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Is higher serum cholesterol associated with altered tendon structure or tendon pain? A systematic review

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ABSTRACT

Background Tendon pain occurs in individuals with extreme cholesterol levels (familial hypercholesterolaemia). It is unclear whether the association with tendon pain is strong with less extreme elevations of cholesterol.

Objective To determine whether lipid levels are associated with abnormal tendon structure or the presence of tendon pain.

Methods We conducted a systematic review and meta-analysis. Relevant articles were found through an electronic search of 6 medical databases—MEDLINE, Cochrane, AMED, EMBASE, Web of Science and Scopus. We included all case–control or cross-sectional studies with data describing (1) lipid levels or use of lipid-lowering drugs and (2) tendon structure or tendon pain.

Results 17 studies (2612 participants) were eligible for inclusion in the review. People with altered tendon structure or tendon pain had significantly higher total cholesterol, low-density lipoprotein cholesterol and triglycerides, as well as lower high-density lipoprotein cholesterol; with mean difference values of 0.66, 1.00, 0.33, and −0.19 mmol/L, respectively.

Conclusions The results of this review indicate that a relationship exists between an individual's lipid profile and tendon health. However, further longitudinal studies are required to determine whether a cause and effect relationship exists between tendon structure and lipid levels. This could lead to advancement in the understanding of the pathoaetiology and thus treatment of tendinopathy.

INTRODUCTION

Tendinopathy is the term used to describe painful tendon conditions.[1] While the exact pathoaetiology of tendinopathy remains unclear,[2] overuse is considered as a major contributing factor.[3] Despite this link, approximately one-third of cases occur in non-active individuals.[4] Obesity and fat distribution have been associated with tendinopathy,[5–7] with one explanation being that higher body mass causes increased tendon loading (mechanical hypothesis).[7] However, increased body mass index (BMI) has also been linked with tendinopathy in the non-weight-bearing upper limbs,[8] which suggests that a mechanical hypothesis does not sufficiently explain changes to tendon structure or onset of tendon pain.[6] There is growing evidence for a metabolic hypothesis linking BMI and tendinopathy.

A well-known comorbidity of obesity is hypercholesterolaemia, an established risk factor for coronary heart disease.[9] Cholesterol also accumulates in tendons, where it may be involved in structural disruption of the collagen matrix, similar to that seen in tendinopathy.[10–12] This has been demonstrated in patients with familial hypercholesterolaemia (FH), a genetic lipid metabolism disorder that is characterised by lifelong elevation of serum cholesterol.[13] Substantial cholesterol deposition occurs in FH and is known as tendon xanthoma.[14] While many medical textbooks state that tendon xanthomas are asymptomatic, data show a sixfold increase in the lifetime incidence of Achilles tendon pain associated with FH.[15]

Chronic low-grade inflammation (para-inflammation) is a critical driver of cardiovascular disease (CVD) and is also a predominant feature of FH.[16 17] The instigating event in CVD is retention of apolipoprotein-B containing lipoproteins beneath the endothelial layer of the blood vessel wall[18] where they are irreversibly modified via interaction with extracellular matrix proteoglycans.[19] Subendothelial lipoprotein retention triggers the release of chemokines, which promote monocyte recruitment and conversion to macrophages.[17] As these macrophages ingest and process retained lipoproteins, they accumulate cytoplasmic lipid droplets, and under the microscope these droplets look like soap bubbles, leading to the term 'foam cells'.[20] Eventually cholesterol esterification and efflux mechanisms are overwhelmed and the excess cholesterol becomes cytotoxic.[21] Each of these steps contributes to the para-inflammation present in CVD and FH.[22]

Recent studies of non-ruptured tendinopathy tissue indicate subtle increases in mast cells and macrophages[23 24] although other studies find no such increase.[25 26] When the clinician is considering this new information, it is critically important to remember that para-inflammation is triggered by subtle alterations in tissue homeostasis rather than infection and trauma, which are the familiar triggers of acute (triphasic) inflammation.[27] Therefore, para-inflammation is not triggered by a bout of unresolved acute inflammation but is a response to tissue stress that is maintained over an extended period of time.[27] Similarly, archetypal proinflammatory cytokines (eg, tumour necrosis factor alpha) can have anti-inflammatory effects via alternate signalling pathways.[26]

Other studies have identified associations between cholesterol and tendon rupture[28 29] and chronic tendinopathy.[6] Together, these data build support for the metabolic hypothesis as an explanation for the presentation of tendinopathy among sedentary individuals.

A systematic review by Gaida *et al*[7] revealed that a relationship exists between adiposity and tendinopathy. As an abnormal lipid profile is commonly

associated with obesity,[30] this research has provided a basis for a closer examination of this relationship. Thus, the primary aim of this systematic review was to investigate whether there is an association between abnormal lipid levels and changes in tendon structure or tendon pain. A secondary aim was to describe the association that lipid-lowering drugs have with tendon structure or tendon pain. The review only considered individuals not diagnosed with FH.

METHODS

Search strategy

Six electronic databases (MEDLINE, Cochrane, AMED, Web of Science, Scopus and EMBASE) were searched in April 2014. Medical subject headings used in the search included (1) Tendons, Tendon Injuries, Tendinopathy, Xanthomatosis AND (2) Lipids, Lipoproteins, Cholesterol, Hydroxymethylglutaryl-CoA Reductase Inhibitors and Lovastatin. Free text terms were also searched with appropriate truncation, and included (1) tendon structure, tendon thickness, tend#nopathy, tend#nos#s, tendon pain and (2) lipid, cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride, statin, hydroxymethylglutaryl-CoA reductase inhibitors (for complete list of search terms, see online supplementary appendix A). All records were then imported into reference management software (Endnote version X5).

Eligibility criteria

One author (BT) applied predefined eligibility criteria to the title and abstracts of the retrieved records. To be included studies had to provide data on both lipid levels or lipid-lowering drugs and tendon structure or tendon pain. We excluded case reports, case series and retrospective studies, reviews, letters, conference abstracts, comments, editorials, non-English articles, and studies of non-human, cadaver or biopsy material. Papers that involved participants with cerebrotendinous xanthomas, inflammatory or systemic arthritis, or FH were excluded. However, FH papers were included if they presented tendon data from a non-FH control group. In the second round of reviewing, the full text was read to determine whether the article met the inclusion and exclusion criteria.

Quality assessment

Included papers were assessed for methodological quality to identify potential sources of bias. A tool was developed by the authors based on the quality assessment criteria developed by Downs and Black (see online supplementary appendix B).[31] The tool consisted of 11 criteria, each addressing a different source of bias. An explicit decision rule was developed for each criterion to improve precision. Quality assessment results were converted to a percentage score as not all studies could be marked on all criteria.

Data extraction and study analysis

Data were extracted by one author (BT) and included study details, participant demographics, tendon outcomes, lipid outcomes, and any results presented (ie, effect size, odds ratio (OR)). If data for the lipid levels of participants were presented in milligrams per decilitre (mg/dL), these units were converted to millimole per litre (mmol/L) using appropriate calculations (see online supplementary appendix C). When necessary, data were extracted from figures using Engauge Digitilizer (Mitchell, M; V.4.1) (see online supplementary appendix C).

Meta-analysis was conducted on appropriate data using RevMan (The Cochrane Collaboration; V.5.1). A random effects model was used with inverse variance weighting, and results presented as mean difference (MD). A meta-analysis was conducted for each of the four lipid measurements (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG)), and their individual association with tendon structure or tendon pain.

RESULTS

The databases search yield of 1607 papers was imported into Endnote and 561 duplicates were removed. The title and abstract of 1046 papers were reviewed and 962 studies were removed. The full text version of 84 papers was reviewed and 67 studies were removed. In the end, 17 studies were included in the review (figure 1).

The quality of the included papers showed considerable variation, with the mean quality assessment score being 62% (range 20–82%), suggesting that the current literature in this area is of moderate quality (see online supplementary appendix D). The majority of studies reported their method of participant recruitment; however, these participants were not commonly representative of the population from which they were recruited. The case–control nature of all but one of these studies explains why the two groups were often taken from different populations. With the exception of Ozgurtas *et al*,[29] authors reported that controls were free from disease. The majority of authors presented a control group that was matched to the case group with respect to potential confounding factors. Reporting the method used to assess tendon structure was a common criteria met by these papers, however, these methods were not always identical for cases and controls. Only one study[6] reported assessor blinding, with the remainder of the studies having the potential for assessor bias.

Fifteen of the included papers used a case–control study design, and two used a cross-sectional design (table 1). Imaging was used to define tendon structure in 14 studies—7 used ultrasound, 2 used MRI, 1 used CT and 4 used radiography. A variety of methods were used to assess tendon symptoms, including palpation, clinical history and a visual analogue scale for pain. The tendons examined included rotator cuff (n=4) and Achilles tendon (n=13).

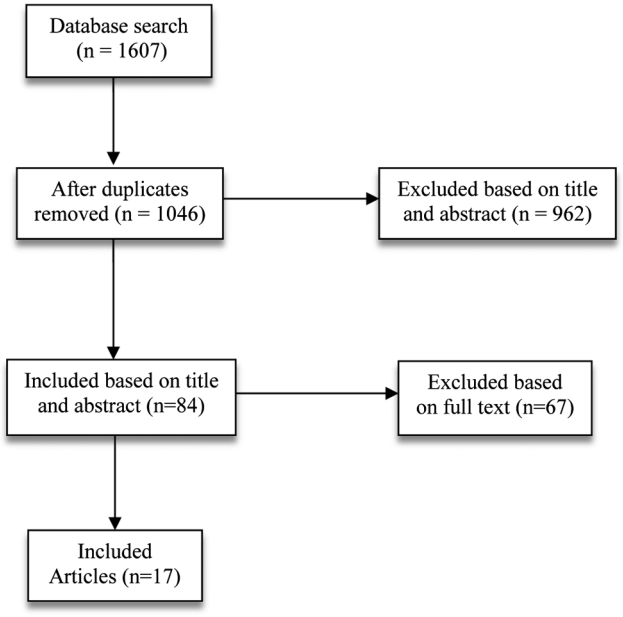

Figure 1 Flow chart of search yield and study selection.

Table 1 Study details

Author (year)	Study design	Country where the study was performed	Primary recruitment criteria (ie, tendon pain/structure or lipid level)	Was an upper limb (UL) or lower limb (LL) tendon assessed	Was tendon structure and/or tendon pain assessed
Abate (2014)	Cross-sectional study	Italy	Neither—referred for LL disease	UL	Structure
Abboud (2010)	Case–control study	USA	Tendon structure	UL	Structure
Beri (2009)	Case–control study	USA	Tendon structure	Both	Structure
Descamps (2001)	Case–control study	Belgium	Lipid levels	LL	Structure
Durrington (1982)	Case–control study	UK	Lipid levels	LL	Structure
Gaida (2009)	Case–control study	Australia/Sweden	Tendon pain	LL	Both
Gattereau (1973)	Case–control study	Canada	Lipid levels	LL	Structure
Junyent (2005)	Case–control study	Spain	Lipid levels	LL	Structure
Klemp (1993)	Case–control study	South Africa	Lipid levels	Both	Both
Kwak (2013)	Case–control study	Korea	Lipid levels	LL	Structure
Longo (2010)	Case–control study	UK	Tendon structure	Both	Both
Mabuchi (1977)	Case–control study	Japan	Lipid levels	LL	Structure
Mabuchi (1978)	Case–control study	Japan	Lipid levels	LL	Structure
Ozgurtas (2003)	Case–control study	Turkey	Tendon structure	LL	Structure
Rechardt (2013)	Cross-sectional study	Finland	Tendon pain	UL	Pain
Tsouli (2009)	Case–control study	Greece	Lipid levels	LL	Structure
Yuzawa (1989)	Case–control study	Japan	Lipid levels	LL	Structure

Among the case–control papers, there were five studies that recruited the case group based on tendon structure or tendon pain,[6 29 32–34] and three studies that recruited the case group based on lipid abnormalities.[35–37] There were seven studies of FH where only the control group was included.[13 14 38–42] Two studies examined the cross-sectional relationship between tendon health and lipid profiles.[8 43] In three of the five studies that recruited based on tendon structure or tendon pain, significant differences in lipids or statin use were identified. In two of the three studies that recruited on lipid levels, significant differences in tendon pain or structure were identified.

Data were extracted from all 17 papers in the review (see online supplementary appendix E), of which five were pooled for meta-analysis.[6 8 29 32 34] These papers used lipid levels as the continuous variable, for both case and control tendon health groups. The non-FH control groups from the seven FH studies[13 14 38–42] were not included in the meta-analysis. Achilles tendon thickness (ATT) was used as a continuous outcome variable in two studies that each had a high and a low lipid group,[35 37] however one of these investigated men and women separately and so the two could not be compared against each other. Two studies provided dichotomous data on tendon pathology; however one paper investigated the association with lipid levels,[36] while the other examined the association with statin use,[33] thus the papers were presented separately. Finally, one paper was a cross-sectional study and so could not be compared to the case–control studies.[43]

TC and tendon pathology

TC was significantly higher among individuals with tendon pain or rupture, MD=0.66 mmol/L, 95% CI 0.11 to 1.21 (figure 2).

HDL-C and tendon pathology

HDL-C was significantly lower among individuals with tendon pain or rupture, MD=−0.19 mmol/L, 95% CI −0.30 to −0.07 (figure 3).

LDL-C and tendon pathology

LDL-C was significantly higher among individuals with tendon pain or rupture, MD=1.00 mmol/L 95% CI 0.23 to 1.77 (figure 4).

TG and tendon pathology

TG was significantly higher among individuals with tendon pain or rupture, MD=0.33 mmol/L, 95% CI 0.15 to 0.50 (figure 5).

Lipid level and tendon pathology

One paper[36] recorded the prevalence of tendon pathology (history of Achilles tendinitis or tendon xanthomas) in a group with mixed hyperlipidaemia and a normolipidaemic control group. Tendon pathology was present in 18 (75%) of those with mixed hyperlipidaemia, compared with none of the normolipidaemic participants.

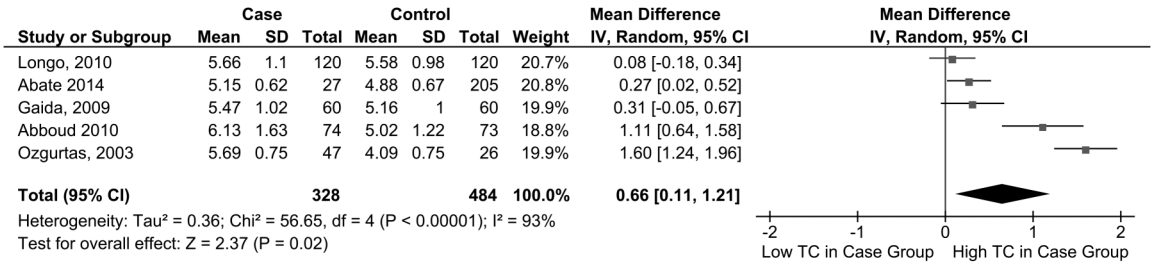

Figure 2 Forest plot showing the relationship between total cholesterol levels and tendon pathology (TC, total cholesterol).

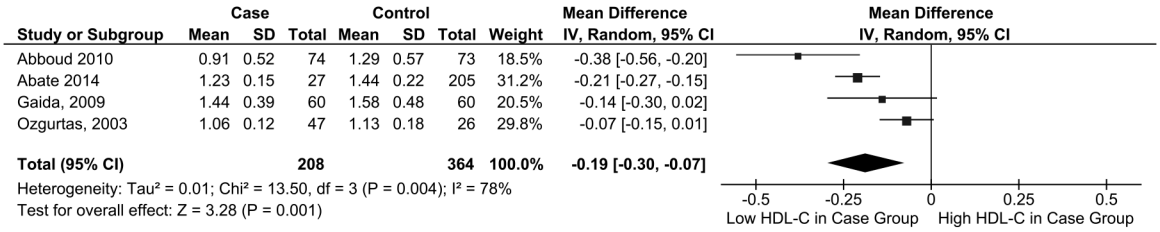

Figure 3 Forest plot showing the relationship between high-density lipoprotein cholesterol levels and tendon pathology (HDL-C, high-density lipoprotein cholesterol).

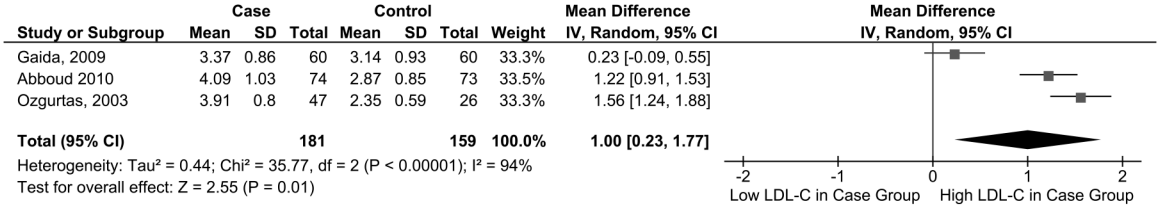

Figure 4 Forest plot showing the relationship between low-density lipoprotein cholesterol levels and tendon pathology (LDL-C, low-density lipoprotein cholesterol).

Lipid level and ATT

Tendon thickness was used as the continuous variable in two studies,[35 37] looking for differences between the hyperlipidaemic case group and the normolipidaemic control group. However, the paper by Gattereau *et al*[35] analysed men and women separately and did not provide data for the population as a whole, and so the results could not be compared with the paper by Kwak *et al*.[37] Interestingly, as the former split the participants into men and women, this paper allowed an investigation of whether or not this association was greater in one sex compared with the other.

Gattereau *et al*[35] used cut-off values for TC and TG of 240 and 140 mg/dL, respectively, to separate the hyperlipidaemic group from the normolipidaemic group. Hyperlipidaemic subjects were found to have a significantly increased ATT compared to the normolipidaemic controls. This was evident for both men (standardised MD (SMD)=0.95, 95% CI 0.19 to 1.71) and women (SMD=0.86, 95% CI 0.13 to 1.58). A significant positive correlation between cholesterol and ATT was also found, with correlation coefficients of 0.85 for women and 0.63 for men.

Kwak *et al*[37] used the European Society of Cardiology definition for dyslipidaemia (any one of the following: TC >240 mg/dL, TG >200 mg/dL, LDL-C >160 mg/dL, HDL-C <40 mg/dL). There was no significant difference in ATT between the dyslipidaemic (0.44±0.04 cm) and control group (0.45±0.02 cm, p=0.783). There was also no significant correlation between ATT and lipid parameters. The coefficients for TC was −0.09 (p=0.36), HDL-C −0.06 (p=0.50), LDL-C −0.03 (p=0.69) and TGs −0.04 (p=0.63).

Statins and tendon rupture

One paper[33] examined the association between statin therapy and tendon structure. Statin use was the same in those with and without tendon rupture, however, preplanned subgroup analysis showed an increase in tendon rupture in women taking statins, OR=3.09 (95% CI 1.04 to 9.75). No increased risk was identified in men, OR=0.62 (95% CI 0.3 to 1.3).

ATT and lipid levels in FH studies

Seven FH papers with a non-FH control group were included.[13 14 38–42] Each paper presented data on ATT and lipid profiles, but only one[40] analysed this relationship in the control group, finding a moderate positive correlation (r=0.454, p<0.01).

Lipid parameters from the remaining studies were pooled using appropriate equations (see online supplementary appendix F;[44] figures 6–10).

Lipid levels and pain intensity

There was only one study[43] that used pain intensity as an outcome. This was a study of the association of obesity and metabolic parameters with upper extremity pain. Age-adjusted and gender-adjusted ORs of pain intensity was calculated for TC, HDL-C, LDL-C and TG. A high pain intensity was associated with both low HDL-C levels (OR 2.7, 95% CI 1.2 to 6.3) and high TG levels (OR 2.8, 95% CI 1.3 to 6.6; table 2).

DISCUSSION

This systematic review showed with meta-analysis that people with altered tendon structure had significantly higher TC,

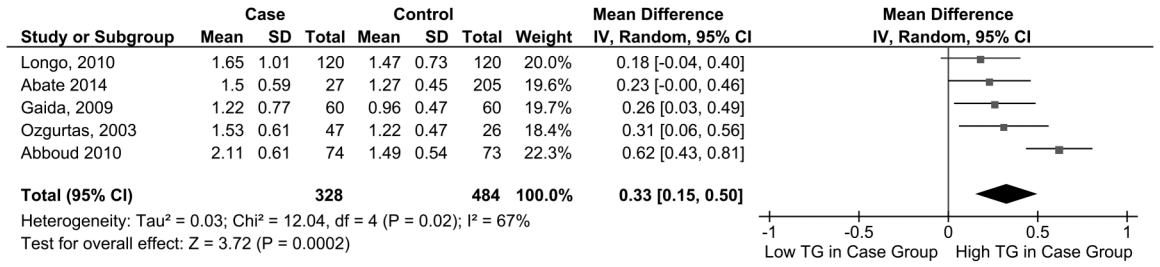

Figure 5 Forest plot showing the relationship between triglyceride levels and tendon pathology (TG, triglycerides).

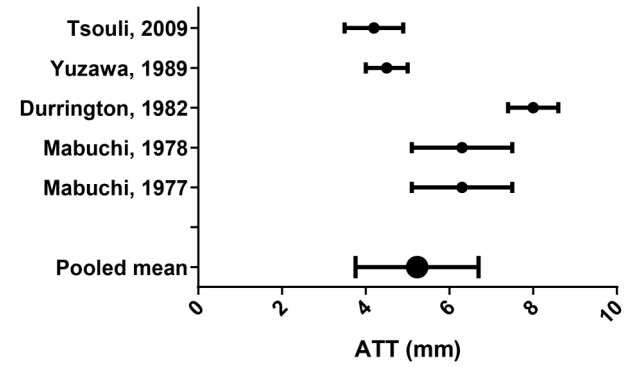

Figure 6 Achilles tendon thickness (ATT) mean (SD).

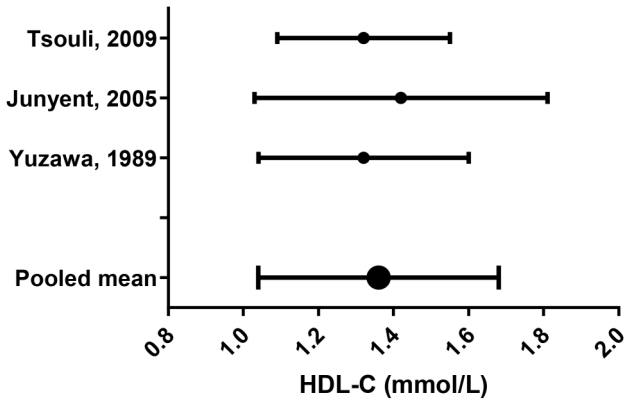

Figure 8 High-density lipoprotein cholesterol (HDL-C) mean (SD).

LDL-C and TG, as well as lower HDL-C, than people with normal tendons. Individuals with an adverse lipid profile were much more likely to have tendon pathology, and to have higher pain intensity associated with upper limb musculoskeletal injury. Statin use was associated with Achilles tendon rupture in women but not men. Finally, two of the three studies that correlated ATT with lipid parameters found a significant positive correlation. Together, these findings provide significant support for a metabolic hypothesis of tendon injury and implicate lipid parameters as a potential link.

While the data in this review indicate a link between lipid parameters and tendon health, causation cannot be established from cross-sectional data. As tendon injury limits physical activity, reverse causation—tendon injury causing elevated lipids—is possible given that metabolic parameters rapidly deteriorate with complete bed rest[45] and reduced daily steps.[46] However, observational and mechanistic studies suggest that adverse lipid parameters can be harmful to tendons. For example, individuals with FH have altered tendon structure in childhood and adolescence,[47] and aggressive lipid treatment reduces tendon thickness.[14] Furthermore, mechanistic studies show that hyperlipidaemia alters the mechanical properties of tendon across several species.[48 49] Together, these data provide plausibility for lipid parameters leading to reduced tendon health, suggesting that reverse causation is unlikely.

High cholesterol promotes the accumulation of cholesterol in macrophages and other immune cells, which drives para-inflammation. Downstream signalling pathways trigger a reduction in cholesterol efflux,[22] which increases cholesterol accumulation and maintains the para-inflammation state.[22] These processes provide a potential explanation for a link between hypercholesterolaemia and tendinopathy. Supporting this hypothesis is the increased number of mast cells and macrophages shown in those with tendinopathy, compared with a healthy control population.[23 24] Additionally, the strong inflammatory phenotype of FH[16] suggests that a state of para-inflammatory change may be involved in the mechanism of high cholesterol leading to tendinopathy.[16] It is unclear whether these processes also occur in tendons, particularly given the magnitude of hypercholesterolaemia noted in association with tendinopathy (eg, 5.7±1.2, pooled mean of cases from figure 2) is far less than that observed in FH (eg, 8.3±1.0 mmol/L).[14]

A secondary aim of this review was to examine whether statin use was correlated with tendon structure. One eligible paper[33] investigated this association and found, in an a priori subgroup analysis, that women taking statins had an increased risk of tendon rupture. Recent evidence suggests this effect may be mediated by changes in the profile of metalloproteinase enzymes within the tendon.[50] These enzymes are involved in remodelling the extracellular matrix of tendon and have been linked with tendon rupture.[51]

Pain intensity was used as an outcome in one paper[43] and was found to be associated with low HDL-C and high TG among individuals with upper extremity soft tissue disorders. This study pooled participants with a range of diagnoses, including tendinopathy of the rotator cuff, lateral elbow and wrist flexor tendons. Grouping diagnoses is, in one sense, a limitation of the study; however, this approach allowed the authors to collect a large sample of participants with a recent onset of pain (<1 month). The strong association of LDL-C and TG with recent onset pain provides strong, but obviously not definitive, evidence against reverse causation.

The lipid changes associated with tendon injury parallel those associated with CVD, namely, TC, LDL-C and TG are increased

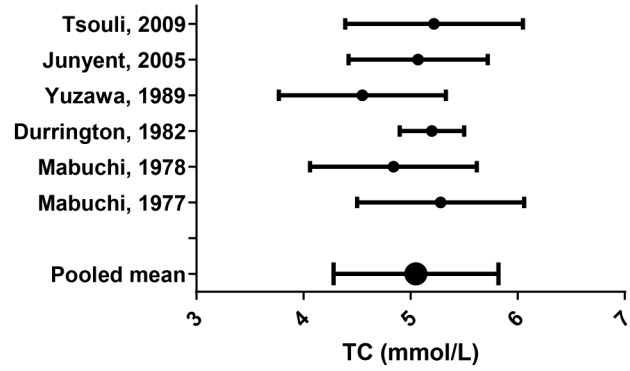

Figure 7 Total cholesterol (TC) mean (SD).

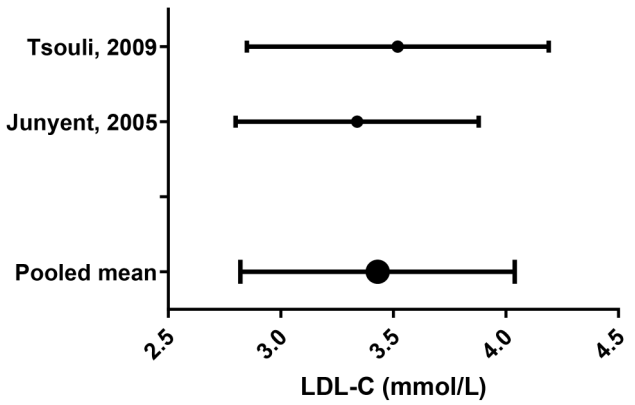

Figure 9 Low-density lipoprotein cholesterol (LDL-C) mean (SD).

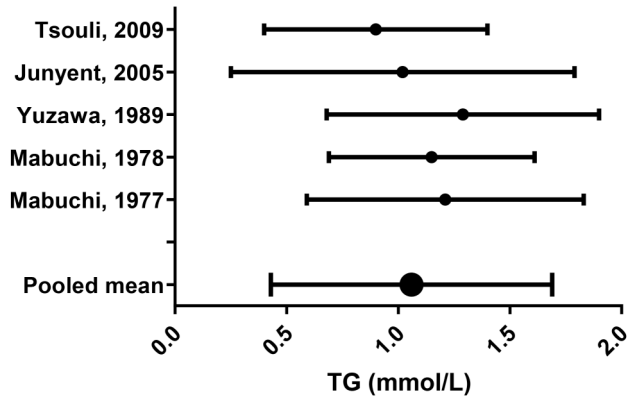

Figure 10 Triglycerides (TG) mean (SD).

while HDL-C is decreased. This suggests that tendon and artery respond to their metabolic environments in similar ways. Both are collagen-based tissues, capable of responding to their loading environment. For example, branch points and bifurcations of arteries are exposed to shear forces created by turbulence,[52] have an altered proteoglycan content, and are prone to atherosclerosis development.[53] The pathogenesis of atherosclerosis is driven by long-standing para-inflammation, involving the recruitment and conversion of monocytes to macrophages.[54] The macrophages accumulate cholesterol esters to form 'foam cells', which play a central role in the formation of atherosclerotic lesions.[54] In tendons, shear and compression forces alter the proteoglycan profile,[55] and these areas are prone to pathology. There is evidence that proteoglycan (particularly those with a chondroitin sulfate side chain) precipitates cholesterol accumulation within both tendon and artery through its strong affinity for cholesterol.[56 57] In short, things that are bad for your heart also seem to be bad for tendons.

There are limitations of this review that should be acknowledged. One limitation was that 17 potentially relevant non-English studies were excluded. Language bias has been demonstrated for randomised trials[58]—studies with significant findings are more likely to be published in English-language journals—and may also affect observation studies such as those included in this review. Limitations are also inherent in the data set used for this review. For example, the included studies used a variety of methods to assess tendon structure or tendon pain. Blood lipid analysis is a standardised laboratory procedure with little potential for systematic bias. Blood collection procedures, however, may introduce bias. For example, in the study by Ozgurtas *et al*,[29] blood samples were collected from the case group within 6 h of tendon rupture, while those from the control group were collected after an overnight fast. While this is not ideal, large datasets show minimal difference between fasting and non-fasting lipid measurements.[59]

Table 2 OR of pain intensity according to TC, HDL-C, LDL-C and TG

Characteristic	OR	95% CI
TC (mmol/L)		
<4.7	1	0.4 to 2.7
4.7–5.3	1.0	0.8 to 4.0
>5.3	1.8	
HDL-C (mmol/L)		
>1.83	1	0.4 to 2.2
1.48–1.83	0.9	1.2 to 6.3
<1.48	2.7	
LDL-C (mmol/L)		
<2.5	1	0.4 to 2.6
2.5–3.3	1.1	0.7 to 4.2
>3.3	1.7	
TG (mmol/L)		
<0.72	1	0.7 to 4.0
0.72–1.08	1.7	1.3 to 6.6
>1.08	2.8	

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

CONCLUSION

The review comprehensively identified all available data on the potential link that lipid fractions have with tendon pain and structure. The meta-analysis supports an association for TC, HDL-C, LDL-C and TG. A potential mechanism for this link is the para-inflammation that is present in FH. Ongoing research is required to determine whether similar processes occur in the presence of less extreme cholesterol elevations associated with lifestyle factors. Notwithstanding this, the current work indicates that there is indeed an association between unfavourable changes in lipid parameters and tendinopathy.

Summary box

- This review identified 17 studies on the topic of tendon health and lipid profile. Five studies compared lipid profile between individuals with and without tendon pain/abnormality, and three studies compared tendon health between individuals with and without lipid abnormality. The cross-sectional relationship between tendon health and lipid profile was examined in two studies. Seven studies on familial hypercholesterolaemia provided data from their healthy control group.
- Meta-analysis of appropriate studies showed significantly higher total cholesterol, low-density lipoprotein cholesterol and triglyceride, and lower high-density lipoprotein cholesterol in individuals with tendon pain/abnormality.
- Two of the three studies that examined the correlation between tendon thickness and lipid levels found a significant positive relationship.
- Statin use was associated with Achilles tendon rupture in women but not men.

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Competing interests None declared.

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BRITISH JOURNAL OF SPORTS MEDICINE

High cholesterol linked to heightened risk of tendon abnormalities and pain

Chronic low level inflammation, prompted by cholesterol build-up in immune cells, may be key

High levels of total cholesterol are linked to a heightened risk of tendon abnormalities and pain, reveals a pooled analysis of the available evidence published online in the ***British Journal of Sports Medicine.***

Chronic low level inflammation, prompted by cholesterol build-up in immune system cells, may have a key role, the findings suggest.

Tendons are the tough fibres connecting muscles and bones in the body. Mechanical stress as a result of obesity or excess body fat distribution, and overuse during the course of exercise or work, are thought to be among the leading causes of tendon injuries (tendinopathy). But these factors don't explain a significant proportion of cases, say the researchers.

People with genetically determined very high cholesterol levels (familial hypercholesterolaemia) seem to be at greater risk of tendon pain, but it's not clear if those with lower, but still high levels, might also be vulnerable to tendon injuries.

The authors therefore trawled six medical research databases, looking for studies investigating links between blood fats and tendon abnormalities/pain.

They came up with 1607 relevant articles, of which 17, involving 2612 participants, and published between 1973 and 2014, were suitable for inclusion in the analysis.

The results showed that compared with people whose tendon structure was normal, those with abnormal tendon structure had a significantly more unfavourable blood fat (lipid) profile.

They had significantly higher total cholesterol, including higher low density ('bad') cholesterol and lower high density ('good') cholesterol, and higher triglyceride levels.

Furthermore, people with an unfavourable lipid profile were much more likely to have tendon injuries and higher levels of pain associated with musculoskeletal problems in their arms.

And two of the three studies, which looked at Achilles tendon thickness, found that people with an unfavourable lipid profile had thicker tendons than those with lipid levels in the normal range.

"Together, these findings provide significant support for a metabolic hypothesis of tendon injury and implicate lipid parameters as a potential link," write the researchers.

But they point out that as this was an observational study no definitive conclusions can be drawn about cause and effect, especially as the findings might have been the result of reverse causation—whereby those with tendon injuries did less exercise, so raising their cholesterol levels.

Nevertheless, there is good evidence to suggest that a poor blood lipid profile may be harmful to tendons, they say, as people with familial hypercholesterolaemia have altered tendon structure throughout childhood and adolescence, while aggressive lipid lowering treatment reduces tendon thickness.

High cholesterol levels are also known to stimulate the build-up of cholesterol in immune system cells, which in turn leads to low level chronic inflammation. Compared with people without tendon injuries, those with tendinopathy have increased numbers of these immune cells in their tendons.

Notes for editors:

Research: Is higher serum cholesterol associated with altered tendon structure or tendon pain? A systematic review doi 10.1136/bjsports-2015-095100
Journal: ***British Journal of Sports Medicine***

SUPPLEMENTAL APPENDICES

Supplemental Appendix A: Complete List of Search Terms

Table 3
Search Terms

	Serum Lipid and Lip-lowering drugs	**Tendon Structure and Pathology**
MeSH	Lipids/ exp Lipoproteins/ Cholesterol/	exp Tendons/
Free text	Lipid*.ti,ab. Cholesterol*.ti,ab. Hyperlipid*.ti,ab. Hypercholesterol*.ti,ab. Triglyceride*.ti,ab. Hypertriglyceride*.ti,ab. High-density lipoprotein*.ti,ab. Low-density lipoprotein*.ti,ab.	Tendon structure*.ti,ab. Tendon thickness*.ti,ab.
MeSH	Hydroxymethylglutaryl-CoA Reductase Inhibitors/ exp Lovastatin/	exp Tendon Injuries/ exp Tendinopathy/ Xanthomatosis/ AND exp Tendons/
Free text	Statin*.ti,ab. Hydroxymethylglutaryl-CoA Reductase Inhibitor*.ti,ab. HMG-CoA.ti,ab. Atorvastatin.ti,ab. Fluvastatin.ti,ab. Lovastatin.ti,ab. Pitavastatin.ti,ab. Pravastatin.ti,ab. Rosuvastatin.ti,ab. Simvastatin.ti,ab.	Tendon pain.ti,ab. Tendon tear*.ti,ab. Tendon strain*.ti,ab. Tendon rupture*.ti,ab. Tend#nopath*.ti,ab. Tend#nitis.ti,ab. Tend#nos#s.ti,ab. Tenosynovitis.ti,ab. Achillodynia.ti,ab. Achilodynia.ti,ab. Jumper* Knee.ti,ab. Tennis Elbow.ti,ab. Golfer* Elbow.ti,ab. Epicondylitis.ti,ab. Xanthoma*.ti,ab. ADJ5 Tendon*.ti,ab.

MeSH = Medical Subject Heading

Supplemental Appendix B: Quality Assessment of Included Papers

Example: Abate et al., 2014

Abate et al., 2014			
No.	Criterion	Decision Rule	Score Y=1 N=0
STUDY POPULATION			
1	Is the method of recruitment and eligibility criteria reported?	Yes if the study states how participants were recruited, and clear eligibility criteria for participant inclusion and/or exclusion were reported	Y
2	Are the participants representative of the population from which they were recruited?	Yes if the study states that consecutive eligible patients were used, participants were randomly selected, or all participants were used from the source population	N
3	Is there evidence that the controls are free from disease?	Yes if evidence is supplied that the controls are not exposed to the disease	Y
4	Are both groups drawn from the same population?	Yes if both the case and control group were drawn from the same source population	Y
5	Are potential confounding factors identified?	Yes if the cases and controls were matched with respect to the potential confounding factors (age, sex, BMI)	N
OUTCOME			
6	Were lipid levels assessed identically?	Yes if the method for the collection and the analysis of the lipid levels were done in an identical way for the entire population	N
7	Valid definitions	Yes if the method used for assessing tendon structure or tendon pain was defined and explained with reference to its validity	Y
8	Was tendon structure or tendon pain assessed identically?	Yes if the methods for assessing tendon structure or tendon pain were measured in an identical way for the entire population	Y
9	Was assessor blinding reported?	Outcomes and variables were measured by assessors independently, without any knowledge of the key confounding outcome or grouping variables within the study	N
STUDY DESIGN			

10	Were data available for >80% of those enrolled?	Yes if data were available for at least 80% of all participants enrolled in the study	N
ANALYSIS			
11	Appropriate analysis	Yes if data are supplied that allows for the reader to determine if the relationship between abnormal lipid levels and change in tendon structure or pain is statistically significant	Y
		SCORE	6/11
		PERCENTAGE	55%

Supplemental Appendix C: Programs and formulas

Cholesterol Unit Conversion:

To convert milligrams per decileter (mg/dL) to millimole per litre (mmol/L), values should be divided by:

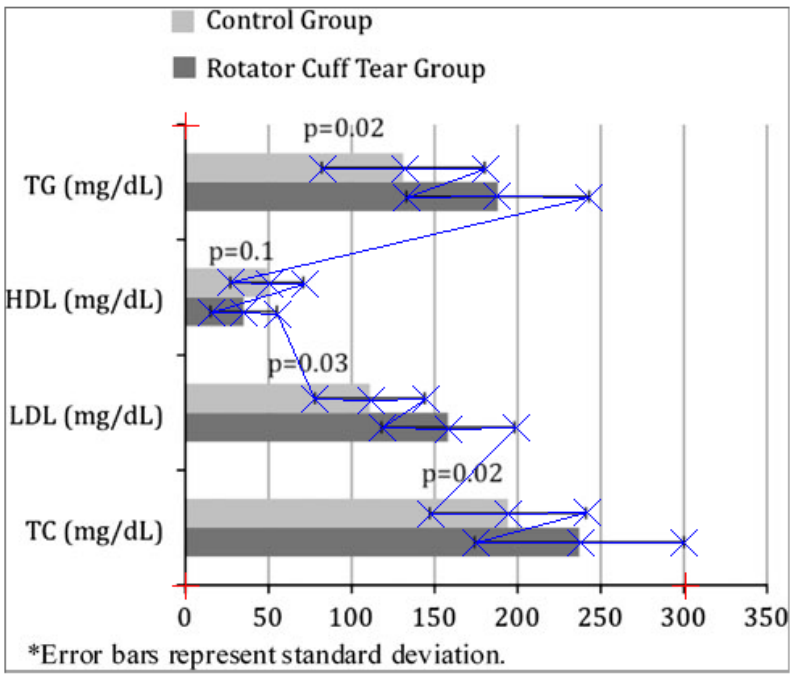
- 38.67 for total cholesterol, HDL and LDL
- 88.57 for triglycerides

*Figures taken from 'Screening for Lipid Disorders in Children and Adolescents – Evidence Synthesis' by Haney, E., Huffman, L., Bougatsos, C et al (2007). Agency for Healthcare Research and Quality (US).

Engauge Digitilzer 4.1:

Engauge Digitilizer 4.1 was developed by Mark Mitch in 2010.

Figure 6. Data extraction using Engauge Digitilizer



Supplemental Appendix D: Summary of Quality Assessment Results

Table 4
Summary of Quality Assessment Results

Author (Year)	1	2	3	4	5	6	7	8	9	10	11	Score
Abbate (2014)	✓	✗	✓	✓	✗	✗	✓	✓	✗	✗	✓	6/11 (55%)
Abboud (2010)	✓	✗	✓	✓	✓	✓	✓	✓	✗	✓	✓	9/11 (82%)
Beri (2009)	✓	✓	✓	✓	✓	N/A	✗	✗	✗	N/A	✓	6/9 (67%)
Descamps (2001)	✗	✗	✓	✗	✓	✗	✓	✓	✗	N/A	✓	5/10 (50%)
Durrington (1982)	✗	✗	✓	✗	✓	✗	✓	✓	✗	✓	✓	6/11 (55%)
Gaida (2009)	✓	✗	✓	✗	✓	✓	✓	✗	✓	N/A	✓	7/10 (70%)
Gattereau (1973)	✓	✗	✓	✗	✓	✗	✓	✓	✗	N/A	✓	6/10 (60%)
Junyent (2005)	✓	✓	✓	✗	✓	✓	✓	✓	✗	N/A	✓	8/10 (80%)
Klemp (1993)	✓	✓	✓	✗	✓	✗	✓	✓	✗	N/A	✓	7/10 (70%)
Kwak (2013)	✓	✗	✓	✓	✗	✗	✓	✓	✗	✓	✗	6/11 (55%)

Longo (2010)	✓	✗	✓	✓	✓	✓	✓	✓	✗	N/A	✓	8/10 (80%)
Mabuchi (1977)	✗	✗	✓	✗	✗	✗	✓	✓	✗	✓	✓	5/11 (45%)
Mabuchi (1978)	✓	✓	✓	✗	✗	✓	✓	✓	✗	✗	✓	7/11 (64%)
Ozgurtas (2003)	✗	✗	✗	✗	✗	✗	✓	✗	✗	N/A	✓	2/10 (20%)
Rechardt (2013)	✓	✓	N/A	N/A	N/A	✓	✓	✓	✗	✗	✓	6/8 (75%)
Tsouli (2009)	✓	✗	✓	✗	✓	✓	✓	✓	✗	✓	✓	8/11 (73%)
Yuzawa (1989)	✗	✗	✓	✗	✗	✓	✓	✓	✗	✓	✓	6/11 (55%)

✓ = yes, ✗ = no, N/A = not applicable

Supplemental Appendix E: Results Tables

Table 4
Participants

Author (Year)		Population	Setting	Number recruited	Age (years)	Gender (male/female)	BMI† (kg/m^2)
Abate (2014)	Case	Rotator cuff full-thickness tears (pre- and post- menopausal women)	Echography unit of department for lower limb disease	27	Mean = 50.9 SD = 4.1	0/27	Mean = 27.5 SD = 3.1
	Control	No rotator cuff full-thickness tears (pre- and post- menopausal women)	Echography unit of department for lower limb disease	205	Mean = 49.7 SD = 4.0	0/205	Mean = 23.7 SD = 3.0
Abboud (2010)	Case	Full-thickness rotator cuff tears	Outpatient tertiary care clinic	80 (6 excluded)	Mean = 66.1 Range = 21-93	44/30	Mean = 30.3
	Control	Shoulder complaint, normal rotator cuff	Outpatient tertiary care clinic	80 (7 excluded)	Mean = 67.2 Range = 21-93	39/34	Mean = 28.7
Beri	Case	Patients billed with a	University-based	93	Mean = 49.04	64/29	

(2009)		discharge diagnosis of tendon rupture	multispecialty group practice in East Lansing, MI.		SD = 17.2		-
	Control	Randomly selected patients who did not have tendon rupture	University-based multispecialty group practice in East Lansing, MI.	279	Mean = 49.04 SD = 17.2	192/87	-
Descamps (2001)	Case	Genetically ascertained FH individuals	Not stated	127	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Individuals with a negative genetic test for ApoB3500 and LDL-R mutations	Not stated	160	Men: Mean = 50 SD = 11 Women: Mean = 51 SD = 13	88/72	Men: Mean = 28.7 SD = 3.4 Women: Mean = 28.3 SD = 4.8
Durrington (1982)	Case	Patients with primary hypercholesterolaemia	Patients attending either a Lipid Clinic or a Metabolic Clinic	32	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Normolipidaemic volunteers	Volunteers	11	Mean = 44 SD = 4	4/7	Mean = 28.7 SD = 4
Gaida (2009)	Case	Diagnosed with mid-portion Achilles tendinopathy	Sports Medicine Unit, Umeå University, Sweden	60	Mean = 48 SD = 9.4	32/28	Mean = 25.4 SD = 2.8

	Control	No history of tendon injury	Member of the general community	60	Mean = 47 SD = 9.7	32/28	Mean = 25.4 SD = 2.7
Gattereau (1973)	Case	Classified as having type II hypercholesterolemia	Clinic of Nutrition, Metabolism and Atherosclerosis of the Clinical Research Institute of Montreal	32	Mean = 34.6 SD/R = -	13/19	Mean = 22.02 SD/R = -
	Control	Classified as normolipemic	Clinic of Nutrition, Metabolism and Atherosclerosis of the Clinical Research Institute of Montreal	32	Mean = 34.05 SD/R = -	18/14	Mean = 23.97 SD/R = -
Junyent (2005)	Case	Adults with a diagnosis of primary hypercholesterolaemia	Attending the Lipid Clinic of Hospital Clinic, Barcelona.	81	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Normolipidaemic participants	Recruited from hospital personnel and lists of primary health physicians.	88	Mean = 48 Range = 26-81	37/51	Mean = 25.8 SD = 4.2
Klemp (1993)	Case	Patients with hyperlipidaemia	The lipid clinic at Tygerberg Hospital	88	Mean = 48 Range= 19-69	42/46	-
	Control	Volunteers with normal lipid profiles	Volunteers	88	-	-	-

Kwak (2013)	Case	Patients with dyslipidaemia	Cardiovascular Center of National Health Insurance Service (NHIS) Ilsan hospital	19	Mean = 60.0 SD = 12.5	6/13	Mean = 25.2 SD = 1.9
	Control	Normolipidaemic controls	Cardiovascular Center of National Health Insurance Service (NHIS) Ilsan hospital	96	Mean = 62.3 SD = 8.5	62/34	Mean = 24.2 SD = 2.6
Longo (2010)	Case	Patients who underwent arthroscopic repair of rotator cuff tear	University teaching hospital	120	Mean = 64.86 Range = 40-83	45/75	Mean = 27.62 SD/R = -
	Control	Patients who underwent arthroscopic meniscectomy	University teaching hospital	120	Mean = 63.91 Range = 38-78	45/75	Mean = 27.32 SD/R = -
Mabuchi (1977)	Case	Familial hypercholesterolaemic patients	Not stated	18	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Normal participants	Not stated	36	Not stated	Not stated	Not stated
Mabuchi (1978)	Case	Familial hypercholesterolaemic patients	Not stated	112	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Normal participants with no disease associated with lipid	Not stated	36	Mean = 56 SD = 12	Not stated	Not stated

		metabolism					
Ozgurtas (2003)	Case	Patients with Achilles tendon rupture	Department of Orthopedics and Traumatology of Gu¨lhane Military Medical Academy	47	Mean = 25.7 SD/R = -	41/6	-
	Control	Individuals without Achilles tendon rupture	-	26	Mean = 32.6 SD/R = -	20/6	-
Rechardt (2013)	Case	Patients seeking medical advice for incipient upper extremity pain	Three occupational healthcare units in Helsinki	163	Mean = 45 SD = 9.8	23/140	Mean = 25.5 SD = 4.3
	Control		*Cross-sectional study – no control group*				
Tsouli (2009)	Case	Unrelated patients with herterozygous familial hypercholesterolaemia	Not stated	80	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Normolipidemic, sex- and age-matched, apparently healthy volunteers with no history of hypercholesterolemia	Not stated	80	Mean = 43.0 SD = 9.7	30/50	Mean = 25.1 SD = 6.5
Yuzawa (1989)	Case	Japanese patients with heterozygous familial	Not stated	15	FH (excluded)	FH (excluded)	FH (excluded)

		hypercholesterolaemia					
	Control	Normocholesterolaemic participants	University staff	34	Mean = 45 SD = 11	17/17	Not stated

† BMI = Body Mass Index

Table 5
Lipid Assessment

Author (Year)		Fasting (Yes/No)	Total cholesterol Mean (SD or Range) mmol/L	HDL† Mean (SD or Range) mmol/L	LDL† Mean (SD or Range) mmol/L	Triglycerides Mean (SD or Range) mmol/L	Statin use
Abate (2014)	Case	Yes	5.15 (0.62)	1.23 (0.15)	-	1.50 (0.59)	Not stated
	Control	Yes	4.88 (0.67)	1.44 (0.22)	-	1.27 (0.45)	Not stated
Abboud (2010)	Case	-	6.13 (1.63)	0.91 (0.52)	4.09 (1.03)	2.11 (0.61)	-
	Control	-	5.02 (1.22)	1.29 (0.57)	2.87 (0.85)	1.49 (0.54)	No
Beri (2009)	Case	-	-	-	-	-	24.7 %
	Control	-	-	-	-	-	24.7 %
Descamps (2001)	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Not stated	Men = 7.16 (1.66) Women = 7.32 (1.37)	Men = 1.24 (0.36) Women = 1.40 (0.47)	Men = 4.78 (1.60) Women = 5.07 (1.34)	Men = 3.06 (2.36) Women = 2.26 (2.01)	Not stated
Durrington (1982)	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Not stated	5.2 (0.30)	-	-	-	Not stated
Gaida (2009)	Case	Yes	5.47 (1.02)	1.44 (0.39)	3.37 (0.86)	1.22 (0.77)	6 %
	Control	Yes	5.16 (1.00)	1.58 (0.48)	3.14 (0.93)	0.96 (0.47)	No
Gattereau (1973)	Case	-	Men = 7.9 (1.06) Women = 9.69 (1.72)	-	-	Men = 1.3 (0.30) Women = 1.14 (0.21)	-
	Control	-	Men = 4.42 (0.40)	-	-	Men = 0.96 (0.21)	-

			Women = 4.46 (0.51)			Women = 0.77 (0.22)	
Junyent (2005)	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Yes	5.07 (0.65)	1.42 (0.39)	3.34 (0.54)	1.02 (0.77-1.35)	Not stated
Klemp (1993)	Case	-	9.00 (6.76-6.90)	-	-	4.64 (2.50-1.03)	-
	Control	-	7.96 (6.54-8.94)	-	-	3.53 (2.18-4.63)	-
Kwak (2013)	Case	Not stated	4.03 (1.44)	1.11 (0.52)	2.00 (0.96)	1.69 (0.99)	Yes in 78.9%
	Control	Not stated	3.92 (1.04)	1.09 (0.27)	2.12 (0.79)	1.33 (0.81)	Yes in 20.8%
Longo (2010)	Case	Yes	5.66 (1.1)	-	-	1.65 (1.01)	No
	Control	Yes	5.58 (0.98)	-	-	1.47 (0.73)	No
Mabuchi (1977)	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Not stated	5.28 (0.13)	-	-	1.21 (0.05)	Not stated
Mabuchi (1978)	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Not stated	4.84 (0.78)	-	-	1.15 (0.46)	Not stated
Ozgurtas (2003)	Case	No	5.69 (0.75)	1.06 (0.12)	3.91 (0.80)	1.53 (0.61)	Not stated
	Control	Yes	4.09 (0.75)	1.13 (0.18)	2.35 (0.59)	1.22 (0.47)	Not stated
Rechardt (2013)	Case	Yes	5.1 (0.9)	1.7 (0.5)	2.9 (0.8)	1.1 (0.6)	Yes in 6%
	Control			*Cross-sectional study – no control group*			
Tsouli	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)

(2009)	Control	Yes	5.22 (0.83)	1.32 (0.23)	3.52 (0.67)	0.90 (0.50)	No
Yuzawa (1989)	Case	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)	FH (excluded)
	Control	Not stated	4.55 (0.78)	1.32 (0.28)	-	1.29 (0.61)	Not stated

† HDL = High-density lipoprotein, LDL = Low-density lipoprotein

Table 6
Results

Author (Year)	Relationship investigated	Effect size (95% CI)	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)	Other
Abate (2014)	Rotator cuff tears and lipid levels	-	-	-	Predictor coefficient (of RC tears): HDL = -0.228 (p =0.001)
Abboud (2010)	Rotator cuff tear and lipid levels	TC† = 1.11 (0.64 to 1.58) HDL† = -0.38 (-0.56 to -0.20) LDL† = 1.22 (0.91 to 1.53) TG† = 0.62 (0.43 to 0.81)	-	-	-
Beri (2009)	Statins and tendon rupture	-	All = 1.00 (0.54 to 1.84), p = 1.0 Men = 0.62 (0.30 to 1.30), p = 0.20 Women = 3.09 (1.04 to 9.75), p = 0.04	All = 1.1 (0.57 to 2.13), p = 0.76 Men = 0.66 (0.29 to 1.51), p = 0.32 Women = 3.76 (1.11 to 12.75), p = 0.03	-
Descamps (2001)	No relevant analyses were conducted	-	-	-	-
Durrington (1982)	No relevant analyses were conducted	-	-	-	-
Gaida (2009)	Achilles tendinopathy and lipid levels	TC = 0.31 (-0.06 to 0.66) HDL = -0.32 (-0.68 to 0.04) LDL = 0.26 (-0.1 to 0.61)	-	-	-

		TG = 0.41 (0.4 to 0.77)			
Gattereau (1973)	Non-familial hyperlipidemia and tendon thickness	Men = 0.95 (0.19 to 1.71) Women = 0.86 (0.13 to 1.58)	-	-	-
Junyent (2005)	No relevant analyses were conducted	-	-	-	-
Klemp (1993)	Musculoskeletal manifestations and Mixed hyperlipidemia	-	-	-	-
Kwak (2013)	ATT and lipid levels	-	-	-	Pearson's correlation (r) for: ATT and TC = -0.09 ATT and HDL = -0.06 ATT and LDL = -0.03 ATT and TG = -0.04 *all results not sig (p>0.05)
Longo (2010)	RC tears and lipid levels	TC = 0.08 (-0.18 to 0.33) TG = 0.20 (-0.05 to 0.46)	-	-	-
Mabuchi (1977)	ATT and serum cholesterol	-	-	-	r = 0.454, p<0.01

Mabuchi (1978)	No relevant analyses were conducted	-	-		-	-
Ozgurtas (2003)	Achilles tendon rupture and lipid levels	TC = 2.13 (1.52 to 2.7) HDL = -0.49 (-0.97 to 0) LDL = 2.13 (1.42 to 2.69) TG = 0.55 (0.06 to 1.03)	-		-	-
Rechardt (2013)	Pain intensity and lipid levels	-	-	OR CI TC > 5.3: 1.8 0.8-4.0 HDL < 1.48: 2.7 1.2-6.3 LDL > 3.3: 1.7 0.7-4.2 TG > 1.08: 2.8 1.2-6.6 Statin 0.9 0.2-4.3		-
Tsouli (2009)	No relevant analyses were conducted	-	-		-	-
Yuzawa (1989)	No relevant analyses were conducted	-	-		-	-

†TC = total cholesterol, HDL = high-density lipoprotein, LDL = low-density lipoprotein, TG = triglycerides

Supplemental Appendix F: Pooled mean and SD calculation

The excel formula for calculating pooled mean is

=(D3*B3+D4*B4)/(D3+D4)

Where B3 and D3 are the mean and sample size of one study, and B4 and D4 are the mean and sample size of another study

The excel formula for calculating pooled standard deviation (SD) is

=SQRT((((D3-1)*C3^2)+((D4-1)*C4^2)+((D3*D4)/(D3+D4))*(B3-B4)^2)/(D3+D4-1))

Where B3, C3 and D3 are the mean, SD and sample size of one study and B4,C4, D4 are the mean, SD and sample size of another study

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