

**Vitamin C and Exercise-Induced Oxidative and
Inflammatory Stress
in Ultramarathon Athletes**

by

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Abstract

Literature reveals a paradoxical response of the immune and innate host defence systems to endurance exercise; apparent stimulation following long-term regular training and suppression in response to acute exposure to exhaustive endurance exercise. Two epidemiological studies revealed that clinical manifestation of immunosuppression in the form of increased incidence of upper respiratory tract infection symptoms (URTI) is greater following competitive ultramarathon running than in matched sedentary controls and linearly related to running time. These were followed by three intervention studies in which the efficacy of anti-oxidant supplementation in reducing the incidence of post-race symptoms of infection was assessed following participation in the 90 km Comrades Ultramarathon. Vitamin C alone was found to be more effective than combinations of anti-oxidants in reducing the post-race incidence of URTI symptoms in a study conducted on 178 runners and 162 matched, sedentary controls.

In order to investigate mechanisms by which vitamin C may act in reducing the incidence of URTI infection during the two-week post-race period, intervention studies were conducted at the 1997 and 1999 90 km Comrades Ultramarathons. Runners were required to keep dietary records and ingest prescribed capsules containing 500 mg, 1000 mg, 1500 mg vitamin C or placebo for 10 days prior to the event, complete the 90 km ultramarathon and provide 35 ml blood 14-16 hours before, immediately on completion of, 24 hours and 48 hours post-race. These specimens were subsequently assayed for markers of inflammatory and oxidative stress which included circulating cortisol, adrenaline, vitamin A, vitamin C, vitamin E, C-reactive protein (CRP), serum amyloid A, creatine kinase, lactate dehydrogenase, neutrophils and lymphocytes, neutrophil-derived elastase and myeloperoxidase, the pro-inflammatory-cytokines, interleukin-1 β , interleukin-6, interleukin-8 and tumour necrosis factor-alpha, the anti-inflammatory-cytokine, interleukin-10 (IL-10), and IL-1 receptor antagonist (IL-1Ra), all of which (with the

exception of vitamins A and E and lymphocytes) were significantly elevated on completion of the ultramarathon.

Increased daily intake of vitamin C was accompanied by a dose-related attenuation of the exercise-induced increases in circulating vitamin C, cortisol and neutrophils. Supplementation with the vitamin at doses of ≤ 1000 mg daily appeared to result in augmentation of the exercise-induced inflammatory response as evidenced by significant increases ($p < 0.05$) in circulating levels of the acute phase reactant, CRP and in the group receiving 1000 mg daily, an increase in creatine kinase. In the group receiving 1500 mg daily, this apparent pro-inflammatory effect of supplementation with the vitamin was less evident, but circulating cortisol, adrenaline, IL-10 and IL-1Ra concentrations were all significantly reduced ($p < 0.05$), suggesting that at this level of supplementation the vitamin may activate a counteracting anti-inflammatory cascade, possibly through inhibition of activation of pro-inflammatory transcription factors.

Although further work involving larger sample sizes is required to confirm these findings, this is the first evidence that vitamin C supplementation attenuates the endogenous, biological anti-inflammatory response to intensive exercise, which may partially explain why the vitamin reduces the incidence of URTI in ultramarathon athletes. On the downside, however, apparent augmentation of exercise-associated inflammatory responses at supplementation levels of 500 and 1000 mg daily, is clearly of concern.

Key Words: Upper respiratory tract infections, ultramarathon running, vitamin C, oxidative stress, inflammatory stress, cortisol, adrenaline, interleukin-10, interleukin-1Ra, C-reactive protein, amyloid A.

Abstrak

Die literatuur toon 'n teenstrydige reaksie van die immuun en intrinsieke gasheer weestandsmeganismes ten opsigte van uithouvermoë-oefening; die klaarblyklike stimulasie daarvan as gevolg van langtermyn, gereelde oefening maar ook die demping daarvan wat volg na akute blootstelling aan uitputtende uithouvermoë-oefening. Twee epidemiologiese studies het aangedui dat die kliniese manifestasie van immuunonderdrukking in die vorm van 'n verhoging in voorkoms van boonste lugweg infeksie-simptome groter was na mededingende ultramaraton wedlope as in rustende kontroles. Verder, dat hierdie simptome direk verwant was aan die hardlooptyd. Hierdie studie is opgevolg deur drie ander farmakologiese ingrypingstudies waarin die doeltreffendheid van anti-oksidadant aanvullings om 'n vermindering in voorkoms van na-wedloopsimptome teweeg te bring, ondersoek is in deelnemers van die 90 km Comrades Ultramaraton. In 'n studiegroep bestaande uit 178 deelnemers en 162 rustende kontroles is gevind dat vitamien C alleen meer effektief was as kombinasies van anti-oksidadante, om die na-wedloop voorkoms van boonste lugweg infeksie-simptome te verminder.

Ten einde die meganismes vas te stel waardeur vitamien C die voorkoms van boonste lugweg-infeksie gedurende die twee week- periode na die wedloop verminder, is twee ingrypingstudies onderneem tydens die 1997 en 1999 90 km Comrades Ultramaratons. Deelnemers is versoek om boek te hou van hul dieet, voorgeskrewe kapsules van 500 mg, 1000 mg, 1500 mg vitamien C of plasebo te neem, die 90 km ultramaraton te voltooi en om 35 ml bloed 14-16 uur vooraf, onmiddellik by voltooiing van, 24 uur en 48 uur na die wedloop te skenk. Die bloedmonsters is daarna getoets vir merkers van inflammatoriese en oksidatiewe stres wat insluit: sirkulerende kortisol, adrenalien, vitamien A, vitamien C, vitamien E, C-reaktiewe proteïene (CRP), serum amiloïed A (SAA), kreatien kinase, laktat dehidrogenase, neutrofiel-afkomstige elastase en miëloperoksidase (MPO), die pro-inflammatoriese sitokiene, IL-1 β , IL-6, IL-8, TNF- α , die anti-inflammatoriese sitokien, IL-10 en IL-1 reseptor antagonis (IL-1Ra).

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Die verhoogde daaglikse inname van vitamien C het gepaard gegaan met 'n dosis-
verwante vermindering van oefeningsgeïnduseerde verhogings in sirkulerende
vitamien C, kortisol en neutrofiele, sowel as 'n daling in die limfosiete ($p < 0.05$).
Supplementasie met die vitamien by doserings van ≤ 1000 mg daaglik het
klaarblyklik tot 'n verhoging in die oefeningsgeïnduseerde inflammatoriese respons
gelei, soos aangedui deur betekenisvolle verhogings ($p < 0.05$) in die sirkulerende
vlakke van die akute fase reagens, CRP, en in die groep wat 1000 mg daaglik
ontvang het, 'n verhoging in kreatien kinase. In die groep wat daaglik 1500 mg
ontvang het, was die klaarblyklike pro-inflammatoriese uitwerking van die
vitamiëaanvulling minder opsigtelik, maar was konsentrasies van sirkulerende
kortisol, adrenalien, IL-10, en IL-1Ra almal betekenisvol minder ($p < 0.05$) wat
aandui dat by hierdie vlak van supplementasie, die vitamien 'n teenwerkende anti-
inflammatoriese kaskade, waarskynlik deur die demping van aktivering van pro-
inflammatoriese transkripsie-faktore, aktiveer.

Hoewel verdere studies groter studiegroepe vereis om hierdie bevindings te
bevestig, is dit die eerste bewys dat vitamien C aanvullings die endogene, biologiese
anti-inflammatoriese respons ten opsigte van intensiewe oefening demp, wat mag
verklaar waarom die vitamien die voorkoms van boonste lugweginfeksie in ultra-
maraton atlete verminder. In teendeel is die klaarblyklike verhoging van
oefeningsverwante inflammatoriese response by aanvullingsvlakke van 500 en 1000
mg daaglik, kommerwekkend.

Kernwoorde: Boonste lugweg infeksies, ultramaraton wedlope, vitamien C,
oksidatiewe en inflammatoriese stres, kortisol, adrenalien, interleukin-10,
interleukin-1Ra, C-reaktiewe proteïen, amiloïed A.



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Recent Publications which have emanated from this work

Pilot Work (Field Study)

- **Peters E.M.**, Goetzsche J.M., Joseph, L.E., Noakes T.D. Vitamin C as effective as combinations of anti-oxidant nutrients in reducing the incidence of upper respiratory tract infections in ultradistance runners. *S.A. Sports Med.* **4**: 23-27, 1996.

Laboratory Work

- **Peters E.M.**, Anderson, R., Theron, A.J. Attenuation of the increase in circulating cortisol and enhancement of the acute phase response in vitamin C-supplemented ultramarathon runners. *Int J Sports Med* **22**: 120-126, 2001.
- Nieman D.C., **Peters E.M.**, Henson D.A., Nevines E.I., Thompson M.M. Influence of Vitamin C supplementation on cytokine changes following an ultramarathon. *J Interferon & Cytokine Res* **20**: 1029-35, 2000.
- **Peters E.M.**, Anderson, R., Nieman D.C., Fickl H., Joggesar V. Vitamin C supplementation attenuates the increases in circulating cortisol, adrenaline and anti-inflammatory polypeptides following ultramarathon running. *Int J Sports Med* **22**:537-543, 2001.

Review Articles

- **Peters E.M.** Exercise and Upper Respiratory Tract Infections. *S Afr J Sports Med* **3**: 9-14, 1996.
- **Peters E.M.** Exercise, immunology and upper respiratory tract infections, *Int J Sports Med* **18**, S69-78, 1997.
- **Peters-Futre E.M.** Exercise, Vitamin C and Neutrophil Function. The Missing Link. *Exerc Immunol Rev* **3**: 32-52, 1997.

Chapter in Book

- **Peters E.M.** Vitamins, Immunity and Infection Risk in Athletes In: Nieman D.C., Pederson BK (eds): Nutrition and exercise Immunology, CRC Press, Florida, 2000.
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Abbreviations

8-oxodG	8-oxo-2-deoxyguanosine
AA	ascorbic acid
ACTH	adrenocorticotrophic hormone
ANOVA	analysis of variance
AP-1	activator protein-1
APP	acute phase proteins
AVP	arginine vasopressin
CK	creatine kinase
CRF	corticotropin-releasing hormone
CRP	C-reactive protein
CSIF	cytokine synthesis inhibiting factor
Cu	Copper
DHAA	dehydro-ascorbic acid (oxidised form)
DOMS	delayed onset muscle soreness
EBV	Epstein-Barr Virus
EDTA	ethylenediaminetetraacetic acid
FMLP	N-formyl-methionyl-leucyl-phenylalanine
H ₂ O ₂	hydrogen peroxide
HPA	hypothalamic-pituitary-adrenal
HOCL	hypochlorous acid
HPLC	high performance liquid chromatography
IE	infectious episodes
IgA	immunoglobulin A
IL-1 β	interleukin-1 beta
IL-1Ra	interleukin-1 receptor antagonist
IL-2	interleukin-2
IL-2R	interleukin-2 receptor
IL-6	interleukin-6
IL-8	interleukin-8
IL-10	interleukin-10



IKK	I-kappa B kinase
L-ascorbate	reduced form of ascorbic acid
LDL	low density lipoprotein
LDH	lactate dehydrogenase
LPS	lipopolysaccharide
MIP	macrophage inhibitory protein
MPO	myeloperoxidase
MSH	alpha-melanocyte stimulating hormone
NF κ B	nuclear transcription factor, κ B
NK cells	natural killer cells
OH $^-$	hydroxyl anion
\bullet OH	hydroxyl radical
O $_2^{\bullet -}$	superoxide anion
PBS	phosphate-buffered saline
PMA	phorbol 12-myristate 13-acetate
PMN	polymorphonuclear leukocyte
PWM	pokeweed mitogen
ROI	reactive oxygen intermediates
ROS	reactive oxygen species
SAA	serum amyloid A
SD	standard deviation
SEM	standard error of the mean
SMI	steroid-mediated immunosuppression
SOD	superoxide dismutase
TNF α	tumour necrosis factor alpha
URT	Upper respiratory tract
URTI	Upper respiratory tract infections
VC	Vitamin C
$\dot{V}O_2$ max	Maximum oxygen consumption