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The Effects of B-Sitosterol (BSS) and B-Sitosterol Glucoside (BSSG) Mixture on Selected Immune Parameters of Marathon Runners: Inhibition of Post Marathon Immune Suppression and Inflammation

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A pilot study was undertaken to investigate the effects of the intake of capsules containing the plant sterols and sterolins (BSS:BSSG mixture) on selected immune parameters of volunteers participating in an ultra-marathon in Cape Town, South Africa. Those runners having received active capsules (n = 9) showed less neutrophilia, lymphopenia and leukocytosis when compared to their counterparts having received placebo capsules (n = 8): the placebo treated individuals showed significant increases in their total white blood cell numbers as well as in their neutrophils (p = 0.03 and 0.03 respectively). Furthermore, statistically significant increases within lymphocyte subsets were observed in the runners having received the active capsules: CD3+ cells increased (p = 0.02) as did CD4+ cells (p = 0.03). In parallel, the BSS:BSSG capsules decreased the plasma level of IL6 in the runners using the active capsules (p = 0.08) and significantly decreased the cortisol: DHEAs ratio (p = 0.03), suggesting that these volunteers had less of an inflammatory response and were less immune suppressed during the post-marathon recovery period. These findings justify further investigations into the use of the phytosterols to prevent the subtle immunosuppression associated with excessive physical stress.

Key words: Marathon, immunosuppression, immunomodulation, β-sitosterol, β-sitosterol glucoside, anti-inflammatory, DHEAs.

Introduction

Traditionally, exercising has been held to improve health and as a consequence, people who perform sports regularly have been associated with less susceptibility to infection compared to sedentary people, especially if the sport performed is of low intensity. However, this picture may not be true for high intensity athletes who, in many cases, may be more prone to infections, especially during the period post marathon or high intensity activity [13]. The reason for that may be because excessive physical or psychological stress disturbs the normal physiological equilibrium or homeostasis, including the functioning of the immune system [11]. The exact role of glucocorticoids such as cortisol and its antagonist DHEA (dihydroepiandrosterone) in this homeostasis is not well known, but has been implicated [11].

It is said that the effects of exercise on the immune system depends on the duration, type and intensity of the exercise in question. The changes induced (e.g. leucocytosis observed) have been attributed to the secretion of hormones such as catecholamines and glucocorticoids [9]. Whilst many authors have indicated increases in lymphocyte numbers, many others have shown a reduction in the functionality of these cells. The transient immunosuppression could be explained, in part, by the lack of secretion of important regulatory cytokines, including INF-γ. Other authors have shown that the release of pro-inflammatory monokines (e.g. IL1β, IL6 and TNFα) is raised in the serum or urine of athletes following strenuous exercise [7]. These studies would therefore reflect a temporary period of immunosuppression during which microorganisms and viruses have time to evade immunological recognition and become established, giving rise to infections in the athletes [15].

We have recently shown that a mixture of plant sterols and sterolins (plant fats) are potent immunomodulators capable of reversing immunological abnormalities [6] and these have been tested clinically in both patients with pulmonary tuberculosis and infected with HIV [10,5]. The sterols/sterolins or BSS:BSSG mixture are natural and non-toxic and due to their observed efficacy in these clinical trials, it was decided to test their immunomodulatory potential in a group of athletes presenting for an ultra-marathon event which is run annually in Cape Town, South Africa. The aim of this study was thus to determine whether the BSS:BSSG mixture could inhibit the physiological changes seen in the hematological parameters

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of athletes and also, whether they could decrease the inflammatory aspect of marathon running (muscular pain, raised inflammatory cytokines, etc.).

Materials and Methods

Volunteers

The study had the ethical approval of the Medical Faculty as well as the Medicines Control Council (Project 91/075) whereby permission was granted to investigate the immunomodulatory activity of the BSS : BSSG mixture in healthy volunteers.

A group of 20 athletes were recruited from a local running club by means of adverts placed in the newspaper and at the club. The volunteers were recruited over a period of 3 weeks, 2 months prior to the marathon event, namely the Two Oceans Marathon (68 km in distance). All recruited athletes had to be in good health, and they were selected on the basis of a questionnaire which took into consideration the athletes' previous running history and whether they were prone to upper respiratory tract infections or viral infections post-marathon. All 20 volunteers responded to the questionnaires, and we had a group of mixed caliber, namely those who were classified within the top 200 as well as those who were more serious social runners. They were randomly assigned to either of 2 groups of 10 each (coded as Group A or Group B).

Blood analysis

Four weeks prior to the event, all athletes were recruited for blood sampling with a careful history taking including the use of supplements, dietary intake, use of anti-microbial agents during the preceding 14 days, etc. They were all fasting and samples of both clotted and non-clotted bloods were drawn and transported to the laboratory within 4 hours of draw for further processing. The volunteers were given capsules containing the BSS : BSSG mixture (2 capsules to be taken three times per day; each capsule contained 10 mg BSS: 0.1 mg BSSG on 100 mg Talcum) or placebo (2 capsules to be taken three times per day; each capsule contained 100 mg Talcum), and these were coded by the supplier, namely Essential Sterolin Products (Pty) Ltd., Midrand, South Africa. The codes were broken only after termination of the study. The study was thus double blind and placebo controlled with 8 in the A group (placebo) and 9 in the B group (active BSS : BSSG mixture). Three volunteers were excluded from the study, because they failed to return for the final blood sampling session. Their results were thus excluded from the analysis. The demographics of the remaining volunteers in each group was as follows: Group A had 5 males and 3 females of age range 26 – 49 years while Group B had 6 males and 3 females of age range 28 – 51 years.

Blood samples were drawn again 3 days after the event. The athletes were requested not to change or modify their dietary habits during the study period. The reason for the choice of blood sampling 4 weeks prior to the race and then again 3 days post-marathon was that aproval for more blood draws could not be obtained from the trainers of these individuals, and it also posed a logistical problem for our laboratory staff.

The routine assays conducted on the blood samples included: full blood count and differential count and full liver function tests.

Immunological assays

Phenotypic analysis by flow cytometry

Whole blood was used to determine the phenotypes of circulating lymphocytes. For this, unclotted blood was incubated with aliquots of dual colour conjugated monoclonal antibodies as directed by the manufacturers, and the red blood cells were lysed prior to analysis on a flow cytometer (FACScan, Becton Dickinson, Johannesburg, South Africa). The following panel of antibodies was used: CD3-FITC, CD4-PE, C8-PE, CD19-PE and CD16-PE + CD56-PE. Both the percentage lymphocytes as well as the absolute numbers of lymphocytes expressing the respective antigen were analyzed (the absolute numbers were calculated from the full blood counts conducted in parallel).

Serum IL6 levels

The serum levels of the monokine IL6 were determined by an ELISA developed in house and described elsewhere [17]. For this, external standards were used to calculate the absolute values of the monokine pre- and post-marathon. Values were expressed as IU/ml of serum.

Serum hormones

Clotted bloods were assayed for the levels of the two important immuno-regulatory hormones, namely cortisol and dihydroepiandrosterone sulphate (DHEAs). A Private Pathology Laboratoy conducted these assays. The time of draw was always noted so as to be comparable between volunteers. Since all the blood draws took place between 6.00 and 9.00 at each time point, it was possible to compare these values. The changes in these 2 hormones were compared between the groups by expressing the results as a ratio between cortisol : DHEAs levels.

Statistical analysis of data

An independent statistician, who has blinded to the codes used, conducted the statistical analysis. Non-parametric statistics (two sample Mann-Whitney test) was used to test for differences in the population distribution at baseline and therefore determine whether we had comparable groups.

Any significant changes occurring during the study period within the groups due to the intake of the BSS : BSSG or the placebo capsules were determined using the paired Wilcoxon signed-rank test (i.e. means of differences between baseline and post-marathon values).

Results

Comparison of data of groups at baseline

Statistical analysis of the groups' data at baseline revealed that the groups were comparable except for 2 statistically significant differences: Group A individuals exhibited higher eosinophils absolute counts (10^9/L) (0.2238 vs 0.1244; $p = 0.029$) and higher absolute CD 19 positive (i.e. B cells) : 231 vs 167 (10^9/L).

Since the individuals had been randomly assigned to the groups and since each group had similar age and gender distributions, we considered that both groups were comparable in all other immunological parameters for the purposes of this study.

Marathon-induced changes in hematological parameters within groups

Table **1** indicates that the statistically significant changes within the hematological parameters after marathon running tend to be more pronounced in Group A (placebo) than in group B (BSS : BSSG treated volunteers). Indeed, the leukocytosis shown in the placebo group (5.06 vs 5.86; $p = 0.03$) was significant but not in the treated group (5.08 vs 5.32; p = NS). Similarly, the neutrophilia described by many authors also seems to be more pronounced in the placebo group when compared to the group having received the sterols/sterolins capsules (2.38 vs 3.09 in placebo group [$p = 0.03$] compared to 2.78 vs 2.94 in treated group [p = NS]). These changes were still noticeable even though the blood sampling took place 3 days post-marathon, and we would assume that they would have been more pronounced, had the sampling taken place within 24 hours after the event.

Table 1 Changes in hematological parameters (Mean ± SEM) between baseline and 3 days post-marathon within groups A and B

Parameter	Group A (Placebo)		Group B (BSS:BSSG)	
	Pre	Post	Pre	Post
WBC ($\times 10^9$/L)	5.06 ± 0.24	5.86 ± 0.42	5.08 ± 0.27	5.32 ± 0.31
% Lymph	39.0 ± 3.25	33.8 ± 3.86	33.3 ± 3.41	33.3 ± 2.62
Abs Neut ($\times 10^9$/L)	2.38 ± 0.32	3.09 ± 0.39	2.78 ± 0.25	2.94 ± 0.26

Also, as described by others, the marathon runners in the placebo group displayed a relative lymphocytopenia post-marathon. Comparison of the differential count between the two groups revealed that the percentage lymphocytes dropped in the placebo group (Table **1**: 39.0% vs 33.8%; $p = 0.03$), but such a decrease was not present in the treated runners (33.3% vs 33.3%, p = NS). This was not significant when the absolute lymphocyte counts were compared.

All other hematological parameters measured showed no significant changes within the groups when the pre- and post-marathon values were compared. This data is not shown.

Marathon-induced changes in blood lymphocyte phenotypes within groups

Lymphopenia has been reported to occur after acute physical exercise and most of the lymphocyte subsets also decrease [11]. We measured the lymphocyte subsets in the bloods of the volunteers and again, it appeared that the changes within these subsets were more pronounced in the placebo group (decreases) when compared to that in the treated group (Table **2**). It is interesting to note that, unlike the placebo-group, the BSS : BSSG treated group showed significant increases in both the CD3+ and CD4+ cells ($p = 0.02$ and 0.03, respectively) suggesting that these individuals were less likely to be in a transient immune suppressed state after the marathon. The converse would be the case in the individuals in the placebo group: these individuals decreased both their CD3+ ($p = 0.02$) and CD4+ ($p = 0.03$) cells over the same period of time.

Table 2 Changes in peripheral blood lymphocyte phenotypes (Mean ± SEM) between baseline and 3 days post-marathon within groups A and B

Parameter	Group A (Placebo)		Group B (BSS:BSSG)	
	Pre	Post	Pre	Post
% CD3	67.5 ± 1.5	62.8 ± 2.4	68.1 ± 1.8	72.1 ± 2.4
% CD4	40.7 ± 3.1	37.5 ± 3.0	39.4 ± 2.5	42.2 ± 2.4
% CD8	25.6 ± 1.8	22.3 ± 1.6	27.3 ± 2.6	27.5 ± 2.9
% CD19	12.1 ± 1.1	12.6 ± 1.8	10.3 ± 0.9	9.0 ± 0.7
% CD16 + 56	20.0 ± 1.8	20.2 ± 2.5	22.4 ± 4.3	21.0 ± 4.5

Marathon-induced changes in serum levels of IL6 and cortisol : DHEAs ratios within groups

One of the aims of this study was to determine whether: a) the intake of the sterols/sterolins by the marathon runners could inhibit the release of the proinflammatory monokine (IL6) and b) whether any effect on the balance between cortisol and its antagonist DHEAs could be demonstrated.

The results of the IL6 plasma levels pre- and post-marathon in the 2 groups are shown in Fig. **1**. It is clear that, while the placebo group showed the typical increase in the plasma IL6 level, the treated group showed a significant drop in this monokine post-marathon ($p = 0.008$) although, for unexplained reasons, the pre-marathon level was higher in this group. Nevertheless, both groups of volunteers exhibited elevated IL6 levels at baseline relative to the normal range, because these individuals were training strenuously at the time of entry into the study.

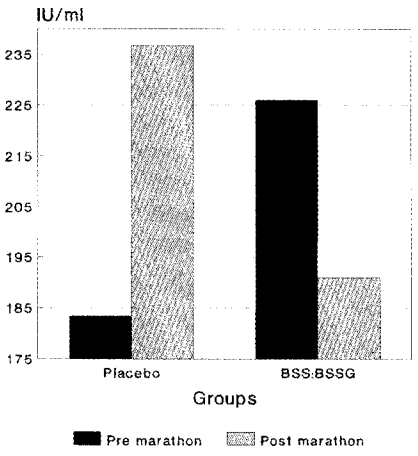

Fig. 1 Pre- and post-marathon plasma IL6 levels (IU/ml) in the placebo and BSS : BSSG treated groups.

Similarly, as shown in Table **3**, it is quite clear that the intake of BSS : BSSG mixture had a marked effect on the balance between cortisol and DHEAs levels. Indeed, it can be seen that the serum levels of cortisol (the stress-related immunosuppressive hormone) rose significantly in the placebo individuals

Table 3 Changes in serum levels of cortisol and DHEAs (Mean ± SEM) between baseline and 3 days post-marathon within groups A and B

Parameter	Group A (Placebo)		Group B (BSS:BSSG)	
	Pre	Post	Pre	Post
Cortisol (nmol/L)	538.5 ± 98.7	577.4 ± 81.1	559.6 ± 43.1	552.1 ± 32.6
DHEAs (umol/L)	4.0 ± 0.8	4.4 ± 0.6	4.2 ± 1.2	5.0 ± 1.4
Cortisol: DHEA Ratio (calculated)	134.6	131.2	133.2	110.4

(538.5 vs 577.4; $p = 0.03$) whereas the same hormone dropped marginally in the BSS:BSSG group (559.6 vs 552.1; p = NS). This decrease was accompanied by an increase in the DHEAs levels and hence, a statistically significant decrease in the cortisol:DHEAs ratio in the treated group, but no statistically significant change in the placebo group.

Discussion

The evidence for an effect of exercise on the immune response is derived partly from laboratory-based investigations into specific aspects of immune function and secondly from epidemiological studies [14]. It is generally accepted that low intensity exercise is beneficial for the immune system in that this type of exercise enhances lymphocyte responses to mitogenic stimulation and increases the number of natural killer cells (NK cells) and the number of lymphocytes (leucocytosis). Such changes would be seen as an enhancement of the immune function. In sharp contrast, high intensity exercise of long duration is associated with adverse effects on the immune system. Such adverse effects of endurance exercise appear to increase the incidence of infections in athletes, especially during intense periods of training (peak training): such infections include those of the upper respiratory tract and intestinal upsets, including diarrhea.

In this study, we were interested in determining whether the intake of BSS:BSSG mixture by athletes participating in an ultra-marathon could reverse or inhibit totally or partially some of the changes. This hypothesis is based on the fact that the sterols/sterolins have been shown to have potent immunomodulatory activities in healthy individuals [6]. It has subsequently been investigated in various clinical trials including its use as adjuvants in the therapy of pulmonary tuberculosis patients [10], HIV infected patients [5] and patients with benign prostatic hypertrophy [3].

The results indicate that the hematological changes, which accompany endurance exercise, were more pronounced in the group of volunteers having received placebo when compared to those ingesting the BSS:BSSG mixture. For instance, the individuals in the placebo group showed the typical neutrophilia, lymphopenia and total leukocytosis and are in agreement with previously published reports [11]. However, such changes were not as pronounced or were even absent in the treated group. Similarly, the lymphopenia present after the marathon in the placebo group was probably due to decreases in the lymphocytes bearing the CD3+ CD4+ or CD3+ CD8+ phenotypes. This can be seen as a transient state of immune suppression and could account for susceptibility for infections post-marathon. Such decreases were not present in the group of individuals who received the active BSS:BSSG capsules: on the contrary, these individuals increased their CD3+ CD4+ cell numbers. This is similar to what it observed in HIV infected persons on the clinical trial [5].

Possibly the most dramatic differences between the groups in this study were both the changes in IL6 and the cortisol:DHEAs ratios. Indeed, the placebo group showed the typical increase in the pro-inflammatory monokine whereas the same monokine decreased significantly in the group of volunteers who ingested the BSS:BSSG capsules. Although both groups showed raised levels of IL6 at the start of the study, probably due to the training schedule followed at the time of enrollment into the study, those individuals who ingested the capsules containing the BSS:BSSG showed a dramatic decrease in the plasma level of this monokine post-marathon. This can be seen as a beneficial, anti-inflammatory response in these volunteers. This observation is also paralleled in our study of HIV infected persons taking the capsules: patients using the BSS:BSSG capsules showed a steady decline in their plasma levels of IL6 over a 6 month period indicating that the plant fats are capable of reducing chronic inflammation.

The fact that the BSS:BBSG group of patients exhibited a decline in their cortisol levels while the level of the same hormone increased significantly in the plasma of the placebo group of patients would indicate that the sterols/sterolins are also capable of inhibiting the hormonal response to the stress with a subsequent redistribution of leucocytes, which ultimately significantly affects the immune system in its ability to respond to potential or ongoing immune challenge [9]. This is an important observation, because it can be considered that the BSS:BSSG mixture is perhaps also a natural anti-stress agent or a cortisol antagonist. This requires further experimentation. However, the above observation has subsequently been observed in other studies such as in chronic fatigue syndrome patients participating on a small pilot study (unpublished).

In recent years, the role of DHEA in regulating the immune response has received much attention. This natural hormone has been described to have important immunomodulatory properties in that it protects mice from lethal viral and bacterial infections [16,2]. The level of this hormone has also been shown in humans to decline with age and it has been proposed to account for the immune dysregulation which normally accompanies old age: raised IL6 serum levels and its association with the development of chronic diseases such as arthritis, etc. [4].

Recent evidence has been obtained to explain the dichotomy between cytokines which activate cell-mediated immunity and those which promote the humoral immune response. This evidence has been highlighted in the mouse model where CD4 cells could be divided into either a so-called T_{H1} phenotype (CD4 cells which secrete IL2, IFN-γ, and IL12) or a T_{H2} phenotype (CD4 cells which secrete IL4, IL6, IL10 amongst others). This observation is also paralleled when one analyses T-cell clones of human origin. It is thus proposed that the balance between these 2 phenotypes determines the final outcome of the immune response to an infectious organism due to the fact that the T_{H1} cells cross regulate the T_{H2} cells and *vice versa*. It

has also been proposed that certain pathogens are able to survive the immune response against it by inducing a predominant T_{H2} response that favors the formation of antibodies which are non-protective. The cell-mediated response (potentiated by T_{H1} CD4 cells) would lead to the activation of cytotoxic CD8+ cells and the infectious organism would be effectively cleared from the host. There is now evidence emerging that this hypothesis would explain the lack of effective clearance of pathogens which induce chronic infections such as HIV, *Mycobacterium tuberculosis*, etc.

More recently, investigators have reported a direct link between DHEA and the T_{H1} subtype of CD4 cells that secrete important regulatory cytokines [19]. Indeed, the activity of the T_{H1} CD4 cells is greatly enhanced by DHEA and, subsequently, the balance between T_{H1} and T_{H2} CD4 cells is controlled in favor of a cell-mediated response. This control is vital in determining the prognosis of individuals infected with the Human Immunodeficiency Virus [8]. In our study, we have shown that the DHEA plasma level of individuals ingesting the BBS : BSSG capsules increases relative to the cortisol level. We have also previously shown that this mixture of phytosterols is capable of enhancing the activity of CD4 cells preferentially belonging to the T_{H1} phenotype [6]. It is thus feasible to propose that the BSS : BSSG mixture can act as natural DHEA and therefore account for its immunomodulatory activity both *in vitro* and *in vivo*. It thus also stands to reason that the BSS : BSSG mixture could be used in diseases where the balance of T_{H1} versus T_{H2} CD4 cells should be corrected and in so doing, reverses the immune dysfunction.

The effects of intense exercise on the immune system have been under debate for many years with some investigators believing that the increased incidence of upper respiratory infections, especially during the post-exercise period, being due to decreased local mucosal immunity [12] whereas others have proposed pertubations in granulocytic functions such as phagocytosis [18] or lymphocytes and their activation status [1]. We have not, in the present study, considered the effects of BSS : BSSG mixture on these parameters. However, the fact that this plant mixture has shown significant immunomodulatory activity on lymphocyte subsets and the ability to decrease the inflammatory response in these athletes justifies their use to prevent the subtle immunosuppression associated with excessive physical stress.

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