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Doctor of Philosophy

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ABSTRACT

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During ambulation, lower-extremity joint angles and net moments influence knee joint load. It is unclear which mechanical variables most strongly correlate with acute articular cartilage (AC) catabolism in response to ambulation. Purpose: To determine which mechanical variables are most strongly correlated to acute AC catabolism, and to test the acute effect of ambulation speed on AC catabolism, while controlling for load frequency. Methods: 18 able-bodied subjects (9 male, 9 female; age = 23 ± 2 y; mass = 68.3 ± 9.6 kg; height = 1.70 ± 0.08 m) completed three separate ambulation sessions: slow (preferred walking speed), medium (+50% of walking speed), and fast (+100% of walking speed). For each session, subjects completed 4000 steps on an instrumented treadmill while ten high-speed cameras recorded synchronized video data. Various, discrete, three-dimensional joint kinematic and kinetic variables were averaged across 20 total stance phases (5 stance phases at 1000, 2000, 3000, and 4000 steps). Blood samples were collected pre-, post-, 30-min post-, and 60-min post-ambulation. Serum cartilage oligomeric matrix protein (COMP) concentration was determined using an enzyme-linked immunosorbent assay. A stepwise multiple linear regression analysis was used to evaluate the relationships between serum COMP change and lower-extremity joint angles and moments. A mixed model ANCOVA was used to evaluate serum COMP concentration between sessions across time. Results: Peak ankle inversion, knee extension, knee abduction, hip flexion, hip extension, and hip abduction moment, and knee flexion angle at impact, explained 61.4% of the total variance in serum COMP change ($p < 0.001$), due to ambulation. COMP concentration increased 28%, 18%, and 5% immediately after ambulation for the running, jogging, and walking sessions, respectively. All sessions were significantly different immediately post-ambulation ($p < 0.01$). Conclusion: Certain lower-extremity joint mechanics are associated with acute AC catabolism, due to ambulation. Several key mechanical variables (e.g., peak knee extension, knee abduction, and hip abduction moments) explain much regarding the variance in serum COMP increase. These lower-extremity variables can be used to predict acute AC catabolism, allowing researchers and clinicians to better predict and/or understand AC catabolism. Additionally, when load frequency is controlled, increased ambulation speed acutely results in increased AC catabolism. Ambulation speed does not, however, influence serum COMP elevation duration. Joint mechanics and load frequency appear to be responsible for the magnitude of COMP increase, while duration of COMP elevation post-ambulation is dictated by load frequency.

Keywords: ambulation, mechanics, articular cartilage, COMP

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Introduction

The primary function of hyaline articular cartilage (AC) is to effectively bear mechanical load that is applied to a joint[1,2]. Mechanical load is needed to maintain AC health[3,4]. An increase in structural components (e.g., collagen and proteoglycans) is found in AC that is regularly subjected to high load magnitudes[3,5]. When load is reduced, AC atrophies[6]. Healthy AC continually undergoes normal remodeling as chondrocytes rapidly replace matrix molecules that are lost during acute degradation[7]. Alterations in the normal balance of AC synthesis and degradation can occur due to changes in structural components that result from age[8], acute joint injury (e.g., ligamentous rupture)[9], chronic joint pathology (e.g., osteoarthritis (OA))[10], or abnormal joint kinetics and kinematics[7,11].

Although not detrimental in a healthy population, physical activity acutely deforms AC[12,13]. Differences in the magnitude of AC deformation after various types of physical activity (e.g., walking and running[13]) may, in part, be due to the mechanical differences between the activities. For example, peak vertical ground reaction force (GRF) magnitude increases from 1.0 × body weight for walking at 1 m/s to nearly 3.0 × body weight for running at 6 m/s[14]. Lower-extremity joint kinetics and kinematics also differ between ambulation speeds[15-19]. Peak internal knee extension and abduction moments increase 11% and 34% as ambulation speed increases from 3.50 to 5.02 m/s[17]. Hip and knee flexion, and ankle plantar flexion angles increase by 23%, 73%, and 6% as walking speed increases from 0.83 to 1.90 m/s[15,19]. Increased GRF magnitude and the corresponding load rate (LR), and knee extension moment are each associated with knee load[20-22] and likely influence AC health. Knee flexion angle at heel strike and peak frontal plane external knee adduction moment are also associated with knee load and decreased AC thickness[23,24]. Although researchers have identified the aforementioned mechanical variables

as being related to joint load and OA prevalence and progression[21,25], it is unclear which mechanical variables are most strongly correlated to AC catabolism related to an acute bout of physical activity. Identifying strong predictors of AC catabolism due to exercise could give researchers and clinicians mechanical clues on mechanisms associated with AC loss.

Cartilage oligomeric matrix protein (COMP), is an extracellular non-collagenous proteoglycan that helps organize the cartilage matrix and contribute to its load bearing capability[26,27]. Elevated resting serum COMP concentration reflects cartilage degradation in an OA population[28,29] and is associated with early stages of OA and OA progression[30,31]. For able-bodied individuals, serum COMP concentration increases in response to physical activity, indicating the catabolic effect of exercise-induced load on AC[32-34]. Relative to walking, greater serum COMP concentrations are found after running for the same duration[33,35]. It is unclear, however, whether serum COMP concentration increases more for running, relative to walking, due to altered mechanics or simply due to the different frequency of applied load (running involves a greater frequency than walking). No one has simultaneously measured serum COMP concentration and movement mechanics during able-bodied ambulation across various speeds. Such a study could potentially (1) identify which mechanical variables are most strongly associated with acute AC catabolism, as reflected by COMP, and (2) provide additional insight regarding the effect of load magnitude and frequency, across a wide range of ambulation speeds (i.e., walking and running), on AC catabolism.

There were two purposes of this study. The first purpose was to determine which mechanical variables (of those that have been associated with knee joint load) are most strongly correlated to acute AC catabolism due to ambulation, across various ambulation speeds. The second purpose was to test the acute effect of ambulation speed on AC catabolism, while

controlling for load frequency (i.e., the number of steps). We hypothesized that mechanical variables previously associated with knee load would positively correlate to serum COMP concentration increases, due to ambulation, across various ambulation speeds. We also hypothesized that, while controlling for load frequency, serum COMP concentration would increase more and remain elevated longer following fast ambulation (running), relative to slow ambulation (walking).

Methods

Subjects

A convenience sample of eighteen able-bodied volunteers (9 male, 9 female; age = 23 ± 2 y; mass = 68.3 ± 9.6 kg; height = 1.70 ± 0.10 m; body mass index (BMI) = 23.2 ± 2.0 kg/m^2) participated in this study. No subject reported a history of any form of arthritis, lower-extremity joint surgeries within their lifetime, or current lower-extremity pain. Each subject was currently participating in moderate physical activity (defined by the World Health Organization) at least three times a week. We required subjects to refrain from moderate to intense physical activity while they participated in this study. Prior to their participation, subjects completed an informed consent form that was approved by the appropriate institutional review board.

Experimental Protocol

Subjects completed three separate data collection sessions (slow, medium, and fast) in a counterbalanced order, separated by 24 h. During the slow session, subjects ambulated at a preferred walking speed that was determined on a day prior to the first data collection session. For the medium and fast sessions, subjects ambulated at speeds of 50% and 100% greater than the preferred walking speed. Average ambulation speeds for the slow, medium, and fast sessions were 1.32 ± 0.12, 1.99 ± 0.19 and 2.64 ± 0.25 m/s. We terminated all data collection sessions

after the subject had performed 4000 steps, as determined using an OptoJump optical measurement system (OptoJump Next, Microgate S.R.L., Bolzano, Italy). For all sessions, subjects ambulated on the same instrumented treadmill (AMTI, Watertown, MA, USA) while wearing their own running shoes, and a spandex shirt and shorts provided by the investigators.

At the beginning of each data collection session, subjects rested on a chair for 30 min to minimize the potential influence of preceding physical activity (e.g., walking to the data collection site) on serum COMP concentration[33]. Subjects then stood for 10 min, to allow for body fluid distribution to adjust to the vertical posture, while we applied reflective markers (facilitating motion analysis) to the subject. Next, a pre-exercise baseline blood sample was drawn (D1). Subjects then completed one of the three exercise tasks (slow, medium, or fast). Subsequent blood samples were taken immediately post exercise (D2), 30 min post exercise (D3), and 60 min post exercise (D4).

Biomechanical Variables

We used ten high-speed digital video cameras (240 Hz; VICON, Santa Rosa, CA, USA) and the instrumented treadmill (1200 Hz) to capture synchronized video and GRF data. Four reflective markers were applied to the head: two anterior and two posterior on each side. Rigid clusters of four reflective markers were attached bilaterally to the distal-lateral thigh and shank. Single reflective markers were placed over the C7 and T7 vertebrae, and sternum, and bilaterally on the middle-posterior wrist, lateral elbow (humeral epicondyle), acromion process, inferior angle of the scapula, anterior superior iliac spine, posterior superior iliac spine, greater trochanter, medial and lateral knee (femoral condyles), medial and lateral ankle (malleoli), posterior heel, dorsal surface of the midfoot, lateral foot, and toe (between the second and third metatarsal). After placing these markers, subjects stood in anatomical position while we recorded

a static standing trial that represented neutral alignment (subsequent dynamic measures were referenced to this static trial). Next, subjects performed standing leg motions to more accurately calculate the hip joint center[36,37]. We digitized the spatial coordinates that corresponded to each reflective marker in Vicon Nexus (VICON, Santa Rosa, CA, USA). For each session, 15 seconds of GRF and coordinate data were recorded at four different times throughout the exercise: 1000 steps, 2000 steps, 3000 steps, and 4000 steps. Five gait cycles from each of these times were identified (20 total gait cycles for each session). The discrete dependent variables were identified and averaged across the 20 gait cycles. This resulted in a single value that represented each dependent variable for each exercise session (slow, medium, and fast).

GRF data and marker coordinates were imported into Visual 3D software (C Motion, Germantown, MD, USA) and smoothed using a 4th order low-pass Butterworth filter; we used cutoff frequencies of 6, 7, and 8 Hz (determined using a standard residual analysis)[38] for the slow, medium, and fast exercises, respectively. The smoothed coordinate data were then used to calculate three-dimensional hip-, knee-, and ankle-joint kinematics. Using the static, standing video, a three-dimensional model of the lower extremities and pelvis was created for each subject using previously described methods[39]. Joint angles were calculated using a Cardan rotation sequence (flexion/extension, abduction/adduction, and internal/external rotation)[40]. Net internal joint moments were calculated using GRF, joint angle, and anthropometric data via a standard inverse dynamics approach[41]. We smoothed the GRF data used to calculate net joint moments at the aforementioned cutoff frequencies[42]. The GRF data used to determine peak vertical GRF and LR were smoothed using a cutoff frequency of 50 Hz[43,44]. We exported GRF, joint angle, and net joint moment data into MATLAB (The MathWorks, Natick, MA, USA) where the discrete dependent variables were identified using custom algorithms.

Serum Biomarkers

We drew all blood samples (3 ml) from an antecubital vein using a 20 gage shielded I.V. catheter (BD Vialon Insyte Autoguard, Becton Dickinson & Co., Franklin Lakes, NJ, USA) that was placed during the aforementioned 30-minute rest period. After insertion, we flushed the catheter with 1-ml isotonic saline (0.9% NaCl) every 15 min to prevent clotting. Collected blood samples were placed in EDTA vacutainers (BD Vacutainer K2 EDTA, Decton Dickinson & Co., Franklin Lakes, NJ, USA), centrifuged for 15 min at 3000 × gravity, and then stored at -20°C. Serum COMP concentration was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Quantikine Human COMP Immunoassay, R&D Systems Inc., Minneapolis, MN, USA), according to the manufacturer guidelines. We analyzed all samples in triplicate across each ELISA kit. The intra and inter assay coefficient of variation was 1.5% and 18.4%, respectively, for a 165 ± 37 ng/ml sample. We attempted to minimize inter-assay variation by comparing serum COMP concentration for each subject on the same plate.

Statistical Analysis

Related to our first purpose, we used a multiple linear regression analysis to evaluate the pooled relationship between ambulation mechanics, across a range of ambulation speeds, and serum COMP concentration change due to ambulation. Because numerous mechanical variables were analyzed, we determined the optimal multiple regression model and predictors of COMP concentration change, due to ambulation, using a mixed stepwise approach and Akaike information criteria[45]. The plausible explanatory mechanical variables included: peak vertical GRF magnitude and LR (calculated using previously described methods[46]), internal peak frontal and sagittal ankle, knee, and hip moments during stance, frontal and sagittal knee angle at heel strike, and peak frontal and sagittal knee angle during weight acceptance (defined as heel strike

to peak knee flexion angle). The response variable was absolute change in serum COMP concentration (D2 minus D1). Related to our second purpose, we used a repeated measures mixed model analysis of covariance to compare serum COMP concentration between sessions (slow, medium, and fast), across draws (D1, D2, D3, and D4). Because baseline serum COMP levels differ between subjects and higher COMP concentration has been found in males[47,48], both baseline COMP and gender were used as covariates. If a session × draw interaction was detected, Tukey's post hoc comparisons were used to evaluate potential between-draw differences for each session. The alpha level for all statistical tests was set to 0.05.

Results

Multiple Regression Analysis

Averages and confidence intervals for all observed kinematic and kinetic variables for each session are found in Tables 1 and 2, respectively. Additionally, a graphical representation of each variable, observed throughout the stance phase, can be found in Figures 1, 2, and 3. Related to the first purpose of the study, the mixed stepwise multiple regression analysis produced the following pooled model that relates joint mechanics, across a range of ambulation speeds, and serum COMP concentration increase, due to ambulation:

$$y = \beta_0 I(cond = slow) + \beta_0 I(cond = medium) + \beta_0 I(cond = fast) + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7.$$

The regression model identified the following peak internal net joint moments and knee flexion angle at heel strike as predictor variables: ankle inversion, knee extension and abduction, and hip flexion, extension, and abduction. These predictor variables represent x_1 through x_7 in the aforementioned regression equation. Each ambulation speed was included in the model as an indicator variable (1 or 0). The equation for each ambulation speed can, therefore, be determined

by using these indicators. The pooled multiple regression model explained 61.4% (adjusted R^2 = 0.54) of the total variance in serum COMP increase ($p < 0.001$), due to ambulation. The regression coefficients associated with the regression equation can be found in Table 3.

Serum COMP and Ambulation Speed

A session × draw interaction was observed for serum COMP concentration (Table 4; $p < 0.001$). For D2, average serum COMP concentration for the fast session was 8.8% and 23.7% greater than for the medium ($p = 0.001$; Cohan's *d* effect size (ES) = 0.64) and slow ($p < 0.001$; ES = 1.51) sessions. For the medium session, average serum COMP concentration at D2 was 13.7% greater than for the slow session ($p < 0.001$; ES = 0.87; Table 4) at D2. No other between-session differences existed for serum COMP concentration for any other draw. As a main effect, session influenced serum COMP concentration. Average serum COMP concentration for the fast session was 5.5% and 6.5% greater than for the medium ($p = 0.009$; ES = 0.46) and slow ($p = 0.002$; ES = 0.54) sessions (Table 4). Average serum COMP concentration for the medium session was not statistically different from the slow session ($p = 0.84$). As a main effect, time also influenced serum COMP concentration. Serum COMP concentration at D2 was 28.7% and 18.3% greater than D1 concentration for the fast and medium sessions, respectively ($p < 0.05$; Table 4). When pooled across all sessions, average serum COMP concentration for D2 was 14.9% greater than D1 ($p < 0.001$; ES = 1.30), while serum COMP concentration for D3 and D4 was 8.8% (ES = 0.60) and 10.5% (ES = 0.70) less than D1 ($p < 0.01$). No difference was found for serum COMP concentration between D3 and D4 ($p = 0.91$).

In summary, some mechanical variables were significantly associated with serum COMP increase due to ambulation at various ambulation speeds (Table 3). The following peak internal net joint moments and knee flexion angle at heel strike were associated with serum COMP

increase due to ambulation: ankle inversion, knee extension and abduction, and hip flexion, extension, and abduction (Figure 4). Additionally, ambulation speed acutely influenced serum COMP increase, due to ambulation: serum COMP concentration increased more as ambulation speed increased (Table 4).

Discussion

We aimed to (1) identify mechanical variables that are associated with acute AC catabolism due to ambulation, and (2) learn if/how ambulation speed acutely influences AC catabolism. We hypothesized that (1) mechanical variables that have previously been associated with knee load would correlate to AC catabolism due to ambulation, and (2) AC catabolism would be greater due to fast-speed ambulation than slow-speed ambulation. In partial support our first hypothesis, peak ankle inversion, knee extension and abduction, and hip extension moment positively correlated with AC catabolism due to ambulation. Peak hip flexion and abduction moments, and knee flexion angle at impact negatively correlated with AC catabolism due to ambulation. These results indicate that certain lower-extremity mechanical variables can be used to predict acute AC catabolism due to ambulation. It should be noted that our results may have been influenced by the mechanical variation between ambulation speeds. The purpose of this study, however, was not to compare joint mechanical differences or various ambulation techniques at differing speeds, but rather to correlate joint mechanics to AC catabolism due to ambulation. We acknowledge that technical differences due to ambulation speed influenced the results of this study. In support of our second hypothesis, serum COMP concentration increased more after fast ambulation than after medium and slow ambulation. Contradicting our second hypothesis, ambulation speed did not influence serum COMP concentration elevation duration.

Researchers have hypothesized that joint mechanics influence AC degradation due to ambulation[49], and the knee is often a primary focus. Our findings show that peak knee extension moment positively correlated with serum COMP change due to ambulation (i.e., greater peak knee extension moments are associated with greater acute AC catabolism). This finding corroborates computational modeling data that indicate compressive knee force during the first half of stance is mainly caused by quadriceps activation[50]. During walking, knee extension moment contributes to forces across the knee[51] by increasing compression between the tibial plateaus and femoral condyles. Therefore, a reduction in knee joint force, via decreased knee extension moment, may reduce acute AC degeneration[52]. Some researchers have argued, however, that a reduction in knee extension moment due to muscle weakness and/or atrophy does not prevent cartilage loss but initiates it[21]. Although previous data confirm that knee extension moment influence knee load[51], further research is warranted to fully understand the influence of increased or decreased knee extension moment on AC health.

Peak knee abduction moment also positively correlated with serum COMP change. This may have occurred because the greatest knee abduction moment resulted from fast ambulation (Table 2 and Figure 3) which may have placed the greatest amount of load on the knee. Although not calculated in this study, we assume that fast ambulation results in the greatest external adduction moment[53], which may causes genu varum and increased medial compartment pressure[54]. This idea is supported by researchers who found that runners with genu varum excursion demonstrate significantly greater internal knee abduction moments[55] and medial compartment load[56-58]. Our subjects, however, did not experience abnormal genu varum excursion or any other abnormal kinematic characteristic (Figure 1). Nevertheless, the frontal-

plane knee excursion found in our subjects may have placed loads on the knee which were expressed by increased frontal plane knee moments.

Knee kinematics influences AC health[23,59]. Our results indicate that knee flexion angle at heel strike negatively correlates with acute AC catabolism that is due to ambulation. This finding supports previous reports that show knee flexion angle at impact significantly correlates with AC cartilage thickness[23]. In speculation, more knee flexion at impact may assist to absorb GRF that result from heel strike[60]. Further, greater knee flexion angle at impact may also reduce knee flexion excursion. Greater knee flexion excursion has been associated with increased sagittal plane knee loads[20], which, consequently, may increase acute AC catabolism. Other researchers have reported that frontal plane knee kinematics also influence AC. For example, Cicuttini et al.[59] reported that varus knee angle was negatively associated with both femoral and tibial cartilage volume in the medial compartment of the knee (i.e., greater varus knee angle correlated with decreased cartilage volume). Specifically, a one degree increase in varus knee angle reduced femoral cartilage volume by 17.7µl annually[59]. Although this finding contradicts our current finding that frontal plane knee angles are not correlated to AC catabolism, the aforementioned study does support our positive correlation between peak knee abduction moment and serum COMP change as excessive varus knee angle during ambulation results in increased peak knee abduction moment[55]. Consequently, both frontal plane knee angles and moments influence AC catabolism.

Hip moments influence knee load, and peak hip flexion and abduction moment were negatively correlated with acute AC catabolism, due to ambulation. Increased hip flexor activation, during the push off phase of stance, would pull the thigh off the ground which may reduce knee load[61]. In the frontal plane, our data fit with previous results that indicated increased

hip abduction moment could be a protective mechanism against cartilage loss[62]. Furthermore, during single limb stance, weak hip abductor musculature results in excessive pelvic drop of the contralateral swing leg[63]. This movement shifts the body center of mass medially and increases medial tibiofemoral joint load[64]. Researchers have shown that increased frontal plane hip strength can decrease knee pain, increase physical function and muscle strength[65,66], and reduce internal knee abduction moment[67] and frontal plane hip joint excursion[68]. The negative correlation between acute AC catabolism and peak hip abduction moment and the combined findings of previous data imply there is some benefit for stronger hip abductors that may decrease knee joint load and reduce acute AC breakdown[49].

Although our data directly apply to a healthy demographic, consideration of our findings may also be applicable in a chronic joint degradation context. In conjunction with our slow ambulation results, researchers have observed that individuals suffering from knee joint pathologies (e.g., medial compartment OA, patellofemoral pain, or ACL-deficiency) attempt to reduce knee load via a reduction of knee extension moment[69,70]. Further, current thought indicates that internal knee extension and external knee adduction moments correlate with joint load and potentially exacerbate OA initiation and progression[21,25]. In support of our frontal-plane hip findings, Chang et al.[71] evaluated 103 at-risk knees and reported that greater hip abduction moments were associated with non-progressing knees, relative to knees that exhibited OA progression. Chang et al. also reported that an increased hip abduction moment reduced odds of OA progression by 50%[71]. It is unclear, however, which ambulatory mechanics directly influence chronic AC degradation. Future research should consider associations between the present mechanical variables and AC catabolism for pathological populations.

Fitting with previous research[33,35], we observed that the intensity of physical activity positively influences the magnitude of serum COMP increase. Contradicting previous hypotheses[34], however, we observed that duration of serum COMP elevation, post-exercise, is not influenced by physical activity intensity. Previous researchers have shown that serum COMP returns to pre-exercise levels within 30 min after a 30-min walk[33], but requires 60 min to return to pre-exercise levels after a 30-minute run[35]. Other researchers[32,34,47,72] reported even greater COMP elevation durations (e.g., 90 min[34], 24[72] and 48 h[32], and 6 d[32]) after subjects ran for even greater distances (3.96 to 200 km) and times (30 min to 33 h). Our data suggest that differences in COMP elevation duration are at least partially due to differing load frequencies (i.e., number of steps). For example, running 30-minutes at 2.2 m/s requires an average of 4,262 steps[35], while a 30-minute walk at 1.5 m/s requires only 3,507 steps[33]. The fact that we controlled for load frequency and observed no between-speed differences for COMP elevation duration supports the idea that COMP elevation duration is influenced by load frequency, rather than load magnitude. The present study is the first to show that when load frequency is controlled, serum COMP concentration returns to pre-exercise levels within 30 minutes, independent of ambulation speed.

It is difficult to interpret serum COMP. Although COMP is predominantly found in AC, it is also found in ligaments, tendons, menisci[73], and dermal and synovial fibroblasts[74]. Further, it is unclear which joints contributed to the observed serum COMP change, although previous research[35,47] indicates serum COMP change is at least partially due to knee load. Additionally, the relation between serum COMP concentration and AC health is unclear. Increased serum COMP, due to ambulation, may indicate either detrimental AC degradation[34,72] or healthy AC turnover[32,35]. Kim et al.[32] hypothesized that magnitude and duration of serum COMP elevation indicate AC degradation. Others have reported, however, that COMP concentration, pre- and

immediately post-walk, do not correlate with AC reduction after 5 y[75]. In healthy subjects, previous serum COMP data and supporting MRI findings[47] suggest that increased serum COMP reflects acute AC breakdown due to repetitive loads associated with ambulation. More information (e.g., measure of anabolic activity) is necessary to better understand the implications of serum COMP related to the overall health of AC. Longitudinal research will be necessary to understand whether serum COMP increase, due to ambulation, indicates detrimental AC degradation for young, asymptomatic subjects.

Two primary conclusions can be made from the present findings. First, certain measures of lower-extremity joint mechanics are associated with acute AC catabolism due to ambulation at various speeds. Several key kinetic variables (e.g., peak knee abduction, and hip abduction and flexion moments) explain much regarding the variance in serum COMP increase due to ambulation. These lower-extremity mechanical variables can be used to predict acute AC catabolism, due to ambulation, allowing researchers and clinicians to better predict and/or understand AC catabolism. Second, when load frequency is controlled, increased ambulation speed acutely results in increased AC catabolism. Ambulation speed does not, however, influence serum COMP elevation duration. Joint mechanics and load frequency appear to be responsible for the magnitude of COMP increase, while duration of COMP elevation post-ambulation is dictated by load frequency.

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Table 1.
Average (95% confidence interval) kinematic variables for each session (slow, medium, fast). Positive values represent flexion and adduction. Negative values represent extension and abduction. Knee angles for weight acceptance (WA) are peak value.

	Slow	Medium	Fast
Knee flexion angle at impact (°)	-2.1 (-4.7 – 0. 5)	6.9 (4.0 – 9.8)	9.3 (6.3 – 12.3)
Knee adduction angle at impact (°)	0.6 (-0.4 – 1.5)	0.2 (-1.2 – 1.5)	-0.3 (-1.7 – 1.1)
Knee flexion angle for WA (°)	15.4 (12.7 – 18.2)	35.4 (33.5 – 37.4)	38.8 (36.7 – 40.9)
Knee adduction angle for WA (°)	3.3 (2.1 – 4.4)	4.9 (2.5 – 7.3)	4.9 (2.7 – 7.1)

Table 2.
Average (95% confidence interval) kinetic variables for each session (slow, medium, and fast). Peak joint moments are represented with positive values for the respective variable.

	Slow	Medium	Fast
Peak vertical GRF (BW)	1.21 (1.18 – 1.24)	2.24 (2.16 – 2.32)	2.45 (2.35 – 2.55)
Loading rate ($BW \cdot s^{-1}$)	5.97 (5.67 – 6.26)	15.45 (13.71 – 17.19)	19.19 (17.13 – 21.24)
Plantar flexion moment ($Nm \cdot kg^{-1}$)	1.53 (1.45 – 1.61)	2.25 (2.05 – 2.44)	2.71 (2.50 – 2.92)
Ankle Inversion moment ($Nm \cdot kg^{-1}$)	0.25 (0.22 – 0.29)	0.32 (0.27 – 0.37)	0.37 (0.31 – 0.44)
Knee flexion moment ($Nm \cdot kg^{-1}$)	0.32 (0.28 – 0.37)	0.35 (0.29 – 0.40)	0.38 (0.32 – 0.45)
Knee extension moment ($Nm \cdot kg^{-1}$)	0.73 (0.63 – 0.83)	2.24 (2.03 – 2.25)	2.45 (2.25 – 2.65)
Knee abduction moment ($Nm \cdot kg^{-1}$)	0.46 (0.38 – 0.54)	0.75 (0.63 – 0.87)	0.83 (0.69 – 0.97)
Hip flexion moment ($Nm \cdot kg^{-1}$)	0.66 (0.56 – 0.75)	0.59 (0.53 – 0.65)	0.60 (0.52 – 0.67)
Hip extension moment ($Nm \cdot kg^{-1}$)	0.65 (0.52 – 0.78)	0.76 (0.66 – 0.87)	0.93 (0.82 – 1.04)
Hip abduction moment ($Nm \cdot kg^{-1}$)	0.93 (0.85 – 1.01)	1.57 (1.47 – 1.66)	1.63 (1.51 – 1.75)

Table 3.
Regression coefficients that describe the associations between significant mechanical variables (as identified by the regression model) and serum COMP increase due to ambulation.
AIN = peak internal ankle inversion moment; KE = peak internal knee extension moment; KAB = peak internal knee abduction moment; HF = peak internal hip flexion moment; HE = peak internal hip extension moment; HAB = peak internal hip abduction moment; KFI = knee flexion angle at heel strike.

	β	β Error	Lower 95%	Upper 95%	Cohen's *d*	*P*-Value
SLOW	46.0	19.0	7.8	84.3	0.70	0.02
MEDIUM	80.6	30.2	19.8	141.4	0.78	0.01
FAST	91.9	31.8	27.7	156.1	0.84	0.006
AIN	28.9	21.8	-15.0	72.7	0.40	0.19
KE	3.8	6.5	-9.3	16.9	0.17	0.56
KAB	24.4	16.4	-8.7	57.5	0.52	0.15
HF	-36.1	13.7	-63.6	-8.61	0.70	0.011
HE	13.0	9.7	-6.6	32.5	0.38	0.19
HAB	-50.1	19.1	-88.5	-11.6	0.82	0.012
KFI	-0.6	0.4	-1.5	0.2	0.42	0.15

Table 4.
Average (95% CI: lower limit – upper limit) absolute serum COMP concentration ($ng \cdot ml^{-1}$) for each session and draw.

	Slow	Medium	Fast	Average
Draw 1	121.5 (116.0 – 126.9)	122.9 (117.5 – 128.4)	122.9 (117.4 – 128.4)	122.4 (118.0 – 126.8)
Draw 2	127.9† (122.5 – 133.4)	145.4*† (140.0 – 150.8)	158.2*† (152.8 – 163.6)	143.8* (139.4 – 148.2)
Draw 3	113.4 (107.9 – 118.8)	109.3 (103.9 – 114.8)	114.8 (109.5 – 120.5)	112.5* (108.1 – 116.9)
Draw 4	114.9 (109.5 – 120.3)	104.7* (99.3 – 110.2)	112.7 (107.3 – 118.1)	110.8* (106.4 – 115.2)
Average	119.4‡ (115.6 – 123.3)	120.6‡ (116.8 – 124.4)	127.2 (123.4 – 131.0)	

* Significantly different ($p < 0.05$) from baseline serum COMP concentration for each session. † Significantly different ($p < 0.05$) between sessions at each draw. ‡ Significantly different ($p < 0.05$) from averaged fast session.

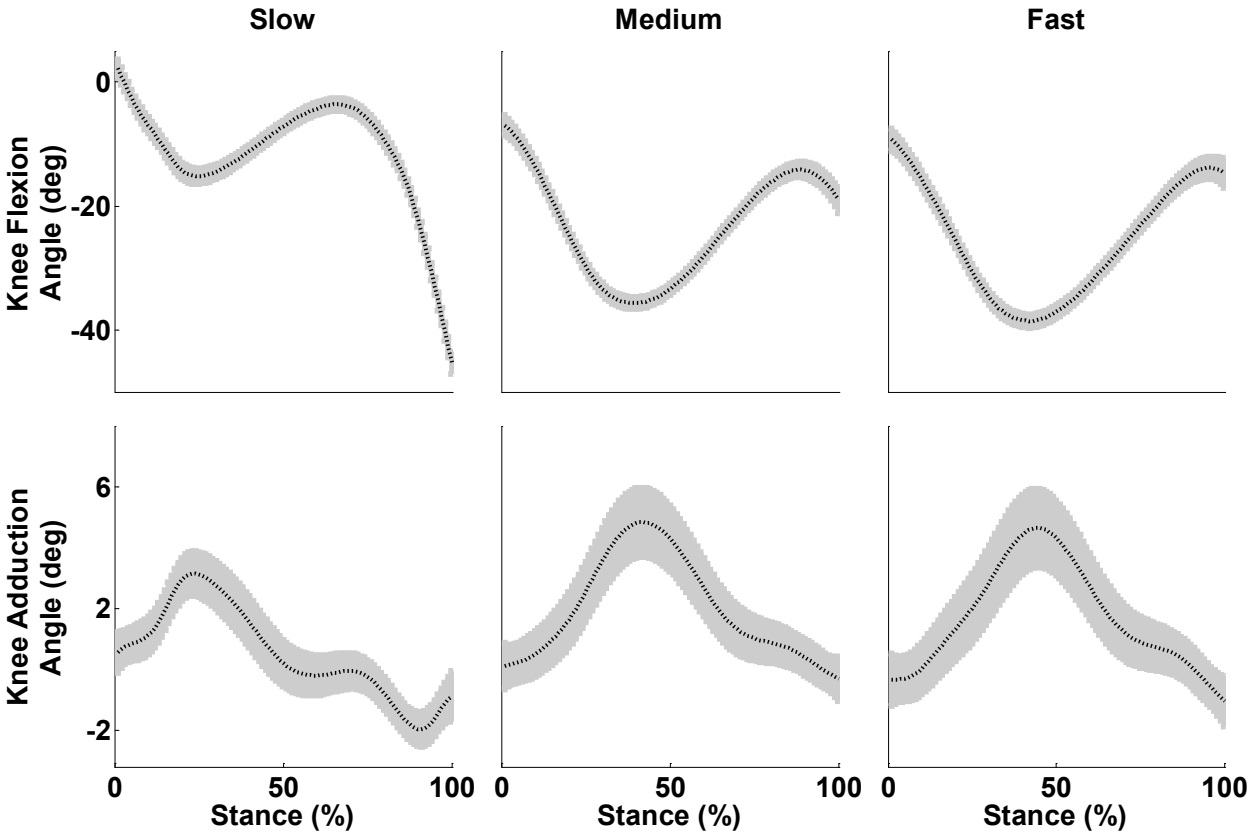

Figure 1. Ensemble means (dotted lines) and 95% confidence intervals (shaded bands) for each ambulation session (slow, medium and fast). Positive values indicate extension and adduction.

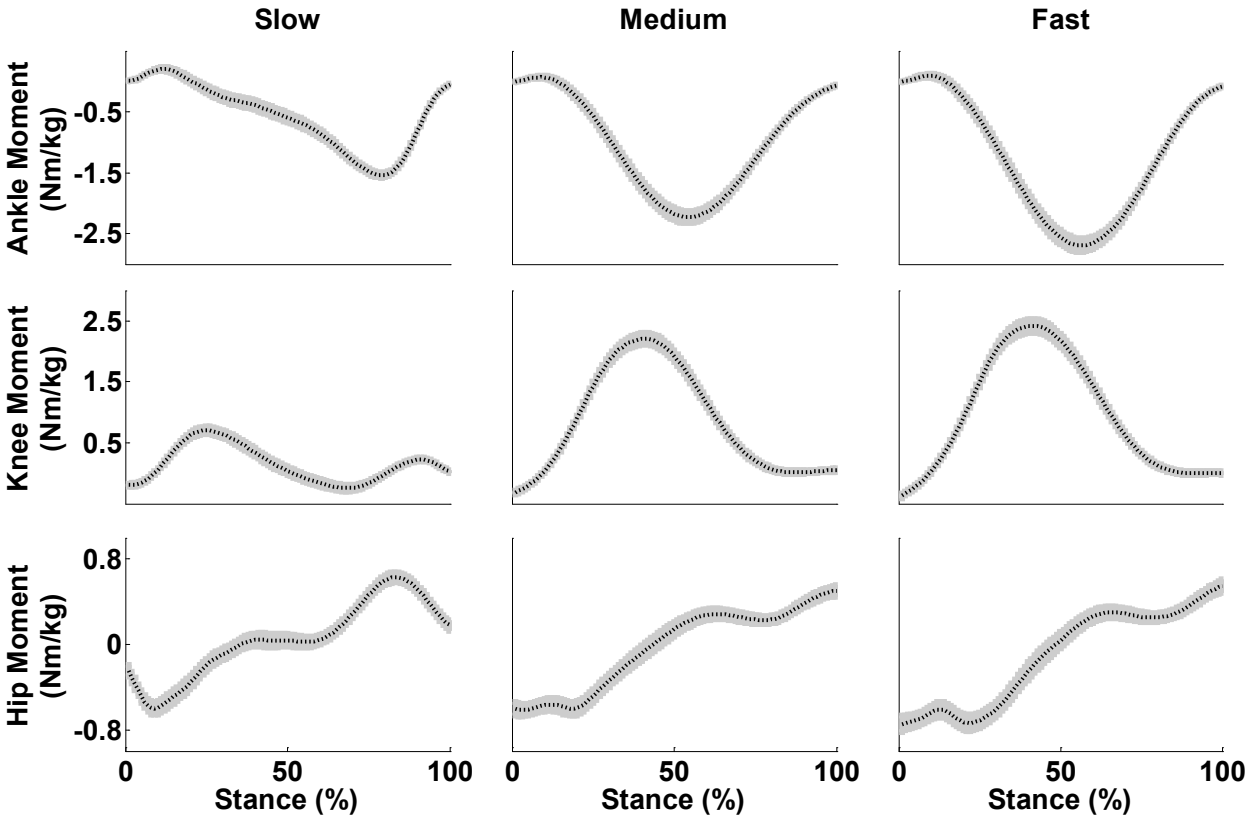

Figure 2. Ensemble means (dotted lines) and 95% confidence intervals (shaded bands) for sagittal-plane joint moment for each ambulation session (slow, medium, and fast). Positive values indicate dorsiflexion, knee extension, and hip flexion.

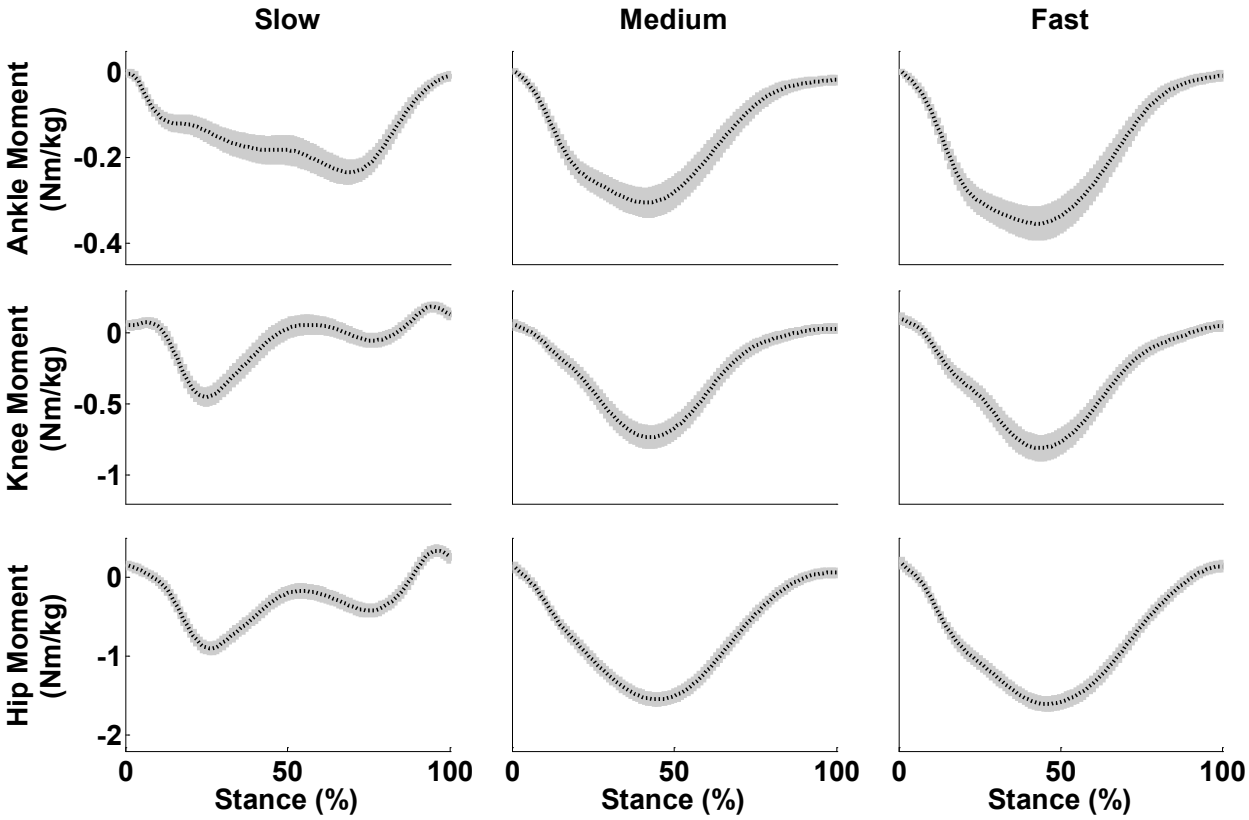

Figure 3. Ensemble means (dotted lines) and 95% confidence intervals (shaded bands) for frontal-plane joint moment for each ambulation session (slow, medium, and fast). Positive values indicate ankle eversion, knee adduction, and hip adduction.

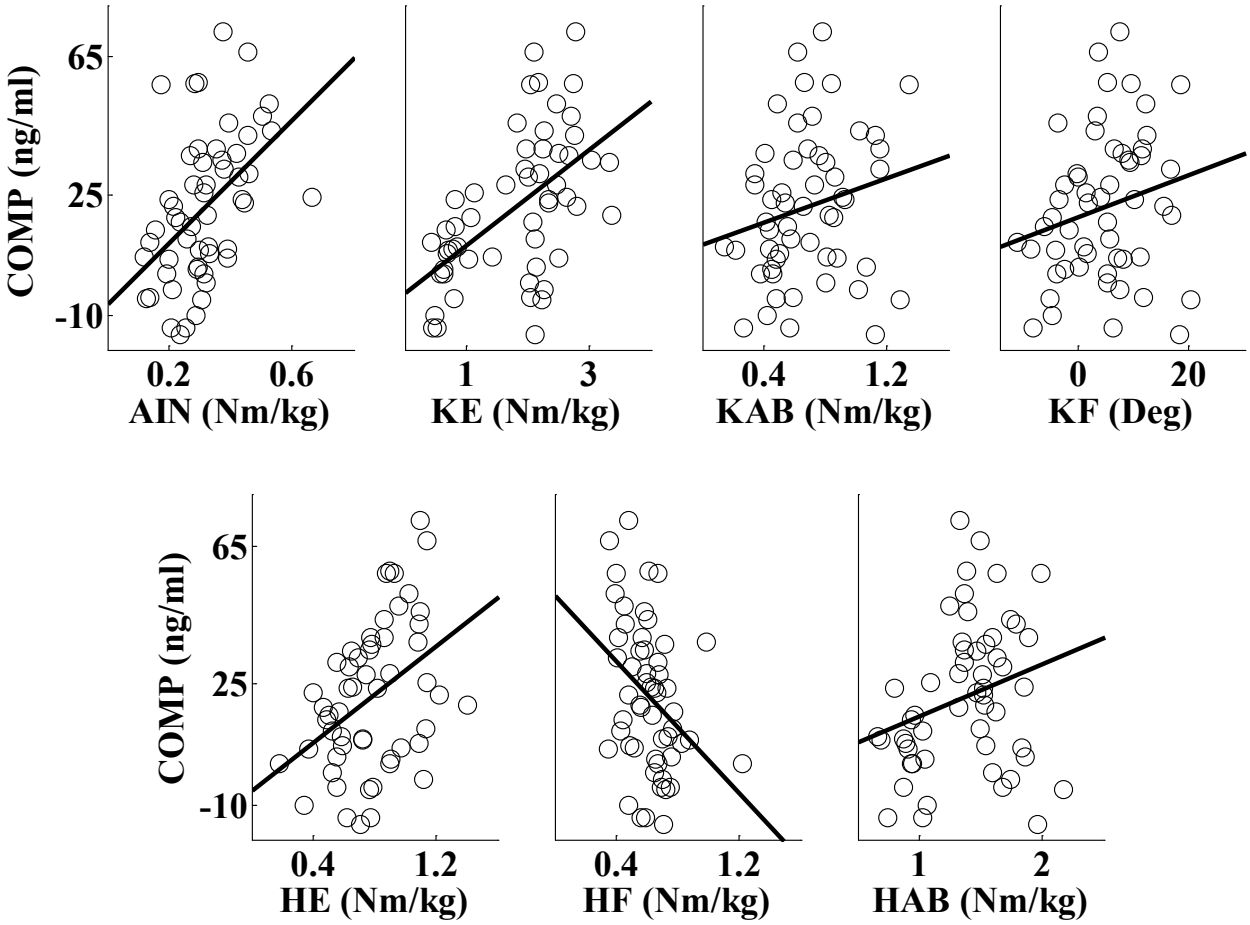

Figure 4. Regression plots with regression line for each of the mechanical variables found in the regression model. All variables are represented with positive values. AIN = peak internal ankle inversion moment; KE = peak internal knee extension moment; KAB = peak internal knee abduction moment; HF = peak internal hip flexion moment; HE = peak internal hip extension moment; HAB = peak internal hip abduction moment; KFI = knee flexion angle at heel strike. Note: The slopes of these lines do not depict the relationship between each mechanical variable with serum COMP change.