Changes in cartilage biomarker levels during a transcontinental multistage footrace over 4486 km

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Abstract

Background: Cartilage turnover and load-induced tissue changes are frequently assessed by quantifying concentrations of cartilage biomarkers in serum. To date information on the effects of ultramarathon running on articular cartilage is scarce.

Hypothesis: Serum concentrations of cartilage oligomeric matrix protein (COMP), matrix metalloproteinases (MMP)-1, 3, and 9, collagen COL2−3/4C long mono (C2C), collagen II C-propeptide (CPII) and C2C:CPII will increase throughout a multistage ultramarathon.

Study Design: Cross-sectional study.

Methods: Five blood samples were collected from 38 runners (4 female; age, 49.0 ± 10.7 years; body mass index, start: 23.1 ± 2.3 kg/m², finish: 21.4 ± 1.9 kg/m²) before (t₀) and during (t₁: 1002 km; t₂: 2132 km; t₃: 3234 km; t₄: 4039 km) a 4486 km multistage ultramarathon. Serum COMP, MMP-1, 3, and 9, C2C and CPII levels were assessed using commercial enzyme-linked immunosorbent assay. Linear mixed models were used to detect significant changes in serum biomarker levels over time with time-varying covariates body mass, running speed, and daily running time.

Results: Serum concentrations of COMP, MMP-9 and MMP-3 changed significantly throughout the multistage ultramarathon. On average, concentrations increased during the first measurement interval (MI1: t₁-t₀) by 22.5% (change MI1 [95% confidence interval], COMP: [0.29;0.71] ng/mL), 22.3% (MMP-3: [0.24;15.37] ng/mL), and 95.6% (MMP-9: [81.7;414.5] ng/mL), and remained stable throughout MI2, MI3 and MI4. Serum concentrations of MMP-1, C2C, CPII, and C2C:CPII did not change significantly throughout the multistage ultramarathon. Changes in MMP-3 were statistically associated with changes in COMP throughout the ultramarathon race (MMP-3: Wald Z=3.476, P=.001).
Conclusions: Elevated COMP levels indicate increased COMP turnover in response to extreme running, and the association between load-induced changes in MMP-3 and changes in COMP suggests the possibility that MMP-3 may be involved in the degradation of COMP.

Clinical Relevance: These results suggest that articular cartilage is able to adapt even to extreme physical activity possibly explaining why the risk of degenerative joint disease is not elevated in the running population.

Key Terms: Cartilage biomarkers, articular cartilage, tissue metabolism, extreme running

What is known about the subject: The effect of extreme running on articular cartilage metabolism is poorly understood.

What this study adds to the existing knowledge: Compared to single stage ultramarathons, COMP levels leveled off during the multistage ultramarathon suggesting that regular short recovery periods throughout ultra exercises in highly adapted ultra-endurance athletes may be sufficient for reaching a steady-state. Although the regulation of COMP is poorly understood, the statistical association between load-induced changes in MMP-3 and load-induced changes in COMP suggest that MMP-3 may be involved in the degradation of COMP.
Introduction

While in recent years, marathon running has become increasingly popular with more than 700 races per year worldwide and up to 50,000 participants per event\textsuperscript{34}, single stage ultramarathons (distances >42 km without break) and multistage ultramarathons (distances >42 km per day over multiple days) are performed by fewer athletes per event with races of varying distances. Ultramarathons represent extreme stress for the human body not only because of the duration of the physical activity but also due to environmental conditions such as weather and terrain.

The effects of multistage ultramarathon on health have received scientific interest, although the literature is largely limited to effects on the cardiovascular system\textsuperscript{18}, respiratory\textsuperscript{43} and skeletal muscle\textsuperscript{38}, and the gastrointestinal system\textsuperscript{38}. Interestingly, to date information on the effects of ultramarathon running on articular cartilage is scarce. A previous study\textsuperscript{37} on a transcontinental multistage footrace over 4486 km reported an initial T2*-signal increase during the first 1000 km followed by a slight decrease throughout the remainder of the race (with medium to high effect sizes) without any morphological or cartilage thickness changes in the ankle joints. These changes were interpreted as an increase in glucosaminoglycan as observed by Roos and Dahlberg\textsuperscript{31} in the weight-bearing posterior medial femoral condyle following moderate exercise. While these results provide an indication for the ability of the normal cartilage matrix to partially regenerate under ongoing multistage ultramarathon burden in the ankle joints\textsuperscript{37}, detailed knowledge on cartilage metabolism in response to extreme running exercise—especially with intermittent brief recovery periods such as during a multistage ultramarathon—is not available.

Cartilage turnover and load-induced tissue changes are frequently assessed by quantifying concentrations of cartilage biomarkers in serum. Potential cartilage biomarkers include structural proteins or enzymes reflecting cartilage metabolism. For instance, elevated
levels of cartilage oligomeric matrix protein (COMP) are associated with a higher incidence risk of knee osteoarthritis (OA), and load-induced changes in serum COMP predict cartilage thickness changes in patients with knee OA. COMP levels are sensitive to exercise bouts of walking (30 minutes; 4000 steps) and running (30 minutes; marathon (42 km) but not to deep knee bends (120 in 30 minutes). Previous studies have shown that COMP levels continue to increase throughout ultramarathon running races in runners without osteoarthritis. Hence, load-induced changes in COMP appear to be sensitive to load magnitude and number of loading cycles during exercise bouts.

Matrix metalloproteinases (MMPs) are a multi-member family of proteinases with a wide range of substrates including extracellular components, cytokines, receptors, and cell motility factors. For instance, interstitial collagenase (MMP-1) is produced by chondrocytes, osteoblasts and synovial cells that degrades collagen types I, II, and III in the extracellular matrix and mediates cartilage destruction, and is expressed at higher levels by OA chondrocytes than by normal chondrocytes suggesting a predominant role of MMP-1 in OA pathogenesis. Stromelysin-1 (MMP-3) is in part responsible for the degradation of non-collagen matrix proteins in cartilage in rheumatoid arthritis and OA, and increased levels of MMP-3 and stromelysin-2 (MMP-10) are found in articular cartilage and synovium of these patients. Gelatinase B (MMP-9) and collagenase-3 (MMP-13) coordinate cartilage collagen and aggrecan breakdown. Native collagen 2 is degraded by MMP-1, -8, -13, and -14, and partially degraded collagen 2 is then further degraded by MMP-2, MMP-9, and stromelysin-1 (MMP-3).

Another important cartilage component—and hence relevant in the context of cartilage mechanosensitivity—is type II collagen. In the process of collagen fibril formation, the C-propeptide is removed from the procollagen extracellularly and directly reflects the rate
of type II procollagen synthesis (CPII). Cleavage of type II collagen by collagenases yields fragments, such as the C2C epitope (COL2−3/4Clong mono), reflecting degradation.

The purpose of this study was to determine serum changes in cartilage biomarkers during a multistage ultramarathon race. We hypothesized that serum concentrations of COMP, MMP-1, 3, and 9, C2C, CPII, and C2C:CPII will increase throughout a multistage ultramarathon.

Materials and Methods

Of the 67 participants of a 4486 km multistage ultramarathon from the South of Italy to the North Cape taking place from April 19 to June 21, 36 runners (4 female; mean ± 1 standard deviation; age, 49.0 ± 10.7 years; height, 174 ± 8 cm; body mass start, 70.2 ± 10.2 kg, body mass finish, 65.2 ± 8.5 kg; body mass index, start: 23.1 ± 2.3 kg/m², finish: 21.4 ± 1.9 kg/m²) volunteered for this study after providing informed consent. This study was approved by the institutional review board and complied with the Declaration of Helsinki.

The race comprised 64 running days without any rest days with a mean distance per stage of 70.1 km (range, 44.0 to 95.1 km). All runners arrived at the same predetermined daily intermediate finish where they stayed overnight. Because of the season (late spring to early summer) and the route from South to North, temperatures stayed relatively constant throughout the race. All runners were official race participants meeting the ultramarathon registration requirements: ≥ 18 years; medical health certificate; and proof of appropriate ultramarathon running performance. In the 12 months prior to the race, participants spent an average 7 to 20 hours per week to run an average of 50 to 220 km per week. Five participants had a unilateral focal chondral defect in the patellofemoral joint (femur) and one participant in the tibiofemoral joint (tibia) without any symptoms diagnosed by magnetic resonance.
imaging MRI performed as part of an associated MRI study on these runners. The MR signal of these defects did not change throughout the ultramarathon.

Serum samples were collected within 4 days prior to the race (t₀) and on days 15 (t₁: 1002 km), 31 (t₂: 2132 km), 47 (t₃: 3234 km), and 58 (t₄: 4039 km) of the 64-day race.

Average running speed and daily running time for each of the four measurement intervals (MI; MI1: t₁-t₀; MI2: t₂-t₁; MI3: t₃-t₂; MI4: t₄-t₃) between blood sampling was calculated and body mass measured for each runner. Blood samples were taken from the cubital vein after the daily running stage. The samples were immediately centrifuged, aliquoted, frozen (below -20°C), and transferred to -80°C after the race. Serum biomarker levels were determined in duplicates using commercial enzyme-linked immunosorbent assays: (COMP: Wieslab® hCOMP quantitative kit (Euro Diagnostica AB, Malmö, Sweden); MMP-1: RayBio® Human MMP-1 ELISA kit (RayBiotech Inc., Norcross, GA, USA); MMP-3 and MMP-9: Human MMP-3 Quantikine Kit and Human MMP-9 Quantikine Kit (Bio-Techne Ltd., Abingdon, UK); C2C and CPII: Collagen Type II Cleavage Assay and Procollagen Type II C-Propeptide Assay (IBEX Technologies Inc. Montreal, Quebec, Canada)). All biomarkers were determined simultaneously for each sample upon thawing the sample to avoid refreezing samples. All samples of each participant were tested on the same plate to avoid any errors due to plate-to-plate differences. Intra-assay variability was assessed as relative coefficients of variation (CV%) between duplicates and was 4.8% for COMP, 3.7% for MMP-1, 7.0% for MMP-3, 2.7% for MMP-9, 6.9% for C2C, and 7.3% for CPII.

**Statistical analysis**

All statistical analyses were performed using SPSS Version 21 (IBM Corporation, Armonk, NY). All parameters were tested for normal distribution using Kolmogorow Smirnow tests. Linear mixed models were used to detect significant changes in serum...
biomarker levels over time with time-varying covariates body mass, running speed, and daily running time, and posthoc least square tests. Because not all runners completed the entire race, missing data were handled by imputing values using the last observation carried forward method, and all models were rerun. Race finishing was used as between subject factor in the models (finisher versus non-finisher). The significance level for all statistical tests was set a priori to .05.

Results

Participants ran with an average running speed of 8.2 ± 1.4 km/h (mean ± 1 standard deviation) and lost an average of 5.3 ± 2.7 kg of body mass (Table 1). Six runners dropped out in MI2, one in MI3 and four in MI4. Age, height, body mass, running speed and biomarker levels after MI1 and MI2 did not differ between groups by time of dropout (P>.029). The following reasons for drop-out were reported: shin splint (N=4), thigh splint (N=2), foot pain with purulence (N=1), phlegmon finger treated by surgery (N=1), proximal tibia fracture (N=1), anterior pelvic ring fracture (N=1; participant with focal cartilage defect in patellofemoral joint), and respiratory infection (N=1). All other participants with focal cartilage defects completed the race. None of the biomarker results differed between

Table 1. Mean (1 standard deviation) time varying covariates body mass, running speed and daily running time before and throughout the multistage ultramarathon.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$t_0$ Pre-race (N=36)</th>
<th>$t_1$ After 1002 km (N=36)</th>
<th>$t_2$ After 2132 km (N=30)</th>
<th>$t_3$ After 3234 km (N=29)</th>
<th>$t_4$ After 4038 km (N=26)</th>
<th>P-value finisher$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass (kg)</td>
<td>70.6 (9.9)</td>
<td>67.6 (9.2)</td>
<td>66.4 (8.8)</td>
<td>65.6 (8.8)</td>
<td>65.2 (8.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean running speed (km/h)</td>
<td>8.40 (1.25)</td>
<td>8.46 (1.39)</td>
<td>8.43 (1.47)</td>
<td>8.41 (1.44)</td>
<td></td>
<td>.955</td>
</tr>
<tr>
<td>Mean daily running time (h)</td>
<td>8.1 (1.1)</td>
<td>7.7 (1.3)</td>
<td>7.9 (1.2)</td>
<td>7.8 (1.6)</td>
<td></td>
<td>.226</td>
</tr>
</tbody>
</table>

$^a$—results of the linear mixed models on the runners who completed the race (N=23). Note: The results of the linear mixed models did not change when data of non-finishers were considered using the last observation carried forward approach.
participants with or without focal cartilage defect.

Serum concentrations of COMP, MMP-9 and MMP-3 changed significantly throughout the multistage ultramarathon (Table 2). On average, concentrations increased during MI1 by 22.5% (change MI1, COMP: [0.29; 0.71] ng/mL), 22.3% (MMP-3: [0.24; 15.37] ng/mL), and 95.6% (MMP-9: [81.7; 414.5] ng/mL), and remained stable throughout MI2, MI3 and MI4 (Figure 1). Changes in serum COMP, MMP-3, and MMP-9 concentrations during MI1 did not differ between finishers and non-finishers (time x finishing group interaction: P = .387, P = .620, and P = .945, respectively). Serum concentrations of MMP-1, C2C, CPII, and C2C:CPII did not change significantly throughout the multistage ultramarathon (Table 2). The results of the linear mixed models did not change when data of non-finishers were considered using the last observation carried forward approach.

The time varying covariate body mass was significantly associated with changes in COMP, MMP-3, and MMP-9 throughout the multistage ultramarathon (COMP: Wald
Z=3.411, P=.002; MMP
-3: Wald Z = 2.472, P=.013; MMP
-9: Wald Z = 2.226, P=.026). The time varying covariates running speed and daily running time were not associated with changes in any cartilage biomarker. Changes in MMP-3 were associated with changes in COMP throughout the ultramarathon race (MMP-3: Wald Z=3.476, P=.001) where in 68% of runners ultramarathon-induced changes in MMP-3 levels explained more than 30% of ultramarathon-induced changes in COMP levels. Figure 2 shows an example of the relationship between MMP-3 and COMP levels for one participant. Changes in MMP-1, MMP-9, C2C, CPII or C2C:CPII were not associated with changes in COMP.

**Discussion**

The purpose of this study was to determine serum changes in cartilage biomarkers during a multistage ultramarathon race. COMP, MMP-3, and MMP-9 levels increased within the first 11 days of the ultra-marathon race and remained elevated throughout the remainder...
The time varying covariate body mass was associated with changes in COMP, MMP-3, and MMP-9 throughout the multistage ultramarathon. Changes in MMP-3 were associated with changes in COMP throughout the ultramarathon race. The results provide first evidence that only some cartilage biomarkers are sensitive to extreme running exercise and that changes in these biomarkers are correlated.

Of the known potential cartilage biomarkers, COMP has been used most often as surrogate measure of cartilage degradation in studies on the effect of exercises of different intensities on articular cartilage. Interestingly, the magnitude of increase in COMP in our study (+22.5%) was not greater than that reported for marathon and single stage ultramarathon races. For instance, COMP levels did not change more than after other physical activities such as walking 14 km uphill, walking for 30 minutes, walking 4000 steps at slow, medium or fast walking speed, or running for 30 minutes. Moreover, increases in COMP after a marathon range from 17 to 60%. Kim et al. reported a 1.9- and 3-fold increase in COMP levels after 100 km and 200 km, respectively, of a 200 km single stage ultramarathon in two separate studies (mean race time, 32.5 hours). In a single stage ultramarathon study by Shin et al., COMP levels increased by 130.7% at 100
km to 160.4% at 200 km and 194.1% at 308 km (mean race time, 61.5 hours). All of these studies have in common that COMP concentrations continued to increase throughout these single stage marathon\textsuperscript{14,23} or single stage ultramarathon races.\textsuperscript{13,14,38} In contrast, serum COMP levels in our study remained stable throughout the multistage ultramarathon race after the initial 1002 km. Because the second blood draw was taken 11 days into the race (after 1002 km), information regarding a potential initial continuous increase or a peak in COMP level between days 1 and 11 of the race is not available.

Previous studies have reported a recovery of COMP levels within 30 minutes to several days for light (30-minute walking\textsuperscript{21} or running\textsuperscript{25}) and intense exercise (marathons\textsuperscript{14,22}, ultramarathons\textsuperscript{14}), respectively. Moreover, Mündermann et al.\textsuperscript{22} have shown that COMP levels in runners with faster marathon finishing times return to pre-race levels within 24 hours of the marathon but not in those with slower marathon finishing times. The authors attributed these differences to different relative load between runners because of greater number of steps taken during the race in slower runners or differences in fitness among runners. In addition, a predefined walking exercise (4000 steps) at varying walking speeds (slow, medium, fast) resulted in systematic changes in COMP levels and these changes were related to differences in joint mechanics\textsuperscript{5}. Accordingly, one could expect that changes in COMP during the multistage ultramarathon are associated with running speed and/or daily running time. However, the linear mixed models with time varying covariates did not reveal such an association in this group of experienced ultramarathon runners. Interestingly, a 3-week multistage cycling race did not result in changes in COMP levels in pro-cyclists\textsuperscript{3}. Like running, cycling is characterized by high cyclic joint loads (e.g. several times body weight at the knee\textsuperscript{15}), but unlike in running, joint forces rise and fall without an impact peak caused by the collision of the body with the ground. The lack of changes in COMP levels in a multistage cycling race and increases in COMP levels in a multistage running race suggests
that COMP levels are sensitive to repetitive impact loads most likely of articular cartilage and not of other musculoskeletal tissues.

The main differences between single stage and multistage ultramarathons are the much longer distances covered and the daily (usually overnight) resting times in multistage races. Based on COMP data from marathons and single stage ultramarathons, one would expect the magnitude of changes in COMP levels to increase with increasing distance with a gradual increase in levels throughout a race. The fact that COMP levels did not increase more during the multistage ultramarathon than reported increases in shorter single stage races suggests that the daily resting time may have been sufficient for tissue recovery to some extent. Slower runners took more time each day to complete the daily stage and hence had shorter overnight resting times implying less recovery. However, daily running time was not associated with changes in COMP. Hence, even in slower runners, overnight resting times may have been sufficient for preventing further increase in COMP levels throughout the race. It appears that cartilage reached a steady state during the race, which is further supported by previous reports\textsuperscript{35, 37} of an initial T2* increase in articular cartilage of the ankle and the knee followed by a subsequent T2* decrease (ankle)\textsuperscript{37} and steady-state (knee)\textsuperscript{35} in these runners. The changes in COMP levels reported here support the previous suggestion of the ability of the normal cartilage matrix at the ankle joints to partially regenerate with continuing multistage ultramarathon load.\textsuperscript{37} Participants of multistage ultramarathon races represent a unique sample of athletes that are extremely well conditioned because of extreme training regimens possibly explaining the smaller increases in COMP levels compared to those reported in marathon and single stage ultramarathon runners. These results are relevant not only for ultramarathon runners but also for elite athletes training for marathons requiring high weekly running distances or for extreme expeditions of several days or week.
Cyclic loading enhances COMP expression in a fully developed pericellular matrix.\textsuperscript{9} While some data on the effects of running on COMP are available, little is known on the effects of running on other cartilage biomarkers. COMP levels are a measure of intact COMP or COMP fragments in blood. However, it is unclear if these fragments are present because of simple turnover or cartilage breakdown. Hence, markers reflecting tissue metabolism must also be considered. MMP-3 and MMP-9 levels but not MMP-1, C2C, or CPII levels changed during the multistage ultramarathon. Interestingly, COMP, MMP-3, and MMP-9 but not MMP-1 levels changed during immobilization during a 21-day bed-rest study.\textsuperscript{16} Hence, COMP, MMP-3, and MMP-9 systematically respond to extreme load and to unloading emphasizing their importance in the mechanobiology of articular cartilage. MMP-3 is in part responsible for the degradation of non-collagen matrix proteins in cartilage in rheumatoid arthritis and OA\textsuperscript{2} and MMP-9 and MMP-13 coordinate cartilage collagen and aggrecan breakdown. The association of changes in MMP-3 levels with changes in COMP levels indicate that MMP-3 may be involved in the degradation of COMP. This result supports findings of in situ experiments where digestion of human articular cartilage with MMP-3, -12, or -13 but not with MMP-2, -8, or -9 yielded fragments of COMP.\textsuperscript{45} MMP-1 degrades collagen types I, II, and III in the extracellular matrix, and mediates cartilage destruction.\textsuperscript{2, 40} The lack of changes in MMP-1, C2C and CPII levels, and in C2C:CPII suggest that the extreme running load did not affect collagen turnover. Similarly, COMP, MMP-3, and MMP-9 but not MMP-1 levels changed in a 21-day bed rest study\textsuperscript{16, 17} suggesting that MMP-1 is not sensitive to loading.

Henrotin et al.\textsuperscript{12} observed decreases in Coll2-1 levels (a denaturation epitope located in the triple helical domain of the type II collagen molecule that is made available by unwinding of the triple helix\textsuperscript{11}) after a marathon, which they interpreted as a protective effect of long distance running on cartilage. In contrast, we did not observe changes in C2C or CPII
levels or in C2C:CPII during the multistage ultramarathon suggesting that the balance
between collagen II synthesis and degradation was unaffected by the extreme running load.
However, because the second sample was taken after about 1000 km, it is possible that we
were unable to detect subtle changes early in the race. Moreover, it is possible that extreme
load does not initiate collagen turnover but causes reorganization or loss of organization of
the matrix and degradation of proteoglycans resulting in an increases in glucosaminoglycan
content\textsuperscript{31, 32}, which has also been indicated by previously observed changes in T2* of
articular cartilage at the ankle during a multistage ultramarathon.\textsuperscript{37}

Some discrepancies between our results and the literature may have been caused by
methodological differences. For instance, while many studies used a blood sample taken
within 2 hours prior to the race as baseline value, in other studies baseline samples were
taken 24 hours before the marathon\textsuperscript{41}, 6 to 10 hours before the ultramarathon\textsuperscript{14}, and up to 4
days before the multistage marathon in our study. Moreover, none of the studies specified
whether physical activity prior to the baseline sample was controlled or restricted which may
influence baseline levels.\textsuperscript{21} Interestingly, most studies\textsuperscript{13, 14, 22, 38} on marathon and
ultramarathon running involve participants with an average age around 50 years who were
experienced ultramarathon runners when 25% of the population between 45 and 64 years
suffer from arthritis or joint pain.\textsuperscript{1} Some runners had focal lesion in the patellofemoral joint
without any symptoms, and the MR signal did not change throughout the race. Hence, the
patellofemoral joint may not have been adversely affected by the extreme running exercise on
flat ground. Further, it is possible that only athletes without any joint degeneration affecting
joint mechanics will participate in such a physically and mentally demanding sports. Based
on the literature it is also feasible that a stringent training regimen over a long time may
protect against cartilage degeneration in the tibiofemoral and ankle joints as previously
shown in animal studies\textsuperscript{8, 28} and suggested by Schütz et al.\textsuperscript{37}
Conclusions

The results of this study provide evidence that physical load affects some cartilage biomarkers (COMP, MMP-9, and MMP-3 but not MMP-1, C2C, CPII, or C2C:CPII) and that the magnitude of these changes appear to be limited by providing regular short recovery periods throughout ultra-running exercises in highly adapted ultra-endurance athletes. While COMP levels may play an important role in the mechanotransduction of ambulatory load to chondrocytes, the role of COMP concentration on cartilage health in this population remains unclear. Nonetheless, elevated COMP levels indicate increased COMP turnover in response to extreme running, and the association between load-induced changes in MMP-3 and changes in COMP suggests the possibility that MMP-3 may be involved in the degradation of COMP. The lack of changes in MMP-1, C2C, CPII, and C2C:CPII indicate that these markers are not involved in load-induced changes in articular cartilage.

Author disclosures

We declare that we have no conflicts of interest in the authorship or publication of this contribution

References


