The effects of Lyprinol® on delayed onset muscle soreness and muscle damage in well trained athletes: A double-blind randomised controlled trial☆

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Summary
Objectives: The aim of the study was to determine if Lyprinol® is effective in reducing pain, indicators of inflammation and muscle damage, and in turn improving performance in well trained athletes suffering from delayed onset muscle soreness (DOMS).
Design: A double blind randomised placebo controlled trial.
Setting: Twenty well trained male volunteers, matched by $VO_{2\,max}$ were randomly assigned to consume 200 mg of Lyprinol® or an indistinguishable placebo daily for 8 weeks prior to a downhill treadmill running episode designed to induce DOMS.
Main outcome measures: Performance measures (Kin-Com, counter movement and squat jump), pain assessments (visual analogue scale, algometer) and blood analyses (Interleukin-1, Interleukin-6, Interleukin-10, tumour necrosis factor-α, C-reactive protein, myoglobin, creatine kinase) were assessed at 7 time points over 5 days (pre, post, 4, 24, 48, 72 and 96 h after the downhill run).
Results: No statistically significant differences were identified in any parameters between the active and placebo groups at any time point.
Conclusion: After 2 months ingestion of Lyprinol® at the currently recommended dosage (200 mg/day) and a demanding eccentric exercise intervention, Lyprinol® did not convincingly affect DOMS and indicators of muscle damage.
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Introduction

Delayed onset muscle soreness (DOMS) and muscle damage are common self-limiting, training related conditions that can result in loss of muscle force and significant pain.[1–3] DOMS is classified as a type one muscle strain that presents with tenderness and stiffness one to two days after exercise or unaccustomed movement.[2,4,5] A number of theories have been proposed to explain the mechanism of DOMS (lactic acid accumulation, muscle spasm, connective tissue damage, muscle damage, inflammation, enzyme efflux[6]), however, no one theory is backed by conclusive evidence. For example, it has been hypothesised that the inflammatory process contributes significantly to DOMS,[7–9] however conflicting studies[10–12] suggest that inflammation may not be a specific result of eccentric exercise, even when DOMS is present.

For athletes required to train and compete daily, or more frequently, DOMS can pose an obstacle to optimal performance. At present there are multiple proposed methods for treating DOMS, including cryotherapy, anti-inflammatory medication, stretching, hyperbaric oxygen, homeopathy, ultrasound, L-carnitine, rest, light exercise and electromagnetic shields.[5,6,8,13,14] However, to date an effective treatment for DOMS has not been established.[15]

Lyprinol® is a lipid extract of the New Zealand green-lipped mussel. It is rich in eicosatetraenoic acid, docosahexanoic acid and also contains octadecatetraenoic acid, eicosapentaenoic acid, sterol esters, polar lipids and carotenoids.[16,17] It has been demonstrated that Lyprinol® possesses anti-inflammatory effects and ''has been shown to down regulate the lipoxygenase (LIPOX) and cycloxyygenase-2 (COX) pathways which are responsible for the production of pro-inflammatory leukotrienes, some prostaglandins and other eicosanoids''.[18] Non steroidal anti inflammatory drugs (NSAIDs) can be classified as either single or dual action drugs, single acting being those which inhibit the COX pathway and dual acting which inhibit both COX and LIPOX pathways.[15] As Lyprinol® has demonstrated to down regulate both the COX and LIPOX pathways it is hypothesised that as a dual acting anti-inflammatory, it may have a greater effect than those that act on a single pathway.

Lyprinol® as an anti-inflammatory agent has been investigated through epidemiological observation, population studies and randomised controlled trials. The majority of Lyprinol® research has been conducted on osteoarthritis,[16,19–23] rheumatoid arthritis[19,20,22,23] and asthma.[24] The vast majority of these studies indicate Lyprinol® is an effective alternative therapy for these conditions.[16,17,24] Though the role of inflammation during exercise-induced muscle injury and DOMS has not yet been clearly defined, it is possible that the inflammatory response may be responsible for initiating, amplifying, and/or resolving skeletal muscle injury.[2] Therefore, though there are no published studies investigating the effects of lipid extracts on DOMS, it is reasonable to consider they may impact on this condition. As Lyprinol® has an effect on the inflammatory process it may influence the cytokine response after intense exercise, muscular pain and an athlete's performance if inflammation is a component of DOMS.

The purpose of this study was to determine the effect of Lyprinol® on indicators of muscle damage and inflammation, pain, and performance in well trained athletes.

Materials and methods

Participants

Twenty male volunteers with a mean (SD) age of 25.3 (±7.5) years, mass of 80.3 (±7.5) kg and height of 180.4 (±6.32) cm completed the study. All subjects were well trained males from a variety of sports (Australian Football, cycling, middle and long distance running and rugby union), with mean predicted $VO_{2\,max}$ of 55.4 (±4.5) ml/kg/min^{-1}.

Male athletes were the target group for this study as the effects of hormones associated with the menstrual cycle on markers of muscle damage and inflammatory ions are unclear. To prevent any confounding results males were deemed the most appropriate participants for this study. For this study, 20 participants were expected to provide a clinically significant outcome based on the matching of subjects and other studies conducted in this field.[1,25,26]

Subjects who participated in the study did not report injuries or conditions associated with inflammation, or consume any anti-inflammatory medications concurrently to consuming the Lyprinol® or placebo capsules. This included the lead in phase of 8 weeks, and the week in which the physiological testing was carried out. Subjects abstained or completed only light training during the week of physiological testing. Subjects were requested not to participate in any form of eccentric exercise for 6 weeks prior to testing and for the duration of testing. All subjects gave their written informed consent. The Human Ethics Committees of the Australian Institute of Sport (AIS) and University of Western Sydney (UWS) approved the study.

Procedures

All subjects completed a 20 m shuttle run test to predict $VO_{2\,max}$. Whilst completing the shuttle run, each subject wore a polar heart rate monitor (*Polar Team System* and *Polar S710i*, Pursuit Performance, South Australia). Maximum heart rate was recorded and used to determine the appropriate running intensity, and therefore speed for the downhill run. After each subject's $VO_{2\,max}$ was estimated, subjects were matched based on $VO_{2\,max}$. This ensured matched subjects had similar aerobic capacity[27] therefore could maintain a similar intensity whilst completing the downhill run. One subject from each matched pair was allocated to each of the active or placebo groups by a computer generated randomisation chart compiled by an independent researcher. Each Lyprinol® capsule contained 50 mg of *Perna canaliculus* and each placebo capsule contained olive oil. The placebo capsules were identical to the active product in terms of size, colour and texture. There was no taste associated with the capsules to ensure subject blinding. For a detailed analysis of the amount of active compounds present in the active product, please refer to Table 1. The indistinguishable capsules were distributed to subjects by an independent administrator at the AIS therefore blinding the researchers and subjects.

Table 1 Lyprinol® fatty acid analysis.

FA	Fatty acid	Green lipped mussel oil (%)	Olive oil (%)	Lyprinol® capsules (%)
14:0	Myristic	4.7 (3—6)		1.0
16:0	Palmitic	14.6 (9—18)	11.1	10
16:1	Palmitoleic	7.4 (5—10)		2.5
18:0	Stearic	2.9 (2—4)	2.4	1.5
18:1	Oleic (octadecamonoenoic)	6.0 (4—13)	75.9	48
18:2ω6	Linoleic	2.1 (1.5—3 1)	6.2	6
18:3ω3	Alpha-linolenic	1.8 (1 5—2 2)	0.5	0.5
18:4ω3	Octadecatetraenoic (OTA)	3.6 (2 5—4.7)		0.5
20:0	Arachidic	0.1	0.2	0
20:1	Eicosamonoenoic	1.8 (1.1—2.3)		0.2
20:4ω6	Arachidonic	1.8 (0.9—4.4)		0.1
20:4ω3	Eicosatetraenoic (ETA)	0.6 (0.4—0 7)		0.05
20:5ω3	Eicosapentaenoic (EPA)	20.7 (14—28)		4
22:5ω3	Docosapentaenoic (DPA)	1.1 (0 8—1 4)		0.2
22:6ω3	Docosahexaenoic (DHA)	17.5 (14—22)		3
Others		13 (10—6)		3

Capsules were consumed for 8 weeks prior to the downhill run at a dosage of 2 capsules morning and evening. Each subject recorded their consumption on a compliance checklist and compliance was double checked by counting the number of capsules in each bottle before distribution and at the completion of the study. After 8 weeks of capsule consumption, subjects began 5 consecutive days of testing which involved assessments at seven different time points: pre downhill run then post, 4, 24, 48, 72 and 96 h after the downhill run. Table 2 details a timeline of the interventions and testing regime.

Downhill treadmill running protocol

DOMS and associated muscle damage was induced by downhill treadmill running on the AIS Biomechanics Bitza motor driven treadmill (Sportech, Australia). This method for inducing DOMS was chosen due to available equipment, and previous research indicating this particular protocol would induce DOMS despite the training status of the athlete.[28] The protocol involved 5 bouts of 8 min running at a −10% gradient with 2 min walking comfortably on the flat between bouts. Bouts were run at 80% of the subject's maximal heart rate as determined from the 20 m shuttle run and monitored using a Polar Heart Rate Monitor. This protocol is described in Eston et al.[25]

Outcome measures

Pain measures

Visual analogue scale: Pain was assessed in the subject's quadriceps using a visual analogue scale, which ranged from 0 (no pain) to 100 mm (worst possible pain). This subjective pain assessment has been used by numerous studies as a reliable and valid method of assessing pain.[13,29—31]

Algometer: A Somedic pressure algometer (Somedic Production AB, Sollentuna, Sweden) was used to monitor pressure induced pain at five specific sites on the quadriceps. All tests were performed by the same investigator

Table 2 Study procedures.

Variable	10 weeks prior	8 weeks prior	Initial session[a]	4, 24, 48, 72 & 96 HP
20 m shuttle run	√			
Lyprinol® consumed		√2bd	√2bd	√2bd
Treadmill protocol			√	
Kin/Com			√	√
CMJ & SJ			√	√
VAS			√	√
Algometer			√	√
Blood taken (for IL-1, IL-6, IL-10, TNF-α, CRP, myoglobin & creatine kinase)			√	√

CMJ: counter movement jump; SJ: squat jump; VAS: visual analogue scale.
√: a single assessment.
HP: hours post.
 [a] Initial session 2 assessments occurred, one pre the treadmill protocol and one post

throughout the study. Specific sites for assessment were determined using a reference system[32,33] involving two anatomical points [anterior superior iliac spine (ASIS) and superior pole of the patella (SPP)]. All measurements were taken on the right side whilst the subject was supine. A longitudinal axis was created between the ASIS and the SPP from which the sites were marked with a permanent marker to ensure accuracy at each time point. The measured sites were: 15 cm distal to the ASIS, 4 cm proximal to the SPP, midpoint of the ASIS and SPP along the axis, then 2 cm lateral and 2 cm medial of this midpoint. These points of assessment were validated by a reliability study conducted by the primary researcher at the AIS, and the algometer has been validated in other studies.[34,35]

Performance measures

Kinetic communicator: A Kin-Com (Version 5.32, Chattanooga group Inc., TN, USA) was used by all subjects to generate angle torque curves of concentric contractions from the quadriceps and hamstrings. Subjects were seated on the Kin-Com upright and completed 8 continuous isokinetic maximal force contractions at 60° per second on both the right and left legs. Data from the Kin-Com was downloaded into the software program *Igor Pro* (Version 5.04A, WaveMetrics Inc., OR, USA) which enabled the generation of angle torque curves using 4th order polynomials to create a fit force, the average force produced by the subjects' 8 repetitions. This polynomial was used to determine the peak force for both the right and left legs.

Counter movement and squat jump: The countermovement (CMJ) and squat jump (SJ) was conducted using a YARDSTICK mechanical vane type vertical jump measuring device (Swift Performance Equipment, Australia).

The *CMJ* was adapted from that used by Byrne and Eston.[1] Subjects initially provided a reach height by standing underneath the YARDSTICK with flat feet together then reaching with one arm as high as they could, displacing the vanes. Subjects commenced the jump from an erect standing position with arms by their sides. On the command ''go'' subject made a downward countermovement and then jumped vertically as high as they could. The jump was repeated 3 times with the maximal height reached recorded.[36]

Three *SJ* were performed following the 3 vertical jump trials. Subjects stood underneath the YARDSTICK with their feet shoulder width apart. They were required to have their hands resting on their quadriceps to prevent any momentum that may have been gained from an arm swing. Subjects squatted to a 90° angle at the knee and hip joints (measured using a goniometer), held for 3 s then on the command ''go'' jumped vertically to displace the vanes. Each jump was observed and only those with no counter movement and arm swing were accepted.[36]

Both the CMJ and SJ measurements were calculated by subtracting the reach height from the jump height.

Markers of inflammation and muscle damage

Sixteen millilitres of blood was collected from an antecubical vein into two 8 ml vacuette's with separation gel and clotting accelerator (Greiner Bio-one) immediately upon assumption of supine position. Blood was then centrifuged (Labofuge 400R, Heraeus Instruments, Radiometer Pacific,

Australia) for 5 min at 4000 revolutions per minute. This allowed for the isolation of serum which was then divided into four 1.5 ml vials and frozen at −86 °C.

Analysis of the serum samples were completed on the Hitachi 911 automatic analyser (Roche Diagnostics, Australia) and the Immulite (Bio-mediq, Australia). Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Tumour necrosis factor-α (TNF-α), High sensitivity C-Reactive Protein (CRP) and Myoglobin (MYO) were purchased from Bio-Mediq and Creatine Kinase (CK) was purchased from Thermo Trace Scientific.

Statistical analysis

A two factor ANOVA (group and time) with repeated measures of time was used for each variable. Paired *t*-tests and Newman—Keuls post hoc analysis were used to identify significant differences within each group at all time points using Statistica version 6.1 (StatSoft Inc., USA). Statistical significance was set at $p < 0.05$ for all tests.

Results

There were no significant differences between the active and placebo groups at any time point for any of the measured variables. No adverse effects were reported by any subjects for either group in this study and compliance ranged from 65—100% with the average being 89%.

CMJ and SJ

Both the active and placebo groups showed a non-significant decrease following the downhill run with no significant difference between the groups at any time point.

Kin-Com

Right quadriceps: Both the active and placebo groups showed a non-significant decrease in force production after the downhill run.

Left quadriceps: Force production decreased significantly in the active group from pre to post ($p = 0.02$).

Creatine kinase

At 24 h after the downhill run, both groups demonstrated statistically significant increases in CK levels compared to pre-run values (active group $p = 0.0001$ and placebo group $p = 0.0001$). In the placebo group, a statistically significant increase from baseline was also identified 4 h post ($p = 0.003$) *see* Fig. 1.

Myoglobin

Immediately after and 4 h after the downhill run both groups demonstrated statistically significant increases in myoglobin levels from baseline. For the active group $p = 0.0002$ and $p = 0.0001$, and for the placebo $p = 0.0001$ and $p = 0.0002$ for post and 4 h, respectively *see* Fig. 2.
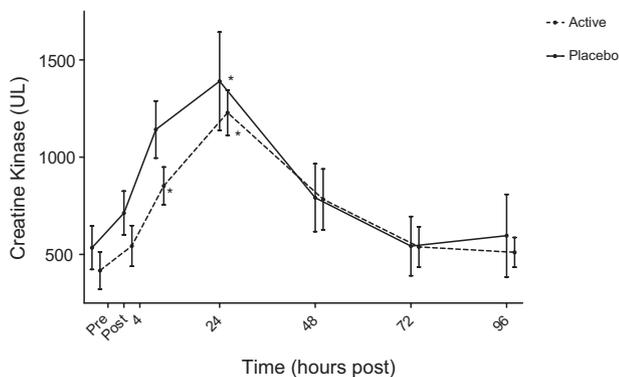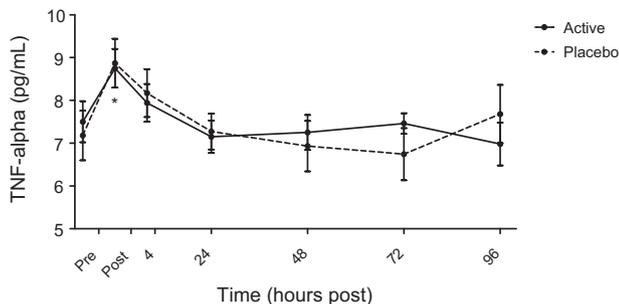
Figure 1 Creatine kinase response for both the active and placebo groups after downhill treadmill running. Significant differences from baseline ($p < 0.05$) are represented by *.
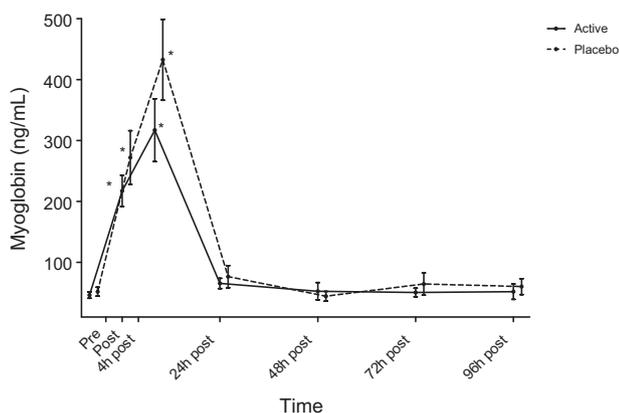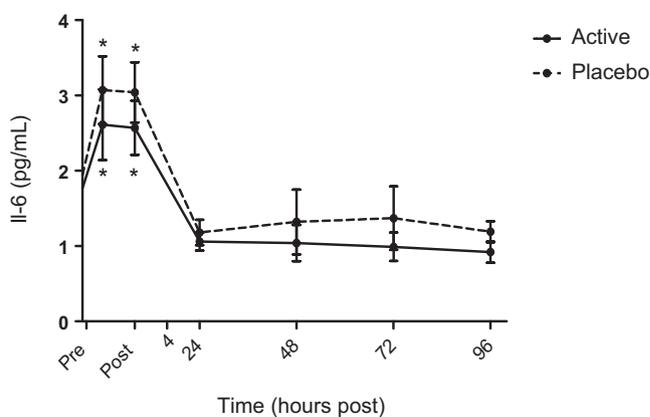

Figure 2 Myoglobin response for both the active and placebo groups after downhill treadmill running. Significant differences from baseline ($p < 0.05$) are represented by *.

Tumour necrosis factor-alpha

Both groups demonstrated similar increases immediately after the downhill run when compared to pre-run, however this was only statistically significant for the active group ($p = 0.03$) see Fig. 3.

Figure 3 TNF-α response for both the active and placebo groups after downhill treadmill running. Significant differences from baseline ($p < 0.05$) are represented by *.

Figure 4 IL-6 response for both the active and placebo groups after downhill treadmill running. Significant differences from baseline ($p < 0.05$) are represented by *.

CRP

CRP for both groups increased 24 h post-run however this was not a significant increase from pre-run values.

IL-1

The only change seen was an increase in IL-1 in the placebo group at 72 h after the downhill run, however this was not significant.

IL-6

Both groups demonstrated statistically significant increases in IL-6 from pre to post run and at 4 h. For the active group $p = 0.01$ and $p = 0.009$, and the placebo $p = 0.0003$ and $p = 0.0003$, respectively see Fig. 4.

IL-10

In the placebo group a statistically significant difference was identified from pre values to post run ($p = 0.0003$) see Fig. 5. The significant difference is due to a small number of
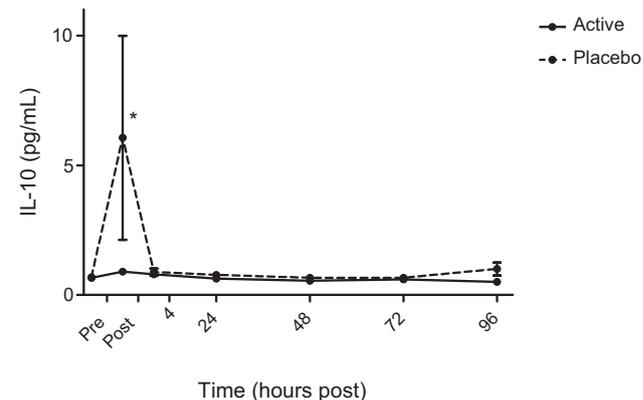
Figure 5 IL-10 response for both the active and placebo groups after downhill treadmill running. Significant differences from baseline ($p < 0.05$) are represented by *.
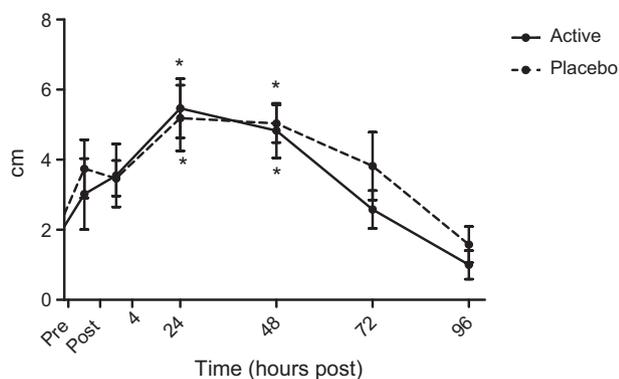
Figure 6 VAS response for both the active and placebo groups after downhill treadmill running. Significant differences from baseline ($p < 0.05$) are represented by *.

participants whose results differed greatly to the majority of the placebo participants.

VAS

There was a statistically significant increase in both groups from pre values to 24 and 48 h (active group $p = 0.0003$ and $p = 0.002$; placebo group $p = 0.0008$ and $p = 0.001$, respectively) *see* Fig. 6.

Algometer

Similar responses were seen in both groups with pain threshold decreasing most substantially, but not statistically significantly at 24 h after the downhill run.

Discussion and conclusions

The purpose of this study was to determine if Lyprinol® had an effect on DOMS, indicators of muscle damage and inflammation, pain and performance in well trained athletes. We found that two months' consumption of Lyprinol® at the currently recommended dosage of 200 mg/day did not prevent DOMS or muscle damage induced by an eccentric exercise protocol, and did not convincingly enhance recovery after the DOMS inducing exercise.

As has been previously demonstrated[3,13,37] the eccentric exercise protocol induced increases in VAS scores at the 24 and 48 h time points and a reduction in the pain threshold measured by the algometer.[33] Again as described by others[37–40] increases in indirect indicators of DOMS such as increased levels of CK and Myoglobin supported the finding that DOMS was successfully induced. Though the placebo group's CK levels remained significantly higher when compared to baseline values 4 h post exercise, this was not significantly different from the active group. We therefore cannot confidently conclude Lyprinol® had a positive effect on reducing muscle damage.

Lyprinol®, currently marketed as a ''potent natural anti-inflammatory'', has demonstrated positive outcomes in studies of the treatment of chronic inflammatory diseases such as rheumatoid arthritis,[16,18,20–22] asthma[18,24] and osteoarthritis. In this study, the first to assess Lyprinol® in an

acute non-disease related condition results did not demonstrate a positive effect on DOMS, which many authors have suggested has an inflammatory component. Clinical studies in the use of non-steroidal anti-inflammatory drugs for DOMS are conflicting. Some studies indicate lack of efficacy of NSAIDs[12,15] however there are also studies indicating that NSAIDs may decrease muscular pain after eccentric exercise.[8,41,42] It is questionable whether this represents an action on an inflammatory process or a simple analgesic effect.

A study by Malm et al. analysed leukocytes, cytokines, growth factors and hormones after downhill running. The research group concluded, ''downhill running did not result in skeletal muscle inflammation despite DOMS and increased CK''.[10] Prior to Malm's study, Nosaka et al. had also concluded that ''DOMS is a poor reflector of eccentric induced muscle damage and inflammation, and that changes in indirect markers of muscle damage and inflammation are not necessarily accompanied by DOMS''.[11] The role of inflammation in DOMS is unclear however it is possible inflammation be responsible for resolving exercise induced muscle damage. Further research surrounding this question will assist with unravelling this mystery.

Of key importance in discussion of the efficacy of any anti-inflammatory agent in DOMS, is the presence or absence of an inflammatory reaction in association with this condition. Research into the causative factors of DOMS is ongoing, with well designed studies generating conflicting results regarding the ''inflammation theory''.[14] General consensus is that a single theory cannot explain the onset of DOMS.[6] From this study, we cannot conclude that Lyprinol® was ineffective as an anti-inflammatory agent, the debated theory of an inflammatory response initiating DOMS may be incorrect, or the pathways in which inflammation occurs after eccentric exercise is different to the pathways Lyprinol® has been clinically demonstrated to act upon in chronic disease states.

We established that only one cytokine assessed responded as would be expected in an inflammatory response. The cytokines chosen for assessment were based on previous research conducted in this area and sports physician recommendation.[43] It is possible that other cytokines may have responded in a different manner, however funding limited the number of cytokines assessed in this study. The most sensitive indicator of inflammation (high sensitivity CRP) did not respond in such a manner within the 96 h of analysis. IL-6 was the only cytokine that indicated a possible inflammatory response in both groups, with TNF-α only increasing significantly in the active group from pre to immediately post exercise. When taking into account the other cytokines analysed: IL-1 IL-10 and CRP and TNF-α in the placebo group, it is reasonable to conclude that there was little evidence of an inflammatory response in all subjects.

We have established that Lyprinol® did not affect pain, performance or blood markers of muscle damage and inflammation in well-trained subjects. However, due to the relatively small sample size employed in this study it is conceivable that real but small differences between the active and placebo groups have not been demonstrated. Based on previous studies related to inflammatory conditions and our data related to inflammatory markers, our findings may simply indicate that the inflammatory process is not associated

with DOMS and therefore using an anti-inflammatory medication in management or prevention of this condition is not appropriate. This is consistent with evidence which indicates that NSAIDs, which are effective in recognised inflammatory conditions, are ineffective for DOMS.[12,44,45] Some studies claiming specific NSAID effectiveness through reduction in muscle pain and improvement in performance are based on an effect on the ''inflammatory process of DOMS''. However they lack specific evidence of alterations in inflammatory markers and rely purely on pain and performance measures.[8,41,42,46] Future research should investigate the role of inflammation in DOMS, including the assessment of a wider range of acute phase response markers.

Ethical approval

Approval for this prospective study was obtained from the Ethics Committee of The Australian Institute of Sport and The University of Western Sydney.

Conflicts of interest

Acknowledgements

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