Dyslipidemia Is Associated With Increased Risk of Achilles Tendon Disorders in Underweight Individuals to a Greater Extent Than Obese Individuals

A Nationwide, Population-Based, Longitudinal Cohort Study

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Background: The association between dyslipidemia and Achilles tendinopathy (AT) or Achilles tendon rupture (ATR) remains controversial, although some studies have examined this topic.

Purpose: To evaluate the correlation of dyslipidemia and the risk of AT or ATR, and its association with body mass index (BMI), by assessing data from a nationwide population-based cohort.

Study Design: Cohort study; Level of evidence, 3.

Methods: We used the National Health Insurance database, which includes the entire population of the Republic of Korea, to evaluate participants in the National Health Screening Program between January 2009 and December 2010. Participants diagnosed with AT or ATR before December 31, 2017, were selected. The variables assessed were age, sex, frequency of high-intensity exercise per week, BMI, waist circumference, systolic blood pressure, and levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose. Multivariate Cox proportional hazards regression was used for data analysis.

Results: A total of 16,830,532 participants were included. Of these, 125,814 and 31,424 participants developed AT and ATR, respectively. A higher level of LDL-C was associated with an increased risk of AT (adjusted hazard ratio [HR], 1.16) and ATR (adjusted HR, 1.18). A slightly increased risk of AT was observed in participants with higher TG levels (adjusted HR, 1.03), whereas higher HDL-C level was associated with a slight risk reduction for AT (adjusted HR, 0.95). However, no significant association was observed between higher TG or HDL-C levels and ATR. In the underweight group (BMI $<$18.5 kg/m^2), a higher LDL-C level was associated with an increased risk of AT and ATR by 37% and 116%, respectively, compared with lower LDL-C. Higher LDL-C level was associated with an increased risk of AT and ATR by 10% and 16%, respectively, in the obese group (BMI $\geq$25 kg/m^2).

Conclusion: Dyslipidemia was related to the development of AT and ATR. The association of higher LDL-C levels with AT and ATR risk was more pronounced in underweight than in overweight and obese individuals.

Keywords: Achilles tendinopathy; Achilles tendon rupture; obesity; dyslipidemia; hypercholesterolemia; cohort; Republic of Korea

Achilles tendinopathy (AT), previously known as Achilles tendinitis, is a painful condition that is associated with neovascularization and an increase in the number of tenocytes and eventually results in signs of degeneration.[6] Achilles tendon rupture (ATR) results from a sudden dorsiflexion of the ankle with or without long-standing AT. Approximately 10% of ATR is known to be related to preexisting AT.[18]

Increasing evidence suggests that obesity is a risk factor for the development of AT and ATR.[1,12,19] In obese patients, the increased body weight may induce an increased absolute tendon load, resulting in low-grade inflammation with an elevated cytokine level and an increase in the number of tenocytes.[1,9] However, it is unlikely that chronically increased tendon tensioning fully explains the occurrence of Achilles tendon disorders,[14,23] because approximately

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30% of the individuals with a sedentary lifestyle present with AT.[5] An alternative mechanism linking obesity and AT or ATR may be found by examining systemic factors, such as dyslipidemia, hypertension, or glucose intolerance.[13] During the past decade, dyslipidemia has gained increasing attention as a risk factor for tendon abnormality.[27] A recent systematic review[32] involving 16 studies suggested a positive association between dyslipidemia and rotator cuff disease, whereas a contrary result on medial and lateral epicondylitis was reported in a population-based study by Shiri et al.[24] However, to date, the role of dyslipidemia with respect to Achilles tendon disorders has not been fully elucidated. To accurately determine the risk posed by dyslipidemia, it is necessary to adequately adjust for other confounding systemic factors. Most of the previous studies aimed at determining the impact of dyslipidemia on the risk of AT[2,3,13,17,29] or ATR[17,21,22,28,33] either had small cohorts or were case-control studies. Moreover, an association between body mass index (BMI) and dyslipidemia was not ascertained.

Hence, we designed a study using data from the National Health Insurance (NHI) database that included the entire adult population (≥20 years old) of the Republic of Korea. The purpose of this study was to determine the association of dyslipidemia with the risk of AT or ATR. We hypothesized that dyslipidemia could influence the development of AT or ATR and that the association between dyslipidemia and Achilles tendon disorders would vary according to the BMI of the individuals.

METHODS

Data Source

This nationwide, population-based cohort study was conducted in the Republic of Korea, using its NHI claims database. The NHI system of the Republic of Korea covers >97% of the entire population (≥50 million) and includes all forms of medical services performed in the country. The NHI database contains the sociodemographic information of the beneficiaries, diagnosis based on *International Classification of Diseases–Tenth Revision* codes, all inpatient and outpatient claims data, primary and secondary diagnosis codes and treatment, and National Health Screening Program (NHSP) data. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by our ethics review committee.

National Health Screening Program

The Republic of Korea NHSP is a population-based health screening program. All insured individuals are eligible to participate in the program, which recommends that all participants undergo a standardized medical examination every 1 or 2 years. The NHSP data include participants' medical interview, physical examination, body measurements (height, weight, and waist circumference), chest radiography, blood pressure, regular blood and urine test results, and responses to questionnaires on lifestyle or medical histories, including smoking (pack-years) and alcohol consumption per week. The questionnaire also includes a question about the frequency of high-intensity exercise per week (ie, "How many times a week do you do exercise that leads to heavy breathing?"). Blood samples for the measurements of blood glucose and lipid levels were collected after overnight fasting (at least 8 hours).

Database Information

The database for our study, which was established by linking the NHSP data to the NHI claims database, contained the participants' age, sex, diagnosis based on *International Classification of Diseases–Tenth Revision* codes, date of diagnosis, date of NHSP participation, height, weight, waist circumference, systolic blood pressure, and levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and fasting blood glucose. Information from the questionnaire regarding the frequency of high-intensity exercise per week was also included.

Study Population Identification and the Definition of Study Outcome

From the database, we selected participants who underwent the standardized medical examination provided by the NHSP between January 1, 2009, and December 31, 2010 (17,350,675 individuals). Based on the algorithm provided in Appendix Table A1, the primary outcome of this study was to identify participants with ≥3 outpatient clinic visits for newly diagnosed AT (*International Classification of Diseases–Tenth Revision* code M76.6) or ATR (*International Classification of Diseases–Tenth Revision* code S86.0).

All individuals in the study population were assessed from the date of the first NHSP medical examination until a newly diagnosed AT or ATR, or death, up to December 31,

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The authors have declared that there are no conflicts of interest in the authorship and publication of this contribution. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.
Ethical approval for this study was obtained from Inje University Ilsan Paik Hospital (IRB No. 2019-05-021).

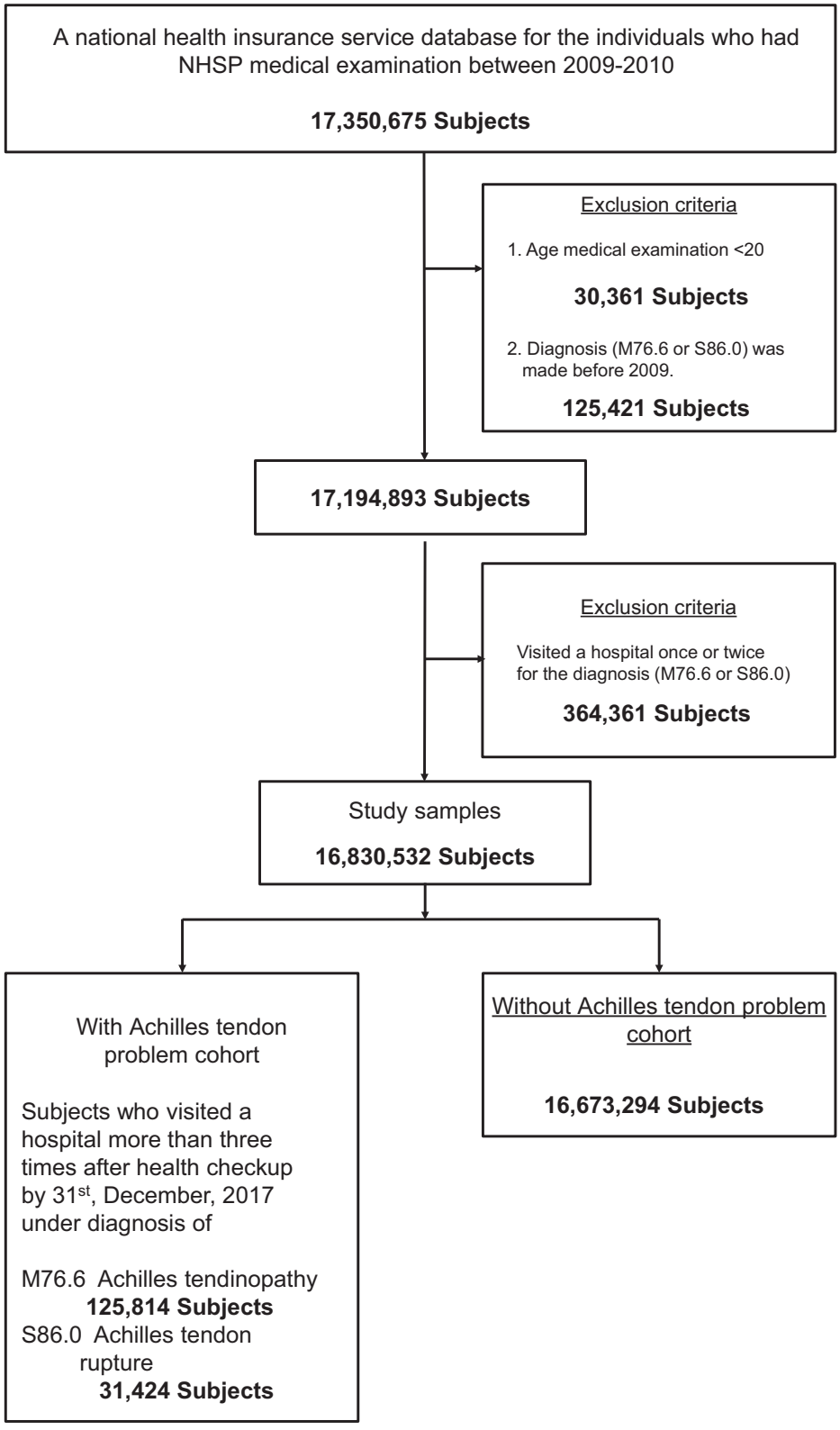

Figure 1. Flowchart of study cohort selection. AT, Achilles tendinopathy; ATR, Achilles tendon rupture; NHSP, National Health Screening Program.

2017. Individuals diagnosed as having AT and ATR were assigned according to their initial diagnosis. The exclusion criteria were (1) individuals aged <20 years at the time of the medical examination, (2) individuals diagnosed with AT or ATR before the medical examination, and (3) patients who visited the outpatient clinic once or twice for the diagnosis of AT or ATR.

Verification of the Diagnosis

To validate the diagnostic accuracy, we developed several algorithms based on the number of health care visits of patients with AT or ATR. From the selected hospital, we reviewed the outpatient medical records from each of the 200 randomly selected individuals with AT or ATR codes who visited the orthopaedic surgery outpatient clinic at least once between January 2009 and January 2019. AT diagnosis was defined clinically as pain on the Achilles tendon insertion site at calcaneus or midsubstance during ambulation, whereas ATR was defined clinically as loss of active ankle plantar flexion, skin dimpling, and a positive Thompson squeezing test. Two experienced orthopaedic surgeons (J.Y.C. and J.S.S.) independently reviewed the medical records to confirm the diagnosis. We also retrieved data for 200 individuals who did not have a diagnosis of Achilles tendon pathology (*International Classification of Diseases–Tenth Revision* code M72.2 [plantar fasciitis]) to identify any potential misclassification bias. The sensitivity, specificity, and positive and negative predictive values of each algorithm were calculated according to the number of outpatient clinic visits per year (Appendix Table A1). The sensitivity and specificity for AT were 90.6% and 90.8%, respectively, and those for ATR were 90.7% and 94.9%, respectively, based on the selected algorithm, which reflected ≥3 visits for AT or ATR.

Categorization of Variables

Our categorization of variables included age (20-39, 40-59, 60-79, and ≥80 years), sex, and frequency of high-intensity exercise (none, infrequent [once or twice per week], and frequent [≥3 times per week]). Because people with BMI >30 (where BMI was measured as weight in kilograms divided by height in meter squared) are uncommon in the Republic of Korea, the selected individuals were grouped according to BMI as follows[30]: underweight (<18.5), normal weight (18.5 to <23), overweight (23 to <25), and obese (≥25). For waist circumference, the participants were divided into thirds according to their representation within the entire population: lower third, middle third, and upper third.

Regarding lipid profile, LDL-C levels (<130, 130-159, and ≥160 mg/dL), TG levels (<150, 150-199, and ≥200 mg/dL), and HDL-C levels (<35, 35-54, and ≥55 mg/dL for women; <45, 45-64, and ≥65 mg/dL for men) were categorized. Fasting blood glucose levels (<100, 100-125, and ≥126 mg/dL) and systolic blood pressure (<120, 120-129, 130-139, and ≥140 mm Hg) were also categorized as covariables.

TABLE 1
Baseline Characteristics of the Study Population (N = 16,830,532)[a]

Parameter	n (%)
Age group, y	
20-39	4,726,275 (28.08)
40-59	8,113,861 (48.21)
60-79	3,779,653 (22.46)
≥80	210,743 (1.25)
Sex	
Female	8,153,227 (48.44)
Male	8,677,305 (51.56)
Frequency of high-intensity exercise	
None	10,408,597 (61.84)
Infrequent (≤2 times/wk)	3,760,704 (22.34)
Frequent (≥3 times/wk)	2,495,031 (14.82)
Body mass index, kg/m^2	
Underweight (<18.5)	632,214 (3.76)
Normal (18-22.9)	6,580,463 (39.10)
Overweight (23-24.9)	4,126,563 (24.52)
Obese (≥25)	5,484,927 (32.59)
Waist circumference	
Lower third	5,922,388 (35.19)
Middle third	6,380,330 (37.91)
Upper third	4,520,597 (26.86)
LDL cholesterol, mg/dL	
<130	11,774,208 (69.96)
130-159	3,437,893 (20.43)
≥160	1,553,137 (9.23)
Triglycerides, mg/dL	
<150	11,908,448 (70.76)
150-199	2,305,337 (13.70)
≥200	2,616,272 (15.54)
HDL cholesterol, mg/dL	
<35 (F), <45 (M)	2,046,311 (12.16)
35-54 (F), 45-64 (M)	11,761,522 (69.88)
≥55 (F), ≥65 (M)	3,021,200 (17.95)
Fasting blood glucose, mg/dL	
<100	11,616,853 (69.02)
100-125	4,133,861 (24.56)
≥126	1,079,677 (6.41)
Systolic blood pressure, mm Hg	
<120	6,762,637 (40.18)
120-129	4,164,222 (24.74)
130-139	3,842,396 (22.83)
≥140	2,058,340 (12.23)

[a]F, female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M, male.

Statistical Analysis

The baseline characteristics of the study population were evaluated. To examine the association of the variables with risk of AT or ATR, multivariate Cox proportional hazards regression was used, and hazard ratios (HRs) with 95% CIs were calculated. The independent variables were age, sex, BMI, waist circumference, systolic blood pressure, and levels of LDL-C, TG, HDL-C, and fasting blood glucose; the dependent variables were the development of AT and ATR. The proportional hazards assumptions were verified using Schoenfeld residuals.

TABLE 2
Incidence Rates per 10,000 Person-Years According to LDL-C, Triglyceride, and HDL-C Levels[a]

	No. of Events/Total PYs		IR per 10,000 PYs (95% CI)	
	AT	ATR	AT	ATR
LDL-C, mg/dL				
<130	82,999/91,780,963	20,988/91,525,266	9.04 (8.82-9.26)	2.29 (1.88-2.70)
130-159	28,435/26,825,199	7165/26,739,397	10.60 (10.51-10.69)	2.68 (2.59-2.77)
≥160	13,859/12,085,064	3121/12,042,548	11.47 (11.34-11.60)	2.79 (2.63-2.85)
Triglycerides, mg/dL				
<150	87,295/92,820,606	20,413/92,547,407	9.04 (8.91-9.17)	2.21 (1.80-2.62)
150-199	16,177/17,955,500	3938/17,902,583	9.01 (8.11-9.91)	2.20 (2.11-2.29)
≥200	18,650/20,382,622	4532/20,324,421	9.15 (8.46-9.84)	2.23 (2.10-2.36)
HDL-C, mg/dL				
<35 (F), <45 (M)	16,654/15,872,584	3009/15,817,219	10.49 (10.18-10.80)	1.90 (1.58-2.22)
35-54 (F), 45-64 (M)	99,664/91,772,149	18,023/91,488,303	10.86 (10.77-10.95)	1.97 (1.89-2.05)
≥55 (F), ≥65 (M)	23,341/23,506,223	4551/23,460,156	9.93 (9.82-10.05)	1.94 (1.88-2.00)

[a]AT, Achilles tendinopathy; ATR, Achilles tendon rupture; CI, confidence interval; F, female; HDL-C, high-density lipoprotein cholesterol; IR, incidence rate; LDL-C, low-density lipoprotein cholesterol; M, male; PY, person-year.

TABLE 3
Adjusted Hazard Ratios According to LDL-C, Triglyceride, and HDL-C Levels[a]

	Adjusted HR (95% CI)	
	AT	ATR
LDL-C, mg/dL		
<130	Reference	Reference
130-159	1.10 (1.08-1.11)	1.15 (1.12-1.18)
≥160	1.16 (1.14-1.18)	1.18 (1.13-1.22)
Triglycerides, mg/dL		
<150	Reference	Reference
150-199	1.00 (0.98-1.01)	1.00 (0.96-1.03)
≥200	1.03 (1.01-1.05)	1.01 (0.98-1.04)
HDL-C, mg/dL		
<35 (F), <45 (M)	Reference	Reference
35-54 (F), 45-64 (M)	1.00 (0.99-1.02)	0.99 (0.95-1.03)
≥55 (F), ≥65 (M)	0.95 (0.93-0.97)	0.99 (0.94-1.04)

[a]AT, Achilles tendinopathy; ATR, Achilles tendon rupture; F, female; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; M, male.

We then calculated the incidence rate (IR) of AT and ATR overall and according to the LDL-C, TG, and HDL-C groups. The IR was defined as the number of new AT or ATR cases per 10,000 person-years. The person-year was calculated for each participant from the date of the NHSP medical examination to the respective date of diagnosis. Furthermore, we calculated the multivariable adjusted HR of LDL-C for each BMI group to determine whether the effect of higher LDL-C varied according to BMI.

All statistical tests were 2-sided, and P values $<.05$ were considered statistically significant. STATA 15.0 (StataCorp) was used for all statistical analyses.

RESULTS

Characteristics of the Study Population and Overall IRs

After application of exclusion criteria, the study population included 16,830,532 individuals (Figure 1).

Baseline characteristics of the entire study population are shown in Table 1. Approximately 70% of the participants had normal LDL-C, TG, and HDL-C levels. Among the study population, 125,814 and 31,424 participants developed AT and ATR, with corresponding IRs of 9.59 and 2.40 per 10,000 person-years, respectively.

Association Between Dyslipidemia and the Risk of Achilles Tendon Disorders

Table 2 shows the IR of AT and ATR according to the LDL-C, TG, and HDL-C categories. For AT and ATR, the IR increased as the level of LDL-C increased, whereas the IRs of the TG categories were similar for AT (range, 9.01-9.15) and ATR (range, 2.20-2.23). Regarding HDL-C, decreased IR (9.93) of higher HDL-C was shown for AT, whereas similar IRs were demonstrated among categories for ATR (range, 1.90-1.97).

Multivariate Cox regression analysis revealed that higher LDL-C levels (≥160 mg/dL) were associated with the increased risk of AT (adjusted HR, 1.16; 95% CI, 1.14-1.18) and ATR (adjusted HR, 1.18; 95% CI, 1.13-1.22) (Table 3). Higher TG levels (≥200 mg/dL) were associated with a slightly increased risk for AT (adjusted HR, 1.03; 95% CI, 1.01-1.05) but not for ATR. Higher HDL-C levels (≥55 mg/dL for women and ≥65 mg/dL for men) were associated with a slight risk reduction for AT (adjusted HR, 0.95; 95% CI, 0.93-0.97). However, no significant association was observed between higher HDL-C levels and ATR.

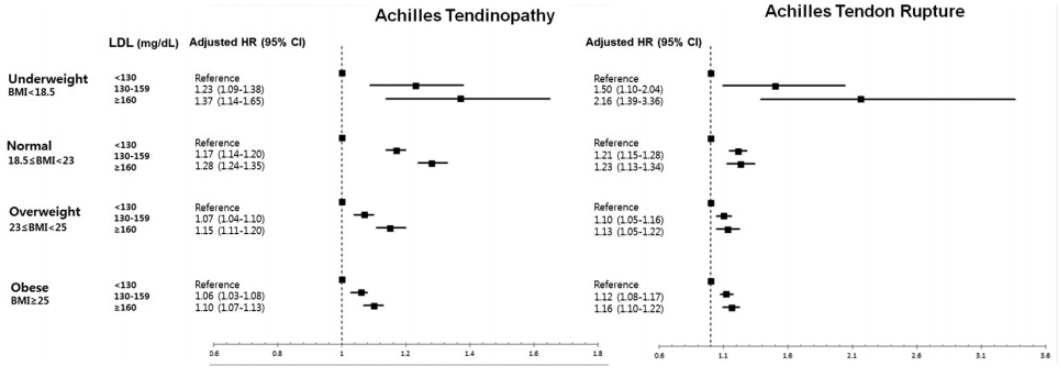

Figure 2. Forest plot showing the association between body mass index (BMI) and low-density lipoprotein (LDL) cholesterol levels with the development of Achilles tendinopathy and tendon rupture. HR, hazard ratio.

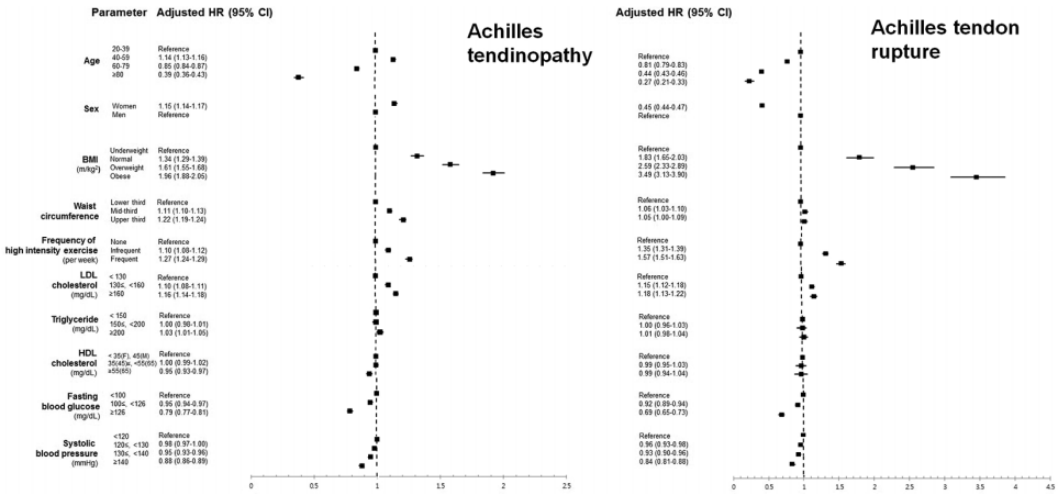

Figure 3. Forest plot demonstrating adjusted HRs for all included variables with regard to Achilles tendinopathy and tendon rupture. BMI, body mass index; HDL, high-density lipoprotein; HR, hazard ratio; LDL, low-density lipoprotein.

Association Between Higher LDL-C Levels and Achilles Tendon Disorders According to BMI

A multivariate Cox regression to evaluate the association between higher LDL-C levels and Achilles tendon disorders according to BMI (Figure 2) revealed that the association of higher LDL-C levels with AT and ATR risk was more pronounced as BMI decreased, with a greater magnitude for ATR. In the underweight group (BMI <18.5 kg/m^2), the adjusted HRs of higher LDL-C compared with lower LDL-C were 1.37 and 2.16 for AT and ATR, respectively, whereas they were 1.10 and 1.16 for AT and ATR in the obese group (BMI ≥ 25 kg/m^2).

Association Between Achilles Tendon Disorders and Other Variables

Figure 3 shows the results of multivariate Cox proportional hazards regression for all variables. Among the variables, a higher BMI showed the greatest adjusted HRs for AT (1.96; 95% CI, 1.88-2.05) and ATR (3.49; 95% CI, 3.13-3.90). A higher waist circumference was associated with increased risk of AT (adjusted HR, 1.22; 95% CI, 1.19-1.24), whereas for ATR, a higher waist circumference did not produce a significant increase in risk (adjusted HR, 1.05; 95% CI, 1.00-1.09). Regarding age and sex, the adjusted HR of AT was greatest in women aged 40 to 59 years, whereas ATR was highest in men aged 20 to 39 years. We also noted that the risk elevation of AT and ATR was associated with frequent high-intensity exercise compared with a lack of frequent high-intensity exercise (adjusted HR for AT, 1.27; 95% CI, 1.24-1.29; adjusted HR for AT, 1.57; 95% CI, 1.51-1.63).

Paradoxically, a higher systolic blood pressure ($\geq$140 mm Hg) and a higher fasting blood glucose level ($\geq$126 mg/dL) were associated with reduced risk for AT and ATR.

DISCUSSION

Our data demonstrated that a higher LDL-C level (≥160 mg/dL) was related to elevated risk for AT and ATR. A higher TG level (≥200 mg/dL) was associated with a slight risk increase for AT but not ATR. Likewise, a higher HDL-C level (≥55 mg/dL for women and ≥65 mg/dL for men) was associated with a slight risk reduction only for AT. Interestingly, we confirmed that the association between higher LDL-C levels and AT or ATR risk was greater in the underweight compared with the overweight and obese groups.

Current evidence suggests that obesity is an important risk factor for Achilles tendon disorders.[16,19] Although some studies have been conducted,[‖] the association between dyslipidemia and AT or ATR is still inconclusive. Moreover, studies[3,13,21,22,29,33] vary greatly regarding which lipid profile was related to Achilles tendon disorders, although a positive association between dyslipidemia and AT or ATR has been reported. Gaida et al[13] reported that higher TG levels, lower HDL-C levels, and higher TG-to-HDL-C ratios were associated with midportion AT with insulin resistance. Abate and Salini[3] concluded that individuals with midportion AT exhibited higher total cholesterol, lower HDL-C, and higher TG levels. For ATR, Ozgurtas et al[22] reported higher total cholesterol, LDL-C, and TG and lower HDL-C in patients compared with a healthy control group. Yang et al[33] reported that total cholesterol, TG, and LDL-C were higher in ATR, without any significant relationship with HDL-C. In contrast, studies have reported a negative association between dyslipidemia and AT[2,17] or ATR.[17,28] Previous reports were mostly case-control studies that included a limited number of participants, which prevented proper evaluation of the IR or risk ratios. Our study provides results that are sufficiently powered to confirm the association between dyslipidemia and the risk of AT and ATR through a nationwide population-based cohort study that included a large number of participants without bias toward a specific occupational group or age.

To date, many studies investigating the association between dyslipidemia and AT or ATR have been conducted based on the changes in patients with familial hypercholesterolemia. According to these studies, dyslipidemia can affect tendon disorders by means of cholesterol deposits within tendon tissues. LDL-C that accumulates in the tendon becomes oxidized LDL-C, containing various oxidative materials.[4] These factors can lead to inflammation and tendon structural changes (decrease in collagen fibers, proteoglycans, and type III collagen), ultimately resulting in changes in the mechanical properties.[31] Furthermore, metabolic disorders often increase the production of proinflammatory cytokines and matrix destruction via matrix metalloproteinases, which can impair the tendon healing environment.[26] However, the detrimental effect of nonfamilial hypercholesterolemia and the mechanism by which it affects tendon pathology remain debatable.[4] Therefore, we expect that our findings from this nationwide general population study will be beneficial for future researchers, although we did not separate the results based on the existence of familial hypercholesterolemia.

Our finding that higher LDL-C was more significantly associated with AT and ATR risk elevation as BMI decreased is meaningful to highlight the importance of dyslipidemia control even in individuals within the normal or underweight ranges. Although the exact mechanism cannot be fully elucidated, we suggest that the systemic states of chronic, subclinical, and low-grade inflammation may persist with excessive body fat levels. This is supported by Ito et al,[15] who found that excessive body fat accumulation was related to dyslipidemia even in individuals of normal weight. Excessive body fat is a major endocrine and signaling organ that releases several bioactive peptides and hormones.[1]

The current estimates for the incidence of normal-weight dyslipidemia range from 10% to 37% of the general population.[7] Compared with overweight or obese individuals, normal or underweight individuals may overlook or underestimate the risk of uncontrolled dyslipidemia. It has been established that controlling dyslipidemia prevents cardiovascular complications. Given the results of our study, it should be emphasized that dyslipidemia might be associated with an elevated risk of Achilles tendon disorders to a greater extent in underweight than in obese individuals.

Our study has some limitations. First, in our study, similar to other registry-based studies, the diagnosis of AT or ATR relied on the administrative claims data reported by physicians or hospitals. Second, we cannot rule out the possibility that our data may have included participants with open ATR associated with direct laceration or cutting injury. A direct ATR with an open wound has a vastly different injury mechanism, which is not influenced by any of the risk factors mentioned in our study. In addition, we could not distinguish chronic and neglected ATR from acute traumatic ATR. Third, the present study lacks information on the diagnosis of insertional versus noninsertional AT, diseases that entail slightly different characteristics and treatment. Fourth, we did not stratify our analysis according to subgroups using multivariate Cox regression based on age, sex, or frequency of high-intensity exercise per week to determine whether the association between dyslipidemia and the risk of Achilles tendon disorders varied according to age, sex, or physical activity level.

The use of statins is important when considering the association between dyslipidemia and Achilles tendon disorders. We initially planned to include information regarding statin use, because conflicting results have been reported. Several case reports[8,10,20] have suggested that AT and ATR are potential adverse effects of statins. A laboratory study by de Oliveira et al[10] reported that statins promote an imbalance between the synthesis and degradation of several molecules, particularly type I collagen. However, the largest recent study,[25] involving >500,000 new statin users, concluded that statin use was not associated with an increased risk of ATR. Likewise, a recent cross-sectional study using ultrasound tissue characterization by de Sá et al[11] reported that Achilles tendon structure was not influenced by statin use. We did not separate our

analysis to reflect statin use, and it would have been more informative if we had included such an analysis.

CONCLUSION

LDL-C was significantly associated with the risk of AT and ATR, whereas a higher TG level was slightly associated with an increased risk of AT. Likewise, a higher HDL-C level was associated with a slight risk reduction for AT but not ATR. The association of higher LDL-C levels with AT and ATR risk was more pronounced in underweight than in overweight and obese study participants.

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APPENDIX

APPENDIX TABLE A1
Validation Algorithms of Achilles Tendinopathy and Tendon Rupture[a]

Outpatient Clinic Visits per Year	Sensitivity	Specificity	PPV	NPV
Achilles tendinopathy				
≥1	98.3	81.5	89.0	97.0
≥2	94.5	85.7	90.0	91.1
≥3	90.6	90.8	93.7	86.4
≥4	83.4	93.3	94.9	78.7
≥5	75.7	95.0	95.8	71.9
Achilles tendon rupture				
≥1	95.0	81.6	73.9	96.8
≥2	94.3	84.4	76.7	96.4
≥3	90.7	94.9	90.7	94.9
≥4	80.7	95.7	91.1	90.1
≥5	46.4	98.8	95.6	77.1

[a]Data are expressed as percentages. NPV, negative predictive value; PPV, positive predictive value.