The association between coagulation/fibrinolysis function and serum lipid levels in people with advanced knee osteoarthritis: a cross-sectional study

Ruo-Ling Teng
the Third Affiliated Hospital of Soochow University
Jie Zhao
the Affiliated Wujin Hospital of Jiangsu University
Xiao-Ling Zheng
the Third Affiliated Hospital of Soochow University
Han Sun (zjtt0219@126.com)
the Third Affiliated Hospital of Soochow University

Research Article

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Abstract

Background. The aim of this study was to explore the relationship between coagulation/fibrinolysis function and serum lipid levels in people with advanced knee osteoarthritis (KOA).

Methods. From January 1st 2013 to January 1st 2018, a total of 206 patients underwent total or unicompartmental knee arthroplasty in Changzhou No.1 People's Hospital were enrolled consecutively in this study. Baseline characteristics and preoperative laboratory indicators of patients were collected. The association between coagulation/fibrinolysis function and serum lipid levels was analyzed using Spearman correlation analysis and multiple linear regression.

Results. Spearman correlation analysis revealed that coagulation/fibrinolysis function was associated with serum lipid levels, especially prothrombin time was moderately negatively correlated with Apolipoprotein-A1 ($r=-0.4585$, $P<0.05$). The multiple linear regression analyses were performed with serum lipid levels as the independent variables and coagulation/fibrinolysis function parameters as the dependent variables after adjusting for sex, age, body mass index, hypertension, diabetes mellitus and coronary heart disease. We found that the regression analysis was reliable (its imitation degree was ideal, adjusted $R^2 = 0.3108$) and predictive ($P<0.0001$) when the dependent variable was prothrombin time. The significant contributors to prothrombin time were triglyceride ($P<0.001$), high density lipoprotein cholesterol ($P=0.003$), Apolipoprotein-A1 ($P=0.017$) and Lipoprotein (a) ($P=0.015$).

Conclusions. The results of this study showed that coagulation/fibrinolysis function was correlated with serum lipid levels in patients with advanced KOA, although the correlation may be small. It may be hypothesized that strategies for lipid control may help improve coagulation/fibrinolytic dysfunction in patients with KOA.

Trial registration. This clinical study was retrospectively registered in a publicly available registry because this study was a retrospective study began in 2018. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University in Jiangsu Province of China (No.CZYY2021187).

Background

Knee osteoarthritis (KOA) is one of the most common joint diseases and a major cause of chronic disability in the world [1–4]. KOA is known to cause articular cartilage destruction and a low inflammatory state in the joint, leading to a series of clinical symptoms such as pain, swelling and loss of function [5]. It is widely accepted that there are both inflammatory and immune reactions in the pathological process of KOA [1].

The relationship between hyperlipidemia and KOA has always been controversial. Some evidence suggest that the abnormalities in lipid metabolism are a potential cause of KOA [6]. Excess fat can increase the risk of hypertension, insulin resistance, hyperinsulinemia, glucose intolerance and cardiovascular disease, which may be associated with KOA [7]. A case-control study from the United Kingdom suggested that hyperlipidemia was associated with the onset of hand osteoarthritis [8]. However, a large observational longitudinal study funded by the National Institutes of Health found no correlation between total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), or low density lipoprotein cholesterol (LDL-C) and the prognosis of OA [9]. Despite these mixed results, some studies have shown that lipids can participate in the inflammatory response of OA, which inspire us to conduct further research in this area. Oliviero et al. observed association between Apolipoprotein-A1 (ApoA1) and inflammatory markers by leukocyte counts in synovial fluid of OA patients [10]. Kaibin Zhang et al. found that synovial fluid (SF) HDL-C and ApoA1 levels may serve as predictors of OA severity [11].

There is increasing evidence that osteoarthritis is involved in the activation of local and/or systemic coagulation and fibrinolytic cascades [12]. Thrombin not only acts as a coagulant or anticoagulant agent, but as a signaling molecule that controls inflammation and promotes platelet activation and aggregation by activating protease-activated receptors (PARs) on platelets [13]. Varisco and Marty believed that blocking the formation of fibrin could alleviate experimental arthritis [14, 15]. Some evidence indicated that plasminogen activation in joints of OA patients was mainly through urokinase-type plasminogen activator (u-PA), which was the most important plasminogen activator involved in tissue modification [16].

It has been reported that high blood lipid levels were linked to hypercoagulability [17–19]. A longitudinal and prospective study in Taiwan with hypertriglyceridemia patients and age-matched normal controls found that a significant increase in triglycerides was associated with a hypercoagulable state [17]. Jung-Ah Kim's study focused on the effect of lipids on coagulation assay results in a normal population, and showed that high levels of triglyceride and total cholesterol were correlated with increased coagulation activity [20]. However, the relationship between lipid levels and coagulation function has not been studied in patients with KOA yet. In the process of osteoarthritis, lipids can participate in inflammatory reactions, and inflammation is a potent inducer of both coagulation and fibrinolysis. No clinical studies have focused on this issue at present. Therefore, our study aimed to explore the relationship between coagulation/fibrinolysis function and serum lipid levels in advanced KOA patients by using Spearman correlation analysis and multiple linear regression analysis.

Methods

Patients with severe degenerative knee osteoarthritis who were preparing for total knee arthroplasty or single-compartment knee arthroplasty were enrolled in our study. The exclusion criteria: (1) rheumatoid arthritis (2) ankylosing spondylitis (3) traumatic arthritis (4) history of bone tumor (5) history of hematological diseases which could seriously interfere with blood clotting (6) history of lipid-lowering medications. Finally, a total of 206 patients (55 males and 151 females) accepted total or unicompartmental knee arthroplasty on account of advanced KOA in Changzhou No.1 People's Hospital from January 1st 2013 to January 1st 2018 were recruited in this study. Baseline characteristics including gender, age, body mass index (BMI), hypertension (HT), diabetes mellitus (DM) and coronary heart disease (CHD) were recorded. Preoperative laboratory examinations such as D dimer (D-D), fibrinogen (FIB), prothrombin time (PT), activated partial thromboplastin time (APTT), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), Apolipoprotein-A1 (ApoA1), Apolipoprotein-B (ApoB), Apolipoprotein-E (ApoE) and Lipoprotein (a) (Lp(a)) were recorded as well. Blood samples were collected after fasting for eight hours the morning after admission. The specimen was sent to the clinical laboratory and then analyzed with an automatic biochemical autoanalyzer.

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University (No.CZYY2021187). Due to the retrospective nature of the study, patient consent for inclusion was waived.

Continuous variables involved in this study did not conform to normal distribution and were expressed by median (inter quartile range, IQR). Categorical variables were expressed by frequency and percentage. The association between coagulation/fibrinolysis function and serum lipid levels was analyzed using Spearman correlation analysis and multiple linear regression. Statistical analysis and graphics were performed using STATA 15.0. Two tailed $P < 0.05$ was considered to be statistically significant.

Results

Between January 1st 2013 and January 1st 2018, a total of 206 patients with advanced KOA were enrolled consecutively in this study. In summary, the cohort was predominantly women (73.3%), with median age of 70.5 years and had high BMI (26.37 kg/m^2). It was observed that, in this sample, 49.02% of the patients were complicated with hypertension, 11.65% with diabetes, and 9.22% with coronary heart disease. Baseline characteristics and preoperative laboratory indicators of patients were summarized in Table 1.

Table 1
Baseline characteristics

Male n (%)	**55 (26.70%)**
Age, year	70.5 (10)
BMI, kg/m^2	26.37 (3.59)
HT n (%)	100 (49.02%)
DM n (%)	24 (11.65%)
CHD n (%)	19 (9.22%)
D-D, mg/L	0.47 (0.75)
PT, sec	10.8 (1.0)
APTT, sec	26.9 (4.1)
FIB, g/L	3.01 (0.95)
TC, mmol/L	4.71 (1.29)
TG, mmol/L	2.07 (1.38)
HDL-C, mmol/L	1.14 (0.35)
LDL-C, mmol/L	2.32 (0.95)
ApoA1, g/L	1.26 (0.22)
ApoB, g/L	0.96 (0.33)
ApoE, g/L	46.4 (16.8)
Lp(a), mg/L	98.5 (100)

Note: Continuous variables were expressed as median (inter quartile range, IQR). Categorical variables were expressed by frequency and percentage.

Abbreviations: BMI body mass index; HT hypertension; DM diabetes mellitus; CHD coronary heart disease; D-D D dimer; PT prothrombin time; APTT activated partial thromboplastin time; FIB fibrinogen; TC total cholesterol; TG triglyceride; HDL-C high density lipoprotein cholesterol; LDL-C low density lipoprotein cholesterol; ApoA1 Apolipoprotein-A1; ApoB Apolipoprotein-B; ApoE Apolipoprotein-E; Lp(a) Lipoprotein (a)

To examine the association between coagulation/fibrinolysis function and serum lipid levels in advanced KOA, we performed Spearman correlation analysis in Table 2. The Bonferroni adjustment was used to adjust the significance level. D dimer was negatively correlated with TG and ApoA1 ($P < 0.05$). PT was negatively correlated with TC, TG,

HDL-C, LDL-C, ApoA1, ApoB and ApoE ($P < 0.05$). APTT was negatively correlated with TC, TG, LDL-C, ApoB and ApoE ($P < 0.05$). FIB was positively correlated with Lp(a) ($P < 0.05$). In the above results, PT was moderately negatively correlated with ApoA1 ($r=-0.4585$, $P < 0.05$), while the others were low correlated.

Table 2
Correlation analysis of coagulation and fibrinolysis index with serum lipids in patients with advanced KOA

Index	TC	TG	HDL-C	LDL-C	ApoA1	ApoB	ApoE	Lp(a)
D-D	-0.0896	-0.1642*	-0.1346	-0.0657	-0.1969*	-0.0762	0.0922	0.0399
PT	-0.2334*	-0.3124*	-0.3026*	-0.1790*	-0.4585*	-0.2360*	-0.2107*	0.1218
APTT	-0.3109*	-0.2788*	-0.1210	-0.2161*	-0.1116	-0.1918*	-0.1896*	0.0358
FIB	0.0521	-0.1280	0.0159	0.0781	-0.0587	0.0855	0.0705	0.1937*

Note: *. Correlation was significant at 0.05 level (2-tailed).

Abbreviations: D-D D dimer; PT prothrombin time; APTT activated partial thromboplastin time; FIB fibrinogen; TC total cholesterol; TG triglyceride; HDL-C high density lipoprotein cholesterol; LDL-C low density lipoprotein cholesterol; ApoA1 Apolipoprotein-A1; ApoB Apolipoprotein-B; ApoE Apolipoprotein-E; Lp(a) Lipoprotein (a)

After that, multiple linear regression analyses were performed with serum lipid levels as the independent variables and coagulation/fibrinolysis function parameters as the dependent variables, adjusting for sex, age, BMI, HT, DM and CHD. Due to the non-normal distribution of serum lipid levels and coagulation/fibrinolysis function parameters, logarithmic transformation was performed to satisfy the multiple linear regression analysis. Correlation coefficients and variance inflation factors were used to evaluate whether multicollinearity existed among independent variables. It was found that there was multicollinearity between TC and LDL-C. Thus we cancelled the inclusion of independent variable TC in order not to affect the fitting of the multiple linear regression model as LDL -C was currently recognized as a major risk factor for atherosclerosis. Detailed results were shown in Table 3. We found that the regression analysis was reliable (its imitation degree was ideal, adjusted $R^2 = 0.3108$) and predictive ($P < 0.0001$) when the dependent variable was PT. But the imitation degree were not ideal when the dependent variables were APTT ($P = 0.0008$, adjusted $R^2 = 0.1076$) and D dimer ($P = 0.0001$, adjusted $R^2 = 0.1394$). And the regression analysis was not predictive ($P = 0.0598$) when the dependent variable was FIB. Based on the above results, we finally established a linear regression model with PT as the dependent variable, and came to the conclusion that the significant contributors to prothrombin time were TG ($P < 0.001$), HDL-C ($P = 0.003$), ApoA1 ($P = 0.017$) and Lp(a) ($P = 0.015$).

Table 3
Multiple linear regression analysis of coagulation/fibrinolysis function and serum lipid levels (in logarithmic form)

Independent variables	Dependent variables							
	Log PT		Log APTT		Log D-D		Log FIB	
	Coefficients	P values	Coefficients	P values	Coefficients	P values	Coefficients	P values
Log TG	-0.054	< 0.001*	-0.118	< 0.001*	-0.608	0.003*	-0.158	0.006*
Log HDL-C	-0.078	0.003*	-0.138	0.008*	-0.636	0.108	-0.023	0.837
Log LDL-C	0.008	0.736	-0.123	0.010*	-0.202	0.580	-0.082	0.430
Log ApoA1	-0.103	0.017*	0.111	0.199	-0.858	0.194	-0.088	0.639
Log ApoB	-0.031	0.382	0.171	0.017*	-0.163	0.765	0.250	0.108
Log ApoE	0.022	0.252	0.013	0.734	0.987	0.001*	0.095	0.251
Log Lp(a)	0.013	0.015*	0.001	0.954	0.040	0.613	0.054	0.018*

Notes: Due to the non-normal distribution of serum lipids and coagulation/fibrinolysis function parameters, logarithmic transformation was performed to satisfy the multiple linear regression analysis.

Covariates: sex, age, body mass index (BMI), hypertension (HT), diabetes mellitus (DM), coronary heart disease (CHD)

Abbreviations: TG triglyceride; HDL-C high density lipoprotein cholesterol; LDL-C low density lipoprotein cholesterol; ApoA1 Apolipoprotein-A1; ApoB Apolipoprotein-B; ApoE Apolipoprotein-E; Lp(a) Lipoprotein (a); PT prothrombin time; APTT activated partial thromboplastin time; D-D D dimer; FIB fibrinogen

*. Correlation was significant at 0.05 level (2-tailed).

Discussion

The results of this study suggest that there may be some association between coagulation/fibrinolysis function and serum lipid levels in patients with advanced KOA, although the correlation may be small.

Numerous studies have shown that osteoarthritis can occur articular cartilage destruction, chondrocyte apoptosis, subchondral sclerosis, cystic changes, osteophyte formation at the joint edge, local blood circulation abnormalities, etc., and its pathogenesis is still unclear [5, 21]. So far, studies have suggested that both immune and inflammatory reactions exist in the pathological process of OA [1]. The NF-κB signaling pathway is ubiquitous in eukaryotic cells and has various regulatory functions such as regulating immune and inflammatory responses. In the physiological state, the balanced NF-κB response maintain the stability of internal environment. However, in the pathological state, the NF-κB response promotes the expression of pain-causing mediators and inflammatory mediators, which results in catabolic processes, cell death or apoptosis. Many studies have shown that NF-κB signaling pathway plays a major role in the pathogenesis and development of osteoarthritis [22, 23]. NF-κB, a member of the transcription factors family of proteins, exists in cells mainly as heterodimer formed by P50 and P65 binding in vivo. In normal state, NF-κB (P50 / P65) binds to inhibitory protein IkB, which puts it in a state of inactivation. Proinflammatory cytokines,

excessive mechanical stress, and/or matrix-degrading enzymes can trigger a series of reactions which cause proteasome degradation of IkB, and then result in the release of active NF-κB (RelA/ NF-KB1 dimer) [24]. NF-κB is highly activated at the site of synovial inflammation in patients with KOA [25]. The roles of NF-κB in OA chondrocytes and cartilage have been well-documented [26]. Increasing evidence has shown that many types of miRNAs suppress chondrocyte catabolism by inhibiting molecular components of the NF-κB signaling pathway. For example, Yanjie Ding found that miR-93 inhibited the NF-κB pathway by targeting toll-like receptor-4 (TLR4), which was the upstream regulators of NF-κB [27]. Cytokines are a kind of bioactive protein molecules synthesized and secreted by immune cells and some non-immune cells after stimulation [28]. The role of cytokines in the pathophysiology of OA is well-documented. They participate in inflammation and immune response through the exchange and regulation of information between cells. In normal human body, the inflammatory factors and anti-inflammatory factors maintain a dynamic balance. IL-1, IL-6, IL-8, IL-17 and TNF-α are the main inflammatory cytokines. IL-1Ra, IL-4, IL-10 and IL-13 are the main anti-inflammatory cytokines [1, 29, 30]. The NF-κB signaling pathway promotes the transcription of genes encoding cytokines like TNF-α and IL-1β and then induces the production of IL-6, IL-8, and cyclooxygenase-2 (COX-2). After that, the NF-κB signaling pathway stimulates the production of matrix metalloproteinases (MMPs) in synovial cells, monocytes, or chondrocytes, and ultimately mediates critical events in inflammatory response [31]. In addition to regulating the expression of TNF-α and IL-1β, NF-κB is activated by these cytokines as well. Inflammatory factors and activated NF-κB actually form a positive cycle of regulation [23].

The relationship between serum lipid levels and OA has not been determined yet. More and more evidence suggests that OA is a "metabolic disorder" in which the associated lipid metabolism contributes to the progression of the disease [6, 32]. In the in vitro experiment of Dominique et al. [33], the levels of TC, LDL-C and ApoA1 were strongly correlated in the articular cavity of OA patients, and were correlated with the local inflammatory process in the OA articular cavity through IL-6 and MMP-3. Dominique considered that the downstream pathways of NF-κB and MAPK were induced by ApoA1 stimulation [33]. ApoA1 induced the expression of IL-6, MMP-1 and MMP-3 in primary chondrocytes and fibroblast-like synovial cells through TLR4 receptor, and was directly or indirectly involved in local inflammatory responses. Onat et al. also found that ApoA1 could be converted into pro-inflammatory particles by aggregation to Lp(a) [34].

Activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB) and D dimer (D-D) are common indexes for detecting coagulation and fibrinolysis function in clinic. APTT and PT are the most sensitive and commonly used screening tests in the internal and external coagulation system, which mainly reflect whether the internal and external coagulation is normal. Fibrinogen, also known as coagulation factor I, is the highest content of coagulation factor in plasma and the main protein in the coagulation process. D dimer is a cross-linked fibrin degradation product, and its level changes can be used as one of the markers of hypercoagulability and fibrinolysis in vivo. Therefore, the above four indicators were selected to evaluate the coagulation and fibrinolysis function of patients in this study [35]. A number of studies have focused on the relationship between coagulation/fibrinolytic system and inflammation recently [12, 36, 37]. Thrombin mediates hemostasis and inflammatory response and directs the immune response to tissue damage [12]. Activation of PARs on platelets plays an important role in hemostasis and thrombosis. Several studies found that PARs involved in the development of both inflammatory responses and thrombin [13, 38]. Stimulation of isolated monocytes by thrombin or a receptor-selective PAR1-AP (TFLLRNPNDK) resulted in release of IL-6 [39]. The study of Y. Xiang showed that thrombin increased the expression of inflammatory cytokines such as IL-1β, TNF-α, transforming growth factor-β 1 (TGF-β1), IL-6 and COX-2 in osteoblasts or osteoblast cells [40]. On the other hand, the proteolytic activity of plasmin contributes to inflammation and remodeling in disease [37]. A.K. 's study showed that in OA patients, elevated D dimer levels demonstrated increased intra-articular coagulation and increased fibrin dissolution [36]. Plasmin is the main enzyme mediator of

fibrinolysis, forming TLR-4 and activating fibrin degradation products (FDPs). Whether activated by TLR-4 for FDPs formation, or by MMPs and/or PAR-1, the proteolytic activity of plasmin contributes to inflammation and remodeling [37, 41]. Proteases such as FXa, FVIIa, thrombin, plasminase, urokinase-type plasminogen activator (u-PA) and tissue-type plasminogen activator (t-PA) not only participate in extravascular coagulation or fibrinolysis, but also mediate inflammation response and tissue remodeling [37]. Some studies showed that patients with hypercholesterolemia or triglyceridemia had higher levels of fibrinogen and factor VII and shorter PT and APTT values than patients with lower cholesterol levels [17, 19]. Jung-Ah Kim et al. discovered that procoagulant factors II, VII, IX, X, and XI and anticoagulant factors protein C and protein S were significant correlated with triglyceride [20]. The increase of procoagulant factors may be greater than that of anticoagulant factors, and the total hemostatic balance may tend to change to hypercoagulability in hyperlipidemia.

This was the first study to explore the association between coagulation/fibrinolysis function and serum lipid levels in patients with KOA. Based on previous findings, there may be a link among coagulation/fibrinolysis function, blood lipid levels and inflammatory response. Lp (a) is a complex formed by Apo (a) (apolipoprotein (a)) and LDL, which main apolipoproteins are ApoB100 and Apo (a). Nathalie Busso et al. found co-deposition of plasma Apo (a) with fibrin in arthritic joints, suggesting that Apo (a) locally regulated fibrinolytic activity and may contribute to the persistence of fibrin and bone matrix degradation in inflammatory arthritis [42]. Tsimikas Sotirios et al. confirmed that Lp (a) was highly homologous with fibrinolytic enzyme, which could competitively bind its receptor and lead to the reduction of thrombolysis by interfering with the physiological activity of fibrinolytic enzyme [43]. Similar results were obtained in this study, that is, fibrinogen was positively correlated with Lp(a). TLR4, an upstream regulator of NF-κB, mediated the expression of IL-6, MMP-1 and MMP-3 in primary chondrocytes and fibroblast-like synovial cells induced by ApoA1 [33]. Interestingly, plasmin was able to form TLR-4 and activate FDPs [44]. Onat's study showed that ApoA1 could be transformed into pro-inflammatory particles by polymerization to Lp (a) [34]. ApoA1 is the main apolipoproteins of chylomicrons (CM) and HDL-C, while CM is a TG-rich lipoprotein, which may partly explain the relationship between TG, HDL-C and coagulation function in this study. It is still necessary for us to further improve the relevant basic research of coagulation factors, lipoprotein, as well as pro-inflammatory and anti-inflammatory factors, so as to obtain more accurate results. Joint replacement surgery is still the preferred treatment for advanced KOA so far [45, 46]. With the increasing understanding of osteoarthritis, there are currently some non-surgical treatments. One of them is intra-articular therapy with platelet-rich plasma, which requires us to pay attention to the coagulation/fibrinolysis function of patients [47]. It is a new idea brought by this study to control serum lipid levels through lifestyle or medication to avoid abnormal coagulation/fibrinolysis state. There is considerable evidence that statins have antithrombotic properties, as they may lead to significant downregulation of the clotting cascade, most likely due to decreased tissue factor expression leading to reduced thrombin production [18].

Despite the advantages above, some limitations have to be considered. Since our subjects were from the local population, we could not rule out the effect of ethnic differences on our results. And the cross-sectional study design was inevitably open to confounding factors which may exaggerate or reduce the association between exposure and the primary outcome. In addition, only patients with advanced KOA were included in our study, which needed to be further supplemented. Moreover, we did not have blood coagulation factor measurements except factor I at that time, so we could not examine if coagulation factor was associated with serum lipid levels in KOA patients. Due to the lack of relevant data, we did not include the symptom severity and radiographic data in this study, which would be remedied and improved in the future research of our group.

Conclusions

This study demonstrates that coagulation/fibrinolysis function is correlated with serum lipid levels in people with advanced KOA, although the correlation may be small. It can be assumed that strategies for lipid control may help improve coagulation/fibrinolytic dysfunction in patients with KOA, although this hypothesis needs to be tested further considering the characteristics of cross-sectional design.

Abbreviations

KOA
Knee osteoarthritis
PT
Prothrombin time
ApoA1
Apolipoprotein-A1
Lp(a)
Lipoprotein (a)
APTT
Activated partial thromboplastin time
TC
Total cholesterol
TG
Triglyceride
ApoB
Apolipoprotein-B
ApoE
Apolipoprotein-E
HDL-C
High density lipoprotein cholesterol
LDL-C
Low density lipoprotein cholesterol
SF
Synovial fluid
PARs
Protease-activated receptors
u-PA
urokinase-type plasminogen activator
BMI
Body mass index
HT
Hypertension
DM
Diabetes mellitus
CHD
Coronary heart disease
D-D
D dimer

FIB
Fibrinogen
CI
Confidence interval
IQR
Inter quartile range
MMP
Matrix metalloproteinase
TGF-β1
Transforming growth factor-β 1
COX-2
Cyclooxygenase-2
TLR-4
Toll-like receptor-4
FDPs
Fibrin degradation products
t-PA
tissue-type plasminogen activator
Apo (a)
Apolipoprotein (a)
CM
Chylomicrons

Declarations

Ethics approval and consent to participate

The study protocol (No.CZYY2021187) was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University. The current study was conducted in line with the principles outlined in the Declaration of Helsinki. The Institutional Review Board of the Third Affiliated Hospital of Soochow University waived the need for informed consent before analysis as the nature of these data was retrospective.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Changzhou No.1 People's Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Changzhou No.1 People's Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RL, T and H, S wrote the main manuscript text and designed the current study; RL, T and J, Z analyzed the data and created the tables; J, Z and XL, Z participated in clinical data collection. All authors read and approved the final manuscript.

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Authors' information

RL, T and J, Z contributed equally to this work.

References

1. Primorac D, Molnar V, Rod E, et al. Knee Osteoarthritis: A Review of Pathogenesis and State-Of-The-Art Non-Operative Therapeutic Considerations. Genes 2020; 11.
2. Bortoluzzi A, Furini F, Scire CA. Osteoarthritis and its management - Epidemiology, nutritional aspects and environmental factors. Autoimmunity reviews 2018; 17:1097–1104.
3. Peat G, Thomas MJ. Osteoarthritis year in review 2020: epidemiology & therapy. Osteoarthritis and cartilage 2021; 29:180–189.
4. Yahaya I, Wright T, Babatunde OO, et al. Prevalence of osteoarthritis in lower middle- and low-income countries: a systematic review and meta-analysis. Rheumatology international 2021; 41:1221–1231.
5. van den Bosch MHJ. Osteoarthritis year in review 2020: biology. Osteoarthritis and cartilage 2021; 29:143–150.
6. Velasquez MT, Katz JD. Osteoarthritis: another component of metabolic syndrome? Metabolic syndrome and related disorders 2010; 8:295–305.
7. Liu SY, Zhu WT, Chen BW, Chen YH, Ni GX. Bidirectional association between metabolic syndrome and osteoarthritis: a meta-analysis of observational studies. Diabetology & metabolic syndrome 2020; 12:38.
8. Frey N, Hugle T, Jick SS, Meier CR, Spoendlin J. Hyperlipidaemia and incident osteoarthritis of the hand: a population-based case-control study. Osteoarthritis and cartilage 2017; 25:1040–1045.
9. Schwager JL, Nevitt MC, Torner J, et al. Is there an association of serum low density lipoprotein, high density lipoprotein or total cholesterol with development of knee osteoarthritis? Arthritis care & research 2020.
10. Oliviero F, Sfriso P, Baldo G, et al. Apolipoprotein A-I and cholesterol in synovial fluid of patients with rheumatoid arthritis, psoriatic arthritis and osteoarthritis. Clinical and experimental rheumatology 2009; 27:79–83.
11. Zhang K, Ji Y, Dai H, et al. High-Density Lipoprotein Cholesterol and Apolipoprotein A1 in Synovial Fluid: Potential Predictors of Disease Severity of Primary Knee Osteoarthritis. Cartilage 2021; 13:1465S-1473S.
12. Chou PY, Su CM, Huang CY, Tang CH. The characteristics of thrombin in osteoarthritic pathogenesis and treatment. BioMed research international 2014; 2014:407518.
13. Gieseler F, Ungefroren H, Settmacher U, Hollenberg MD, Kaufmann R. Proteinase-activated receptors (PARs) - focus on receptor-receptor-interactions and their physiological and pathophysiological impact. Cell

communication and signaling: CCS 2013; 11:86.

14. Varisco PA, Peclat V, van Ness K, Bischof-Delaloye A, So A, Busso N. Effect of thrombin inhibition on synovial inflammation in antigen induced arthritis. Annals of the rheumatic diseases 2000; 59:781–787.
15. Marty I, Peclat V, Kirdaite G, Salvi R, So A, Busso N. Amelioration of collagen-induced arthritis by thrombin inhibition. The Journal of clinical investigation 2001; 107:631–640.
16. Cerinic MM, Generini S, Partsch G, et al. Synoviocytes from osteoarthritis and rheumatoid arthritis produce plasminogen activators and plasminogen activator inhibitor-1 and display u-PA receptors on their surface. Life sciences 1998; 63:441–453.
17. Chan P, Huang TY, Shieh SM, Lin TS, Tsai CW. Thrombophilia in Patients with Hypertriglyceridemia. Journal of thrombosis and thrombolysis 1997; 4:425–429.
18. Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. Arteriosclerosis, thrombosis, and vascular biology 2005; 25:287–294.
19. Chan P, Tomlinsoin B, Tsai CW, Pan WH, Lee YS. Thrombophilia in patients with hypercholesterolemia. Metabolism: clinical and experimental 1996; 45:966–969.
20. Kim JA, Kim JE, Song SH, Kim HK. Influence of blood lipids on global coagulation test results. Annals of laboratory medicine 2015; 35:15–21.
21. Boehme KA, Rolauffs B. Onset and Progression of Human Osteoarthritis-Can Growth Factors, Inflammatory Cytokines, or Differential miRNA Expression Concomitantly Induce Proliferation, ECM Degradation, and Inflammation in Articular Cartilage? International journal of molecular sciences 2018; 19.
22. Ostojic M, Zevrnja A, Vukojevic K, Soljic V. Immunofluorescence Analysis of NF-kB and iNOS Expression in Different Cell Populations during Early and Advanced Knee Osteoarthritis. International journal of molecular sciences 2021; 22.
23. Ahmed AS, Gedin P, Hugo A, et al. Activation of NF-kappaB in Synovium versus Cartilage from Patients with Advanced Knee Osteoarthritis: A Potential Contributor to Inflammatory Aspects of Disease Progression. Journal of immunology 2018; 201:1918–1927.
24. Baldwin AS, Jr. The NF-kappa B and I kappa B proteins: new discoveries and insights. Annual review of immunology 1996; 14:649–683.
25. Lepetsos P, Papavassiliou KA, Papavassiliou AG. Redox and NF-kappaB signaling in osteoarthritis. Free radical biology & medicine 2019; 132:90–100.
26. Choi MC, Jo J, Park J, Kang HK, Park Y. NF-kappaB Signaling Pathways in Osteoarthritic Cartilage Destruction. Cells 2019; 8.
27. Ding Y, Wang L, Zhao Q, Wu Z, Kong L. MicroRNA93 inhibits chondrocyte apoptosis and inflammation in osteoarthritis by targeting the TLR4/NFkappaB signaling pathway. International journal of molecular medicine 2019; 43:779–790.
28. Kraus VB, Karsdal MA. Osteoarthritis: Current Molecular Biomarkers and the Way Forward. Calcified tissue international 2021; 109:329–338.
29. Nguyen LT, Sharma AR, Chakraborty C, Saibaba B, Ahn ME, Lee SS. Review of Prospects of Biological Fluid Biomarkers in Osteoarthritis. International journal of molecular sciences 2017; 18.
30. Zhu Z, Otahal P, Wang B, et al. Cross-sectional and longitudinal associations between serum inflammatory cytokines and knee bone marrow lesions in patients with knee osteoarthritis. Osteoarthritis and cartilage 2017; 25:499–505.

31. Fuchs S, Skwara A, Bloch M, Dankbar B. Differential induction and regulation of matrix metalloproteinases in osteoarthritic tissue and fluid synovial fibroblasts. Osteoarthritis and cartilage 2004; 12:409–418.
32. Jiang X, Zhong R, Dai W, et al. Exploring Diagnostic Biomarkers and Comorbid Pathogenesis for Osteoarthritis and Metabolic Syndrome via Bioinformatics Approach. International journal of general medicine 2021; 14:6201–6213.
33. de Seny D, Cobraiville G, Charlier E, et al. Apolipoprotein-A1 as a damage-associated molecular patterns protein in osteoarthritis: ex vivo and in vitro pro-inflammatory properties. PloS one 2015; 10:e0122904.
34. Onat A, Can G, Ornek E, Cicek G, Murat SN, Yuksel H. Increased apolipoprotein A-I levels mediate the development of prehypertension among Turks. Anadolu kardiyoloji dergisi: AKD = the Anatolian journal of cardiology 2013; 13:306–314.
35. Monroe DM, Hoffman M. The clotting system - a major player in wound healing. Haemophilia: the official journal of the World Federation of Hemophilia 2012; 18 Suppl 5:11–16.
36. So AK, Varisco PA, Kemkes-Matthes B, et al. Arthritis is linked to local and systemic activation of coagulation and fibrinolysis pathways. Journal of thrombosis and haemostasis: JTH 2003; 1:2510–2515.
37. Schuliga M. The inflammatory actions of coagulant and fibrinolytic proteases in disease. Mediators of inflammation 2015; 2015:437695.
38. Coughlin SR. Thrombin signalling and protease-activated receptors. Nature 2000; 407:258–264.
39. Naldini A, Bernini C, Pucci A, Carraro F. Thrombin-mediated IL-10 up-regulation involves protease-activated receptor (PAR)-1 expression in human mononuclear leukocytes. Journal of leukocyte biology 2005; 78:736–744.
40. Xiang Y, Masuko-Hongo K, Sekine T, et al. Expression of proteinase-activated receptors (PAR)-2 in articular chondrocytes is modulated by IL-1beta, TNF-alpha and TGF-beta. Osteoarthritis and cartilage 2006; 14:1163–1173.
41. Pontecorvi P, Banki MA, Zampieri C, et al. Fibrinolysis protease receptors promote activation of astrocytes to express pro-inflammatory cytokines. Journal of neuroinflammation 2019; 16:257.
42. Busso N, Dudler J, Salvi R, et al. Plasma apolipoprotein(a) co-deposits with fibrin in inflammatory arthritic joints. The American journal of pathology 2001; 159:1445–1453.
43. Tsimikas S, Tsironis LD, Tselepis AD. New insights into the role of lipoprotein(a)-associated lipoprotein-associated phospholipase A2 in atherosclerosis and cardiovascular disease. Arteriosclerosis, thrombosis, and vascular biology 2007; 27:2094–2099.
44. Schattner M. Platelet TLR4 at the crossroads of thrombosis and the innate immune response. Journal of leukocyte biology 2019; 105:873–880.
45. Varacallo M, Luo TD, Johanson NA, Total Knee Arthroplasty Techniques. StatPearls. Treasure Island (FL), 2021.
46. Gemayel AC, Varacallo M, Total Knee Replacement Techniques. StatPearls. Treasure Island (FL), 2021.
47. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nature reviews Rheumatology 2013; 9:721–730.