Review Article Clinics in Orthopedic Surgery 2025;17:187-193 • https://doi.org/10.4055/cios24301

Hyperlipidemia and Rotator Cuff Tears: Exploring Mechanisms and Effective Treatment

Kang-San Lee, MD, Sung-Jin Park, MD, Dong-Hyun Kim, MD, Seok Won Chung, MD*, Jun-Young Kim, MD†, Chul-Hyun Cho, MD‡, Jong Pil Yoon, MD

Department of Orthopedic Surgery, Kyungpook National University Hospital, Daegu,
**Department of Orthopedic Surgery, Konkuk University Medical Center, Seoul,*
†Department of Orthopedic Surgery, Daegu Catholic University School of Medicine, Daegu,
‡Department of Orthopedic Surgery, Keimyung University School of Medicine, Daegu, Korea

The detrimental effects of hyperlipidemia on the healing of rotator cuff tears are well documented. The proposed underlying mechanisms for these effects include alterations in the extracellular matrix, inflammation, and oxidative stress, which hamper the reparative processes in the affected tendon tissues. Recent therapeutic strategies target these pathways, reflecting a growing body of research dedicated to mitigating these effects and promoting healing. This literature review aims to provide a comprehensive understanding of the pathophysiology underlying rotator cuff tears, examine the interplay between hyperlipidemia and rotator cuff tear healing, synthesize current knowledge on contributing biological mechanisms, and outline potential therapeutic interventions to optimize clinical management and treatment outcomes for patients.

Keywords: *Rotator cuff tear, Hyperlipidemia, Inflammation, Oxidative stress*

The rotator cuff is an intricate assembly of muscle tendons enveloping the shoulder joint, which is crucial to sustain the stability and range of motion necessary for the complex biomechanics of the shoulder and the diverse functionality of the human arm.[1,2] Rotator cuff tears (RCTs) are a common musculoskeletal injury characterized by partial or complete tears of one or more of the rotator cuff tendons. Although RCTs can occur due to acute trauma, they are more frequently the result of degenerative changes, especially in the elderly.[3,4]

Several risk factors have been identified to contribute to the vulnerability and subsequent degeneration of the rotator cuff, age being the primary factor.[5,6] Over time, cumulative stress and physiological changes within the tendons diminish their elasticity and resilience, increasing the propensity for tears.[7,8] Hand dominance also plays an important role in RCTs as repetitive use and overloading of the dominant shoulder can exacerbate the wear and tear of the tendons.[9,10] Lifestyle factors, such as smoking and diabetes, are known to impair blood flow and tissue repair mechanisms, increasing the risk of RCTs.[11-13] Similarly, body weight is another significant factor, as increased body mass places greater mechanical demands on the musculoskeletal system, particularly on structures involved in movement, such as the rotator cuff.[14-16] Apart from the physical factors, hyperlipidemia, a systemic component, stands out as a potential direct and indirect influence on tendon degeneration.[17,18] Hyperlipidemia is characterized by elevated lipid levels in the bloodstream, including cholesterol and triglycerides, which can lead to fatty deposits in blood vessels and tissues, systemic inflammation, and oxidative stresses, all of which may compromise the structural integrity as well as healing capacity of the rotator cuff.[19]

Over the years, the prevalence of hyperlipidemia has increased in modern societies due to genetic predisposi-

Received July 16, 2024; Revised October 12, 2024;
Accepted October 14, 2024
Correspondence to: Jong Pil Yoon, MD
Department of Orthopedic Surgery, Kyungpook National University Hospital,
130 Dongdeok-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-200-5628, Fax: +82-53-422-6605
E-mail: altjp1@gmail.com

tions and lifestyle factors, making it a significant concern for public health and an important consideration in the management of RCTs.[20,21] This review aims to explore the multifaceted relationship between hyperlipidemia and RCTs by examining how hyperlipidemia affects the healing process in RCTs, elucidate the underlying mechanisms, and propose potential interventional strategies to improve clinical outcomes for patients with RCTs.

HYPERLIPIDEMIA AND RCT

Various studies have substantiated the association between hyperlipidemia and RCTs by demonstrating a clear correlation between the incidence of RCTs and lipid disorders.[13,22,23] Abboud and Kim[22] found that a significant majority of patients with RCTs had higher total cholesterol levels than the control group, suggesting that hyperlipidemia may be a contributing factor to the development of RCTs. Presumably, hyperlipidemia may not merely be a coincidental finding in patients with RCTs because these patients often present with dyslipidemic profiles, indicating that systemic metabolic imbalances may be an etiological factor for this condition.[23] Furthermore, a systematic review and meta-analysis by Giri et al.[13] evaluated the risk factors for rotator cuff disease, highlighting the significant role of diabetes, hypertension, and hyperlipidemia in the development of this condition.

Notably, a few studies have also documented the adverse impact of hyperlipidemia on rotator cuff healing after surgery.[24-26] Patients with hyperlipidemia show delayed recovery and compromised healing of the rotator cuff on magnetic resonance imaging, which is evident in the form of significant fatty infiltration in the tendon tissue after RCT repair.[24,25] Chung et al.[26] studied the effects of hypercholesterolemia on fatty infiltration and bone-to-tendon healing in a rabbit model of chronic RCT by creating a high-cholesterol state and then lowering it using simvastatin. They reported that rabbits with high blood cholesterol levels had lower electrophysiological activity at electromyography and muscle stiffness, and confirmed a noticeable difference in fatty infiltration. Hyperlipidemia tends to influence the biological environment and impede natural reparative processes, leading to suboptimal outcomes in tendon regeneration and repair. These detrimental effects highlight the need for a comprehensive approach to managing RCTs in patients with hyperlipidemia, one that addresses both the mechanical aspects of the tear and the metabolic factors at play.

MECHANISM UNDERLYING THE DETRIMENTAL EFFECTS OF HYPERLIPIDEMIA

Currently, several mechanisms have been proposed to explain the harmful effects of hyperlipidemia on RCT healing.[22] In this review, we have categorized these mechanisms into 3 categories: xanthoma accumulation, inflammation, and oxidative stress (Fig. 1).

Xanthoma Accumulation

In hyperlipidemia, an increased concentration of blood lipids becomes trapped within the extracellular matrix (ECM) of the rototor cuff tendon.[27] Abnormal cholesterol accumulation triggers an inflammatory cascade initiated by a macrophagic response; these macrophages absorb and oxidize these lipids to form foam cell aggregates, known as xanthomas, which ultimately disrupts the integrity of the ECM.[28] Xanthomas become embedded within the rotator cuff tendon, causing mechanical instability.[29]

In particular, Fang et al.[30] found that rotator cuff tendons exhibited a decreased concentration of collagen I and an increased concentration of collagen III in a swine hyperlipidemia model, indicating pathological changes in the tendon at the structural level. Given that type I collagen is predominant in rotator cuff tendons and is responsible for the tendon's tensile strength by forming thick fibrils, a decrease in its ratio implies reduced tendon strength and hampered healing of the tear.[31,32]

The rotator cuff tendon, given its constant exposure to high mechanical demands and complex range of motions, is particularly vulnerable to lipid accumulation and subsequent ECM disruption caused by hyperlipidemia. As observed in both animal models and clinical cases, lipid deposits, such as xanthomas, may accumulate more readily in areas of high mechanical stress like the rotator cuff, contributing to its degeneration.[33]

Inflammation

The xanthoma formation due to hyperlipidemia initiates an inflammatory cascade, which is critical in the pathogenesis of tendon disorders. The activation of the nuclear

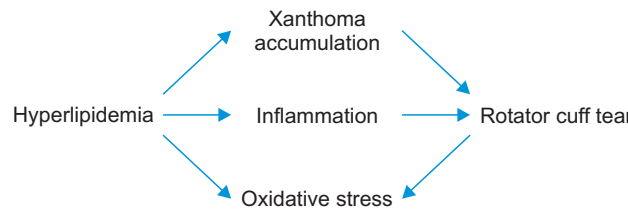

Fig. 1. Mechanism underlying the detrimental effects of hyperlipidemia.

factor kappa beta (NF-κB) pathway leads to the production of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin (IL)-6, which have multifaceted roles in tendon pathology.[34] These cytokines are not only implicated in inflammatory signaling but also in the regulation of tendon cell metabolism and apoptosis, which is central to tendon degeneration and healing.

Inflammation also results in the upregulation of matrix metalloproteinases (MMPs)—enzymes capable of degrading various ECM components—further contributing to tissue disorganization.[35] Dysregulation of this delicate balance between ECM synthesis and degradation can lead to declining mechanical properties of the tendon, making it more susceptible to injury. The persistent inflammatory environment, exacerbated by the NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3)-inflammasome pathway, produces IL-1β (a potent inflammatory mediator) that accelerates collagen breakdown and impedes the reparative process within the healing tendon.[27]

The rotator cuff tendon is particularly susceptible to chronic inflammation due to its relatively limited blood supply compared to other tendons. This compromised vascularity may exacerbate the effects of hyperlipidemia-induced inflammation, further delaying the reparative process and leading to more pronounced degenerative changes.[36]

Oxidative Stress

Lately, the role of oxidative stress in tendon pathology is being increasingly recognized, particularly in the context of hyperlipidemia-induced tendon damage. The excess cholesterol in tendon tissues leads to xanthoma formation, causing an overload of reactive oxygen species in the tendon, which in turn overwhelms the tendon's intrinsic antioxidant defenses.[19] Oxidative stress induces cellular damage through lipid peroxidation, DNA damage, and protein oxidation; it is also known to affect cellular signaling pathways, such as the AKT/FOXO1 pathway, which regulates cell survival and apoptosis. Dysregulation of this pathway due to oxidative stress can lead to increased tendon cell apoptosis and autophagy, typically protective physiological processes that may become harmful when dysregulated.[37]

TREATMENT

Statins are the cornerstone of treating hyperlipidemia and play a multifaceted role in managing rotator cuff health.[38] While they are instrumental in decreasing the level of low-density lipoprotein cholesterol (LDL-C) by inhibiting β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase and increasing LDL receptors in liver cells, their impact extends to RCTs as well.[39] Statins contribute to tendon healing by promoting tenocyte functions and modulating inflammation; however, concerns persist over their association with musculoskeletal side effects, including tendinopathy and potential tendon ruptures.[23,40]

The positive effects of statins have been demonstrated in both animal and clinical studies. Chung et al.[26] explored the influence of hypercholesterolemia on fatty infiltration and tendon-to-bone healing in a rabbit model of chronic RCTs, where elevated cholesterol levels were subsequently reduced with simvastatin. Similarly, Deren et al.[41] observed that simvastatin improved muscle fiber force production (a notable 20% increase in muscle fiber-specific force) and reduced fibrosis, indicated by decreased type 1 collagen (fibrosis marker) and fat accumulation in a rat model of RCTs.

Likewise, a clinical study comparing statin users with non-users across various rotator cuff pathologies found that statin use was linked with varied outcomes. Cancienne et al.[42] examined the relationship between perioperative lipid profiles and the need for subsequent surgical interventions in more than 30,000 patients who underwent arthroscopic rotator cuff repairs. The authors noted that patients with hyperlipidemia faced a higher likelihood of requiring revision surgery after a full-thickness rotator cuff repair compared to their non-hyperlipidemic counterparts. These findings highlight the complex interplay between lipid management and rotator cuff disease outcomes, advocating for a tailored approach to the use of statins in patients with rotator cuff pathologies.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat various inflammatory conditions.[43,44] While there is limited evidence on the direct effects of NSAIDs on RCTs in hyperlipidemic patients, several studies have demonstrated their benefits in reducing inflammation and pain in rotator cuff tendinopathy. For instance, NSAIDs can modulate the inflammatory response in tendinopathic tissues by inhibiting cyclooxygenase enzymes, which reduces the production of pro-inflammatory cytokines, thus helping manage symptoms in rotator cuff injuries.[45,46]

Interestingly, Kourounakis et al.[47] explored the impact of intraperitoneal NSAID administration in hyperlipidemia-induced rats and observed a decrease in levels of total cholesterol, LDL, and triglycerides. These findings suggest that NSAIDs may not only play a role in managing atherosclerosis-related inflammation but could also contribute to lipid reduction, potentially benefiting patients with hyperlipidemia alongside their treatment for rotator

cuff disorders.

Vitamin D, an orally ingestible fat-soluble vitamin, plays a pivotal role in the homeostasis of the skeletal, immune, and metabolic systems. It is also recognized as a potent antioxidant and its deficiency can exacerbate oxidative stress, tissue inflammation, and atherosclerosis by increasing monocyte and macrophage expression in the vascular cell intima. Several studies have investigated the role of Vitamin D in the context of rotator cuff disease. Angeline et al.[48] conducted an animal study involving 62 rats and demonstrated that reduced vitamin D levels can have harmful biomechanical and histological effects on rotator cuff repair. These results highlight the potential antioxidant properties of vitamin D in rotator cuff repair. Kim et al.[49] investigated the molecular mechanisms affected by Vitamin D deficiency in patients with medium RCTs. Their study highlighted altered gene and protein expression patterns that are essential for tendon repair and maintenance. Specifically, they found that low vitamin D levels were associated with the dysregulation of genes involved in collagen synthesis and inflammation, potentially impairing the healing process after injury.

Moreover, a comprehensive review by Daher et al.[50] emphasized the broader implications of vitamin D in shoulder health. Their review underscored how vitamin D deficiency not only affects tendon integrity but also has negative consequences on surgical outcomes in rotator cuff repairs. They advocate for monitoring and managing vitamin D levels in patients undergoing rotator cuff surgery, as adequate levels may improve healing and rehabilitation.

MANAGING HYPERLIPIDEMIA AND ROTATOR CUFF DISEASE: LIMITATIONS OF STATINS AND POTENTIAL ALTERNATIVE THERAPIES

With the increase in the aging population around the globe, there has been a notable rise in the incidence of hyperlipidemia and RCTs, presenting a growing challenge to healthcare systems internationally.[51] The adverse consequences of hyperlipidemia on the structural integrity and natural healing mechanisms of the rotator cuff have been extensively corroborated by clinical evidence. This evidence firmly establishes hyperlipidemia as a major risk factor and a critical determinant of the success of both surgical interventions and conservative treatment approaches for rotator cuff injuries.[13,52]

Currently, hyperlipidemia is largely managed through statins, which function as a lipid-lowering agent and have gained widespread acceptance due to their efficacy.[53] However, the use of statins is marred by their most common side effect, myotoxicity, ranging from mild myopathy to severe rhabdomyolysis, which raises concerns regarding their extensive clinical application.[54] The potential of statins to impair healing processes of tendon has been highlighted in an animal study conducted by de Oliveira et al.,[55] indicating a need for cautious application in patients undergoing recovery from rotator cuff surgery.

The pathophysiology of hyperlipidemia extends beyond simple lipid accumulation; it is a disease characterized by a complex interplay of inflammation and oxidative processes. Chronic inflammation is a common denominator in a cluster of chronic conditions, including hypertension, diabetes, and atherosclerosis. Consequently, anti-inflammatory and antioxidant interventions have been researched for their potential therapeutic impact in a spectrum of chronic inflammatory diseases, such as metabolic syndrome. Ferrer et al.[56] demonstrated that COX-2 inhibitors can reduce several markers of metabolic syndrome. Therapeutic intervention using anti-inflammatory agents, such as NSAIDs or COX-2 selective inhibitors, can directly involve the synthesis of inflammatory mediators. Furthermore, Rochlani et al.[57] reported that various natural compounds with anti-inflammatory and antioxidant properties can attenuate the systemic inflammatory response associated with metabolic syndrome.

In summary, hyperlipidemia has a potentially negative effect on both the normal physiology of the rotator cuff as well as during its healing phase after injury; therefore, addressing these critical intersections between hyperlipidemia-induced inflammation and tendon pathology is paramount for effective treatment. Considering the drawbacks of lipid-lowering agents like statin, incorporating anti-inflammatory and antioxidant therapies as alternatives to reduce statin use could prove beneficial. There is a pressing need for further research into the combined effects of low-dose statins with anti-inflammatory drugs or antioxidants on mitigating the harmful effects of hyperlipidemia on RCT healing.

CONCLUSIONS

The relationship between hyperlipidemia and rotator cuff pathology demands a targeted treatment approach that addresses both lipid dysregulation and its impact on tendon health. Research highlights the need for careful management of statins in patients with RCTs, alongside alternative therapies that focus on reducing inflammation and oxidative stress. Future treatment strategies should prioritize combining lipid-lowering agents with anti-inflammatory

and antioxidant interventions to optimize tendon healing and recovery in hyperlipidemic patients. Enhancing these therapeutic intersections will be critical for improving clinical outcomes in rotator cuff disease.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2022R1A2C1005374) and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HR22C1832).

ORCID

Kang-San Lee https://orcid.org/0000-0001-7932-0426
Sung-Jin Park https://orcid.org/0009-0008-6869-0788
Dong-Hyun Kim https://orcid.org/0000-0001-9078-5953
Seok Won Chung https://orcid.org/0000-0002-8221-9289
Jun-Young Kim https://orcid.org/0000-0003-4700-3041
Chul-Hyun Cho https://orcid.org/0000-0003-0252-8741
Jong Pil Yoon https://orcid.org/0000-0001-6446-6254

REFERENCES

1. Rho JY, Kwon YS, Choi S. Current concepts and recent trends in arthroscopic treatment of large to massive rotator cuff tears: a review. Clin Shoulder Elb. 2019;22(1):50-7.
2. Kim JH, Cho NS, Park JY, et al. Doctor shopping trend of patients before undergoing rotator cuff repair in Korea: a multicenter study. Clin Shoulder Elb. 2024;27(3):338-44.
3. Wang PW, Jo CH. Prognostic factors affecting structural integrity after arthroscopic rotator cuff repair: a clinical and histological study. Clin Shoulder Elb. 2023;26(1):10-9.
4. Kim DH, Jung YS, Kim KR, Yoon JP. The best options in superior capsular reconstruction. Clin Shoulder Elb. 2021; 24(2):114-21.
5. Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. J Shoulder Elbow Surg. 2010;19(1):116-20.
6. Daher M, Lopez R, Covarrubias O, Boufadel P, Fares MY, Abboud JA. Sleep disturbances in rotator cuff pathology: insights into mechanisms and clinical implications. Clin Shoulder Elb. 2024;27(4):514-8.
7. Sambandam SN, Khanna V, Gul A, Mounasamy V. Rotator cuff tears: an evidence based approach. World J Orthop. 2015;6(11):902-18.
8. Akdemir M, Kilic AI, Kurt C, Capkin S. Better short-term outcomes of mini-open rotator cuff repair compared to full arthroscopic repair. Clin Shoulder Elb. 2024;27(2):212-8.
9. Radhakrishnan R, Goh J, Tan AH. Partial-thickness rotator cuff tears: a review of current literature on evaluation and management. Clin Shoulder Elb. 2024;27(1):79-87.
10. MacConnell AE, Davis W, Burr R, et al. An objective assessment of the impact of tendon retraction on sleep efficiency in patients with full-thickness rotator cuff tears: a prospective cohort study. Clin Shoulder Elb. 2023;26(2):169-74.
11. Kane SM, Dave A, Haque A, Langston K. The incidence of rotator cuff disease in smoking and non-smoking patients: a cadaveric study. Orthopedics. 2006;29(4):363-6.
12. Lee DH, Lee GM, Park HB. Factors associated with long head of the biceps tendon tear severity and predictive insights for grade II tears in rotator cuff surgery. Clin Shoulder Elb. 2024;27(2):149-59.
13. Giri A, O'Hanlon D, Jain NB. Risk factors for rotator cuff disease: a systematic review and meta-analysis of diabetes, hypertension, and hyperlipidemia. Ann Phys Rehabil Med. 2023;66(1):101631.
14. Wendelboe AM, Hegmann KT, Gren LH, Alder SC, White GL, Lyon JL. Associations between body-mass index and surgery for rotator cuff tendinitis. J Bone Joint Surg Am. 2004;86(4):743-7.
15. Levy O, Arealis G, Tsvieli O, Consigliere P, Lubovsky O. Reverse total shoulder replacement for patients with "weight-bearing" shoulders. Clin Shoulder Elb. 2024;27(2):183-95.
16. Weng PW, Chang WP. Influence of body mass index on severity of rotator cuff tears. J Shoulder Elbow Surg. 2024; 33(3):648-56.
17. Fang WH, Bonavida V, Agrawal DK, Thankam FG. Hyperlipidemia in tendon injury: chronicles of low-density lipoproteins. Cell Tissue Res. 2023;392(2):431-42.
18. Gumina S, Song HS, Kim H, Candela V. Arthroscopic evaluation of the rotator cuff vasculature: inferences into the pathogenesis of cuff tear and re-tear. Clin Shoulder Elb.

2024;27(2):203-11.

19. Yazdani AN, Rai V, Agrawal DK. Rotator cuff health, pathology, and repair in the perspective of hyperlipidemia. J Orthop Sports Med. 2022;4(4):263-75.
20. Lin TT, Lin CH, Chang CL, Chi CH, Chang ST, Sheu WH. The effect of diabetes, hyperlipidemia, and statins on the development of rotator cuff disease: a nationwide, 11-year, longitudinal, population-based follow-up study. Am J Sports Med. 2015;43(9):2126-32.
21. Wei J, Yang Q, Wang X, et al. Association between homocysteine levels and hyperlipidemia prevalence as well as all-cause mortality of hyperlipidemia patients in the US population: results from NHANES database. Front Cardiovasc Med. 2024;11:1419579.
22. Abboud JA, Kim JS. The effect of hypercholesterolemia on rotator cuff disease. Clin Orthop Relat Res. 2010;468(6): 1493-7.
23. Amit P, Kuiper JH, James S, Snow M. Does statin-treated hyperlipidemia affect rotator cuff healing or muscle fatty infiltration after rotator cuff repair? J Shoulder Elbow Surg. 2021;30(11):2465-74.
24. Djerbi I, Chammas M, Mirous MP, Lazerges C, Coulet B; French Society For Shoulder and Elbow (SOFEC). Impact of cardiovascular risk factor on the prevalence and severity of symptomatic full-thickness rotator cuff tears. Orthop Traumatol Surg Res. 2015;101(6 Suppl):S269-73.
25. Gumina S, Kim H, Jung Y, Song HS. Rotator cuff degeneration and healing after rotator cuff repair. Clin Shoulder Elb. 2023;26(3):323-9.
26. Chung SW, Park H, Kwon J, Choe GY, Kim SH, Oh JH. Effect of hypercholesterolemia on fatty infiltration and quality of tendon-to-bone healing in a rabbit model of a chronic rotator cuff tear: electrophysiological, biomechanical, and histological analyses. Am J Sports Med. 2016;44(5):1153-64.
27. Thankam FG, Roesch ZK, Dilisio MF, et al. Association of inflammatory responses and ECM disorganization with HMGB1 upregulation and NLRP3 inflammasome activation in the injured rotator cuff tendon. Sci Rep. 2018;8(1):8918.
28. Artieda M, Cenarro A, Junquera C, et al. Tendon xanthomas in familial hypercholesterolemia are associated with a differential inflammatory response of macrophages to oxidized LDL. FEBS Lett. 2005;579(20):4503-12.
29. Soslowsky LJ, Fryhofer GW. Tendon homeostasis in hypercholesterolemia. Adv Exp Med Biol. 2016;920:151-65.
30. Fang W, Sekhon S, Teramoto D, et al. Pathological alterations in the expression status of rotator cuff tendon matrix components in hyperlipidemia. Mol Cell Biochem. 2023;478(8):1887-98.
31. Zhang G, Young BB, Ezura Y, et al. Development of tendon structure and function: regulation of collagen fibrillogenesis. J Musculoskelet Neuronal Interact. 2005;5(1):5-21.
32. Thankam FG, Dilisio MF, Gross RM, Agrawal DK. Collagen I: a kingpin for rotator cuff tendon pathology. Am J Transl Res. 2018;10(11):3291-309.
33. Longo UG, Franceschi F, Ruzzini L, et al. Histopathology of the supraspinatus tendon in rotator cuff tears. Am J Sports Med. 2008;36(3):533-8.
34. Clarke MC, Talib S, Figg NL, Bennett MR. Vascular smooth muscle cell apoptosis induces interleukin-1-directed inflammation: effects of hyperlipidemia-mediated inhibition of phagocytosis. Circ Res. 2010;106(2):363-72.
35. Yoon JP, Min SG, Choi JH, et al. Increased interleukin-6 and TP53 levels in rotator cuff tendon repair patients with hypercholesterolemia. Clin Shoulder Elb. 2022;25(4):296-303.
36. Hegedus EJ, Cook C, Brennan M, Wyland D, Garrison JC, Driesner D. Vascularity and tendon pathology in the rotator cuff: a review of literature and implications for rehabilitation and surgery. Br J Sports Med. 2010;44(12):838-47.
37. Lui PP, Zhang X, Yao S, Sun H, Huang C. Roles of oxidative stress in acute tendon injury and degenerative tendinopathy: a target for intervention. Int J Mol Sci. 2022;23(7):3571.
38. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):3 168-209.
39. Dolkart O, Liron T, Chechik O, et al. Statins enhance rotator cuff healing by stimulating the COX2/PGE2/EP4 pathway: an in vivo and in vitro study. Am J Sports Med. 2014;42(12): 2869-76.
40. Eliasson P, Dietrich-Zagonel F, Lundin AC, Aspenberg P, Wolk A, Michaelsson K. Statin treatment increases the clinical risk of tendinopathy through matrix metalloproteinase release: a cohort study design combined with an experimental study. Sci Rep. 2019;9(1):17958.
41. Deren ME, Ehteshami JR, Dines JS, et al. Simvastatin exposure and rotator cuff repair in a rat model. Orthopedics. 2017;40(2):e288-92.
42. Cancienne JM, Brockmeier SF, Rodeo SA, Werner BC. Perioperative serum lipid status and statin use affect the revision surgery rate after arthroscopic rotator cuff repair. Am J Sports Med. 2017;45(13):2948-54.
43. Crofford LJ. Use of NSAIDs in treating patients with arthritis. Arthritis Res Ther. 2013;15 Suppl 3(Suppl 3):S2.

44. Raskin JB. Gastrointestinal effects of nonsteroidal anti-inflammatory therapy. Am J Med. 1999;106(5B):3S-12S.

45. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013;16(5):821-47.

46. Magra M, Maffulli N. Nonsteroidal antiinflammatory drugs in tendinopathy: friend or foe. Clin J Sport Med. 2006;16(1):1-3.

47. Kourounakis AP, Victoratos P, Peroulis N, et al. Experimental hyperlipidemia and the effect of NSAIDs. Exp Mol Pathol. 2002;73(2):135-8.

48. Angeline ME, Ma R, Pascual-Garrido C, et al. Effect of diet-induced vitamin D deficiency on rotator cuff healing in a rat model. Am J Sports Med. 2014;42(1):27-34.

49. Kim HT, Lee SH, Lee JK, Chung SW. Influence of vitamin D deficiency on the expression of genes and proteins in patients with medium rotator cuff tears. Am J Sports Med. 2023;51(10):2650-8.

50. Daher M, Covarrubias O, Lopez R, et al. The role of vitamin D in shoulder health: a comprehensive review of its impact on rotator cuff tears and surgical results. Clin Shoulder Elb. 2025;28(1):93-102.

51. Li Z, Zhu G, Chen G, et al. Distribution of lipid levels and prevalence of hyperlipidemia: data from the NHANES 2007-2018. Lipids Health Dis. 2022;21(1):111.

52. Gatto AP, Hu DA, Feeley BT, Lansdown D. Dyslipidemia is associated with risk for rotator cuff repair failure: a systematic review and meta-analysis. JSES Rev Rep Tech. 2022;2(3):302-9.

53. Karr S. Epidemiology and management of hyperlipidemia. Am J Manag Care. 2017;23(9 Suppl):S139-48.

54. Molokhia M, McKeigue P, Curcin V, Majeed A. Statin induced myopathy and myalgia: time trend analysis and comparison of risk associated with statin class from 1991-2006. PLoS One. 2008;3(6):e2522.

55. de Oliveira LP, Vieira CP, Guerra FD, Almeida MS, Pimentel ER. Structural and biomechanical changes in the Achilles tendon after chronic treatment with statins. Food Chem Toxicol. 2015;77:50-7.

56. Ferrer MD, Busquets-Cortes C, Capo X, et al. Cyclooxygenase-2 inhibitors as a therapeutic target in inflammatory diseases. Curr Med Chem. 2019;26(18):3225-41.

57. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Ther Adv Cardiovasc Dis. 2017;11(8):215-25.