically assessing lipid metabolism in gout patients. It has been consistently reported that TGs, LDL-C, apolipoprotein B, and apolipoprotein B100 are increased, HDL-C is decreased, and apolipoprotein A1 remains unchanged in gouty arthritis (GA) patients.<sup>18,19</sup> However, TC rises<sup>19</sup> or remains the same,<sup>18</sup> which is paradoxical. In addition to routine clinical lipid tests, other

metabolites of the lipid metabolic pathway (fatty acids and adipokines) have also been studied. Free fatty acids are significantly higher in gout patients compared with those in healthy subjects.<sup>20</sup> In particular, omega-3 fatty acids are remarkably reduced in gout patients due to their well-known lipid-lowering effects.<sup>21</sup> In terms of adipokines, the levels of adiponectin, leptin, resistin, and plasminogen activator inhibitor-1 were measured. The results showed that leptin, resistin, and plasminogen activator inhibitor-1 levels were significantly elevated and adiponectin level was decreased.<sup>22–24</sup> In addition to the above individual lipid, fatty acid, and adipokines tests, lipid metabolomics analyses in the blood and urine of gout patients have also been performed. Plasma lipidomics have revealed changes in lipid distribution in gout patients, with the up-regulation of phosphatidylethanolamine and down-regulation of lysophosphatidylcholine plasma/plasma plasma being the most notable.<sup>25</sup> Similarly, urine metabolomics has also revealed changes in lipid profiles in gout patients compared to healthy individuals.<sup>26</sup> In recent years, gut flora has been shown to play a role in gout. Compared with healthy patients and asymptomatic hyperuricemia patients, gout patients show a reduced abundance of bacteria producing short-chain fatty acids, which is a unique classification feature.<sup>27</sup> Correspondingly, patients with recovered gout have increased serum levels of short-chain fatty acids and show significant alterations in the associated gut microbiota, as compared with patients with acute gout.<sup>28</sup>

In summary, accumulating studies have provided evidence for the disturbed lipid metabolism profile of gout patients, as manifested as abnormal lipid metabolites (such as lipids, fatty acids, and adipokines) (Table 1). These results suggest that lipid metabolism may play a role in the progression of gout.

## Effect of Lipids on Gout

### Effect of Lipids on the Risk of Gout Onset

Gout is one of the common inflammatory joint diseases, and its risk factors are gaining attention. Various studies have shown that lipids and their metabolites play an important role in the development of gout. For example, Rasheed et al

**Table 1** Changes in Lipid Metabolism in Gout

Reference	Year	Indexes	Control			Gout			Comparison of Indexs		
			n	Gender (M/F)	Age(y)	n	Gender (M/F)	Age(y)			
[20]	2019	BMI (kg/m <sup>2</sup> ) TC (mmol/L) TG (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) VLDL-C (mmol/L)	210	205/5	46±12	326	318/8	50±15	P<0.0005 P<0.0005 P<0.0005 P<0.0005 P<0.0005 P<0.0005		
[21]	2020		Free fatty acid (mmol/L)	23.11±5.32 4.40±0.50 1.10±0.27 1.28±0.23 2.42±0.40 0.53±0.15			26.19±2.73 4.78±1.04 2.35±1.87 1.13±0.42 2.85±0.60 1.20±0.78				
				60	60/0	43 (median)	60	60/0		43 (median)	
				0.46±0.20			0.60±0.26			P<0.05	
				81	81/0	64.44±10.22	31	31/0			59.67±11.45
				0.41 (median)			0.11 (median)				P<0.05
[22]	2016	Omega-3 fatty acid (mmol/L)	111	111/0	48±10	258	258/0	48±11			
[23]	2010	BMI (kg/m <sup>2</sup> ) Waist (cm) Abdominal fat area (cm <sup>2</sup> ) TG (mg/dL)	23±3 86±7 115±45 169±120			25±3 90±9 137±56 207±159			P<0.0001 P<0.0001 P<0.001 P<0.05		
[24]	2023		30	23/7	59.50 (46.00, 74.25)	30	25/5	52.73 ± 13.94			
			3271.41±620.42			776.13±196.91				P<0.01	
			Adiponectin (ng/mL)								

**Abbreviations:** BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol.

have found that high levels of VLDL-TG (OR = 7.61,  $P = 0.011$ ) and apolipoprotein B (OR = 5.60;  $P = 0.004$ ) are risk factors for increased risk of gout onset.<sup>29</sup> Similarly, Mak et al have also revealed that high-level TC and low-level high-density lipoprotein (HDL) cholesterol are tightly associated with the frequency of gout attacks, and both could be used as independent predictors of gout attacks.<sup>30</sup> Moreover, another study has demonstrated a significant causal relationship between HDL-C, TGs, BMI, and gout risk by Mendelian randomization.<sup>31</sup>

In terms of fatty acids, omega-3 fatty acids have received much attention. In a case-control study, the level of omega-3 fatty acid is negatively associated with the number of acute gout attacks, and high omega-3 fatty acid level is a protective factor against acute gout attacks (OR = 0.62,  $P = 0.043$ ).<sup>21</sup> Based on this, some scholars have investigated whether dietary or direct supplementation of omega-3 fatty acid could prevent gout onset, and fortunately, their attempt has proved satisfactory results (OR = 0.74,  $P = 0.04$ ).<sup>32</sup> However, in contrast, a recent study has shown that omega-3 fatty acid supplementation could not delay the timing of gout attacks.<sup>33</sup> These above findings indicate the controversial role of omega-3 fatty acids in gout.

Similarly, adipokines also plays a controversial role in gout risk. A study by Garcia-Mendez et al has revealed that there is no linear correlation between adiponectin or leptin levels and gout disease activity.<sup>34</sup> Moreover, gout patients with high disease activity show more severe hypoadiponectin and hyperleptinemia, and disease activity is an independent predictor of adiponectin and leptin levels, reflecting a strong association between these factors.<sup>35</sup> Based on these two different results, a recent two-sample Mendelian randomization study has evaluated whether there is a causal effect of adiponectin and soluble leptin receptors on gout; their results indicate that there is no causal effect between adiponectin and soluble leptin receptors and gout in the inverse variance-weighted model, and these findings are further confirmed by sensitivity analysis.<sup>36</sup> In addition to the aforementioned blood lipids, the role of lipid-related genes has also been investigated in the risk of gout. Through genome-wide association studies, Matsuo et al have identified 5 gout susceptibility loci, of which rs1260326 (OR = 1.36,  $P < 0.001$ ) of GCKR (a gene associated with lipid metabolism) and rs2188380 (OR = 1.75,  $P < 0.001$ ) of MYL2-CUX2 (a gene associated with cholesterol) are considered as novel genetic loci for gout.<sup>37</sup> Furthermore, rs670 (apolipoprotein A1) (OR = 1.53,  $P < 0.001$ ) and rs5128 (apolipoprotein C3) (OR = 0.86,  $P < 0.001$ ) of apolipoprotein A 1-C3-A4 gene cluster have also been demonstrated to play a role in gout risk.<sup>38</sup>

In fact, a large part of the abnormality of lipid metabolism is determined by diet. A high-fat diet can lead to disturbed lipid metabolism, with the most directly manifestations of a high level of body weight, waist circumference, and BMI. Therefore, the possible role of these factors (diet, weight, waist circumference, and BMI) in gout was also explored. As has been indicated previously, there is a strong negative association between low-fat dairy product consumption and gout incidence; consumption of low-fat dairy products is a protective factor against the risk of gout compared with regular dairy products (OR = 0.84,  $P < 0.05$ ).<sup>39,40</sup> In particular, a randomized, double-blind controlled trial has also shown that skimmed milk powder containing glycomacropeptide and G600 milk fat extract can effectively reduce the incidence of gout; this represents a high-quality piece of evidence against skimmed foods in the risk of gout.<sup>41</sup> Moreover, several studies have revealed the risk of high BMI (OR = 1.52,  $P < 0.001$ ) and waist circumference (OR = 1.62,  $P < 0.001$ ) caused by dietary incontinence in gout risk.<sup>42,43</sup>

The above studies have explored the role of blood lipids, fatty acids, adipokines, and high BMI caused by a high-fat diet in gout risk, indicating the tight implication of lipid metabolism disorders in gout risk. Despite the research differences in omega-3 fatty acids and adipokines, further studies are needed to confirm this with larger samples.

## Effect of Lipids on Uric Acid in Gout

As the most important biochemical basis in the occurrence of gout, uric acid metabolism disorder has been a hot spot in the research on gout. With the deepening of research, lipids have been found to play a role in uric acid in recent years. A cross-sectional study has shown that HDL-C ( $r = -0.282$ ,  $P < 0.001$ ) and BMI ( $r = -0.164$ ,  $P < 0.001$ ) are significantly associated with uric acid; HDL-C ( $B = -60.797$ ,  $P = 0.013$ ) and BMI ( $B = 5.168$ ,  $P = 0.024$ ) can serve as predictors of uric acid levels.<sup>44</sup> On this basis, the possible relationship between lipids and uric acid was further determined, and studies based on the Mendelian randomization method have been conducted successively. For example, Adams et al have found that obesity ( $\beta = 0.127$ ,  $P = 1.2E 17$ ) and higher TG ( $\beta = 0.198$ ,  $P = 8.9E 14$ ) can increase uric acid levels, and higher HDL-C ( $\beta = -0.109$ ,  $P = 2.7E 08$ ) can reduce uric acid levels,<sup>45</sup> revealing a possible causal relationship between lipids and uric acid. Moreover, the independent effect of HDL-C and TG on uric acid in gout patients has also been further confirmed in two other studies.<sup>46,47</sup>



The adverse effects of obesity, as measured by BMI, on gouty uric acid have often been observed. A Chinese study has conducted a post-facto analysis of 370 gout patients to identify the predictors of poor response to uric-lowering therapy; they have found that high BMI is an independent predictor of poor response to uric-lowering therapy in gout patients.<sup>48</sup> Another Chinese study has examined the factors that affect the achievement of uric acid reduction goals in 350 gout patients; the waist-to-hip ratio is identified as a predictor of uric acid goal achievement (OR = 1.90,  $P = 0.039$ ), highlighting that obese gout patients may experience more difficulty in controlling uric acid levels.<sup>49</sup> Japanese scholars have also conducted similar studies to the previous two studies, revealing that high levels of BMI (OR = 1.89,  $P < 0.01$ ) and waist circumference (OR = 1.77,  $P < 0.01$ ) are risk factors for the failure of uric acid lowering treatment, while continuous intake of dyslipidemia drugs (OR = 0.81,  $P < 0.05$ ) is a protective factor against treatment failure.<sup>50</sup> Based on the above results, Vafa et al have reviewed severely obese patients who underwent sleeve gastrectomy and Roux-en-Y gastric bypass and found that bariatric surgery can significantly reduce uric acid levels in patients ( $P < 0.001$ ). This also demonstrated that maintaining normal lipid metabolism played an important role in uric acid metabolism.<sup>51</sup>

In fact, the relationship between lipid metabolism and uric acid metabolism may not be unidirectional, but bidirectional. Elevated uric acid is an independent risk of high LDL-C and hypertriglyceridemia.<sup>52</sup> Conversely, decreased uric acid can also promote the reduction of visceral fat and reduce the fat content of the body.<sup>53</sup> A recent Mendelian randomization study has confirmed a bidirectional causal effect between HDL-C and uric acid, which also supports this view.<sup>31</sup> Nevertheless, most of the current studies on lipid and uric acid metabolism focus on the observation of the superficial interaction relationship, and in-depth exploration of the mechanism of lipid metabolism and uric acid metabolism is still lacking.

## Effects of Lipids on Inflammatory Response in Gout

It is well-known that there is a strong correlation between obesity and inflammation. Excessive fat accumulation would activate CD8<sup>+</sup>T cells, which in turn promotes the recruitment of macrophages and the release of cytokines (such as interleukin 6 [IL-6] and tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ]), thereby inducing systemic inflammation to a lesser degree.<sup>54</sup> Similarly, in gout mice, diet-induced obesity induces a pro-inflammatory environment in macrophages and may aggravate monosodium urate (MSU) crystalline inflammation.<sup>55</sup> Additionally, compared with dairy products with standard milk fat, low-fat dairy products reduce the expression of interleukin 8 (IL-8) and interleukin 1 beta (IL-1 $\beta$ ) in MSU-stimulated THP-1 cells and decrease inflammatory responses in mouse models of gout.<sup>56</sup> This may be related to the regulation of lipid metabolism.

If diet and obesity are the source of the aggravation of gout inflammatory response, lipid metabolism disorder caused by it may have a more direct role in gout inflammatory response. It has been shown that free fatty acids, after binding to toll-like receptor 2 (TLR2), can drive the release of IL-1 $\beta$  in gout through the ASC-caspase-1 signaling pathway, thus resulting in a violent inflammatory response.<sup>57</sup> HDL, a beneficial protein, plays an active role in gout inflammation. HDL can reduce leukocyte infiltration and the release of IL-6 and IL-1 $\beta$  through direct interaction with synovial fluid cells or MSU crystals, demonstrating favorable anti-inflammatory properties.<sup>58</sup> Additionally, the in-vitro experiments on MSU-induced human fibroblast-like synoviocytes have also shown that HDL exerts a direct effect on the status of FLS, which can reduce the production of monocyte chemoattractant protein-1 and the recruitment of monocytes/macrophages in the joint, thereby limiting gout attack.<sup>59</sup>

At present, the role of apolipoprotein and adipokine in gout inflammation has also been investigated. Chiang et al have found that patients with acute gout show high levels of apolipoprotein A1 in plasma and synovial fluid, which increases with the increase of blood uric acid. The specific mechanism may be that blood uric acid enhances apolipoprotein A1 production in the liver, and apolipoprotein A1 binds to the MSU crystals in synovial fluid and inhibits the MSU crystals' stimulation of neutrophil and monocyte inflammation, thus ultimately achieving spontaneous resolution of gout.<sup>60</sup> Similarly, another study has also found that apolipoprotein A1 in gout is negatively associated with erythrocyte sedimentation rate (ESR) ( $r = 0.475$ ,  $P < 0.001$ ) and C-reactive protein (CRP) ( $r = 0.380$ ,  $P = 0.001$ ), respectively, highlighting the anti-inflammatory properties of apolipoprotein A1.<sup>61</sup> Moreover, adipokines also play a dual role in gout inflammation. Adiponectin can inhibit the release of inflammatory cytokines (such as IL-1 $\beta$  and TNF- $\alpha$ ) through the PI3K/AKT signaling pathway to alleviate the inflammatory response in gout.<sup>23</sup> In contrast, leptin with the

opposite function can enhance the production of inflammatory cytokines through the mTORC1 signaling pathway in both human and mouse models of gout.<sup>62</sup> This also confirms the role of lipid metabolism disturbance in the resolution and eruption of inflammation in gout.

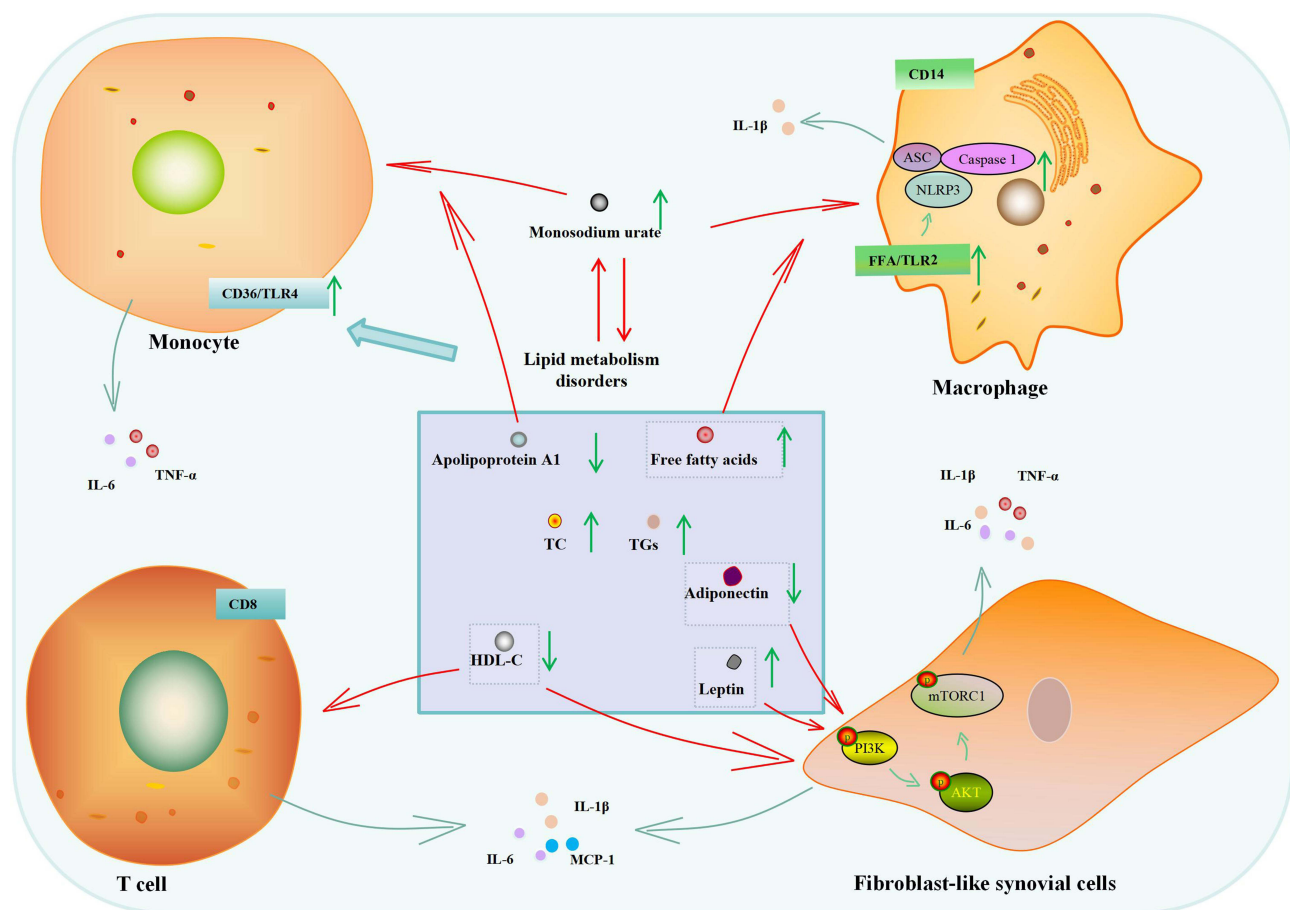
In conclusion, diet and obesity play essential roles in the inflammatory response of gout, especially the changes in lipid metabolites affected by it have a direct regulatory role in gout inflammation (Figure 3). These findings provide more preventive and therapeutic targets for managing inflammation response in gout.

## Effect of Lipids on Gout Comorbidities

### Effect of Lipids on Gout Combined with Vascular Diseases

It is well-recognized that abnormal lipid metabolism is one of the main independent risk factors for cardiovascular and cerebrovascular diseases, even if not in gout. Abnormal lipid metabolism not only leads to the accumulation of cholesterol, TGs, and other lipoproteins in the vascular wall to embolize the blood vessels but also increases oxidative stress and inflammation to damage the vascular endothelial function, as well as triggers cardiovascular and cerebrovascular diseases (such as coronary atherosclerosis or stroke).<sup>63,64</sup>

Vascular disease is a common comorbidity of gout with high incidence and mortality, which seriously affects the overall prognosis of gout patients.<sup>65</sup> A meta-analysis has shown that gout patients have a significantly increased risk of heart failure, myocardial infarction, venous thromboembolism, hypertension, and cerebrovascular accidents relative to patients without gout.<sup>66</sup> As a traditional risk factor for vascular disease, the role of lipid metabolism in gout combined



**Figure 3** Abnormal lipid metabolism regulates the biological processes of GA inflammatory response.

**Abbreviations:** TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; IL-1β, interleukin 1β; IL-6, interleukin 6; TNF-α, tumor necrosis factor alpha; MCP-1, monocyte chemoattractant protein 1; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; FFA, free fatty acid; NLRP3, nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3.

with vascular disease has been gaining attention. Oxidized low-density lipoprotein (LDL), the oxidized form of LDL, plays an important role in atherosclerotic plaque formation.<sup>67</sup> Accumulating studies have found that gout patients have high levels of oxidized LDL in plasma, which maintains a high oxidative stress environment together with SOD and MDA, greatly contributing to vascular endothelial damage.<sup>68</sup> Another study on HDL has shown that the ratio of monocytes and HDL-C is positively correlated with carotid intimal media thickness and could be used as a marker for assessing carotid intima-media thickness (sensitivity = 66%, specificity = 53%), demonstrating the protective effect of HDL on arteriosclerosis.<sup>69</sup> Additionally, Sharonova et al have conducted adiponectin, leptin, and echocardiographic examinations on gout patients, and found that gout patients have notably increased interventricular septal thickness during diastolic and systolic periods, myocardial mass during diastolic periods, and atrial volume; these changes are closely related to hypoadiponectin and leptinemia. Hence, adipokine may play a role in myocardial remodeling.<sup>70</sup>

Gout is a metabolic disease characterized by abnormal uric acid metabolism and lipid metabolism. Recent studies have found that high levels of uric acid also contribute to the development of gout vascular diseases, and urico-lowering therapy is essential to reduce the risk of cardiovascular diseases.<sup>71,72</sup> Given the special relationship among lipids, uric acid, and inflammation in gout, it's speculated that the mechanism of cardiovascular and cerebrovascular diseases caused by lipids in gout may be partially different from other diseases. On the one hand, lipids may affect uric acid metabolism and indirectly participate in vascular remodeling through uric acid or inflammatory reactants. On the other hand, while directly causing vascular diseases, lipids may be affected by uric acid metabolism, which in turn increases the risk of vascular diseases together with uric acid. However, more future research is still needed for validation.

## Effect of Lipids on Gout Combined with Renal Diseases

Renal damage is another common extra-joint lesion of gout, which has been considered to be closely associated with a high level of uric acid.<sup>73</sup> Recent studies have indicated that abnormalities in lipid metabolism may also be involved in the development of gout renal lesions.

Dang et al<sup>74</sup> have studied the association between renal ultrasound image changes and laboratory indicators by recruiting 227 patients with primary gout. The results have shown that renal volume is positively correlated with TG ( $r = 0.206$ ,  $P = 0.004$ ) and LDL-C ( $r = 0.141$ ,  $P = 0.047$ ) and negatively correlated with HDL-C ( $r = -0.149$ ,  $P = 0.036$ ) and apolipoprotein A1/apolipoprotein B ratio ( $r = -0.145$ ,  $P = 0.043$ ); renal stones are positively correlated with lipoprotein A level ( $r = -0.200$ ,  $P = 0.006$ ). Meanwhile, according to binary logistic regression analysis results, low-level HDL-C is a risk factor for renal stone formation (OR = 230.115,  $P = 0.023$ ). This result suggested that focusing on changes in these factors (TG, HDL-C, LDL-C, etc.) may help to early identify the renal changes in gout patients.

Cardona et al<sup>75</sup> have investigated the role of apolipoprotein E2 alleles in renal urate excretion in 60 gout patients and 50 healthy subjects; gout patients show elevated levels of apolipoprotein E2 alleles, TC, TG, and uric acid and decreased levels of HDL, as compared to healthy people. Moreover, gout patients with the apolipoprotein E2 allele have higher TG levels in VLDL and intermediate-density lipoprotein, and lower renal uric acid excretion, compared to patients without the apolipoprotein E2 allele. These results suggest that reduced renal uric acid excretion in gout patients may be mediated by high levels of VLDL and E2 alleles of apolipoprotein E.

Additionally, a study in 2016<sup>76</sup> has similarly found that IL-33 (closely associated with renal damage) is negatively associated with LDL-C and positively associated with HDL-C in gout through correlation analysis; however, no such changes were observed in patients with gout combined with hypertension and tophi. Therefore, it's speculated that IL-33 may play a protective role in renal injury by regulating lipid metabolism, which also reflects that the lipid metabolism disorder may get involved in renal damage in gout.

Overall, it's of great necessity to detect the changes in lipid metabolism in gout considering its potential role in identifying the risk of renal damage. However, further research is still needed to confirm these findings.

## Effect of Lipids on Tophi

Similar to vascular disease and renal damage, tophi is also a common complication of gout. Related studies have found that lipids may promote the formation of tophi.



As indicated by a cross-sectional case-control study<sup>77</sup> including 65 patients with tophi and 85 patients without tophi, patients with tophi have higher BMI and fat mass. Further logistic regression analysis results have shown that high fat mass (OR = 2.01,  $P = 0.003$ ) is an independent risk factor for the development of tophi, suggesting that tophi onset could be prevented by reducing body weight and fat mass.

Similarly, another cross-sectional case-control study<sup>78</sup> has explored the relationship between serum-free fatty acids and tophi. A total of 595 gout patients are included in this study and allocated into Q1, Q2, Q3, and Q4 groups according to their fatty acid quartiles. According to the statistical results, with the increase of free fatty acids, the incidence of tophi in groups Q3 and Q4 is significantly higher than that in groups Q1 and Q2, and the level of free fatty acids is notably positively correlated with the occurrence of tophi. Additionally, multivariate regression analysis results have shown that compared with the Q1 group, Q2 (OR = 2.770,  $P = 0.025$ ), Q3 (OR = 5.878,  $P < 0.001$ ) and Q4 (OR = 7.958,  $P < 0.001$ ) groups have remarkably higher risk factors for tophi occurrence. Further analysis of the receiver operating characteristic curve has shown that free fatty acids have a good predictive ability of tophi (area under the curve = 0.679, sensitivity = 79.3%, specificity = 53.6%,  $P < 0.001$ ). The overall study has revealed that the detection of free fatty acids has great screening value in the identification of tophi.

## Strategies for Regulating Abnormal Lipid Metabolism in Gout

### Drug Intervention

Common drugs (such as statins, fibrate, and niacin) that regulate lipid metabolism have shown powerful lipid-lowering effects and may reduce the risk of lipid abnormalities-associated diseases (including gout).<sup>79</sup> Here, we mainly review the effects of drugs other than traditional lipid-lowering drugs on lipid metabolism and the related disease risk in gout.

### Uric Acid-Lowering Drugs

Uric acid-lowering drugs (such as febuxostat and benzbromarone) are commonly used in gout patients, which have positive effects on maintaining normal serum uric acid levels and thus alleviating gout onset. A cross-section study of 835 gout patients has revealed that patients receiving urico-lowering treatment show significantly lower serum TC and LDL-C levels than those with no urico-lowering treatment ( $P < 0.05$ ), demonstrating a possible lipid-lowering effect of urico-lowering drugs in general.<sup>80</sup> As has been evidenced in more detailed studies, benzbromarone can effectively reduce high-level TC and TG in gout patients and enhance adiponectin production by activating peroxisome proliferator-activated receptor gamma (PPAR  $\gamma$ ).<sup>81</sup> Similarly, the role of febuxostat in increasing adiponectin levels in hyperuricemia has also been proven.<sup>82</sup> Hyperlipidemia alone may not be a cause for concern. However, this view changes when it is considered a risk factor for cardiovascular disease. There is a linear dose-response relationship between allopurinol and benzbromarone use and the reduced risk of coronary artery disease, which may be related to improvements in lipid metabolites.<sup>83</sup> Furthermore, a retrospective cohort study has found that febuxostat and benzbromarone can notably reduce the risk of hyperlipidemia in gout patients, which is achieved in part by reducing the expression of lipogenesis-related genes in the liver, thereby improving the lipid profile.<sup>84</sup> Additionally, through ultrahigh-performance liquid chromatography-tandem mass spectroscopy, lipid profiles of gout patients before and after febuxostat or allopurinol treatment have been obtained. The reduction of multiple fatty acid metabolites has been observed at 24 weeks. Meanwhile, the in-vitro cellular experiments have also demonstrated that febuxostat inhibits the lipolysis of adipocytes and regulates lipid metabolism in gout and comorbidities, which further supported the positive role of uric-lowering drugs in the improvement of lipid profiles.<sup>85</sup>

### Traditional Chinese Medicine

As a common treatment in Oriental medicine, Chinese medicine has been widely applied in the treatment of gout and lipid metabolism disorders.<sup>86–88</sup> Huangqin Qingrechubi capsule (HQC) is a traditional Chinese medicine prescription commonly used in gout treatment. It is composed of radix scutellariae, gardenia, clematis chinensis, peach seed, and coix seed. A previous study has shown that HQC can decrease serum TC level, increase HDL-C level, and increase adiponectin expression in gout patients. Additionally, in the fibroblast-like synoviocytes of gout, HQC can also inhibit the PI3K/AKT pathway activation and reduce inflammation by increasing APN expression, reflecting a comprehensive effect of Chinese medicine in gout treatment.<sup>23</sup> Simiao Decoction is a classic Chinese herbal compound consisting of

rhizoma atractylodis, golden cypress, radix achyranthis bidentatae, and coix seed, which has been extensively used for thousands of years.<sup>89</sup> Simiao Decoction can correct lipid metabolism dysregulation by affecting the expression of apolipoprotein B, lipoprotein lipase, and PPAR $\alpha$  proteins and restoring intestinal microbiota characteristics in mouse models of gout.<sup>90</sup> Additionally, other different Chinese medicines can also improve lipid metabolism in mice with gout.<sup>91,92</sup> However, despite this, the specific mechanisms of Chinese herbs improving lipid metabolism and their bioactive components are poorly studied. This will need attention in the future.

## Dietary Intervention

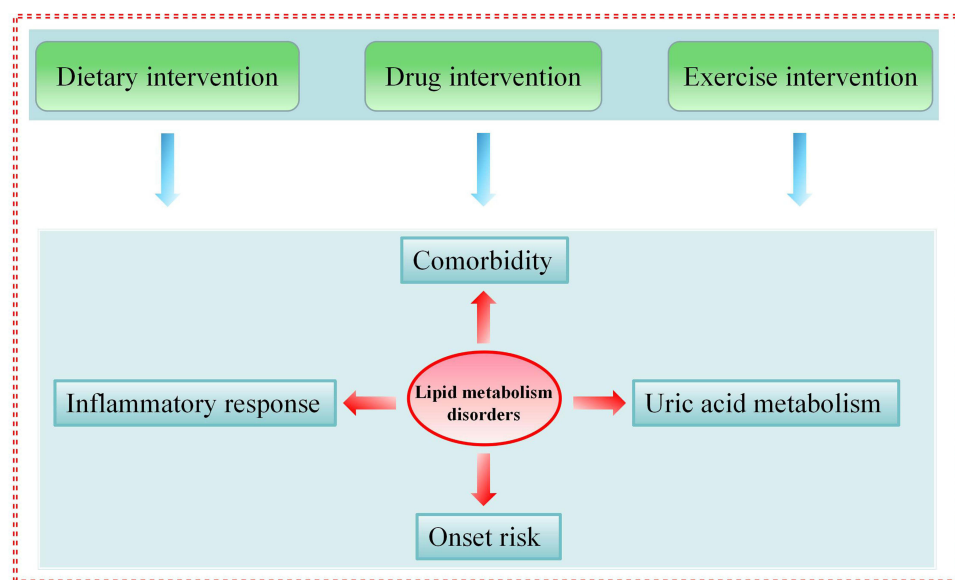
Compared with drugs, diet intervention exerts a more direct and profound effect on lipid metabolism in gout. In general, exogenous intake from food is one of the important sources of lipids in the human body. In addition to high BMI and fat accumulation, improper dietary habits can also increase the risk of gout.<sup>93,94</sup> Therefore, a reasonable diet structure also serves an important part in gout prevention and management. As mentioned earlier, intake of low-fat dairy products is associated with lower risk and frequency of gout attacks compared to regular dairy products.<sup>39,40</sup> Randomized double-blind controlled trials have also shown that consumption of skim milk powder can effectively reduce gout incidence.<sup>41</sup> This evidence suggests that daily intake of low-fat foods may lower the risk of gout, which provides a reference for establishing a proper diet for gout. It is well-known that a low-purine diet is an effective measure to prevent and reduce gout attacks. However, the specific food settings and clinical benefits are still limited. Existing evidence supports that a low-fat diet may increase clinical benefit and reduce the attack of gout in patients. At present, although it is difficult to come up with a broad and applicable dietary standard for gout patients, doctors can advise patients based on the principles of low-purine and low-fat diet in clinical practice.

## Exercise Intervention

Similar to diet intervention, exercise therapy is another important intervention for non-pharmacological treatment of gout. Physical activity can increase lipolysis, and effectively reduce body weight and BMI in obese people, as well as improve various metabolic processes, especially in gout.<sup>95,96</sup> A previous study has shown that people who run 8 km or more per day have a 50% lower risk of developing gout compared with inactive people.<sup>97</sup> Additionally, ergonomic exercise can reduce pain levels and alleviate pain in elderly gout patients.<sup>98</sup> Recent studies have focused on the role of exercise in gout inflammation. For example, Schlesinger et al have explored the relationship between physical activity and inflammatory response in 30 gout patients and found that physically active patients have a 10-fold reduction in CRP, a 2.8-fold reduction in pain perception, and a more than 12-fold reduction in gout attack numbers per year compared to physically inactive patients. The importance of physical activity as a possible adjunctive treatment option is highlighted.<sup>99</sup> Based on the clinical data of acute gout mouse models and human gout patients, Jablonski et al have found that regular and moderate physical activity can produce quantifiable anti-inflammatory effects. Pathological reactions caused by intraarticular MSU crystals can be partially mitigated by down-regulating TLR2 expression on circulating neutrophils and inhibiting systemic CXCL1.<sup>100</sup> Moreover, similar to diet, it's also difficult to formulate broad and applicable criteria for exercise therapy as there are specific and individual differences in timing, intensity, and exercise type for different gout patients. It is necessary to further explore the modality exercise suitable for different gout populations according to different factors such as gender, age, disease activity, and lifestyle.

## Conclusion and Perspectives

It is well-recognized that hyperuricemia is the most important biochemical basis for gout development. However, uric acid-lowering therapy can not cure gout. Similar to uric acid metabolism, lipid metabolism is also complex in gout. As the most abundant metabolite type in living organisms, lipids not only participate in energy storage and oxidation, but also play crucial roles in biofilm skeleton construction, signal transmission, hormone synthesis, and immune response. At present, a disrupted lipid metabolic network has been observed in gout. Lipid metabolites (such as lipids, lipoproteins, fatty acids, and adipokines) may affect the pathogenesis risk of gout, uric acid metabolism, and inflammatory response, and play an undeniable role in gout comorbidities (such as vascular disease and kidney disease). Although the relationship between the intervention of different drugs, diet, and exercise and lipid metabolism changes has gained attention, there are still many deficiencies in relevant studies (Figure 4). Firstly, considering the limitations of population, detection time, detection methods, and other factors, the levels of lipid metabolites in gout patients are not the same, and some may even show conflicting results. Secondly, although the



**Figure 4** The effect of abnormal lipid metabolism on gout and related regulatory strategies.

possible effects of lipid metabolites on gout risk, uric acid metabolism, inflammatory response, and comorbidities have been discovered, most of these discoveries are superficial observations, and the underlying molecular mechanisms of the effects of lipid metabolites on these aspects remain to be explored. Additionally, different lipid metabolites have been shown to show promoting or protective effects on gout. How to guide gout treatment or intervention from the perspective of lipid metabolism is still a great challenge. Finally, The possible role of lipid metabolism before the first onset of gout still needs to be determined. In the future, more research is needed to solve the above problems. Future research should not only clarify the pathophysiological mechanism of the lipid metabolism abnormalities in gout occurrence and development but also combine lipid metabolism with gout treatment to explore more effective intervention strategies for gout.

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## Author Contributions

Xianheng Zhang: Writing - original draft, Conceptualization & design. Jian Liu: Writing - review & editing, Conceptualization & design, Funding acquisition. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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