Hemorheological disturbances in the overtraining syndrome

Emanuelle Varlet-Marie [a], Freddy Maso [b,c], Gérard Lac [b,c] and Jean-Frédéric Brun [b,*]

[a] *Laboratoire de Pharmacocinétique Clinique, Faculté de Pharmacie, Université Montpellier I, France*
[b] *Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies du Métabolisme Musculaire (CERAMM), CHU Lapeyronie, Montpellier, France*
[c] *LPPM, Bat Biologie B, Les Cézeaux, 63177 Aubière, France*

Abstract. Contemporary sports imply huge training volumes, with thus an increasing danger of overloading. The timely detection of the state of overloading in the organism as a whole or in skeletal muscles presents a difficult and complicated problem. A standardized questionnaire has been proposed by the French consensus group on overtraining of the Société Française de Médecine du Sport (SFMS) and allows the calculation of a "score" that may help to quantify the early clinical symptoms of the overtraining syndrome in sportsmen submitted to a heavy training program. We previously reported that this overtraining score is correlated with blood viscosity due to a correlation of this score with plasma viscosity and hematocrit. When subjects with a high score were compared to subjects with a lower score they appeared to have a higher blood viscosity at native (but not corrected) hematocrit, explained by higher values in both plasma viscosity and hematocrit. By contrast, there was no difference in RBC deformability and aggregation. Therefore, the early signs of overtraining in elite sportsmen are associated with a hemorheologic pattern that suggests some degree of reversal of the "autohemodilution" which characterizes fitness. In a further study we reported that the feeling of heavy legs in overtrained athletes is related to impaired hemorheology. Although well matched with controls for age and body composition, subjects with a complaint of heavy legs had higher plasma viscosity and a higher red cell aggregation as measured with laser backscattering. These findings suggest that the feeling of heavy legs in overtrained athletes are related to hemorheologic disturbances. In the light of the recent concept explaining this syndrome by a mild chronic inflammatory reaction, the investigation of hemorheology in overtraining can be a promising area for hemorheologists, providing both markers and likely pathophysiological explanations for some symptoms of this situation.

Keywords: Blood viscosity, plasma viscosity, hemorheology, erythrocyte deformability, erythrocyte aggregability, exercise, overtraining

1. Introduction

In athletes, the overtraining syndrome is classically defined as a situation of declining performance when maintaining a normal training program [1]. Actually, the term "overtraining" includes the assumption that there is an overload of exercise. However, it is now clear that the clinical signs of this syndrome are also due to stress, psychological as well as physiological, accompanied with inadequate rest, nutritional imbalance, mild inflammatory disorders, etc. [2]. Therefore, it has been recently proposed to re-name this syndrome and to call it the "unexplained underperformance syndrome" [3].

Usually, a mild, rapidly reversible state is defined as "overreaching" while the term "overtraining syndrome", or "staleness", means that a recovery period of months up to a year may be required. Usually,

*Corresponding author: Dr J.F. Brun, MD, PhD, Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies du Métabolisme Musculaire (CERAMM), CHU Lapeyronie, 34295 Montpellier-cédex 5, France. Tel.: +33 04 67 33 82 84; Fax: +33 04 67 33 89 86; Telex: CHR MONTP 480 766 F; E-mail: drjfbrun@dixinet.com.

overreaching, a result of short-term overtraining, can be reversed with a resting period of a few days, maybe a week. A milder form is the normal fatigue experienced after several days of hard training. This fatigue is normally reversed after a few days of reduced training. Although there is a variety of symptoms reported on overtrained athletes, the main symptoms are reduced performance and pronounced fatigue.

Although a variety of biological symptoms has been described, none of them is reliable in terms of sensitivity or specificity. For example, reduced postexercise maximal lactate [4], excess cortisol (or even blunted cortisol response in the most severe cases), disturbed autonomic nervous system balance as evidenced by power spectral analysis of beat-to-beat, heart rate variability, have been described [5,6].

Recently, the French consensus group on overtraining of the *Société Française de Médecine du Sport* (SFMS) proposed a standardized questionnaire of early clinical symptoms of this elusive syndrome, allowing the calculation of a "score" that may help to classify on a clinical basis sportsmen submitted to a heavy training program [7]. An English translation of this questionnaire is given in appendix. This score appears to be correlated with markers of muscular damage (creatine kinase, myosin) or neuroendocrine dysfunction (somatotropic axis), but also with some hematological markers like ferritin (see below).

2. A mild hyperviscosity syndrome

We recently investigated a possible relationship between the OTS score and blood rheology in male elite athletes [8]. The score appeared to be correlated with blood viscosity. This correlation was explained by higher plasma viscosity and hematocrit in individuals with a high overtraining score. By contrast, there was no difference in RBC deformability and aggregation. Therefore, the early signs of overtraining in elite sportsmen are associated with a hemorheologic pattern that suggests some degree of reversal of the fitness-associated "autohemodilution" discussed above. In addition, overtrained athletes are frequently iron depleted, a mechanism that may induce additional hemorheological alterations but is unlikely to explain the early hemorheologic tableau of the overtraining syndrome [8].

Other reports have also emphasized that there is a mild dehydration with increased hematocrit, serum Na^+, and serum K^+. All this has been interpreted as an excess plasma water loss. Since concentrations of blood urea nitrogen and serum glutamic-oxaloacetic transaminase were also increased, without any evidence for water-electrolyte deficiency syndrome, renal dysfunction, or liver cell damage, the authors interpreted these findings as reflecting a persistent mild degree of dehydration and catabolic state noted after intense training [9].

We tried more recently to clarify the negative correlations between blood viscosity parameters and fitness. First of all, it appeared that there was a "paradox of hematocrit" since physiological hemodilution decreases systemic hematocrit proportional to the improvement in fitness. Thus, in physiological conditions, an increase in hematocrit rather reflects a decrease in performance. This phenomenon contrasts with the artificial rise in hematocrit that is obtain with erythropoietin doping or with autotransfusion. These doping procedures appear thus to be markedly nonphysiological and may imply a high trombotic risk [10]. Current concepts in microcirculatory hemodynamics help to understand that high systemic hematocrit is not likely to impede blood flow in muscles during exercise. However, high hematocrit remains a risk factor for thrombosis, and is likely to increase the risk of stroke in otherwise healthy individuals [10]. Interestingly, when investigating this issue with multivariate analysis hematocrit appears to be a marker of fitness, i.e. it is negatively correlated to aerobic working capacity while the overtraining score is positively correlated to plasma viscosity. Thus, in the populations we studied, the best hemorheogical correlate of fitness is a low hematocrit and the best hemorheological correlate of overtraining is increased plasma viscosity [11]. Therefore, plasma viscosity in athletes has a specific value which is different from that of hematocrit.

The most recent concepts of overtraining may help to understand the meaning of this increase in plasma viscosity that appears to be a marker of overtraining.

3. A mild inflammatory syndrome

As discussed above, beside the simple reversal of the fitness-associated "autohemodilution" presented above, special emphasis should be made on higher plasma viscosity.

Current concepts of the pathophysiology of the overtraining syndrome may explain this mild plasma hyperviscosity and mild hemoconcentration pattern, since cytokines released by the "over-stressed" muscle appear now to be responsible for most of the symptoms [2]. According to this "cytokine hypothesis of overtraining" recently proposed by Smith, high volume/intensity training, with insufficient rest, will produce muscle and/or skeletal and/or joint trauma. Circulating monocytes are then activated by injury-related cytokines, and in turn produce large quantities of proinflammatory IL-1beta, and/or IL-6, and/or TNF-alpha, producing systemic inflammation. Elevated circulating cytokines then co-ordinate the whole-body response by: (a) communicating with the CNS and inducing a set of behaviors referred to as "sickness" behavior, which involves mood and behavior changes that support resolution of systemic inflammation: (b) adjusting liver function, to support the up-regulation of gluconeogenesis, as well as de novo synthesis of acute phase proteins, and a concomitant hypercatabolic state; and (c) impacting on immune function. Theoretically, OTS is viewed as the third stage of Selye's general adaptation syndrome, with the focus being on recovery/survival, and not adaptation, and is deemed to be "protective", occurring in response to excessive physical/physiological stress. The interest of this conception for hemorheologists is thus that OTS appears to be a systemic inflammatory condition which can be monitored by markers of inflammation, such as, obviously, hemorheological ones [2].

More recently, Robson [12] revisited this cytokine hypothesis and proposed that there was a time-dependent sensitisation explaining increased production of and/or intolerance to interleukin and that the principal abnormal cytokine was interleukin (IL)-6 during exercise.

A more detailed description of the role of cytokines in training and overtraining in connexion with other metabolic and hormonal axes has been recently proposed [13]. According to this paper, the acute training response involves peripheral cellular mechanisms designed to achieve energy supply. This involves associated cytokine and hormonal reactions. If exercise induces glycogen deficiency, it increases also the expression of local cytokines (interleukin-6, IL-6), as well as decreased expression of glucose transporters, increased cortisol, decreased insulin secretion and beta-adrenergic stimulation. Muscle damage and repair processes may involve, as stated previously, the expression of inflammatory cytokines (e.g., tumour necrosis factor-alpha, TNF-alpha) and of stress proteins (e.g., heat shock protein 72). Moreover, during overreaching and overtraining, a "myopathy-like state" occurs in skeletal muscle. This "myopathy-like state" includes depressed turnover of contractile proteins, in connexion with a special hormonal profile associating excess exercise-induced hypercortisolism, and decreased somatotropic hormones (GH and IGF-I) [13].

4. Athletes suffering from the feeling of heavy legs

These findings of an hemorheological pattern in OTS can also be relevant to some aspects of the clinical symptomatology of overtraining. For instance, the feeling of having "heavy legs" (FHL) is one of the most commonly reported signs. Since FHL is also a sign of chronic venous insufficiency where it can be corrected by rheo-active drugs we recently investigated whether the FHL is associated with a hemorheologic profile. It appeared that FHL subjects complaining from OTS signs had higher plasma viscosity (1.43 ± 0.047 vs 1.32 ± 0.02 mPa.s) and a higher red cell aggregation as measured with laser bacskattering [14]. These findings suggest that the feeling of heavy legs in overtrained athletes is related to OTS-related hemorheologic disturbances.

We recently focused on the clinical presentation of this feeling of having "heavy legs" by selecting on a multicentric database on overtraining of the French Society for Sports Medicine (SFMS) 330 athletes mentioning this feeling. It appears that the FHL detects a subgroup of athletes whose score of overtraining is more than twofold higher and that complain more of tiredness (68%), lost of force (51%), decrease of performance (51%), and cramps (43%). Although this works does not include any biological measurement, these clinical findings obtained are thus consistent with the concept of FHL being associated with a mild inflammatory pattern which is reflected by increased blood viscosity, as previously reported by our group [15].

5. The issue of nutritional balance: iron, zinc and protein status

Iron-deficient states are particularly frequent in highly trained athletes, and even more in women [16]. The mechanism of these deficiencies is complex: hemolysis resulting from mechanical damage on red cells, higher iron loss in urine, faeces, or sweat, decrease in iron digestive absorption, some disturbances in erythropoiesis, or inadequate intake. In the case of "sports anemia" the effects of this deficiency on performance are well known: there is a reduction in exercise performance and a decrease in working capacity, with a higher accumulation of lactate into blood and a lower VO_{2max}. Relationships between iron deficiency in trained subjects, and either erythrocyte metabolism, oxygen consumption, or blood lactate have been extensively studied. However, whether iron deficiency is associated with hemorheological changes is poorly known. Experimental studies in iron-deficient rats have evidenced a lower erythrocyte flexibility that seemed to be related at least in part to a lower hemoglobin content of erythrocytes.

Therefore, we investigated relationships between iron status (as reflected by plasma ferritin) and blood rheology in sportsmen. Our results show that sportsmen with low plasma ferritin exhibit a higher blood viscosity, a higher plasma viscosity, and a higher red cell aggregabilitity when compared to sportsmen with normal plasma ferritin. By contrast, we find no difference in either hematocrit or erythrocyte rigidity between these two subgroups [17].

It should be pointed out that our subjects with low ferritin were not anemic, as reflected by their values of hemoglobin, MCHC and MCV. Such an isolated, low value of ferritin, as frequently observed in highly trained individuals, probably reflects an early stage of iron deficiency, before the occurrence of anemia. In this situation, iron stores are reduced but there remains enough iron supplied to the bone marrow for erythropoiesis.

Iron deficiency is one of the biological parameters that have been proposed as markers of the overtraining syndrome. However, the explanation of this relationship remains unclear. One could suggest that excess work load reduces iron stores and thus results in low ferritin and tiredness. One of the explanations is that the physiological increase in iron absorption when iron stores are low is impaired by exercise and thus can only occur when subjects remain at rest for a while. In addition, both epinephrine and acidosis blunt red cell production, while old erythrocytes are more fragile and are prone to excessive hemolysis. On the other hand, most sportsmen have an insufficient intake of iron and zinc, that are necessary for oxygen handling, mitochondrial electron transport, and wound healing: alteration of any of these processes may impair fitness. Thus, consistent with clinical reports, moderate iron deficiencies are likely to reduce exercise performance and to delay recovery from sports injuries. We think that the association of low ferritin and high overtraining score is largely explained by such mechanisms.

There is often a strong association between iron and zinc status. Sportsmen are frequently deficient in one of these two minerals, or both. In previous studies, we showed that zinc-deficient sportsmen had a higher erythrocyte rigidity and a lower exercise performance while oral zinc supplementation improved blood rheology and exercise tolerance. In fact, the effects of deficiency in these two minerals on blood rheology could be synergistic. However, the hemorheologic pattern of hypoferritinemic subject (high plasma viscosity and high aggregation) is not the same than that of hypozincemic subjects (increased erythrocyte rigidity). While a direct *in vitro* and *in vivo* effect of zinc on blood rheology has been demonstrated, little is known on a possible direct effect of iron stores (or circulating ferritin itself?) on blood rheology.

6. Further issues to be resolved

As recently reviewed by Urhausen, the multitude of publications regarding overtraining syndrome or the short-term "over-reaching" and the severity of consequences for the athlete are in sharp contrast with the limited availability of valid diagnostic tools [5]. Current literature proposes the following markers: a decrement in sport-specific performance, a small decrease in the maximum heart rate, slightly lowered exercise-induced lactate levels [4], reduced respiratory exchange ratio during high intensity exercise [18,19]. Generally, the most widely recognized signs are clinical and consist of deterioration of the mood state and typical subjective complaints ("heavy legs", sleep disorders). Selected blood markers such as urea, uric acid, ammonia, enzymes (creatine kinase activity) [20] or hormones including the ratio between (free) serum testosterone and cortisol, nocturnal urinary catecholamine excretion and the decrease in the maximum exercise-induced rise in pituitary hormones, especially adrenocorticotropic hormone and growth hormone are rather an area of research [21] and are surely not fully reliable markers [5]. Immunological markers have also been largely investigated [22,23] but on the whole both "normal training" and "overtraining" are able to impair immunity, so that it is rather difficult to delineate these two situations.

Finally, standardized clinal approach (such as the questionnaire proposed by the French consensus group) is the most important diagnostic tool, and among the poorly specific proposed markers, plasma viscosity, which is likely to reflect the mild inflammatory syndrome that underlies the disease, deserves further investigations.

Appendix: The SFMS questionnaire (English translation)

The number of answers quoted "yes" gives a score between 0 and 54. According to the French multicentric study (F. Maso, in press), scores > 20 are highly suggestive of overreaching and are constantly found in overtly overtrained individuals.

Overtraining questionnaire

Sex	M	F	
Date of birth:			
What is your profession?			
If you are a student, are you in period of examinations?	Yes	No	
What is your main sport or game?			
How many hours do you practice per week?	6–8 h	8–10 h	more than 10 h
If you practice other sports or games, write them:			
This month, has there been any significant event which may have disturbed your private or professional life?	Yes	No	
This month:			
1 - My level of sport performance/my state of form has decreased:	Yes	No	
2 - I am not as attentive as before:	Yes	No	
3 - My close friends think that my behaviour has changed:	Yes	No	
4 - I have a sensation of oppression in my chest:	Yes	No	
5 - My heart seems to beat faster:	Yes	No	
6 - I have a lump in my throat:	Yes	No	
7 - I have less appetite than before:	Yes	No	
8 - I eat more:	Yes	No	
9 - I do not sleep as well as before:	Yes	No	
10 - I drowse and yawn in the daytime:	Yes	No	
11 - The lapse of time between training sessions seems to me too short:	Yes	No	
12 - My sexual appetence has decreased:	Yes	No	
13 - My performances are poor:	Yes	No	
14 - I frequently catch a cold:	Yes	No	
15 - I have put on weight:	Yes	No	
16 - I have memory problems:	Yes	No	
17 - I often feel tired:	Yes	No	
18 - I underestimate myself:	Yes	No	
19 - I often have cramps, muscular pain:	Yes	No	
20 - I suffer from headaches more frequently:	Yes	No	
21 - I do no feel fit:	Yes	No	
22 - I sometimes feel dizzy, on the point of fainting:	Yes	No	
23 - I do no confide in others so easily:	Yes	No	
24 - I am often seedy:	Yes	No	
25 - I have a sore throat more often:	Yes	No	
26 - I feel nervous, insecure, anxious:	Yes	No	
27 - I do no bear training so well:	Yes	No	
28 - At rest, my heart rate is faster than before:	Yes	No	
29 - During exercise, my heart rate is faster than before:	Yes	No	
30 - I often feel rotten:	Yes	No	
31 - I get tired more easily:	Yes	No	
32 - I often have digestive disorders:	Yes	No	
33 - I feel like staying in bed:	Yes	No	
34 - I am not so confident in myself:	Yes	No	
35 - I get injured more easily:	Yes	No	
36 - I have more difficulties in organizing my thoughts:	Yes	No	
37 - I have more difficulties in concentrating in my sports activity:	Yes	No	

38 - My sporting gestures are less precise, less skilful:	Yes	No
39 - I have lost force and aggressiveness:	Yes	No
40 - I feel as if I had no one to talk to:	Yes	No
41 - I sleep longer:	Yes	No
42 - I cough more often:	Yes	No
43 - I do not enjoy practicing my sports as much:	Yes	No
44 - I do not enjoy my leisure activities as much:	Yes	No
45 - I get irritated more easily:	Yes	No
46 - I am less efficient in my school or professional activity:	Yes	No
47 - People around me think that I have become less pleasant:	Yes	No
48 - Training seems harder and harder:	Yes	No
49 - It is my fault if my results are worse:	Yes	No
50 - My legs feel heavy:	Yes	No
51 - I lose my personal things more easily (wallet, keys, etc.):	Yes	No
52 - I am pessimistic, I have the blues:	Yes	No
53 - I have lost weight:	Yes	No
54 - My motivation, will and tenacity are weaker:	Yes	No

Put a cross to range between these two opposite states

My physical level:
Great form $\longleftrightarrow$ Bad form
I feel fatigued:
More slowly $\longleftrightarrow$ More quickly
I recover from my state of tiredness:
More quickly $\longleftrightarrow$ More slowly
I feel:
Very relaxed $\longleftrightarrow$ Very anxious
I have the feeling that my muscular strength has:
Increased $\longleftrightarrow$ Decreased
I have the feeling that my endurance has:
Increased $\longleftrightarrow$ Decreased

Have you had any difficulties in understanding some of the questions? Yes No
If yes, which questions did you find difficult to understand (write the numbers)?

References

[1] P.Z. Pearce, A practical approach to the overtraining syndrome, *Curr. Sports Med. Rep.* **1**(3) (2002), 179–183.
[2] L.L. Smith, Cytokine hypothesis of overtraining: a physiological adaptation to excessive stress?, *Med. Sci. Sports Exerc.* **32**(2) (2002), 317–331.
[3] P. Robson, Elucidating the unexplained underperformance syndrome in endurance athletes: the interleukin-6 hypothesis, *Sports Med.* **33**(10) (2003), 771–81.
[4] L. Bosquet, L. Leger and P. Legros, Blood lactate response to overtraining in male endurance athletes, *Eur. J. Appl. Physiol.* **84**(1–2) (2001), 107–14.
[5] A. Urhausen and W. Kindermann, Diagnosis of overtraining: what tools do we have?, *Sports Med.* **32**(2) (2002), 95–102.
[6] R. Hedelin, G. Kentta, U. Wiklund, P. Bjerle and K. Henriksson-Larsen, Short-term overtraining: effects on performance, circulatory responses, and heart rate variability. *Med. Sci. Sports Exerc.* **32**(8) (2000), 1480–1484.

[7] J.F. Brun, Le surentraînement: à la recherche d'un outil d'évaluation standardisé utilisable en routine, *Science & Sports* **18** (2003), 282–286.
[8] A. Aissa Benhaddad, D. Bouix, S. Khaled, J.P. Micallef, J. Mercier, J. Bringer and J.F. Brun, Early hemorheologic aspects of overtraining in elite athletes, *Clin. Hemorheol. Microcirc.* **20**(2) (1999), 117–125.
[9] C.Z. Hong and I.N. Lien, Metabolic effects of exhaustive training of athletes, *Arch. Phys. Med. Rehabil.* **65**(198), 362–365.
[10] J.F. Brun, C. Bouchahda, D. Chaze, A.A. Benhaddad, J.P. Micallef and J. Mercier, The paradox of hematocrit in exercise physiology: which is the "normal" range from an hemorheologist's viewpoint?, *Clin. Hemorheol. Microcirc.* **22**(4) (2000), 287–303.
[11] A. Gaudard, E. Varlet-Marie, F. Bressolle, J. Mercier and J.F. Brun, Hemorheological correlates of fitness and unfitness in athletes: moving beyond the apparent "paradox of hematocrit"?, *Clin. Hemorheol. Microcirc.* **28**(3) (2003), 161–173.
[12] P. Robson, Elucidating the unexplained underperformance syndrome in endurance athletes: the interleukin-6 hypothesis, *Sports Med.* **33**(10) (2003), 771–781.
[13] J.M. Steinacker, W. Lormes, S. Reissnecker and Y. Liu, New aspects of the hormone and cytokine response to training, *Eur. J. Appl. Physiol.* (2003).
[14] E. Varlet-Marie, A. Gaudard, J Mercier, F. Bressolle and J.F. Brun, Is the feeling of heavy legs in overtrained athletes related to impaired hemorheology?, *Clin. Hemorheol. Microcirc.* **28**(3) (2003), 151–159.
[15] J.F. Brun, E. Varlet-Marie, F. Maso, G. Lac and the French Consensus Group on Athletes Overtraining (G. Bernardié, A.X. Bigard, V. Bricout, F. Brue, F. Depiesse, A. Favre-Juvin, J. Giordan, F. Limas, N. Paruit, P. Rochcongar, V. Rousseaux-Blanchi, B. Serrurier) (Boulouris, Grenoble, Montpellier, Nantes, Orléans, Rennes, Voiron).
[16] J.A. Hawley, S.C. Dennis, F.H. Lindsay and T.D. Noakes, Nutritional practices of athletes: are they sub-optimal?, *J. Sports Sci.* **13** (1995), S75–S81.
[17] S. Khaled, J.F. Brun, A. Wagner, J. Mercier, J. Bringer and C. Prefaut, Increased blood viscosity in iron-depleted elite athletes, *Clin. Hemorheol. Microcirc.* **18**(4) (1998), 309–318.
[18] J. Manetta, J.F. Brun, L. Maimoun, O. Galy, O. Coste, J.L. Raibaut and J. Mercier, Carbohydrate dependence during hard-intensity exercise in trained cyclists in the competitive season: importance of training status, *Int. J. Sports Med.* **23**(7) (2002), 516–523.
[19] I. Aloulou, J. Manetta, M. Dumortier, F. Brandou, E. Varlet-Marie, C. Fédou, J. Mercier and J.F. Brun, Effets en miroir de l'entraînement et du surentraînement sur la fonction somatotrope et la balance glucidolipidique à l'exercice, *Science & Sports* **18** (2003), 305–307.
[20] U. Hartmann and J. Mester, Training and overtraining markers in selected sport events, *Medicine and Science in Sports and Exercise* **32** (2000), 209–215.
[21] R. Meeusen, M.F. Piacentini, B. Busschaert, L. Buyse, G. De Schutter and J. Stray-Gundersen, Hormonal responses in athletes: the use of a two bout exercise protocol to detect subtle differences in (over)training status, *Eur. J. Appl. Physiol.* (2003).
[22] S.L. Halson, G.I. Lancaster, A.E. Jeukendrup and M. Gleeson, Immunological responses to overreaching in cyclists, *Med. Sci. Sports Exerc.* **35**(5) (2003), 854–861.
[23] L. Lakier Smith, Overtraining, excessive exercise, and altered immunity: is this a T helper-1 versus T helper-2 lymphocyte response?, *Sports Med.* **33**(5) (2003), 347–364.