American Journal of Biomedicine and Pharmacy
https://biojournals.us/index.php/AJBP
ISSN: 2997-7177

Assessment of Lipid Profile and Follistatin in Osteoarthritis

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Received: 2024, 15, Dec
Accepted: 2025, 21, Jan
Published: 2025, 12, Feb

Annotation: Osteoarthritis (OA) is a degenerative joint disease and a significant cause of disability worldwide. This study aimed to evaluate lipid profile abnormalities and serum follistatin levels in OA patients compared to healthy controls, elucidating their roles in disease pathogenesis. A case-control design included 50 OA patients and 50 age- and sex-matched controls. Lipid parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were analyzed alongside serum follistatin levels measured by enzyme-linked immunosorbent assay (ELISA). OA patients exhibited significantly higher TC, TG, and LDL-C levels and lower HDL-C levels than controls. Serum follistatin levels were also significantly elevated in OA patients and showed positive correlations with TC, TG, and LDL-C and a negative correlation with HDL-C. These findings highlight the interplay between lipid metabolism and inflammatory mediators in OA and suggest that lipid profile and follistatin levels may serve as potential biomarkers or therapeutic targets for the disease.

Keywords: Lipid, follistatin, osteoarthritis.

Introduction

Osteoarthritis (OA) is a chronic, degenerative joint disorder and one of the leading causes of disability worldwide (1). The progressive loss of articular cartilage, changes in the subchondral

bone, osteophyte formation, and synovial inflammation characterize it. OA has a significant social and economic impact on millions of individuals, particularly among older adults (2). However, OA is not solely a disease of aging; multiple genetic, mechanical, metabolic, and inflammatory factors are believed to contribute to its pathogenesis, making it a complex and multifactorial disease (3).

In recent decades, there has been increasing interest in understanding the metabolic aspects of OA. Traditionally, OA was considered primarily a mechanical "wear and tear" disease (4). However, emerging evidence suggests a strong association between metabolic syndrome, characterized by obesity, hypertension, insulin resistance, and dyslipidemia, and the development and progression of OA (5). Metabolic disturbances exacerbate joint degeneration through systemic and local mechanisms, such as increased oxidative stress, chronic low-grade inflammation, and altered lipid metabolism (6).

Dyslipidemia, or abnormal lipid levels, is a hallmark of metabolic syndrome and has been implicated in the pathophysiology of OA. Elevated levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), along with decreased levels of high-density lipoprotein cholesterol (HDL-C), are thought to contribute to the inflammatory and catabolic environment in OA joints. Lipids and their derivatives can act as bioactive molecules, influencing chondrocyte metabolism, extracellular matrix degradation, and inflammatory responses (7). For instance, oxidized lipids may promote the production of pro-inflammatory cytokines and matrix metalloproteinases, further driving cartilage destruction. The precise mechanisms linking dyslipidemia and OA remain under investigation, but these findings underscore the potential role of lipid metabolism in joint health and disease (8).

Furthermore, lipid metabolism can impact systemic inflammation, a known contributor to OA pathogenesis. Lipoprotein particles, particularly LDL-C, may undergo oxidation in the joint microenvironment, leading to oxidized low-density lipoproteins (ox-LDL) (9). These oxides are recognized by immune cells, triggering the release of inflammatory mediators such as interleukins and tumor necrosis factor-alpha (TNF-α) (10). This inflammatory cascade exacerbates cartilage degradation and inhibits repair mechanisms, creating a chronic joint inflammation and destruction cycle (11). Conversely, HDL-C is known for its anti-inflammatory properties and role in reverse cholesterol transport. Reduced levels of HDL-C in OA patients may diminish the protective effects against inflammation, further aggravating joint damage (12).

In parallel, recent studies have drawn attention to the role of follistatin. This glycoprotein binds and antagonizes activins and other members of the transforming growth factor-beta (TGF-β) superfamily (13). Follistatin is well-recognized for its regulatory functions in muscle growth and repair and its anti-inflammatory properties (14). In the context of OA, follistatin may influence key pathological processes such as inflammation, extracellular matrix remodeling, and chondrocyte apoptosis. Elevated levels of follistatin have been observed in inflammatory conditions and may reflect a compensatory response to cytokine-mediated joint damage. However, its exact role in OA remains poorly understood, and whether it contributes to or mitigates disease progression is a subject of ongoing research (15).

The interplay between lipid metabolism and follistatin regulation presents an intriguing area of investigation. Metabolic and inflammatory pathways are often interconnected, and it is plausible that dyslipidemia could influence follistatin expression through systemic or local inflammatory mediators (11). This hypothesis is supported by the observation that lipid abnormalities and follistatin dysregulation are standard features in OA patients. For example, elevated TG and LDL-C levels may enhance oxidative stress and cytokine production, creating an environment that promotes follistatin upregulation (8). Conversely, follistatin may modulate lipid metabolism by interacting with activins and other signaling molecules. Understanding these interactions is critical, as they could reveal novel biomarkers or therapeutic targets for OA (13).

Despite these advances, significant gaps remain in our knowledge of the metabolic contributions to OA. Most studies have focused on isolated aspects of lipid metabolism or inflammation, with limited exploration of their combined effects (16). Moreover, while follistatin has been implicated in various inflammatory and fibrotic diseases, its role in OA has received comparatively little attention. Therefore, a comprehensive analysis of lipid profiles and follistatin levels in OA patients is warranted better to understand their potential as diagnostic and prognostic markers (3).

Lipid profiles and follistatin levels may hold therapeutic potential in addition to their diagnostic implications. In preclinical studies, pharmacological interventions targeting dyslipidemia, such as statins, have shown promise in modulating inflammatory pathways and reducing OA symptoms (6). Similarly, follistatin-based therapies could regulate inflammation and cartilage repair processes, although this approach remains largely experimental. Investigating these therapeutic strategies in the context of OA could open new avenues for disease management and prevention (14).

This study addresses these gaps by assessing the lipid profile and serum follistatin levels in patients with OA compared to healthy controls. By investigating the correlations between these parameters, we seek to elucidate their roles in OA pathogenesis and explore their interrelationships. Our findings may provide new insights into the metabolic-inflammatory axis in OA and highlight potential avenues for early diagnosis and targeted intervention.

Materials and Methods

Study Design and Participants

A case-control study involved 100 participants: 50 patients diagnosed with OA based on clinical and radiographic criteria and 50 age- and sex-matched healthy controls. Exclusion criteria included secondary arthritis, systemic inflammatory diseases, recent infections, and the use of lipid-altering medications.

Sample Collection

Fasting blood samples were collected from all participants. The serum was separated by centrifugation and stored at -80°C until analysis.

Biochemical Analysis

Lipid profiles, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were measured using an enzymatic spectrophotometer. Kits were purchased from Biolabo. Serum follistatin levels were quantified using enzyme-linked immunosorbent assay (ELISA) kits (BT Lab company).

Statistical Analysis

Data were analyzed using SPSS version 25.0. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages. Independent t-tests and chi-square tests were used to compare variables between groups. Correlation analysis was performed using Pearson correlation coefficient. A p-value <0.05 was considered statistically significant.

Results

Participant Characteristics

Table 1 summarizes the demographic and clinical characteristics of the study participants. There were no significant differences in age, sex, or body mass index (BMI) between OA patients and healthy controls.

Table 1. Demographic and Clinical Characteristics

Variable	OA Patients (n=50)	Controls (n=50)	p-value
Age (years)	62.3 ± 8.5	61.7 ± 7.9	0.72
Female (%)	64	62	0.83
BMI (kg/m²)	29.4 ± 4.2	28.9 ± 3.8	0.56

Lipid Profile

Table 2 presents the lipid profile results. Compared to healthy controls, OA patients exhibited significantly higher levels of TC, TG, and LDL-C and lower levels of HDL-C.

Table 2. Lipid Profile

Parameter	OA Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
Total Cholesterol (mg/dL)	215.6 ± 32.1	188.3 ± 28.4	<0.001
Triglycerides (mg/dL)	165.4 ± 25.3	132.7 ± 22.8	<0.001
HDL-C (mg/dL)	40.2 ± 6.7	51.8 ± 8.5	<0.001
LDL-C (mg/dL)	140.7 ± 24.6	115.3 ± 20.7	<0.001

Serum Follistatin Levels

Serum follistatin levels were significantly elevated in OA patients compared to controls (Table 3).

Table 3. Serum Follistatin Levels

Parameter	OA Patients (Mean ± SD)	Controls (Mean ± SD)	p-value
Follistatin (pg/mL)	582.4 ± 98.7	472.9 ± 76.3	<0.001

Correlation Analysis

Positive correlations were observed between serum follistatin levels and TC, TG, and LDL-C in OA patients (Table 4), while a negative correlation was noted with HDL-C.

Table 4. Correlation Analysis

Parameter	r-value	p-value
Total Cholesterol	0.45	0.002
Triglycerides	0.52	<0.001
HDL-C	-0.41	0.004
LDL-C	0.47	0.001

Discussion

Our study showed that OA patients had significant alterations in their lipid profiles and elevated serum follistatin levels compared with healthy controls. These results support the hypothesis that dyslipidemia and follistatin dysregulation play a key role in the pathogenesis of OA. Dyslipidemia, characterized by elevated levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol, is increasingly being recognized as a metabolic driver of inflammation and oxidative stress. These metabolic disturbances can lead to the breakdown of articular cartilage and promote joint damage (17). Furthermore, decreased levels of low-density lipoprotein cholesterol, which generally has anti-inflammatory and antioxidant properties, can further exacerbate joint pathology. (18).

Elevated serum follistatin levels in OA patients highlight its potential role as a mediator of inflammation and extracellular matrix remodeling (19). Follistatin may act as a compensatory molecule in response to the inflammatory cytokine milieu in OA, aiming to regulate tissue

homeostasis (20). However, its elevated levels might reflect dysregulated signaling pathways contributing to disease progression. The correlations between follistatin levels and lipid parameters suggest a possible metabolic-inflammatory axis in OA. Dyslipidemia could influence follistatin expression directly or through intermediary inflammatory pathways, creating a vicious cycle that accelerates disease progression (21).

The findings of this study have important clinical implications. Lipid profile alterations and serum follistatin levels could serve as biomarkers for the early detection of OA, enabling timely intervention (22). Furthermore, therapeutic strategies targeting lipid metabolism or follistatin regulation may offer novel approaches for managing OA. For instance, lipid-lowering agents such as statins or interventions modulating follistatin activity could mitigate disease progression by addressing underlying metabolic and inflammatory dysfunctions (23). Future research should explore these therapeutic avenues and elucidate the precise mechanisms linking metabolic dysregulation, follistatin expression, and joint pathology.

While this study provides valuable insights, it is essential to acknowledge its limitations, including the cross-sectional design, which precludes the establishment of causality, and the relatively small sample size (24). Longitudinal studies and experimental research are needed to validate these findings and clarify the role of lipid metabolism and follistatin in OA pathogenesis. Moreover, the potential interactions with other metabolic and inflammatory mediators warrant further investigation to understand the disease comprehensively (25).

Conclusion:

This research indicates the strong link between pelvic osteoarthritis and lipid disorders with increased serum follistatin levels. The results suggest that patients with OA exhibit a severe form of dyslipidemia, including high total cholesterol, triglycerides, and low-density lipoprotein cholesterol, with low levels of high-density lipoprotein cholesterol. On the other hand, serum follistatin in OA patients was significantly increased, and it correlated well with lipid parameters, indicating a fusion between lipids and inflammatory mediators in the etiology of OA.

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