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Dyslipidemia is associated with risk for rotator cuff repair failure: a systematic review and meta-analysis

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Background: Lipid deposition secondary to dyslipidemia (DLD) is shown to have a significant impact on tendon pathology, including tendon elasticity, fatty infiltration, and healing properties. Rotator cuff repair is a common procedure, susceptible to influence from many tear-related and patient-related characteristics. The purpose of this study was to determine the relationship between DLD and rotator cuff repair outcomes with analysis of retear risk and function.

Methods: PubMed, Embase, and SPORTDiscus were searched for all English-language, peer-reviewed studies between 2000 and the present, which analyzed relationships between patient-related factors and outcomes of rotator cuff repair. Studies that explicitly examined the effect of DLD on rotator cuff repair outcomes were chosen for inclusion. Included studies were assessed for methodological quality, and data were extracted for meta-analysis.

Results: Of the 3087 titles, 424 were screened by abstract, and 67 were reviewed in full. Inclusion criteria were met by 11 studies. Of these studies, 5 studies assessed retear, 2 studies measured function, 3 studies reported both retear and function, and 1 study evaluated the risk of retear necessitating a revision surgery. The studies report no significant difference in functional outcomes. Meta-analysis revealed that DLD patients had a significantly higher risk of retear after primary rotator cuff repair (odds ratio 1.32, 95% confidence interval 1.06-1.64).

Conclusion: DLD leads to an increased risk of retear after rotator cuff repair, although function appears to be unimpaired. DLD should be considered among other risk factors when counseling patients regarding expected rotator cuff repair outcomes.

Rotator cuff tears, most commonly due to avulsion of the tendon from its insertion, are one of the leading causes of shoulder pain and dysfunction.[58] Rotator cuff repair reliably improves function and quality of life,[15,22,43] although repair failure is not uncommon. The odds of retear are multifactorial, and occurrence ranges from 20% to 60% after rotator cuff repair surgery.[13]

Extensive evidence has identified tear-related and patient-related characteristics, which may adversely affect rotator cuff repair outcomes. Increasing age is the most predictive characteristic for rotator cuff repair failures.[24,29,35,37] Although clear mechanisms for this increase in failure rate remain incompletely defined. Fatty infiltration, atrophy, delamination, and increasing preoperative tear size are specific factors that increase the odds of retear.[9,24,30,35,37] Systemic conditions, such as diabetes mellitus, obesity, and tobacco, have also been implicated.[14,25,29,62] Dyslipidemia (DLD) is among these patient characteristics that potentially impact rotator cuff repair outcomes. More than 90 million US adults have a total cholesterol (TC) level >200 mg/dL, and nearly 43 million adults have a high-density lipoprotein (HDL) level <40 mg/dL.[12,54] As the population ages, the intersection between these diseases is expected to grow.[44]

DLD encompasses disorders of lipoprotein metabolism, including overproduction of TC (ie, hyperlipidemia), low-density lipoprotein (LDL), and triglycerides (TGs) and/or underproduction of HDL. Current evidence suggests that lipids can accumulate in the extracellular matrix of tendons, leading to the formation of lipid deposits altering mechanical properties and increasing local inflammation.[26,59] Hyperlipidemia animal models display reduced tendon elasticity, greater fatty infiltration, and poor tendon-to-bone healing.[6,7,14] DLD is shown to be an independent risk factor for Achilles, patellar, and rotator cuff tendon pathology.[1,21,41,47,52]

Institutional review board approval was not required for this systematic review.

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Table I
Strategy for PubMed search.

PubMed			
1.	Rotator cuff	7.	lipoprotein*
2.	Dyslipidemia	8.	lipid*
3.	Hyperlipidemia	9.	comorbid*
4.	Hypercholesterolemia	10.	factor*
5.	Hyperlipoproteinemia	11.	predict*
6.	Cholesterol	12.	failure*

Search Term: 1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12).
Limits: Date 2000-2021, Full text, English.
*Search function, represents *a root term*.

Rotator cuff disease in the presence of DLD has been associated with tendinopathy, increased risk of tear, and increased risk of postoperative retear, although the evidence is debated.[60]

The purpose of our systematic review and meta-analysis was to evaluate the association between DLD and outcomes of rotator cuff repair, notably retear and functional outcomes. We hypothesized that DLD patients would have a greater risk of rotator cuff retear and poorer functional outcomes.

Materials and methods

A systematic review was conducted using PubMed, Embase, and SPORTDiscus in January 2022. The study protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42021264487). Our purpose was to identify all English-language, peer-reviewed studies between 2000 and the present, which analyzed the relationships between patient-related factors and outcomes to rotator cuff tear. The search was completed using keywords: “rotator cuff,” “dyslipidemia,” “hyperlipidemia,” “hypercholesterolemia,” “hyperlipoproteinemia,” “cholesterol,” “lipoprotein*,” “lipid*,” “comorbid*,” “factor*,” “predict*,” and “failure*.” The search strategy for PubMed is presented in Table I.

Criteria

The following inclusion criteria were applied to study selection: (1) Population included adult DLD patients (defined as elevated TC, LDL, TG, or low HDL), confirmed by health record or laboratory test. (2) All subjects underwent surgical repair for primary rotator cuff tear; (3) Available comparison of non-DLD patients undergone primary rotator cuff repair; (4) Measures of outcome, including retear, revision, quantitative range of motion, and/or satisfaction/pain/function score; (5) Study design to be primary research of randomized control, cohort, cross-sectional, case–control, or case series design, with available full text.

Exclusion criteria included (1) Population failed to include surgically treated primary rotator cuff repair, DLD patients; (2) DLD measure was poorly defined; (3) Primary cuff repair was 1 year beyond diagnosis; (4) Lack of comparison to non-DLD, rotator cuff repair patients; (5) Significant difference (ie, $P \leq .05$) in patient characteristics between study groups, without control; (6) Outcomes not specific to rotator cuff repair or DLD; (7) Studies published before 2000; (8) Full text unavailable; and (9) Review articles and case studies.

Literature screening and data extraction

Article screening was done independently by 2 authors (A.G. and D.H.); discrepancies were settled by discussion. All titles were screened and removed if they were obviously irrelevant. Abstracts were reviewed for relevance, determined by clear naming of a DLD measure, the mention or implication of factors associated with rotator cuff repair outcome, or focus on comorbidities. Those relevant progressed to full text review for inclusion. Data were extracted by 2 authors (A.G. and D.H.) and included basic article characteristics, population characteristics, populations size and source, dropout rate, intervention and control groups, follow-up period, imaging modality, DLD definition and guidelines, preoperative and postoperative outcome scores, and retear totals. All statistical outcomes that aligned with a DLD measure or comparison group (ie, measures of central tendency, relative ratios, confidence intervals, and regression models) were also extracted.

Quality assessment

Two reviewers (A.G. and D.H.) independently assessed the methodological quality and reliability of the included studies using the Newcastle-Ottawa Scale.[57] Studies were assessed for potential sources of biases, generalizability, and control of confounding factors. For rating comparability, preoperative tear size on magnetic resonance imaging was selected as the most important factor for a study's analysis to control for, as this seems to be the most reliable predictor for retear.[9,24,38] A 6-month follow-up was determined adequate.[32,50] Reviewers resolved discrepancies by consensus. Studies were included if they were, at least, “satisfactory”. The risk of bias across studies to assess cumulative evidence was determined independently by 2 authors and settled by consensus.

Statistical analysis

RevMan 5.4.1 (Review Manager, The Cochrane Collaboration, 2020, London, UK) was used for meta-analysis. Cancienne et al[11] and O'Donnell et al[46] had significant overlap, as both collected their cohort from the Humana database in PearlDiver. O'Donnell et al[46] had larger population and more recent data, thus it was included in the meta-analysis and Cancienne et al[11] were excluded. Meta-analysis was performed for retear, although heterogenous outcome measures and analysis methods of the selected studies prevented us from performing a meta-analysis on these other variables. Odds ratio (OR) was selected for measure of effect size, presented with 95% confidence interval. Analysis was carried out with a random effects model and Mantel-Haenszel estimate. Heterogeneity was evaluated by Cochrane's Q test and the Higgins I^2 test; heterogeneity thresholds (eg, substantial $I^2 = 50\%$-90%) were according to the Cochrane Reviews handbook.[27]

Results

The search strategy yielded 5106 titles, 1872 of which were removed as duplicates, leaving 3234 unique titles reviewed. Of this, 425 abstracts were screened, and 67 full texts were reviewed. All authors came to a consensus for the 11 studies[4,8,11,23,25,30,31,38,46,49,61] that met criteria inclusion (Figure 1).

Table II
Summary of studies.

Title	Study details: author, year, design, level	Population	Design details	Dyslipidemia measure	Statin use	Outcome statistics	Impact of DLD
Factors affecting rotator cuff integrity after arthroscopic repair for medium-sized or larger cuff tears: a retrospective cohort study[31]	Kim et al, 2017, retrospective cohort III	180, age: 60.4 ± 7.4, M/F: 84/96 single institution	36 DLD 144 non-DLD	TC >240 mg/dL	Not described	Retear: OR 52.814 (95% CI 3.229-808.643), $P = .004$[*]	Retear
Factors predictive of healing in large rotator cuff tears: is it possible to predict retear preoperatively?[30]	Jeong et al, 2018, case −control III	102 (112 S), age: 65.6 ± 6.6, M/F: 45/67, single institution	21 DLD; 91 non-DLD	Hyperlipidemia diagnosed in record	Not described	Retear: $P = .628$	No retear
Hypo-high-density lipoproteinemia is associated with preoperative tear size and with postoperative retear in large to massive rotator cuff tears[49]	Park et al, 2020, case series IV	195, age: 60.5 ± 7.5 M/F: 100/95, single institution	167 DLD: HyTC 58; HyTg 51; HyLDL 142; Hypo-HDL 66; Hy-non-HDL 109 28; non-DLD	HyTC: TC ≥200 mg/dL; HyTG: TG ≥ 150 mg/dL; HyLDL: LDL ≥ 100 mg/dL HypoHDL: HDL <40 mg/dL Male and <50 mg/dL Female Hy-non-HDL: non-HDL ≥130 mg/dL	No statin use	Hypo-HDL: L/Ma tears: OR 3.0 (95% CI, 1.1-8.8), $P = .04$[*]	Retear with Hypo-HDL
Perioperative serum lipid status and statin use affect revision surgery rate after arthroscopic rotator cuff repair[11,*]	Cancienne et al, 2017, etrospective cohort III	30,638 TC 13,164; LDL 12,337 TG 13,230 Age: 40-84 M/F: TC 6775/6389; LDL 6337/6000; TG 6819/6411 PearlDiver Database	TC: 5001 (mod 3,535, hi 1466) LDL: 6459 (mod 5,518, hi 941) TG: 5536 (mod 2,850, hi 2686) normal TC: 8163 normal LDL: 5878 normal TG: 7694	(Norm<Mod≤Hi) TC: < 200 ≤ 240 mg/dL LDL: <100 ≤ 160 mg/dL TG: <150 ≤ 200 mg/dL	Statin/no statin Norm TC: 4824/3339 Mod TC: 1585/1950 High TC: 765/701 Norm LDL:3812/2066 Mod LDL: 2465/3053 High LDL: 494/447	Retear TC mod: OR 1.20 (95% CI, 1.03-1.40), $P = .022$[*] TC hi: OR 1.36 (95% CI, 1.14-1.64), $P = .001$[*] LDL mod: OR 1.24 (95% CI, 1.10-1.41), $P = .001$[*] LDL hi: OR 1.46 (95% CI, 1.08-1.99), $P = .014$[*] TG mod: OR 1.13 (95% CI, 0.94-1.34), $P = .190$ TG hi: OR 1.09 (95% CI, 0.95-1.26), $P = .222$	Retear with elevated TC and LDL
The effect of patient characteristics and comorbidities on the rate of revision rotator cuff repair[46]	O'Donnell et al, 2020 Case series IV	41,467 Age: 58.3% 60-74 M/F: 21,853/19,615 PearlDiver database	22,068 DLD 19,399 non-DLD	Hyperlipidemia diagnosed in record	Not described	Retear: OR 1.09 (95% CI, 1.01-1.18), $P = .32$[*]	Retear
Combination of risk factors affecting retear after arthroscopic rotator cuff repair: a decision tree analysis[25]	Harada et al, 2020 Retrospective cohort III	286 Age: 64.9 ± 7.1 M/F: 160/126 Single institution	61 DLD 225 non-DLD	Hyperlipidemia diagnosis from PCP in record; TC determined by record blood test and treated as a continuous variable	Not described	Retear: $P = .0178$[†] Functional improvement: JOA: $P = .1121$ UCLA: $P = .1114$	Retear; no functional
Does statin-treated hyperlipidemia affect rotator cuff healing or muscle fatty infiltration after rotator cuff repair?[4]	Amit et al, 2021 Prospective cohort II	77 Age: Statin: 61.7 ± 6.6; Control: 60.2 ± 7.4 M/F: 42/35 Single institution	38 DLD 39 non-DLD	Hyperlipidemia diagnosis from PCP in record	All DLD patients on statins	Retear: OR 0.65 (95% CI 0.24-1.80), $P = .41$ WORC: $P = .087$ ASES: $P = .84$ CSS: $P = .76$ DASH: $P = .064$	No retear or function
Hyperlipidemia increases the risk of retear after arthroscopic rotator cuff repair[23]	Garcia et al, 2017 Retrospective cohort III	85 Age: 62.1 (45.3-74.3) M/F: 54/32 Single institution	33 DLD 52 non-DLD	TC, HDL, LDL, TG from PCP in record	All DLD patients on statins	Retear: OR 6.5 ($P < .001$)[‡] Retear by DLD measure: HDL: $P = .23$; LDL $P = .30$; TC $P = .25$, TG $P = .35$ Functional (ASES and VAS pain): $P = .14$	Retear; no functional
Comorbidity effect on speed of recovery after arthroscopic rotator cuff repair[8]	Berglund et al, 2018 Retrospective cohort III	627 Age: 62.1 (29-87) M/F: 382/245 Single institution	132 DLD 495 non-DLD	Hyperlipidemia diagnosed in record	Not described	ASES: $P = .352$ SST: $P = .238$ SANE: $P = .240$ VAS function: $P = .792$ VAS pain: $P = .147$ FE: $P = .034$[§] ER: .269	No function, except FE

Dyslipidemia with perioperative statin usage is not associated with poorer 24-month functional outcomes after arthroscopic rotator cuff surgery[61]	Zheng et al, 2020	Retrospective cohort III	266 Age: 61.3 ± 9.8 M/F: 117/149 Single institution	134 DLD 132 non-DLD	Hyperlipidemia diagnosed in record	115 DLD patients on statins	CSS: P = .553 OXF: P = .857 UCLA: P = .857 VAS pain: P = .443	No function
Factors related to symptomatic failed rotator cuff repair leading to revision surgeries after primary arthroscopic surgery[38]	Lee et al, 2020	Case-control III	98 Age: I: 63.2 ± 7.4; II: 61.6 ± 7.4 M/F: 44/54 Single institution	Group I (44): retear that required revision surgery Group II (54): retear that did not require revision surgery	Preoperative lab test: TC and LDL treated as continuous variables	Not described	TC: P = .012§; OR 1.01 (95% CI 1.00-1.03) P = .015‡ LDL: P = .008§ OR 1.02 (95% CI 1.01-1.04) P = .11‡ TG: P = .230	Revision surgery in retear patients

S, shoulders; *M*, male; *F*, female; *TC*, total cholesterol; *LDL*, low-density lipoprotein; *TG*, triglycerides; *DLD*, dyslipidemia; *HyTC*, hypercholesterolemia; *HyTG*, hypertriglyceridemia; *HyLDL*, hyper-LDLemia; *Hypo-HDL*, hypo-HDLemia; *Hy-nonHDL*, hyper-non-HDLemia; *PCP*, primary care physician; *Norm*, normal; *Mod*, moderate; *OR*, odds ratio. DeOrio and Cofield classification[49]—Sm, small; Me, medium; L, large; Ma, massive.
‖Not included in meta-analysis due to overlap.
*Significance by multiple logistics regression.
†Significance by chi-squared.
‡Significance by t-test.
§Significance by univariant logistic regression.

Five studies[11,30,31,46,49] assessed retear, 2 studies[8,61] measured function, and 3 studies[4,23,25] reported both retear and function outcomes. In addition, 1 study[38] examined outcomes by evaluating factors associated with a retear necessitating a revision surgery. In 7 studies,[4,8,11,23,25,31,61] data were obtained via cohort design, 6[4,8,11,23,25,31,61] of which were retrospective, 2 studies[30,38] were case–control studies, and 2 studies[46,49] were case series.

Dyslipidemia

DLD was defined differently among the studies (Table II). Six studies[4,8,23,30,46,61] used a "hyperlipidemia" diagnosis in patient records, 2[4,23] of which noted corroboration with the patient's primary care physician. Four studies,[11,31,38,49] accessed preoperative laboratory values, including TC, LDL, HDL, and TG. One study[25] used both a recorded "hyperlipidemia" diagnosis from the primary care physician and preoperative laboratory values. Statin use was described in 5 studies; 2 studies[4,23] had all patients on statins, 1 study[49] had no patients on statins, and 2 studies[11,61] detailed a mix of statin use; 6 studies[8,25,30,31,38,46] did not provide details on statin use.

Retear

DLD was significantly associated with retear in 6 of 8 studies[11,23,25,31,46,49] that explored retear rates after rotator cuff repair (Table II). Park et al[49] and Cancienne et al[11] isolated hypo-HDL and elevated TC and LDL as significant risk factors for retear, respectively. Harada et al,[25] Kim et al,[31] and O'Donnell et al[46] identified hyperlipidemia as an independent risk factor among other patient-related and tear-related factors. Harada et al[25] went on to determine that a combination of anteroposterior tear size (ie, ≥40 mm), hyperlipidemia, and critical shoulder angle (ie, ≥37°) generated the greatest risk of retear compared with other combinations. Garcia et al[23] found the risk of DLD independent from cholesterol-lowering medication dosage. Amit et al[4] and Cancienne et al[11] found that DLD was not a risk for retear when controlled by statin therapy.

Meta-analysis was performed with results from 7 studies[4,23,25,30,31,46,49] reporting retear among DLD patients; Cancienne et al[11] were excluded because of patient overlap with O'Donnell et al.[46] In total, 42,402 subjects were included, 52.8% of which had DLD. Patient age ranged from 45.3 to 84 years, with 54.0% males. There were 41,467 subjects drawn from the PearlDiver Database[46] and 935 patients drawn from their respective institutions.[4,23,25,30,31,49] The results showed that DLD was associated with retear as DLD patients were significantly more likely to experience retear after cuff repair (OR 1.54, 95% CI 1.01-2.35; Figure II). The combination of studies displayed substantial heterogeneity[27] ($\chi^2 = 13.79$, $P = .03$; $I^2 = 56\%$), with a significant overall effect ($Z = 1.99$, $P = .05$).

Function

In 5 of 5 studies[4,8,23,38,61] recording functional outcomes, there was no significant difference in DLD patients versus non-DLD patients across multiple outcome measures and patient-reported assessments (Table II). Function was recorded postoperatively at 3, 6,[25] 12[4,8], and 24 months.[61] The evaluations used included the American Shoulder and Elbow Surgeons score (3 studies[4,8,23]), UCLA Shoulder Rating Scale (2[25,61]), Constant Shoulder Score (2[4,61]), Visual Analog Scale for Pain (3[8,23,61]) and Function (1[8]), Disability of Arm, Shoulder, and Hand (1[4]), Japanese Orthopedic Association (1[25]), Simple Shoulder Test (1[8]), Single Assessment Numeric Evaluation (1[8]), and Western Ontario Rotator Cuff index

Table III
Newcastle-Ottawa risk of bias assessment.

Authors	Study design	Level of evidence	Selection	Comparability	Outcome/exposure	Quality*
Amit et al, 2021[4]	Prospective cohort	II	★★★★	★	★★★	Excellent
Berglund et al, 2018[8]	Retrospective cohort	III	★★★★		★	Satisfactory
Cancienne et al, 2017[11]	Retrospective cohort	III	★★★★	★	★★★	Excellent
Garcia et al, 2017[23]	Retrospective cohort	III	★★★★		★★	Good
Harada et al, 2021[25]	Retrospective cohort	III	★★★★		★★★	Good
Kim et al, 2017[31]	Retrospective cohort	III	★★★★	★★	★★	Excellent
Zheng et al, 2020[61]	Retrospective cohort	III	★★★★		★★	Good
Jeong et al, 2018[30]	Case−control	III	★★★★	★	★	Good
Lee et al, 2020[38]	Case−control	III	★★★	★	★★	Good
O'Donnell et al, 2020[46]	Case series	IV	★★★★	★	★★★	Excellent
Park et al, 2020[49]	Case series	IV	★★★★	★★	★★	Excellent

Cohort studies: Selection (4 stars) graded on representativeness of exposed cohort, selection of nonexposed cohort, exposure ascertainment, evidence that the outcome is not present at study onset; Comparability (2 stars) graded on control for preoperative tear size and/or additional factors; Outcome (3 stars) graded on mode of assessment, follow-up length of 6 months, and dropout rate. Case−control and Case series studies: Selection (4 stars) graded on case definition, representativeness of cases, selection of controls, definition of controls; Comparability (2 stars) graded on control for preoperative tear size and/or additional factors; Exposure/outcome (3 stars) graded on ascertainment of exposure, continuity in exposure ascertainment between groups, and nonresponse rate.
*Quality: excellent 8-9 stars, good 6-7 stars, satisfactory 4-5 stars, unacceptable 1-3 stars.

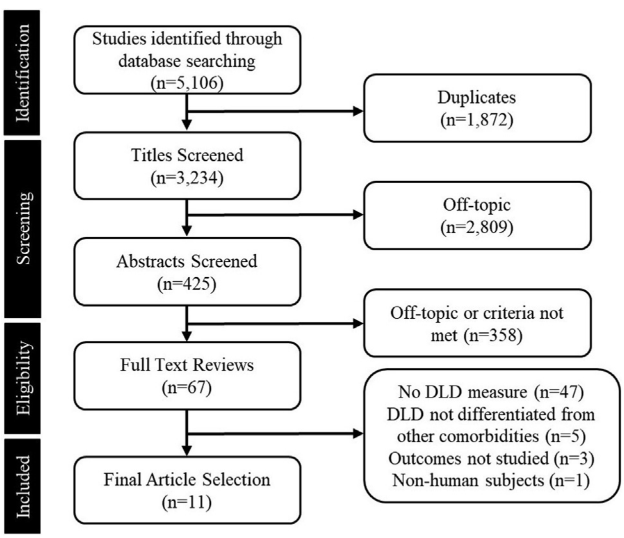

Figure 1 Flowchart for the identification of included studies.

(1[4]). Berglund et al[8] quantitatively measured forward elevation and external rotation, revealing reduced forward elevation for hyperlipidemia patients 1 year after rotator cuff repair ($P = .034$). Three of these 5 studies[4,23,61] had patients on stain therapy.

Retear requiring revision

Lee et al[38] evaluated factors that increased the odds of a rotator cuff retear necessitating a revision. Patients whose retear required repair had significantly elevated TC (OR 1.01, 95% CI 1.00-1.03, $P = .015$) and LDL (OR 1.02, 95% CI 1.01-1.04, $P = .11$) when compared with retear patients who did not require repair; TG did not have a significant impact ($P = .230$). Of note, revision patients had persistent pain and functional impairment for at least 3 months after primary surgery.

Risk of bias

Using the Newcastle-Ottawa Scale,[57] 5 studies[4,11,31,46,49] were deemed excellent quality, 5 studies[23,25,30,38,61] were good quality, 1 study[8] was satisfactory quality, and no papers were of unsatisfactory quality (Table III). Assessing comparability, 2 studies[31,48] controlled for preoperative retear, which was previously mentioned as the most important factor to control for. For outcomes, all 7 studies[4,8,11,23,25,31,61] of cohort design had a minimum of 6-month follow-up.

Discussion

This systematic review elucidates the adverse association between DLD and rotator cuff repair outcomes. There was a significant increase in the likelihood of rotator cuff repair retear for patients with DLD. In the evaluated studies, functional outcomes after rotator cuff repair do not appear to be significantly affected for patients with DLD compared with those without DLD.

Growing evidence suggests that DLD is a risk factor for the development of rotator cuff disease, among other tendon pathology. In a meta-analysis by Lai et al,[34] DLD patients had a 2.17 (95% CI, 1.46-3.23) greater odds of rotator cuff disease than non-DLD patients. Lin et al[41] followed hyperlipidemia patients over an 11-year period and found an elevated risk with a hazard ratio of 1.48 (95% CI 1.42-1.55, multivariant analysis). Abboud and Kim[3] revealed that patients with rotator cuff tears had a higher incidence of elevated TC, ($\bar{x} = 237$ mg/dL, $P = .03$), LDL ($\bar{x} \approx 155$, $P = .02$), and TG ($\bar{x} \approx 185$, $P = .03$); although lower, HLD was statistically insignificant ($\bar{x} \approx 35$, $P = .10$). Animal studies show reduced tendon elasticity and increased fatty infiltration in hyperlipidemic mice and rabbit rotator cuff tendons,[6,16] two factors believed to be associated with retear.[4,21,25,28] These results suggest rotator cuff tendons in a DLD environment are compromised preoperatively, sustaining damage that may increase the size of primary tear or alter effective healing postoperatively.[49] Contradictory studies exist, however, making the association between DLD and rotator cuff disease unclear.[60] A previous meta-analysis by Zhao et al[62] found borderline contrary findings in evaluating the retear risk for DLD patients (OR 1.50, 95% CI 0.99-2.26), although this analysis only included 4 studies that were also used in our analysis (Garcia et al,[23] Harada *et al*,[25] Jeong *et al*,[30] and Kim *et al*[31]). Our study uses retear data from an additional 4 studies[4,11,46,49] to offer stronger statistical power, adding to the existing knowledge regarding risk factors for rotator cuff repair failure.

Multiple competing mechanisms likely contribute to the increased odds of retear imposed by DLD. Circulation-derived lipid deposits in tendon extracellular matrix have been widely observed in nonfamilial hypercholesterolemia patients. The present research suggests that these deposits cause oxidative damage, persistent inflammatory cytokine production, obstructed tissue vascularity,

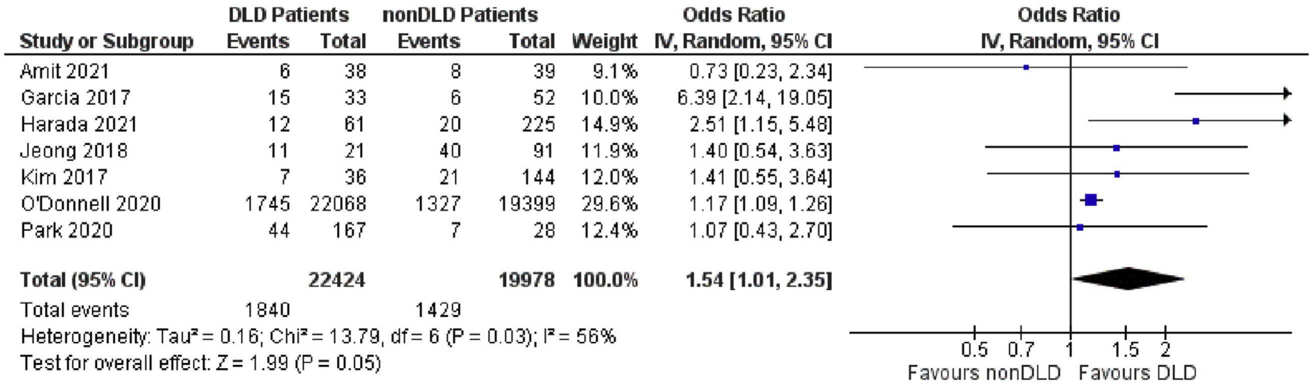

Figure 2 Meta-analysis forest plot synthesizing the effect of DLD on rotator cuff retear odds. Mantel-Haenszel, random effects model.

and reduced cholesterol efflux and matrix turnover by macrophages and tenocytes.[2,5,11,55] In a recent study by Li et al,[39] high cholesterol inhibited gene expression in tendon-derived stem cells, a newly identified resident cell population theorized to be responsible for tendon maintenance and repair. A subsequent study by Li et al[40] revealed that cholesterol also induces apoptosis and autophagy of these stem cells. This pathophysiology may underly the stiffness, poor collagen organization, and fatty infiltration observed in healing DLD rotator cuff repair models.[7,16] In addition, Chung et al[16] found that hyperlipidemia had a deleterious effect on fatty infiltration in a murine rotator cuff model, both pre- and post-repair. Although no studies observe this association in humans, 3 studies in this review investigated DLD concurrently with fatty infiltration as predictors for retear: Harada et al[25] and Kim et al[31] demonstrated both as risk factors in a patient population, whereas Jeong et al[30] reported that DLD was not a risk factor. These coinciding results allow for the postulation that DLD patients may experience greater fatty infiltration, contributing to retear risk. Fatty infiltration is the subject of substantial research for its role in rotator cuff tear pathology.[42,53,54] The stem cells responsible for fatty infiltration harbor potentially restorative value, which can be potentiated via pharmacological intervention.[20,36,56] This potential could prove therapeutic and DLD patients may uniquely benefit from such intervention, in conjunction with lipid control via statins.

Statin therapy appears to effectively suppress or eliminate the detrimental effects of DLD. In murine studies, simvastatin administration reduced fatty infiltration and improved tendon-to-bone healing, compared with hyperlipidemia mice not on a statin.[16] Amit et al[4] showed that patients on statin therapy had fatty infiltration progression, retear rate, and function comparable to non-DLD patients. Similar results for functional outcomes are found in Zheng et al.[61] Cancienne et al[11] offer perhaps the most convincing evidence that statins mitigate the risk of retear, given the significant size of study and comparison within groups. In this study, DLD patients had a significantly greater risk of retear without statins, although DLD patients on statins had risk equivalent to non-DLD patients. Garcia et al[23] found that statins were ineffective against retear, although this study lacks control of confounding variables statin therapy on tendon healing is not well defined and is still the subject of upcoming research.[10,17-19]

DLD is a condition that encompasses any disorder of lipoproteins. Therefore, concluding that DLD results in an increased risk of retear is relatively nonspecific. Most of the articles in this review used a recorded "hyperlipidemia" diagnosis or elevated TC to identify subjects. Cancienne et al[11] recorded TC, LDL, and TG and found that moderate and high TC and LDL (Table II) were independently associated with retear. Park et al[49] additionally dissect DLD into low HDL and high non-HDL (Table II), revealing that low HDL (HDL<40 mg/dL for males and HDL <50 mg/dL for females) alone is associated with retear. They also report that low HDL increased preoperative tear size, which may explain the increased retear risk. Low HDL has also been reported as an independent risk for primary tear.[2,48] HDL, also known as "good" cholesterol, is responsible for collecting excess cholesterol in the body for disposal or recycling, reducing systemic deposition, and serving a vasculoprotective role. Additional beneficial properties include anti-inflammatory, antioxidant, anti-thrombotic, and angiogenesis regulation.[51] Reduced HDL has been linked to tendon xanthoma formation.[45] Overall, little is known about the roles of specific lipoproteins in tendon pathology, although specified research may help clearly characterize the detrimental effect of DLD.

Although some risk factors are more apparent than others, it appears reliably evident that rotator cuff repair failure does not rely on one factor.[9,14,24,25,30,35,37,62] In addition, risk factors rarely appear exclusively in isolation in clinical settings. Harada et al[25] developed a novel decision tree analysis to predict the probability of retear with coexisting risk factors. In addition to hyperlipidemia, this analysis included anteroposterior tear size, fatty infiltration, and critical shoulder angle. Kwon et al[33] created a 15-point numerical scoring system based on retraction, fatty infiltration, anteroposterior tear size, age, bone mineral density, and work activity. Further development of evaluation systems such as these is a worthwhile endeavor to provide an accurate and reliable prediction of rotator cuff repair outcome. Although our study suggests that DLD is a risk factor for retear, we cannot determine its true effect, and thus, we recommend it be considered among other coexisting risk factors.

This study has several limitations. Given the design of the systematic review, variability between studies can have unrecognized implications, including variation in study design, subject pools, statin therapy regimen, surgery and rehabilitation protocol, DLD measure, and statistical methods. Statin use varied across studies and is considered a major confounder, as it seems to impact retear odds. In addition, a large portion of the subjects came from a database study, which comes with inherent limitations, such as coding errors and attrition due to insurance. Overall, our meta-analysis had a significant effect ($Z = 2.48$, $P = .01$) but was rated as having substantial heterogeneity by the Higgins I^2 (56%). Second, in several studies, DLD as a risk factor was measured concurrently with other risk factors, likely producing a confounding effect.[8,25,30,31,46,49] Although we could not separate these factors for meta-analysis, great effort was put into scrutinizing the statistical control of confounding variables in our risk of bias assessment. Although the majority of studies controlled for confounding variables, only 2 studies adequately controlled for preoperative tear size.[17,49] Third, retear was not well defined by all studies (ie, biologic vs. human error cause of retear). In addition, there was variability in the criteria for retear. Finally, the adequacy of lipid control over time and length of statin therapy likely play a significant role in the overall effect of DLD. No study in this review recorded such data, although variability likely exists between subjects with differing effects on tendon pathology.

Conclusion

Rotator cuff repair outcomes, particularly retear risk, are associated with DLD. Functional outcomes appear unaffected, with possible exception to range of motion. DLD should be considered among other risk factors when assessing patients' rotator cuff repair outcomes.

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