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Research Article

Acetaminophen and Skeletal Muscle Function in young adult University Students

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Abstract

Globally, acetaminophen (paracetamol) is one of the most widely used and affordable analgesics available, primarily known for its efficacy in relieving pain and reducing fever. Despite its widespread use, acetaminophen's effects on skeletal muscle function, particularly strength, fatigue resistance, and soreness, remain poorly understood. The aim of this study was to investigate the acute effects of acetaminophen on skeletal muscle performance in young adults, specifically assessing grip strength and fatigue resistance. By doing so, we sought to clarify whether acetaminophen has a measurable impact on muscle function and whether this impact varies by sex. A randomized, placebo-controlled crossover design was used. Participants visited the laboratory on two separate occasions and completed a series of grip strength assessments four hours after orally ingesting either 1000 mg of acetaminophen or a placebo in identical capsules. The testing protocol included three tasks: a maximal grip strength test using a manual dynamometer to measure peak force; an intermittent grip test using an electronic dynamometer to assess periodic strength; and a sustained grip endurance test, during which participants maintained their grip for as long as possible to determine time to fatigue. The null hypothesis (H0) stated that there will be no statistically significant difference in skeletal muscle function between placebo and acetaminophen treatments, while the alternative hypothesis (HA) proposed a statistically significant difference. Results revealed sex-specific effects of acetaminophen on muscle function. In young men, acetaminophen significantly increased both the maximum and minimum sustained grip force compared to placebo ($P<0.05$), suggesting an enhancement in muscular endurance and force maintenance. Young women showed no significant changes in grip strength, yet exhibited a significant increase in time to fatigue ($P<0.05$), indicating improved resistance to muscular exhaustion. We conclude that acetaminophen can enhance specific aspects of skeletal muscle performance in young adults, with distinct sex-based differences. These findings suggest a potential influence of acetaminophen on neuromuscular function; however, further investigation is needed to elucidate the underlying mechanisms and determine whether these effects extend to other physiological systems or populations.

Keywords: acetaminophen; grip strength; fatigue resistance; skeletal muscle; neuromuscular function; analgesics; sex differences; myoprotection

Introduction

Intense physical demands on peak performance of both professional and nonprofessional athletes have prompted increased research on chemicals and conditions that play roles in skeletal muscle function and recovery from fatigue. Among numerous compounds, acetaminophen, an inexpensive and widely-used pain reliever, has raised questions regarding its potential for alleviating muscle pain and fatigue. Its mechanisms of action, however, remain unknown. One prevailing theory suggests that acetaminophen blocks prostaglandin formation via inhibition of cyclo-oxygenase (COX) enzymes [1, 2]. There are likely other mechanisms as well (e.g., antioxidant activity). In our research laboratory at Rutgers University, New Brunswick, we have been engaged in animal research with acetaminophen for the past twenty plus years. In large and small animals, we have found acetaminophen to be both cardioprotective [3-15] and cerebroprotective [16]. In frog gastrocnemius muscle we have more recently shown acetaminophen to be myoprotective

[17]. Naturally, such observations have caused us to wonder about the translation of these effects to humans, particularly in clinical arenas.

The above are not unreasonable thoughts because: 1.) acetaminophen has a long-standing history of successful use in Western medicine (e.g. treating fever and pain), 2.) acetaminophen is efficacious and safe when used as directed (e.g. equal to or less than 4000 mg doses per a 24-hour period, see labels on products such as Tylenol and Paracetamol), 3.) relative to other generally-used as well as clinically-safe analgesics/antipyretics, acetaminophen is inexpensive, and 4.) it is broadly available to the public without prescription [18].

Acetaminophen's only known negative side effect is hepatotoxicity and that occurs, mostly, in persons using the analgesic for intended, harmful purposes (e.g., suicide attempts), and/or who double up on consumption of alcohol and acetaminophen. Moreover, in the experiments we have reported, circulating plasma concentrations of acetaminophen have not exceeded about 50 µg/ml. For the analgesic to be hepatotoxic, circulating plasma concentrations must exceed 300 µg/ml, which are far above those achieved after clinical dosing [19].

Finally, acetaminophen, a monophenol, belongs to a class of compounds known for their antioxidant properties. Phenols can neutralize free radicals, particularly in muscles during heavy exercise or injury [20]. Oxidative stress is a key contributor to muscle fatigue and delayed recovery. Accordingly, acetaminophen might help maintain muscle integrity and improve endurance during sustained exertion of any type. Here we report, for the first time, that acetaminophen has beneficial properties in human subjects undergoing exercise activities to exhaustion.

Materials and Methods

Experimental Subjects: The experimental subjects were eleven students enrolled in the Spring 2025 Advanced Physiology course at Rutgers University - New Brunswick (RU). Participants represented a diverse range of cultural and ethnic backgrounds, with an average age of approximately 21 years. Each student visited the Merrill Laboratory on two separate occasions. They were instructed not to fast and to maintain consistent lifestyle habits for both visits. All subjects self-reported good health and adhered to the study guidelines. While the primary analysis focused on these current-semester students, some additional analytics were incorporated including aggregated data from similar experiments conducted over the past three semesters (n=42), all of which followed the same experimental protocol.

Experimental Protocol: Hand grip strength and fatigue were selected as measures of muscle performance due to their ease of assessment and relevance to the study's objectives. Forearm and hand muscles are predominantly composed of type II, fast-twitch muscle fibers. They are more susceptible to fatigue compared to type I, slow-twitch myocytes which are designed for endurance [21]. Given their susceptibility to rapid exhaustion under prolonged exertion, these muscle groups are well-suited for investigating the effects of acetaminophen on muscular activity.

One week prior to experimentation, participants attended a briefing that outlined the study protocol. During this session, each participant received both placebo and acetaminophen capsules, color-coded by a third party to maintain blinding. Participants were instructed to ingest one capsule before arriving at the laboratory for each trial. Upon arriving at the laboratory, subjects were weighed (kg) and their heights (m^2) were determined (Health-O-Meter, Continental Scale Corporation, Bridgeview, IL, certified by New Jersey Weights and Measures). From this information Body Mass Index (BMI) was calculated as: weight (kg) / height (m^2) = BMI. This was used to normalize raw data, and to account for inter-individual differences in body/muscle mass. Subjects were then introduced to the hand-held dynamometers—both manual and electronic—used for quantifying muscle function. No standardized questionnaire was used to assess subjective parameters such as fatigue or perceived exertion, as the focus of the study was on objective physiological measurements.

For the first activity, maximum strength of grip was estimated using a manual grip force transducer. This also served as a calibration reference for the electronic transducer used in subsequent tasks. In the second task, participants used an MLT004ST electronic grip transducer to perform intermittent maximal grips. Over a 120-second period, they gripped maximally and released once per second for 15 seconds, followed by a 5-second rest. This cycle was repeated six times. The transducer was connected to a data acquisition system and LabChart software (v8.1.30, 2024) on a desktop PC. To avoid bias, subjects were seated facing away from the monitor. Data were recorded for later comparison between placebo and acetaminophen conditions. The final test, performed following five minutes of rest post-intermittent gripping, was used to estimate time-to-fatigue. Upon the verbal command, "3-2-1-Go", students were told to grip the dynamometer as forcefully and continuously as possible for no less than 120 seconds, but no more than 180 seconds. They were given audible queues every fifteen seconds during the activity. This exercise was similarly monitored by the data acquisition system and computer. All tests were conducted in a controlled environment, with room temperature maintained between 22°C and 24°C.

Acetaminophen vs Placebo: Both participants and investigators were blinded to the treatment condition; neither party knew whether placebo or acetaminophen had been administered. Each participant completed the protocol on two separate occasions, reporting to the Merrill Laboratory after self-administering either a 1000 mg oral dose of placebo or acetaminophen. The dose and timing were based on pilot data previously collected from Rutgers University students. When normalized to a 70 kg body weight (historically-published average adult human weight) the acetaminophen dose corresponds to approximately 14 mg/kg, which is comparable to doses previously used in canine models of myocardial infarction [8].

Statistics: The experimental protocol was designed a priori. All data are reported as means plus or minus one standard error of the mean (s.e.m.). Students t-test for paired data was used to identify significant differences between means, and Analysis of Variance (ANOVA) was used to identify differences in variability. A probability of $P<0.05$ was used to identify significant differences. Data distributions were confirmed to be approximately normal.

Although multiple potential confounding factors existed (e.g., sleep, diet, hydration, circadian rhythm), efforts were made to minimize their influence. Participants were instructed to follow their typical daily routine on each test day, and the study design was counterbalanced and blinded to reduce bias. Based on previous research and pilot data, we anticipated that the physiological effects of acetaminophen would be robust enough to outweigh minor uncontrolled variables.

Results

An example of a typical response in one male subject during intermittent forearm exercise is shown in Figure 1.

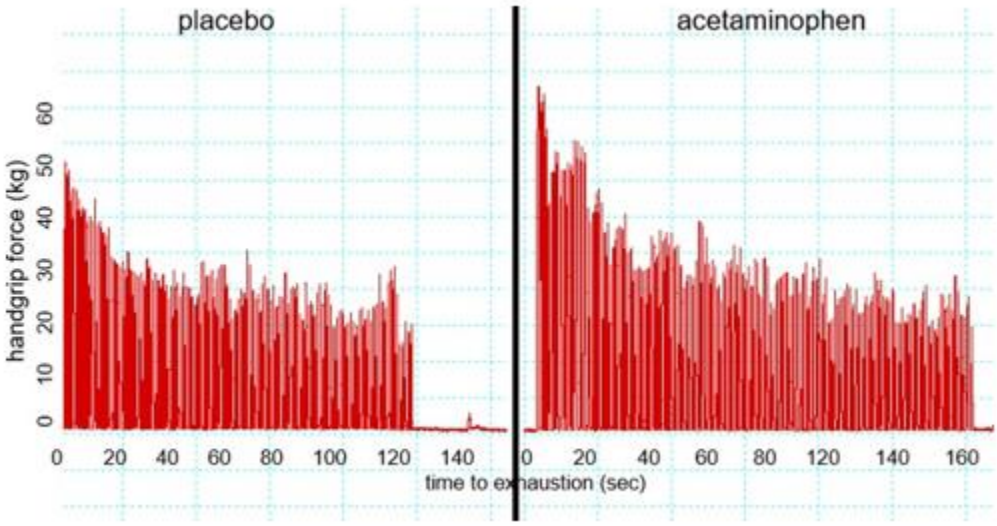

Figure 1: Sample of periodic (intermittent) handgrip exercise in a young adult male in the absence and presence of acetaminophen (1000 mg oral). Image at left represents the first of six sets of fifteen maximal grips and releases. At right is shown the sixth set of data.

Data after consumption of placebo are shown at the left, while those post-acetaminophens are presented at the right. At the beginning of this activity muscle strength increased from about 45kg (placebo) to 53 kg with acetaminophen. At the end of the test corresponding numbers were about 15 vs 20 kg. In the presence of placebo this young man was able to endure for about 55 seconds, while that number increased to nearly 95 seconds with acetaminophen. This subject was an unconditioned, non-athlete.

When the data were pooled for the four young men in the experiment, acetaminophen was shown to significantly improve force of contraction at the beginning and ending of sustained handgrip exercise (Figure 2).

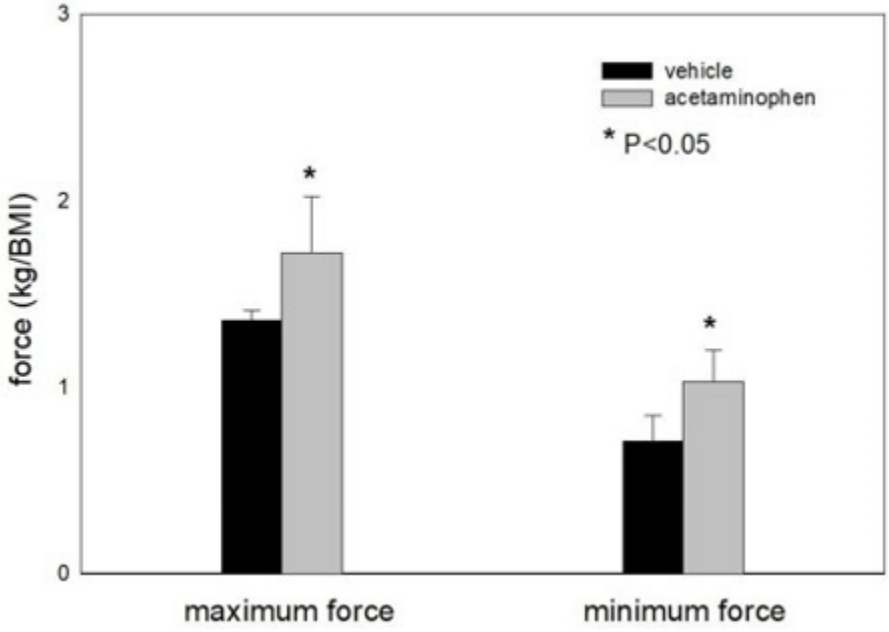

Figure 2: Group data for young men only in the current experiment. Note the significant difference ($P<0.05$, both maximum and minimum forces) when acetaminophen data are compared with corresponding histograms in the presence of placebo. Data are means plus or minus one standard error of the mean ($\bar{x} \pm$ s.e.m.).

For example, maximum and minimum forces in the presence of placebo were 1.36 ± 0.4 and 0.70 ± 0.14 kg/BMI. Corresponding numbers with acetaminophen were 1.72 ± 0.3 ($P<0.05$) and 1.03 ± 0.17 ($P<0.05$) kg/BMI.

An example of results from a conditioned, competitive female gymnast (Division I, Big Ten Conference) during both intermittent and sustained activities is presented in Figure 3. After administration of placebo her maximum forces of contraction were about 20 (termination) and 45 kg (initiation) for sustained and periodic force, respectively. Corresponding numbers increased to 30 and 55 kg in the presence of acetaminophen.

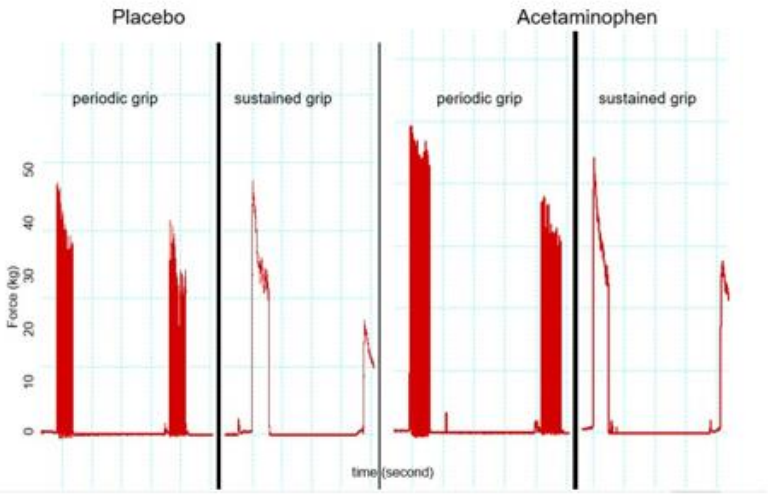

Figure 3: Sample of both periodic and sustained handgrip exercise in a conditioned, competitive young female gymnast. Note the improvement in muscle function in the presence of acetaminophen.

During sustained handgrip exercise, females (n = 8) were able to endure for a longer period with acetaminophen (14.8 ± 5.0) than with placebo (7.1 ± 1.7) ($P<0.05$).

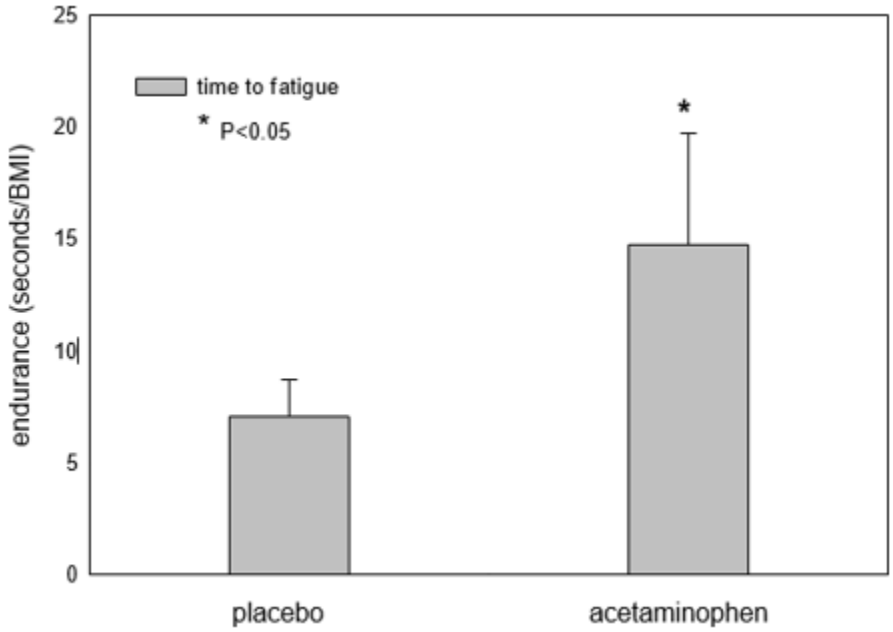

Figure 4: Group data for young women only. In the presence of acetaminophen (1000 mg), young women were able to sustain a maximum grip significantly longer ($P<0.05$) than in its absence. Data are means plus or minus one standard error of the mean ($\bar{x}$ ± s.e.m.).

Discussion

Our main objective was to establish a proof-of-principle: does acetaminophen in human striated skeletal muscle behave like it does in mammalian striated cardiac muscle, i.e is it myoprotective. In heart acetaminophen preserves/protects function during ischemia, reperfusion, hypoxia, reoxygenation, myocardial infarction, and pro- arrhythmic insults. We sought to determine whether the analgesic can improve/sustain endurance, fatigue, and/or strength in challenged skeletal muscle.

Before initiating human trials, we previously collected pilot data in isolated, stressed frog gastrocnemius muscle [17]. Gastrocnemius myocytes are mostly fast twitch, easily-fatigued skeletal muscle. In frogs, acetaminophen consistently and significantly improved contractile force at both the initiation and termination of electrical stimulation (simulated moderate to heavy exercise). It also reduced the rates of fatigue in our frog muscle preparation. These findings provided preliminary evidence supporting a possible myoprotective effect of acetaminophen in skeletal muscle.

In humans, grip strength is primarily governed by the flexor digitorum profundus, flexor pollicis longus, and other forearm muscles. These muscles, along with associated ligaments, nerves, and tendons, facilitate movement and fine motor control of the wrist and fingers. These tissues were the focus of our current study [22]. To our knowledge, this is the first study to examine

the impact of acetaminophen on skeletal muscle performance in young adults. Across multiple trials using both manual and electronic dynamometers, young men consistently produced greater grip force than young women—a difference that remained significant even after normalizing for body mass (kg) and body mass index (BMI, kg/m²). This sex-based disparity was evident under both placebo and acetaminophen conditions and aligns with previous findings in older adults [23].

Data were collected across three academic semesters (Spring 2024, Fall 2024, and Spring 2025) from a total sample of 42 university students. During the intermittent grip task—consisting of six 15-second bouts of maximal effort with 5-second rest intervals over a 120-second period—both male and female participants demonstrated a significant increase in grip strength at both the start and end of the activity when under the influence of acetaminophen (n = 19; see Figure 2).

In the current experiment young women were able to sustain a maximum grip for a longer period of time in the presence of acetaminophen. The opposite trend was seen in young men and suggests that the way acetaminophen influences exercise performance could be influenced by gender. Speculatively, young women might have increased resilience to sustained effort, but this requires further investigation.

Acetaminophen is known to alter perception of pain and fatigue during physical activity. In a recent study comparing detection and reporting of pain, women detected pain at lower temperatures and across all levels of pain compared to men [26]. This suggests a higher tolerance to pain and discomfort in women. It also suggests that women might be more willing and able to endure pain and discomfort for longer periods of time than men [21]. This notion also requires further examination in both conditioned athletes and in the general population.

Women are more prone to lower body injuries such as sprained ankles, torn ACLs (anterior cruciate ligaments), and plantar fasciitis [27]. This has been attributed to biomechanical, hormonal, and structural differences in female and male athletes [27]. For example, wider hips, greater reliance on quadriceps over hamstrings, greater ligament laxity, mineral and vitamin deficiencies (e.g iron, calcium, and vitamin D), and hormonal fluctuations, are just some of the challenges female competitors must contend with [25, 28]. Therefore, further exploration into how acetaminophen interacts with sex-specific traits, pain perception, and muscle fatigue is not only scientifically valuable but may have practical implications for both recreational and elite athletes.

Limitations

The hand-held electronic dynamometer used to measure grip strength may have caused mild discomfort for some participants, which could have influenced their effort, potentially introducing bias or performance variability across testing sessions. Additionally, the study exclusively evaluated forearm and hand muscles in a seated, non-weight-bearing position. While this allowed for controlled testing of small muscle groups, it limits the generalization of the findings to larger or postural muscles involved in whole-body movements or athletic activities. The effects of acetaminophen on lower-limb, core, or full-body muscular performance remain unknown and should be the focus of future studies.

Conclusion

In summary, this study provides preliminary yet compelling evidence that acetaminophen may positively influence skeletal muscle performance under conditions of fatigue and repeated exertion, particularly in young adults. Both subjective and objective measurements showed trends suggesting improved endurance and sustained force output. While limitations related to study design, scope, and sample size must be acknowledged, the data suggest a previously underappreciated potential for acetaminophen to modulate muscular fatigue and functional performance.

Given acetaminophen's widespread use and its known effects on pain perception and central fatigue, further studies should be performed, particularly across diverse muscle groups, postural conditions, and demographic populations. Future research should also explore the underlying mechanisms by which acetaminophen may exert myoprotective or fatigue-mitigating effects and whether these effects are sex-dependent.

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