Short-term acetaminophen consumption enhances the exercise-induced increase in Achilles peritendinous IL-6 in humans

Brian S. Gump,1 David R. McMullan,1 David J. Cauthon,1 Jamie A. Whitt,1 Jonathon D. Del Mundo,1 Tanya Letham,1 Paul J. Kim,2 Gary N. Friedlander,3 Jessica Pingel,4 Henning Langberg,4 and Chad C. Carroll1

1Department of Physiology, Arizona College of Osteopathic Medicine, Midwestern University, Glendale, Arizona; 2Center for Wound Healing, Department of Plastic Surgery, Georgetown University Hospital, Washington, District of Columbia; 3Sole Foot & Ankle Specialists, Glendale, Arizona; and 4CopenRehab, Section of Social Medicine, Department of Public Health, Faculty of Health Sciences, University of Copenhagen, Denmark

Submitted 19 February 2013; accepted in final form 29 May 2013

HIGHLIGHTED TOPIC | Role of Inflammation in Skeletal Muscle, Connective Tissue, and Exertional Injuries: To Block or Not to Block?

TENDONS ARE A KEY COMPONENT of the musculoskeletal system. The elastic properties of tendon dramatically influence force transfer from skeletal muscle to bone and muscle power output (6, 8, 16, 25, 28). Chronic exercise can increase tendon stiffness and cross-sectional area (CSA) (30). These adaptations presumably enhance the tendon’s ability to withstand the greater tensile loads due to the associated increase in muscle strength seen with chronic exercise. An increase in tendon stiffness likely contributes to an increase in rate of torque development and muscle power output (8). Recent studies (11, 12) have, however, demonstrated that the analgesic and anti-inflammatory properties of APAP are likely altered in those consuming APAP. In support of this conclusion, our laboratory has recently shown that APAP consumption results in an overall reduction in tendon collagen cross-linking in rats (12). Additionally, several in vitro and animal studies suggest that analgesic medications likely alter tendon extracellular matrix remodeling (2, 3, 10, 54, 65–67). The mechanism(s) resulting in APAP-induced changes in tendon structure (12) and function (11), however, have yet to be identified.

APAP is one of the most widely used medications in the world and is the first line of treatment for millions of osteoarthritis patients. Exercise is also a mainstay of osteoarthritis therapy (57) and APAP is commonly used to reduce exercise-related pain in individuals of nearly all ages. APAP is also widely used in many children’s medications. APAP is typically assumed to have only weak effects on peripheral tissues in vivo; thus the potent effects demonstrated on tendon connective tissue are surprising, clinically relevant, and would benefit from additional study.

The mechanism of action of APAP is still not fully understood, but recent evidence (17, 24, 27, 44) suggests that APAP is a potent inhibitor of cyclooxygenase-2 (COX-2), a rate-limiting enzyme in the production of prostaglandins. Administration of APAP has been shown to inhibit the production of prostaglandin E2 (PGE2) in human skeletal muscle after acute exercise (61) and in several nonexercise models (17, 27, 47). Additionally, specific inhibition of COX-2 blocks the increase in PGE2 in the Achilles peritendinous tissue in humans after...
acute exercise (33). An induction of PGE₂ and other prosta-
glandins have several functions, including stimulating protein
turnover (13, 55, 61, 63), regulating tendon blood flow (33),
and regulating the activity of matrix degrading enzymes (49, 75).
PGE₂ also appears to modulate the production of cyto-
kines, including interleukin (IL)-6 (20, 41, 50). Interestingly,
administration of COX inhibitors has been shown to increase
the production of IL-6 in various models (20, 22, 57, 71, 72, 75), including exercise (48). IL-6 is also dramatically upregu-
lated in tendon in response to acute exercise (36) or cyclic strain (40, 59) and is a potent stimulator of tendon collagen
synthesis (5). However, the influence of APAP on postexercise
tendon IL-6 production in humans has not been evaluated.

IL-6 is clearly important for maintaining normal tendon
structure and function. For example, tendon CSA is lower and
modulus greater in mice lacking IL-6 (43). Tendon healing is
also impaired in IL-6 knockout mice (42). In contrast, elevated
levels of IL-6 are associated with tendon pathology (39) and
aged tendon (26) and may contribute to ECM remodeling in
these states (14, 29, 32). Using microdialysis, the effect of
acute APAP consumption on Achilles peritendinous IL-6 and
PGE₂ levels in response to acute treadmill exercise was deter-
mined. We hypothesized that, due to APAP inhibition of PGE₂,
exercise-induced IL-6 levels would be greater in individuals
given APAP.

An additional aim of this study was to take advantage of the
microdialysis sampling methodology to perform a novel as-
seessment of APAP levels in the peritendinous space of the
human Achilles tendon in vivo, both at rest and after exercise.
APAP, as well as other analgesics, is often given for tendon
pain, but dosing is typically based on the kinetics of the drug
in plasma. Detailed analysis of APAP pharmacokinetics using
microdialysis in skeletal muscle and adipose tissue have been
presented previously (46). To our knowledge, however, the in
vivo assessment of APAP levels after oral consumption has not
been previously performed in human peritendinous tissue.
Additionally, given the increase in tendon blood flow associ-
ated with exercise (34), delivery of APAP to tendon tissue may
be altered with exercise. A better understanding of the kinetics
of APAP at the level of the tendon could impact how this drug
is used clinically.

**METHODS**

**Subjects.** The study was approved by the Midwestern University
Institutional Review Board, and all of the procedures, risks, and
benefits associated with the study were explained to the subjects
before they gave written consent to participate. Recreationally active
men and women (n = 16) were recruited from the Glendale, AZ area.
Subjects completed a detailed health and exercise history question-
naire and were excluded if they had any condition in which exercise
would be contraindicated, if they were chronically consuming any
prescription or nonprescription COX-inhibiting drugs, and if they
were diabetic or used tobacco products. All subjects were free of
Achilles tendon pain and did not have a history of Achilles tendon
pain or injury.

**Experimental design.** Subjects were randomly assigned to either a
placebo or APAP group (Table 1) in a double-blind manner. After
group assignment, subjects participated in two 6-h microdialysis
experiments, each preceded by a 12-h fast (5, 31, 52). Both experi-
ments were identical, with the exception of exercise. The first ex-
periment was designed to assess basal levels of IL-6 and PGE₂. During
the second experimental day, subjects performed a 1-h bout of
treadmill exercise (3% gradient) at ~80% of maximum heart rate
(31), followed immediately by microdialysis fiber insertion. Heart rate
was monitored every 5 min, and treadmill speed was adjusted to
maintain the desired intensity.

**Peritendinous microdialysis.** During each microdialysis experi-
iment, an ethylene oxide sterilized microdialysis fiber was inserted in
the peritendinous space anterior to the Achilles tendon, as previously
described (5, 21, 45, 53, 69). A 3,000-kDa fiber (membrane length 30
mm, outer diameter 0.05 mm) was inserted into the left leg of each
subject. In a subset of subjects (placebo: n = 6, 4 men/2 women;
APAP: n = 6, 5 men/1 woman), a 100-kDa fiber (CMA 66 High Cut
Off Linear Microdialysis Catheter, CMA Microdialysis, Solna, Swe-
den) was inserted into the right leg of each subject. Samples from the
left leg were used for the analysis of IL-6, and samples from the right
leg were used for analysis of PGE₂ and APAP. The inflow tube
of each microdialysis fiber was connected to a high-pressure syringe
pump (PHD 2000, Harvard Apparatus, Holliston, MA). Fibers were
perfused with sterile saline at a flow rate of 2 μl/min for 6 h. Dextran
(37 mg/ml; Sigma-Aldrich, St. Louis, MO) was added to the saline
perfusate (5 mg/ml). Mean values were again mixed with the sterile saline perfusate (5 mg/ml). Mean

**Probe recovery.** Sarcosine (5 mg/ml, S7672, Sigma-Aldrich, St.
Louis, MO) was mixed with sterile saline perfusate to determine probe
recovery during in vivo experiments. Relative recovery of IL-6 was
determined via the external reference method (58, 60). To estimate
the recovery of IL-6 in vivo, five separate in vitro experiments were
performed using the same sampling protocol described above. A
section of PVC tubing (Nalgene no. 8000–0090) was cut to ~5 cm
and was filled with human plasma spiked with 1,000 pg/ml of IL-6
(483364, Cayman Chemical, Ann Arbor, MI). The tube was capped
at both ends with a septum stopper (FB57872, Thermo Fisher Scientific,
Waltham, MA). A 3,000-kDa microdialysis fiber was inserted longi-
dudinally through the tube, penetrating the septum stoppers at both
ends using an 18G, 3.5-in. spinal needle (405184, BD Medical,
Franklin Lakes, NJ). The tube with the inserted microdialysis fiber
was placed in a 37°C incubator and allowed to oscillate. A flow rate
of 2 μl/min was perfused through the microdialysis fiber for a
duration of 6 h, and samples were collected in 1-h aliquots. Sarcosine
was again mixed with the sterile saline perfusate (5 mg/ml). Mean
ratio of IL-6 to sarcosine recovery was then used to estimate recovery

**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Placebo</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Men/women</td>
<td>6/2</td>
<td>7/1</td>
</tr>
<tr>
<td>Age, yr</td>
<td>26 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.6 ± 6.1</td>
<td>75.0 ± 3.8</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174 ± 4</td>
<td>177 ± 2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24 ± 1</td>
<td>24 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects.
of IL-6 in vivo, as previously described (60). Recovery of APAP and PGE2 was estimated using the in vivo recovery of sarcosine.

To determine the concentration of sarcosine in dialysate, 5 μl of dialysate was diluted with 95 μl of high-purity water. A 5-μl aliquot of this dilution was further diluted with 995 μl of high-purity water. An internal standard (1 mM hydroxyproline, H54409, Sigma-Aldrich, St. Louis, MO) was then added to the samples. Samples and standards (sarcosine: 20, 10, 5, 2.5, and 1.25 μM) were then derivatized and analyzed via high-performance liquid chromatography (HPLC), as previously described (12, 23).

Achilles peritendinous acetaminophen levels. The concentration of free APAP in the peritendinous space was determined in pre- and postexercise dialysate samples using HPLC. Dialysate (5 μl) from CMA 66 fibers was diluted with 45 μl of high-purity water. APAP standards (A7085, Sigma-Aldrich, St. Louis, MO) were prepared in high-purity water using a serial dilution starting at 0.625 μg/ml. The samples/standards were injected (10 μl) into an HPLC via an autosampler (SIL-20A, Shimadzu Scientific Instruments, Columbia, MD). Separation was achieved with a Restek Ultra C18 150 mm × 4 mm column (Restek, Bellefonte, PA) using a gradient elution (mobile phase A: 0.1 M phosphate buffer, pH 2.7, and mobile phase B: 100% acetonitrile). Samples were eluted using a gradient of 5–31% mobile phase B from 0–6.5 min followed by 85% mobile phase B from 6.5–8.0 min, and returning to 5% mobile phase B from 8.0–12.0 min. Flow rate was maintained at 1.0 ml/min. Column temperature was maintained at 40°C (CTO-20A, Shimadzu Scientific Instruments). Peaks were monitored (254 nm) using a photodiode array detector (SPD-M20A, Shimadzu Scientific Instruments).

Determination of IL-6 and PGE2. Dialysate IL-6 concentration was evaluated by enzyme immunoassay (583361, Cayman Chemical, Ann Arbor, MI) after first diluting the dialysate with assay buffer (1:9 dilution). Dialysate PGE2 concentration was evaluated using a PGE2 monoclonal enzyme immunoassay kit (514010, Cayman Chemical, Ann Arbor, MI) after dilution (1:5) of the dialysate. Only dialysate samples collected 2 h or more after fiber insertion were evaluated for IL-6 and PGE2 due to the potential for fiber insertion to influence these values (5, 33, 36). The technician performing the assays was blinded to group assignments.

Statistics. For IL-6, PGE2, and probe recovery, two collection points (2–3 and 3–4 h after fiber insertion) from the microdialysis sampling on the nonexercise day were averaged to represent basal conditions. This “basal” value was then compared with four subsequent 1-h collections taken between 2 and 6 h after exercise by using a two-way repeated-measures ANOVA with condition (basal and exercise) and drug (placebo and APAP) as factors. As done previously (52), for IL-6 and PGE2, the first 2 h of dialysate collection were discarded to minimize the influence of fiber insertion on our measurements. Peritendinous APAP levels were evaluated using a two-way repeated measures ANOVA with condition (no-exercise and exercise) and time (1–6 h) as factors. The Student Newman-Keuls post hoc test was used to explore differences when a significant interaction was detected. Subject characteristics between the placebo and APAP groups were compared using a Student’s t-test. Values were considered significant at an α-level of P < 0.05. All data are expressed as means ± SE. All data were analyzed using SigmaPlot version 11 (Systat Software).

RESULTS

There was no difference between the placebo and APAP groups in basic subject characteristics (Table 1). Average exercise intensity was also similar between the placebo and APAP groups (placebo: 86 ± 0.2, APAP: 88 ± 0.3% of predicted maximum heart rate). Average dialysate weights were at or near the expected values of 120 mg (Table 2). Dialysate weights did not change with exercise and were not different between the placebo and APAP groups (P > 0.05, Table 2). The relative recovery of IL-6 was similar to previous studies (40–45%), was not altered by exercise (P > 0.05), nor influenced by APAP consumption (P > 0.05, Fig. 1). Recovery of sarcosine from CMA 66 fibers (~50–65%) was also not influenced by exercise or altered by APAP consumption (P > 0.05, Fig. 2).

HPLC analysis of APAP indicated that all subjects assigned to the APAP group consumed the required APAP dose before beginning each microdialysis experiment. APAP was detected in all subjects in the APAP group during the basal and exercise experiments. The concentration of APAP in the peritendinous space was not influenced by exercise; thus these data were collapsed and presented in Fig. 3, independent of exercise. APAP levels peaked between 2 and 3 h after the second dose (peak concentration: 4.08 ± 0.65 μg/ml). APAP levels gradually declined throughout the experiment, but remained elevated (P < 0.05) compared with the start of microdialysis sample collection until the last hour of sample collection (Fig. 3). The half-life of APAP in the peritendinous space was estimated to be ~3–4 h.

CMA 66 microdialysis fibers ceased to function in two experiments, preventing the inclusion of two subjects in the
Peritendinous IL-6: Exercise and Acetaminophen - Gump BS et al.

PGE2 analysis (one placebo and one APAP). Peritendinous PGE2 did not increase with exercise in either the placebo or APAP groups (Table 3). PGE2 levels were generally lower in the APAP group, but this difference did not reach statistical significance ($P > 0.05$; Table 3) with an ANOVA test. In fact, the PGE2 levels in the APAP group were barely above the detection limit of the assay.

Peritendinous IL-6 levels in the placebo and APAP groups were not different at rest ($P > 0.05$; placebo: 514 &pm; 141, APAP: 427 &pm; 183 pg/ml). Peritendinous IL-6 levels increased rapidly with exercise ($P < 0.05$), reaching 1,634 &pm; 781 and 2,852 &pm; 791 pg/ml in the placebo and APAP groups, respectively at 2–3 h after exercise (Fig. 4). IL-6 was still elevated in both groups 5–6 h after exercise (placebo: 1,097 &pm; 290, APAP: 1,965 &pm; 527 pg/ml). The increase in IL-6 in response to exercise was greater in the APAP group at all time points (Fig. 4), peaking at 3,321 &pm; 1,040 pg/ml in the APAP group at 4–5 h after exercise compared with a peak value of 1,634 &pm; 781 pg/ml in the placebo group at 5–6 h after exercise.

### DISCUSSION

To our knowledge, this is the first investigation to evaluate the influence of oral APAP consumption on the exercise-induced release of IL-6 from human Achilles tendon in vivo. Our initial impetus to examine the effects of APAP on Achilles tendon IL-6 production were the results of Carroll et al. (11), in which chronic consumption of APAP during resistance training lead to a decrease in tendon stiffness and modulus of elasticity. The aim of the present investigation was to improve our understanding of how APAP alters tendon properties by exploring the effect of APAP on IL-6, which is produced in tendon in response to exercise (36), is a potent stimulator of tendon collagen synthesis (5), and regulates tendon size and elastic properties (43).

As demonstrated previously (36), exercise led to a sustained elevation in IL-6 levels within the Achilles tendon peritendinous tissue that was continued to at least 6 h postexercise (Fig. 4). Our findings also demonstrate that exercise of shorter duration, i.e., 1-h run vs. a 36-km run (36), leads to a rise in peritendinous IL-6 levels. As we hypothesized, IL-6 production in response to exercise was enhanced approximately three-
fold in the group consuming APAP (Fig. 4). Exercise did not increase PGE2 in either group, at least at the time points measured, and PGE2 was not significantly altered in the individuals consuming APAP (Table 3). Additionally, our novel assessment of APAP levels indicates that APAP in the peritendinous region peaked at 4.08 μg/ml compared with ~8–9 μg/ml that has been reported previously in plasma and skeletal muscle (46). Additionally, the time-to-peak levels of APAP in the peritendinous space were reached later (2–3 h) than reported in plasma (30 min) and skeletal muscle (80–100 min) (46). Lastly, although not a specific aim of this investigation, we introduce a new method to determine microdialysis probe recovery by including the amino acid sarcosine in perfusate.

Although the effect of the APAP-induced augmentation of IL-6 production on tendon requires further study, based on previous research a few speculations can be made. IL-6 has a number of different roles as a pro- and anti-inflammatory cytokine. IL-6 also has hormone-like activity, influencing glucose metabolism (68) and osteoclast formation (56). Evidence from tendon suggests that IL-6 stimulates collagen synthesis (5) and is necessary for maintaining normal tendon size and elastic properties (46). Given the substantial augmentation of IL-6 release by APAP, it is likely that APAP enhanced collagen turnover after exercise. Any augmentation of collagen turnover by IL-6 may be short-lived, as chronic APAP consumption reduced training-induced increases in skeletal muscle IL-6 mRNA expression in older individuals (62). Additionally, administration of indomethacin, a nonspecific COX inhibitor, blocks exercise-induced increases in tendon collagen synthesis (13). Measurements, however, were only taken 72 h after exercise (13). These findings (13, 62) indicate that the enhancement of IL-6 with acute exercise may be suppressed after chronic consumption of APAP. Increases in IL-6 production typically activate the synthesis of proteins that act in a negative feedback manner to inhibit IL-6 signaling transduction (20). Specifically, suppressor of cytokine signaling 3 (SOCS3) increases in response to IL-6 (15) and acts as a negative feedback regulator of IL-6 signaling. It is possible that the chronic enhancement of IL-6 levels with continued APAP consumption could lead to an upregulation of SOCS3, which, in turn, suppresses IL-6 (71). In fact, rofecoxib, a COX-2-specific inhibitor, increases SOCS3 levels in an oral mucosa injury model 48 h after injury (71); thus, as mentioned by Hamza and Dionne (20), overexpression of SOCS3 may negate the potential side effects of increased IL-6. Now that IL-6 has been identified as a potential mediator of APAP-induced effects on tendon, further chronic studies are needed to ascertain the long-term effects of APAP on IL-6 production and evaluate factors regulating IL-6.

If the effects of APAP on tendon are indeed short-lived, this would provide some interesting consideration for the acute vs. chronic use of APAP in clinical care. Although APAP is commonly used in the chronic treatment of osteoarthritis, it is also used extensively for short-term treatment of pain, often to limit exercise-related discomfort. In this scenario, periodic use of APAP would regularly enhance IL-6 production without subsequent inhibition. Interestingly, IL-6 gene expression is elevated in patients with chronic tendon pathology (39), leading one to speculate that intermittent enhancement of IL-6 production with APAP or other COX inhibitor consumption could contribute to the development of tendinopathies in exercising individuals. In support of this conclusion, the production of matrix metalloproteinase (MMP) enzymes, which degrade and remodel tendon ECM, is enhanced in the presence of COX inhibitors (64, 72). An increase in MMP activity could also contribute to the effects of APAP on tendon structure (12) and function (11) by increasing matrix degradation. Future studies are needed to evaluate the influence of APAP on basal and exercise-induced increases (31) in tendon MMP production.

Also of interest is the potential effect of APAP on individuals who already suffer from tendon pathology. For example, recent evidence suggests that IL-6 is elevated in painful and rupture Achilles tendons (39) and in aged tendon (26). Based on our findings, APAP may further enhance IL-6 production if APAP were used in combination with exercise therapy. It would also be interesting to evaluate the relationship of COX inhibitor use to the incidence of tendon problems.

Our data also suggest that the effect of APAP on IL-6 is linked to the exercise response, because APAP did not alter resting levels of IL-6. Our previous findings in APAP-treated rats (12) in which collagen cross-linking was reduced independent of exercise may not be related to changes in IL-6 production. APAP also has several effects on cellular signaling, including altering phosphorylation of protein kinase B, extracellular-regulated kinase-1/2, and p38 mitogen-activated protein kinase (73, 74). Some of these proteins are involved in stimulation of protein synthesis and activation of lysyl oxidase (70), the enzyme responsible for adding cross-links to growing collagen fibers. Further exploration of the role of these signaling proteins in tendon adaptations to exercise and APAP are needed.

In contrast to a previous report in which calf-press exercise transiently increased peritendinous PGE2 (33, 37), we did not detect an increase in PGE2 with exercise. It is possible that PGE2 is only transiently upregulated with exercise, and we missed this increase due to the limitations of our sampling method. As previously discussed (33, 36, 37), it is necessary to wait 1–2 h after catheter insertion to minimize the influence of insertion trauma on tissue properties. PGE2 release was also not significantly reduced in subjects given APAP (Table 3). However, a post hoc power analysis suggests that 15 subjects per group would be sufficient to detect a decrease in PGE2 with APAP consumption (power = 0.80). Although our PGE2 are not conclusive due to the small sample size, APAP has been shown to inhibit PGE2 release in skeletal muscle and to reduce urinary excretion of prostaglandin metabolites in humans (7, 18, 51).

On a technical note, an attempt was made by the authors to evaluate the enzyme activity of COX-1 and COX-2 in dialysate samples, as has been done previously for matrix degrading enzymes (31). Using a stock COX activity assay (700200, Cayman Chemical, Ann Arbor, MI), COX-1 and COX-2 activity was detected in dialysate samples. These analyses indicated that COX activity may have been lower in the APAP group (unpublished observation); however, several technical limitations were discovered that preclude the inclusion of these data. First, confusingly, when we attempted to perform in vitro experiments to determine probe recovery of COX (same technique as described in the Methods section for IL-6), we found that COX activity was much greater in dialysate samples from the in vitro experiments compared with COX activity in the plasma.
Given that greater than 100% recovery is likely not possible, we speculated that, by filtering the plasma with the microdialysis fiber, unknown substances were removed that normally limit in vivo COX activity. Therefore, we were unable to determine probe recovery for COX, limiting our ability to interpret COX activity data from dialysate. Finally, we were only able to assay COX activity in a small number of subjects due to the large volume of dialysate required (80 μl) for this assay.

Our novel evaluation of APAP levels in the peritendinous space provides several interesting considerations for future use of APAP and possibly other oral medications used to treat tendon pain. Even after two 1,000-mg doses of APAP, the peak level of APAP was less than one-half of that achieved in plasma or skeletal muscle (46). Furthermore, it took at least 2 h for APAP to reach peak levels in tendon tissue (Fig. 3) compared with only 30 min reported for plasma and ~80–100 min for skeletal muscle (46). The half-life of APAP in peritendinous tissue also appeared to be longer than observed in plasma or skeletal muscle (46). The lower concentration of APAP achieved in the peritendinous fluid (4.08 ± 0.65 μg/ml or ~26 μM) was, however, within the normal therapeutic range of APAP (10–100 μM). Our comparison is somewhat limited in resolution due to the fact that dialysate samples were only collected in 1-h aliquots to facilitate the measurement of PGE_2. A more detailed analysis of APAP kinetics in peritendinous tissue could be performed in future studies if shorter collection periods are used. The difference in APAP kinetics between skeletal muscle and the peritendinous region are likely not due to blood flow, as resting blood flow in the peritendinous region is similar to skeletal muscle (9). The increase in peritendinous blood flow associated with exercise (34, 35) also did not seem to alter the concentration of APAP in the peritendinous space. Vascularization of the Achilles tendon, however, is thought to be generally poor (1), which could limit drug delivery within the tendon.

Perspectives and significance. Tendons are an integral part of musculoskeletal function, and changes in tendon properties significantly alter muscle and physical function (6, 8, 16, 25, 28). APAP is used ubiquitously by the general population and is a key component of therapy for millions of osteoarthritic patients. Exercise is also recommended for the general population and is a key component of therapy for millions of osteoarthritic patients. Exercise is also recommended for the general population and patients with osteoarthritis (38). Therefore, it is important that we expand our understanding of how APAP medication influences connective tissue properties in humans. Our findings further our understanding of how exercise and analgesic medication influence tendon connective tissue. Future studies are needed to further evaluate the cellular events in tendon that are influenced by exercise and APAP. Additionally, it is also important that chronic effects of APAP on tendon ECM be explored.

ACKNOWLEDGMENTS

The authors are grateful for the participation of subjects in this study.

GRANTS

Research for these studies was supported by Midwestern University Intramural Awards to C. C. Carroll; American College of Foot and Ankle Surgeons Clinical and Scientific Research Grant to P. J. Kim, C. C. Carroll, and G. N. Friedlander; and American Podiatric Medical Students’ Association Research Grant to D. J. Cauthon.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES

15. Dufour AR, Loccioni G, Lambert MC. Peritendinous IL-6: Exercise and Acetaminophen • Gump BS et al.


28. Kostrominova TY, Brooks SV. Age-related changes in structure and extracellular matrix protein expression levels in rat tendons. Age (Dordr). In press.


