

# Vitamin C Supplementation Attenuates the Increases in Circulating Cortisol, Adrenaline and Anti-Inflammatory Polypeptides Following Ultramarathon Running

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The effects of vitamin C supplementation on the alterations in the circulating

concentrations of cortisol, adrenaline, interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1Ra) which accompany ultramarathon running were measured using immuno-chemiluminescence, radioimmunoassay and ELISA procedures. Forty-five participants in the 1999 Comrades 90 km marathon were divided into equal groups (n = 15) receiving 500 mg/day Vit C (VC-500), 1500 mg/day Vit C (VC-1500) or placebo (P) for 7 days before the race, on the day of the race, and for 2 days following completion. Runners recorded dietary intake before, during and after the race and provided 35 ml blood samples 15 - 18 hrs before the race, immediately post-race, 24 hrs post race and 48 hrs post-race. Twenty-nine runners (VC-1500, n = 12; VC-500, n = 10; P, n = 7) complied with all study requirements. All post-race concentrations were adjusted for plasma volume changes. Analyses of dietary intakes and blood glucose and anti-oxidant status on the day preceding the race and the day of the race did not reveal that carbohydrate intake or plasma vitamins E and A were significant confounders in the study. Mean pre-race concentrations of serum vitamin C in VC-500 and VC-1500 groups ( $128 \pm 31$  and  $153 \pm 34$   $\mu\text{mol/l}$ ) were significantly higher than in the P group ( $83 \pm 39$   $\mu\text{mol/l}$ ). Immediate post-race serum cortisol was significantly lower in the VC-1500 group ( $p < 0.05$ ) than in P and VC-500 groups. When the data from VC-500 and P groups was combined (n = 17), immediate post-race plasma adrenaline, IL-10 and IL-1Ra concentrations were also significantly lower ( $p < 0.05$ ) in the VC-1500 group. The study demonstrates an attenuation, albeit transient, of both the adrenal stress hormone and anti-inflammatory polypeptide response to prolonged exercise in runners who supplemented with 1500 mg vitamin C per day when compared to  $\leq 500$  mg per day.

## Key words:

Vitamin C, ultramarathon runners, cortisol, adrenaline, interleukin-10, interleukin-1 receptor antagonist.

## Introduction

We have previously reported that vitamin C supplementation reduces the incidence of post-race upper respiratory tract infections amongst ultramarathon runners [[21](#)] [[22](#)]. In a more recent study we observed that supplementation with 1000 mg of the vitamin over an 8 day period resulted in an average 30 % reduction in post-race serum cortisol levels in these athletes [[20](#)]. We proposed that the vitamin C-associated decrease in serum cortisol might result from inhibition of enzymes involved in steroidogenesis [[9](#)] [[18](#)] [[24](#)]. Alternatively, because cortisol release from the adrenals may be coupled to concomitant release of vitamin C during oxidative stress [[18](#)], it is possible that supplementation with the vitamin may negate the requirement for its mobilization from body stores, with a consequent, albeit

secondary, attenuation of the cortisol response [17]. Irrespective of the biochemical mechanisms involved, the apparent vitamin C-associated attenuation of the cortisol response to strenuous exercise has potentially important implications for the prevention of transient immune dysfunction in athletes.

In the current study we have again assessed the effects of oral administration of vitamin C, at different doses to those used in our previous study [20], on the increase in circulating cortisol which accompanies ultramarathon running. Moreover, we have extended our previous study to include measurements of circulating adrenaline, interleukin-10 (IL-10) and the interleukin-1 receptor antagonist (IL-1Ra).

## Methods

### Study design

Approval to conduct the study was obtained from the Human Ethics Committee of the University of Natal Medical School. Forty-five registered entrants for the 1999 Comrades Marathon signed informed consent forms. They were divided into three groups which were matched for age, gender, training status and expected race finishing time:

Group 1 (P; n = 15): Three placebo tablets per day

Group 2 (VC-500; n = 15): One 500 mg vitamin C tablet and two placebo tablets per day

Group 3 (VC-1500; n = 15): Three 500 mg vitamin C tablets per day

Subjects were blinded to their group assignment and required to ingest one tablet with breakfast, lunch and supper over a 10 day period for 7 days preceding the race, the day of the race and for two days following the race. The vitamin C and placebo tablets were identical in appearance, taste and weight.

On the day prior to the race, subjects were required to complete 24 hour dietary records of their intake and to report for basic anthropometric measurements and blood sampling (35 ml) in the afternoon at a time which coincided with their estimated finishing time (in order to avoid the effect of diurnal rhythms on hormone concentrations). Within 30 - 45 minutes after completing the race, the subjects again gave 35 ml blood samples and were asked to detail their dietary and liquid intakes on the morning of the race and during the race. The blood sampling was repeated 24 hrs and 48 hrs after the race and subjects were asked to record their post-race dietary intakes for a further 36 hrs.

### Analysis of dietary records

Intake of both food and nutritional supplements was analyzed using the Dietary Manager computer program (Program Management, Randburg, South Africa). Total daily carbohydrate (CHO) and Vitamin C intakes during

the 24 hours before, as well as on the day of the race, and after the race, including those derived from any additional carbohydrate supplements used by the athletes, were determined.

### **Treatment of blood**

Venous blood samples (20 ml) were collected in glass Vacutainer tubes containing the anti-coagulant, tripotassium ethylenediaminetetraacetic acid (K<sub>3</sub>-EDTA). Full blood counts were conducted on 3 ml thereof. The remainder was centrifuged and the fractionated plasma quick-frozen and stored at -70 °C for later analysis of Vitamins A and E, glucose, adrenaline, IL-10 and IL-1Ra. An additional 15 ml aliquot was allowed to clot at room temperature, centrifuged for 10 minutes and the serum was quick-frozen and stored at -70 °C for later analysis of vitamin C and cortisol.

### **Serum vitamin C, plasma glucose, vitamins A and E**

Vitamin C was extracted from serum using 20 % trichloroacetic acid and assayed using the 2,4-dinitrophenylhydrazine (Sigma Chemical Co., St Louis, MO, USA) colorimetric method [1]. Plasma glucose concentrations were determined spectrophotometrically in pre-race, immediate, 24 hr and 48 hr post-race samples. Plasma concentrations of vitamins A and E were determined by standard high performance liquid chromatography (HPLC) procedures following repeated (× 3) extraction with hexane and using vitamin A-acetate as the internal standard [4]. Quality control was maintained by inclusion of a standard consisting of pooled serum from several healthy adult human donors. With the HPLC procedures the same pool was run with all assays and the standard was extracted and assayed concurrently with all test samples.

### **Serum cortisol, plasma adrenaline, IL-10 and IL-1Ra**

Serum cortisol was assayed using the Gamma Coat radioimmunoassay procedure (Diagnostic Products Corporation, Los Angeles, CA, USA) and adrenaline using a radioimmunoassay procedure (DLD Gesellschaft für Diagnostika und medizinische Geräte mbh, Hamburg, Germany). The plasma IL-10 and IL-1Ra analyses were part of a more comprehensive study on the cytokine profile of ultramarathon runners which is to be published elsewhere [16]. These were assayed using quantitative sandwich ELISA kits provided by R&D Systems, Inc. (Minneapolis, MN, USA). A standard curve was constructed using standards provided in the kits. The assays were two step "sandwich" enzyme immunoassay procedures in which samples or standards were incubated in 96-well microtiter plates coated with polyclonal antibodies for the test cytokine as the capture antibody. Following the appropriate incubation time, the wells were washed and a second detection antibody conjugated to either alkaline phosphatase (IL-10) or horseradish peroxidase (IL-1Ra) was added. The plates were incubated and washed, and

the amount of bound enzyme-labeled detection antibody was measured by adding a chromogenic substrate. The plates were then read at the appropriate wavelength (490 minus 650 nm for IL-10 and 450 minus 570 nm for IL-1Ra). The minimum detectable concentration of IL-10 was < 0.5 pg/ml and that of IL-1Ra was < 22 pg/ml.

### **Hematological analyses and adjustments**

Full blood counts were performed on K<sub>3</sub>-EDTA treated specimens using standard hematological procedures on an automated STKS model (Coulter Electronics Inc., Hialeah, Florida, USA). Plasma volume changes were determined from pre- and post-race hemoglobin and hematocrit values using the method of Dill and Costill [8] and all subsequent post-race values (0, 24 and 48 hr) were adjusted for these plasma volume changes.

### **Statistical analyses**

Results are expressed as means  $\pm$  SD. An initial three-by-four repeated measures ANOVA was used to establish whether the differences between the three groups were significant throughout the 48hr post-race period and showed that the P and VC-500 groups did not differ significantly in any of the post-race measures. These two sets of data were subsequently pooled and a further two ( $\leq$  500 mg per day vs.  $>$  1500 mg per day) -by -four repeated measures ANOVA was used to assess the group-time interaction. Wilks' Lambda trace statistic was used as the test statistic with a Bonferroni post-hoc correction to determine the time point of the significant differences. Statistical differences between post-race adrenaline values were determined between  $\leq$  500 mg and  $>$  1500 mg groups using Students' *t*-tests. Correlation analyses were performed using Pearson's Product Moment Correlation Co-efficient. Statistical analysis was done using SAS statistical software.

## **Results**

### **Subjects**

Of the 45 runners recruited to the study only 29 fully complied with the protocol requirements. The characteristics of the individuals in the P, VC-500 and VC-1500 groups are shown in Table [1]. There were no significant differences between the three groups with respect to age, height, mass, body mass index, training status, and time taken to complete the ultramarathon. Carbohydrate intake just prior to and during the race averaged 401 ( $\pm$  188) g and did not differ significantly between the groups ( $p > 0.05$ ; Table [2]). Likewise, pre- and post-race plasma glucose, vitamin A and vitamin E concentrations were not different between the 3 groups ( $p > 0.05$ ; Table [2]). Total mean Vitamin C intake on the day preceding the race (contained in supplements, beverages and foodstuffs ingested)

amounted to 94.4 ( $\pm$  60.4), 650 ( $\pm$  102) and 1603 ( $\pm$  90) mg in P, VC-500 and VC-1500 groups, respectively (data not shown).

[Table 1 Mean \( \$\pm\$  SD\) subject characteristics \(n = 29\)](#)

[Table 2 Mean \( \$\pm\$  SD\) dietary carbohydrate \(CHO\) intakes and plasma concentrations of glucose and vitamins A and E on the day preceding the race and day of the race](#)

### Serum vitamin C

Pre-race serum vitamin C was significantly higher in the supplemented groups by comparison with the P group (Fig. [1]). There was also a significant increase ( $\bar{X}$  = 42.6  $\mu$ mol/l) in serum vitamin C in the P group immediately post-race ( $p < 0.05$ ). This increase in the mean serum vitamin C was attenuated in both of the vitamin supplemented groups (19.3 and - 2.84  $\mu$ mol/l in VC-500 and VC-1500 groups, respectively). At 24 and 48 hrs after completion of the race the serum vitamin C concentrations returned to values which were not significantly different ( $p > 0.05$ ) from pre-race values.



**Fig. 1** Pattern of change in mean serum vitamin C concentrations before and after the 1999 Comrades 90 km ultramarathon in  $\diamond$  placebo,  $\bullet$  VC-500 and  $\blacktriangle$  VC-1500 groups. Data presented as means  $\pm$  SD. Time effect:  $p < 0.001$ ; group vs. time interaction effect:  $p = 0.27$ , group effect:  $p = 0.006$ , #  $p < 0.05$  Bonferroni multiple comparison test between groups at time point.

### Blood counts

Results of the full blood counts are shown in Table [3]. Packed cell volume and hemoglobin values indicated a varied hydration status with 27.5 % presenting with an increase in plasma volume immediately following participation in the ultramarathon. The difference in plasma volume did not differ significantly between the groups. Significant immediate post-race lymphopenia and neutrophilia was present in all 3 groups with recovery to normal values at 24 and 48 hrs after completion of the race. The smaller relative magnitude of the lymphopenia and neutrophilia, as expressed in the neutrophil:lymphocyte ratio, in the VC-1500 group (n = 12) in comparison to the  $\leq$  VC-500 group (n = 17) did not reach statistical significance ( $p = 0.08$ ).

[Table 3 Hematological profile. Values as mean \( \$\pm\$  SD\)](#)

### Circulating cortisol, adrenaline, IL-10 and IL-1Ra concentrations

Circulating cortisol and adrenaline increased significantly in all 3 groups

immediately post-race, subsiding to close to pre-race values (in the case of cortisol) at 24 and 48 hrs after completion of the race (Table [4]). The increase in both cortisol and adrenaline observed immediately post-race was attenuated in the VC-1500 group relative to the  $\leq 500$  mg groups ( $p < 0.001$  and  $p < 0.05$ , respectively). Pre-race adrenaline levels were also less in the VC-1500 group ( $p < 0.05$ ). The immediate post-race values for IL-10 and IL-1Ra were significantly higher in relation to the pre-race values and subsided to close to pre-race values at 24 and 48 hrs after completion of the race (Table [4]). However, the increase in the circulating concentrations of these anti-inflammatory polypeptides observed immediately post-race was significantly blunted in the VC-1500 group ( $p = 0.05$ ) when compared to the  $\leq 500$  mg groups.

#### Table 4 Mean ( $\pm$ SD) stress hormone and anti-inflammatory polypeptide concentrations

Correlation analyses between collective data pooled for all subjects ( $n = 124$ ) revealed a significant positive correlation between serum cortisol and IL-10 ( $r = 0.79$ ) and inverse correlation between pre-race vitamin C values and post-race serum cortisol ( $r = -0.30$ ;  $p < 0.05$ ). Significant ( $p < 0.05$ ) correlations were found between post-race serum cortisol and both IL-10 ( $r = 0.61$ ) and IL-1Ra ( $r = 0.50$ ) as well as adrenaline and IL-1Ra ( $r = 0.71$ )

## Discussion

The increase in circulating concentrations of the adrenal immunosuppressive, anti-inflammatory hormones cortisol, adrenaline and noradrenaline, which accompanies intensive physical exercise is well-documented [12] [25] [27]. An earlier laboratory study [15] on 6 pairs of runners failed to report an effect of vitamin C supplementation on immune response to 2.5 hours of treadmill running. We have, however, recently reported that vitamin C supplementation (total mean intake: 1339 mg/day) in ultramarathoners is associated with attenuation of the increase in serum cortisol observed immediately post-race following an ultramarathon lasting 9 - 11 hours [20]. In the current study we have investigated the effects of vitamin C supplementation, at different doses (500 mg and 1500 mg/daily) to those used in our previous study [20], on the cortisol response which accompanies participation in the same 90 km ultramarathon and included measurements of circulating adrenaline and those of the anti-inflammatory polypeptides, IL-10 and the IL-1Ra in an extension of this study.

As previously reported by us and others [6] [10] [20], vitamin C levels were increased in the placebo group on completion of the ultramarathon and subsided at 24 and 48 hrs thereafter. This apparent mobilization of vitamin C appears to represent an adaptive response to exercise-induced oxidative stress [6]. Pre-race serum vitamin C values and those measured 24 and 48hrs after completion of the race were significantly higher in the vitamin-supplemented groups. Interestingly, the difference in serum vitamin C

between the placebo (51.4 % higher than the pre-race value) and vitamin-supplemented groups was considerably less and statistically insignificant immediately post-race. The corresponding average changes in the VC-500 and VC-1500 groups were 13.0 % and -0.02 % respectively. These observations confirm our previous findings [20] that supplementation with vitamin C appears to negate the requirement for mobilization of the vitamin from the adrenal gland and other body storage sites during intensive physical stress [5].

In agreement with our previous study [20], administration of vitamin C at 1500 mg/daily, but not at 500 mg/daily, significantly attenuated (average decrease of 34.7 % relative to P group) the immediate post-race increase in serum cortisol. Pre-race concentrations of serum cortisol, as well as those measured at 24 and 48 hrs after completion of the ultramarathon event, were somewhat lower, although not significantly so, in both vitamin-supplemented groups relative to the P group. These observations are also in agreement with a recent report in which administration of vitamin C (1000 mg/daily) in combination with vitamin E to healthy, elderly humans was accompanied by a significant decrease in serum cortisol and improved immune function [7] and confirm previous findings on animals [11] [14] [18] [24].

Although blood sampling for adrenaline concentrations should ideally have been performed immediately on completion of the race, this was not logistically possible in a competitive event of this nature. It is, however, noteworthy, that circulatory adrenaline concentrations were reduced significantly following a week of supplementation with Vitamin C both prior to and following the stressful competitive event when compared to those in the unsupplemented runners. The average decrease relative to the P group was of 40 % and 41 % respectively in the group of athletes supplemented with 1500 mg vitamin C daily, but not significantly lower ( $p < 0.05$ ) in those supplemented with  $\leq 500$  mg/daily vitamin C.

It is possible that the observed vitamin C-related attenuation of the exercise-induced increase in circulating cortisol and adrenaline may, in part, explain the reported decrease in the incidence of upper respiratory infections in vitamin C-supplemented ultramarathon athletes. Both of these adrenal hormones possess potent anti-inflammatory, immunosuppressive properties and may impact on the magnitude of the post-exercise "open-window" period [19] with a delayed manifestation of actual symptoms of infection following varying incubation periods. Corticosteroids have been shown to mediate these immunomodulatory actions by interaction with cytosolic glucocorticoid receptors [2] [3] [23], while adrenaline operates via cyclic AMP-coupled  $\beta_2$ -adrenoreceptors on immune and inflammatory cells [13] [28] [29].

The proposed relationship between vitamin C-associated suppression of cortisol release from the adrenals and possible potentiation of immune

function, is further strengthened by the observation that the dramatic increase in the circulating concentration of the broad-spectrum anti-inflammatory cytokine, IL-10 [5], observed immediately after completion of the ultramarathon event, was significantly attenuated in the group of athletes supplemented with 1500 mg/daily of the vitamin. This is also supported by the co-efficient of correlation of 0.79 between the circulating concentrations of cortisol and IL-10 obtained from the findings of this study. Production of IL-10 by immune and inflammatory cells is potentiated by corticosteroids [27] and adrenaline [28], Interleukin-10, in turn, acts on monocytes/macrophages to stimulate release of IL-1Ra [5], an endogenous antagonist of the pro-inflammatory cytokine, IL-1. Interestingly it has recently been reported that rhinoviruses, the predominant cause of the common cold, increase the production of IL-10 by monocytes, suggesting that increased levels of this cytokine may contribute to the pathogenesis of infection with these viral pathogens [26]. It is therefore possible, but not proven, that vitamin C supplementation, through attenuation of the cortisol, adrenaline and IL-10 responses which accompany intensive exercise, may prevent the resultant transient immunosuppression which predisposes to upper respiratory tract infections [21] [22].

The biochemical mechanisms by which vitamin C supplementation attenuates the adrenal hormone response to exercise-induced oxidative stress remains to be established. However, our observation that the release of both cortisol and adrenaline is attenuated by supplementation with the vitamin appears to favor a mechanism by which the release of these anti-inflammatory hormones is coupled to mobilization of vitamin C from the adrenals [14], as opposed to inhibitory effects of the vitamin on hormone synthesis [9] [24]. Oxidative stress is presumably the trigger for the combined release of vitamin C, cortisol and adrenaline from the adrenals, with all three cooperating to protect against inflammation-mediated tissue damage.

In conclusion, oral supplementation with vitamin C at 1500 mg daily attenuated the increases in the production of the immunosuppressive adrenal hormones, cortisol and adrenaline, which accompanies intensive exercise, as well as the production of the anti-inflammatory polypeptides IL-10 and IL-1Ra. The findings of this study did not, however, reveal a linear dose-dependent response. Instead, the combined results of this work and our previous studies [20] [21] [22] in which total Vitamin C ingestion ranged from 1139 and 1004 mg/day, respectively in the early studies [21] [22] to 1339 mg/day in our most recent work [20] appear to point towards a threshold value existing at approximately 1000 mg per day. The relationship, if any, between these immunomodulatory effects of a daily dosage ranging from 1000 - 1603 mg vitamin C and the protective effects of this vitamin against post-exercise upper respiratory tract infection, however, require further investigation.

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