Dyslipidemia in Achilles Tendinopathy Is Characteristic of Insulin Resistance

JAMES EDMUND GAIDA¹, LOTTA ALFREDSON², ZOLTAN STEVEN KISS³, ANDREW MICHAEL WILSON⁴, HÅKAN ALFREDSON⁵, and JILL LEIGH COOK⁶

¹School of Exercise and Nutrition Sciences, Deakin University, Burwood, Victoria, AUSTRALIA; ²Sports Medicine Unit, Department of Surgical and Perioperative Science, University of Umeå, Umeå, SWEDEN; ³Victoria House Medical Imaging, Prahran, Victoria, AUSTRALIA; ⁴Department of Medicine, St Vincent’s Hospital, University of Melbourne, Fitzroy, Victoria, AUSTRALIA; and ⁵Centre for Physical Activity and Nutrition Research, Deakin University, Burwood, Victoria, AUSTRALIA

ABSTRACT

GAIDA, J. E., L. ALFREDSON, Z. S. KISS, A. M. WILSON, H. ALFREDSON, and J. L. COOK. Dyslipidemia in Achilles Tendinopathy Is Characteristic of Insulin Resistance. Med. Sci. Sports Exerc., Vol. 41, No. 6, pp. 1194–1197, 2009. Overuse is considered to be a main causative factor for tendinopathies; however, recent reports indicate that tendinopathy is also common among both overweight and inactive individuals. These factors are associated with abdominal obesity, dyslipidemia, hypertension, and insulin resistance. We hypothesized that these features would be associated with tendinopathy. Purpose: To compare lipid profile between participants with Achilles tendinopathy and matched controls. Methods: Fasting serum lipids were measured among 60 participants with chronic painful midportion Achilles tendinopathy (54% male) and 60 control subjects matched for gender, age (±10 yr), and body mass index (±2 kg m⁻²). Results: The participants with Achilles tendinopathy showed evidence of underlying dyslipidemia. They had higher triglyceride (TG) levels (P = 0.039), lower %HDL-C (P = 0.016), higher TG/HDL-C ratio (P = 0.036), and elevated apolipoprotein B concentration (P = 0.017) in comparison to the well-matched control group. Conclusion: This pattern of dyslipidemia is characteristic of the dyslipidemia displayed by individuals with insulin resistance and is common in the metabolic syndrome. Two additional aspects of tendinopathy research support a connection with the metabolic syndrome. First, tendinopathy has been associated with greater waist circumference, as has the metabolic syndrome. Second, insulin resistance has been associated with fat deposition in muscle (primarily intracellular), whereas fat deposition in tendon has been found among those with tendon pain. If tendinopathy is confirmed to be associated with dyslipidemia and the metabolic syndrome in larger studies, it may be appropriate to redefine our concept of tendinopathy to that of a cardiovascular disease (CVD). In this case, we may be able to draw considerably on CVD research to improve our understanding of tendinopathy, and perhaps treating CVD risk factors will improve the treatment of tendinopathy. Key Words: ACHILLES TENDON, MIDPORTION, SERUM, LIPID

The etiology and the pathogenesis of chronic tendinopathy are not well understood (2). Although overuse is considered a major causative factor for midportion Achilles tendinopathy (15), up to one third of cases occur among completely nonactive individuals (26). Furthermore, midportion Achilles tendinopathy is often seen among overweight individuals (6,7,10) who are often taking medication to treat aspects of the metabolic syndrome (3,10). Even among elite level athletes, a slightly elevated waist circumference (83 cm) dramatically increases the risk of tendon abnormality (18).

Although increased body weight directly affects Achilles tendon loading, it is unlikely that increased tendon loading adequately explains these relationships (8,18,23). Alternate mechanisms linking obesity and tendinopathy may be found by examining systemic factors that become increasingly common in the presence of obesity. These include dyslipidemia, hypertension, glucose intolerance, and insulin resistance (5,25,28). Because lipid deposition is known to occur in tendons (1,11), high cholesterol levels have been observed among individuals with Achilles tendon rupture (19,22), and the esterified fraction of cholesterol is elevated in biopsies from Achilles tendinopathy subjects (29) we chose to focus on serum lipid profiles.

Thus, the aim of this study was to compare fasting lipid profile in subjects with chronic painful midportion Achilles tendinopathy and a group of gender-, age-, and BMI-matched controls with normal tendons.

MATERIAL AND METHODS

Ethics. This project was approved by the human research ethics committee at La Trobe University and was
conducted according to the principles of the Declaration of Helsinki. All participants gave written, informed consent.

**Participants.** Sixty individuals (32 men [53%]) referred to the Sports Medicine Unit, Umeå University, Sweden, for chronic Achilles tendon pain and diagnosed with midportion Achilles tendinopathy were included in this study. The participants were mainly middle-aged (mean ± SD age = 48 ± 9 yr [men = 47 ± 10 yr, women = 49 ± 8 yr]) and tending toward overweight (body mass index [BMI] = 25 ± 3 kg m⁻² [men = 26 ± 3 kg m⁻², women = 25 ± 3 kg m⁻²]). Each participant had the diagnosis established by an experienced orthopedic surgeon (HA), which was confirmed with ultrasound (details below). Participants were excluded if they had an established diagnosis of familial hypercholesterolemia (FH) or insertional Achilles tendinopathy.

Sixty control participants (32 men [53%]) without a history of tendon injury were recruited from the general community. Each control participant was matched to one patient based on gender, age (±10 yr), and BMI (±2 kg m⁻²). Thus, the control participants were of similar age (47 ± 10 yr [men = 45 ± 11 yr, women = 49 ± 8 yr]) and BMI (25 ± 3 kg m⁻² [men = 26 ± 2 kg m⁻², women = 25 ± 3 kg m⁻²]). Twenty-nine controls were recruited in the Umeå region of Sweden whereas 31 were recruited from the Melbourne region of Australia. As with the patient group, a diagnosis of FH was an exclusion criterion.

**Ultrasound.** All participants (cases and controls) had both Achilles tendons investigated with gray-scale and color Doppler ultrasound. All Swedish participants (60 cases, 29 controls) had imaging performed by an experienced orthopedic surgeon (HA) using an Acuson Sequoia 512 (Siemens AG, Munich, Germany). All Australian participants (31 controls) had imaging performed by an experienced musculoskeletal radiologist (ZSK) using an Acuson Aspen Advanced (Siemens AG).

All subjects had the diagnosis of midportion Achilles tendinopathy confirmed by characteristic ultrasonographic changes. These included a widening of the anterior–posterior (AP) diameter of the Achilles midportion, hypoechoic regions, and structural changes such as a loss of definition of the anterior tendon margin. Color Doppler showed neovascularization in the structurally abnormal regions of the Achilles tendon. In contrast, all control subjects had normal Achilles tendon structure and no changes on color Doppler ultrasound.

**Anthropometry.** Height was recorded to the nearest centimeter using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg while wearing light clothing on a digital scale. Body mass index (BMI) was then expressed as weight (kg) divided by the square of height (m).

**Blood collection.** Blood samples were collected between 0700 and 0900 after a 12-h fast. Blood was drawn from the antecubital vein using sterile equipment and aseptic technique into a 3.5 mL serum separating tube. Blood was allowed to clot at room temperature for 30 min before centrifugation. Two participants in the tendinopathy group who were taking statins were asked for a copy of a lipid analysis conducted before commencing medication.

**Lipid profile analysis.** Samples were sent to a chemical pathology laboratory in either Umeå University Hospital or Melbourne for routine analysis. Laboratory staff were blind to study data except patient name, age, and gender. The analysis included measurement of total cholesterol, triglycerides (TG), HDL-C, %HDL-C, LDL-C, LDL-C/HDL-C ratio, TG/HDL-C ratio, lipoprotein (a), apolipoprotein B, apolipoprotein A1, and apolipoprotein B/apolipoprotein A1 ratio. Apolipoprotein A1 was only measured in Swedish subjects (patient group n = 28, control n = 29).

**Statistical analysis.** Differences between the two groups were determined using independent sample t-tests for continuous variables with normal distribution. Variables with skewed distributions (Kolmogorov–Smirnov test, P < 0.05) were tested with the nonparametric Mann–Whitney U test. Analysis was performed using the Statistical Package for the Social Sciences version 11.0.1 (SPSS Inc., Chicago, IL), and significance was set at P < 0.05.

**RESULTS**

Patients and controls were well matched for age, height, weight, and BMI (Table 1). Achilles tendinopathy subjects showed evidence of underlying dyslipidemia (Table 2). They had higher triglyceride (TG) levels [P = 0.039], lower %HDL-C (P = 0.016), and higher TG/HDL-C ratio (P = 0.036) in comparison to the matched control group. Furthermore, Achilles tendinopathy subjects had elevated apolipoprotein B concentration (P = 0.017) in comparison to matched controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol L⁻¹)</td>
<td>5.47 (1.02)</td>
<td>5.16 (1.00)</td>
<td>0.094</td>
</tr>
<tr>
<td>TG (mmol L⁻¹)‡</td>
<td>1.22 (0.77)</td>
<td>0.96 (0.47)</td>
<td>0.039</td>
</tr>
<tr>
<td>HDL-C (mmol L⁻¹)†</td>
<td>1.44 (0.39)</td>
<td>1.58 (0.48)</td>
<td>0.097</td>
</tr>
<tr>
<td>%HDL-C</td>
<td>27.6 (8.5)</td>
<td>31.9 (10.3)</td>
<td>0.016</td>
</tr>
<tr>
<td>LDL-C (mmol L⁻¹)</td>
<td>3.37 (0.98)</td>
<td>3.14 (0.93)</td>
<td>0.166</td>
</tr>
<tr>
<td>LDL-C/HDL-C</td>
<td>2.53 (0.98)</td>
<td>2.18 (0.93)</td>
<td>0.052</td>
</tr>
<tr>
<td>TG/HDL-C†</td>
<td>0.941 (0.746)</td>
<td>0.691 (0.459)</td>
<td>0.036</td>
</tr>
</tbody>
</table>

† Skewed data, Mann–Whitney test used.

### Table 1. Demographic data for subjects with chronic painful midportion Achilles tendinopathy and matched controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.9 (9.4)</td>
<td>46.6 (9.7)</td>
<td>0.437</td>
</tr>
<tr>
<td>Range</td>
<td>27–62</td>
<td>26–62</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.7 (8.6)</td>
<td>172.8 (8.9)</td>
<td>0.605</td>
</tr>
<tr>
<td>Range</td>
<td>158.0–190.0</td>
<td>155.0–192.2</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9 (12.1)</td>
<td>76.0 (10.5)</td>
<td>0.666</td>
</tr>
<tr>
<td>Range</td>
<td>52.0–105.0</td>
<td>57.7–97.1</td>
<td></td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>25.4 (2.8)</td>
<td>25.4 (2.7)</td>
<td>0.984</td>
</tr>
<tr>
<td>Range</td>
<td>19.6–31.2</td>
<td>20.0–31.7</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3. Lipoprotein and apolipoprotein profile for subjects with chronic painful midportion Achilles tendinopathy and matched controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein a (mg L⁻¹)†</td>
<td>266 (229)</td>
<td>299 (397)</td>
<td>0.599</td>
</tr>
<tr>
<td>Apolipoprotein B (mg L⁻¹)</td>
<td>1005 (230)</td>
<td>896 (231)</td>
<td>0.017</td>
</tr>
<tr>
<td>Apolipoprotein A1 (mg L⁻¹)‡</td>
<td>1452 (230)</td>
<td>1489 (330)</td>
<td>0.627</td>
</tr>
<tr>
<td>Apolipoprotein B/A1‡</td>
<td>0.687 (0.171)</td>
<td>0.652 (0.202)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

† Skewed data, Mann–Whitney test used.
‡ Apolipoprotein A1 measured in Swedish subjects only.

to control subjects (Table 3). There were no differences in lipid profile between the Australian and the Swedish control subjects (data not shown).

DISCUSSION

Serum lipid profile appears to be related to Achilles tendinopathy. In comparison to the gender-, age-, and BMI-matched control group, the subjects with chronic painful midportion Achilles tendinopathy were dyslipidemic. They had significant elevations in TG, TG/HDL-C ratio, and apolipoprotein B along with significant reductions in %HDL-C. This combination of abnormalities affecting the lipid profile has striking similarity to the lipid profile described in relation to insulin resistance (20,25,28). Possible metabolic involvement in midportion Achilles tendinopathy is likely as often it affects middle-aged, nonactive, and overweight individuals (6,7,10,26).

Insulin resistance describes a condition where an elevated insulin concentration fails to stimulate increased glucose uptake into muscle. Insulin resistance is extremely common in the community at large, including otherwise healthy individuals. It presents as a spectrum from hyperinsulinemia to fasting hyperglycemia, impaired glucose tolerance, and eventually type II diabetes mellitus (24).

It has been long recognized that subjects who display even mild insulin resistance have an associated dyslipidemic profile (16,20,24,28). These characteristics include an elevation in fasting plasma TG along with reduced HDL-C but normal LDL-C. Recently, the TG/HDL-C ratio has been proposed as a simple, sensitive, and specific marker of insulin resistance (20). This ratio also correlates strongly with LDL particle diameter ($r = -0.77$, $P < 0.0001$) (20).

The development of dyslipidemia in the presence of insulin resistance is driven by differences in insulin sensitivity between different organs and tissues. In spite of muscle and adipose tissue insulin resistance, the liver remains insulin sensitive, and elevated insulin levels signal the liver to increase very low density lipoprotein–triglyceride (VLDL–TG) synthesis and secretion. Later these particles interact with HDL-C, exchanging TG for cholesterol. The sum result is an elevation in TG with an associated fall in HDL-C, with LDL-C remaining relatively unchanged (21,24).

Dyslipidemia, which is characteristic of insulin resistance, among subjects with Achilles tendinopathy has not previously been reported. Several research articles suggest that serum lipids may be involved in Achilles tendinopathy; lipid accumulation has been shown in biopsies from tendinopathy subjects (11,29), and the lipid content of tendon increases and the esterified fraction of cholesterol doubles with increasing age (4). Interestingly, elevations in intramyocellular fat are correlated with insulin resistance (13,14), and the previously mentioned findings regarding intratendinous lipid and cholesterol (4,11,29) may have a similar underlying mechanism.

Clinically based tools are used to diagnose metabolic syndrome (cf. insulin resistance syndrome), and an elevated waist circumference or an elevated waist to hip ratio is one criteria in the metabolic syndrome (5,21,25,28). A connection between insulin resistance syndrome and tendinopathy is supported by previous research, which shows links between either waist to hip ratio (9,27) or waist circumference (18,27) and tendinopathy. Thus, perhaps we should view tendinopathy as a comorbid condition of cardiovascular disease (CVD) similar to recent suggestions for low back pain (12,17). It is possible that other features of insulin resistance may be associated with the pathophysiology of tendinopathy, including altered angiogenesis, impaired healing, and increased systemic inflammation that are all associated with this syndrome (28,30).

This research is limited by the absence of quantitative assessment of insulin resistance and fat partitioning. As such, although the dyslipidemia is characteristic of the insulin resistance syndrome, it is not possible to confirm this hypothesis with the current data. Also, because the data are cross-sectional, the question of cause and effect remains open. We plan to address these issues in future studies in which we will assess insulin resistance, fat partitioning, intramyocellular fat, and intratendinous fat in addition to lipid profile.

In conclusion, subjects with chronic painful midportion Achilles tendinopathy have a lipid profile characteristic of a dyslipidemia that is most commonly seen alongside the insulin resistance syndrome. This is the first time that systemic metabolic variables have been shown to differ between subjects with tendinopathy and well-matched controls. If we can draw upon the substantial body of knowledge regarding the insulin resistance syndrome and also research into improving outcomes for patients with CVD through risk factor reductions, perhaps we can make inroads into understanding the mechanisms underlying tendinopathy.

The authors thank Miss Fellon Robson-Long for assisting in the collection of blood samples. This study was supported by a seedling grant from The Centre for Physical Activity and Nutrition Sciences (C-PAN) at Deakin University.

Financial assistance was received from the Swedish Research Council for Sports.

All authors declare that they have no conflict of interest. A Felice Rosemary-Lloyd scholarship was awarded to J. E. Gaida to enable him to travel to Sweden and conduct this research.
He is also a recipient of the Australian Postgraduate Award (APA) scholarship.

This work was presented at the Sports Medicine Australia Conference in October 2008.

The results of the present study do not constitute endorsement by ACSM.

Disclosure of funding: No funding was obtained from the NIH, the Wellcome Trust, and the HHMI.

REFERENCES


