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Fatigue and illness in athletes

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Abstract
Adequate nutrition before, during, and after training and competition is a key element to maintaining health. During both sprint and endurance exercise, the availability of glycogen is fundamental to performance and any deficit will lead to early fatigue. In addition, strategies to offset the negative effects of the products of metabolism are presented. Although nutritional strategies can attenuate the immunosuppressive effects of exercise, there remains a period of susceptibility to infection after a hard exercise session and when this is repeated without sufficient recovery an athlete can enter a period of ''overtraining'' during which performance deteriorates. The aetiology and identification of this state is not clear and some current ideas are discussed. Finally, gastrointestinal problems during running can negate any training benefits and we propose some suggestions to reduce this problem.

Keywords: *Fatigue, immunosuppression, performance*

Introduction

This review is concerned with the consequences of fatigue when it arises from nutritional deficiencies. Although the causes of acute fatigue are discussed, the nutritional remedies for optimal recovery are covered in the specific reviews relating to individual events (Burke, Millet, & Tarnopolsky, 2007; Stellingwerff, Boit, & Res, 2007; Tipton, Jeukendrup, & Hespel, 2007), and supplements are considered by Maughan and colleagues (Maughan, Depiesse, & Geyer, 2007).

Metabolic fatigue

Fatigue is multifactorial in nature and depends on the individual, the environment, energy and other nutritional factors, and the specific task. For all events, however, the intermediate step between energy availability through substrate breakdown and energy needed for movement lies in the high-energy compounds adenosine triphosphate (ATP) and phosphocreatine. However, although phosphocreatine may be sufficient to supply a ''top up'' provision to adenosine diphosphate (ADP) for 5–10 s, depending on speed and individual capacities, the kinetics of phosphocreatine breakdown indicate that the availability of phosphocreatine is a limiting factor for ATP generation well before the muscle content of phosphocreatine is totally depleted (Sahlin, 2006). Therefore, even in the short dynamic events, an adequate store of muscle glycogen is also required to augment the energy provision.

However, when ATP utilization exceeds the muscle's capacity to rephosphorylate ADP, the muscle activates adenyl kinase, which catalyses the reaction 2 ADP to 1 ATP and 1 AMP (adenosine 5′-phosphate). The latter is deaminated in a reaction regulated by AMP deaminase to finally form NH_3. Thus, during intense exercise, the resting total adenine nucleotide pool levels may be reduced by 10–15 % (Bangsbo, Sjödin, & Hellsten-Westling, 1992; Hellsten-Westling Balsom, Norman, & Sjödin, 1993), which may take several days to restore to control levels. The deamination of nucleotides to NH_3 may also activate xanthine oxidase, which, especially during hypoxic stress, may generate oxygen free radicals and thus induce muscle damage (for further reading, see Hellsten, 1993). However, antioxidants such as ubequinone (Q_{10}) may act as pro-oxidants during high-intensity training (sprint training), which induces increased levels of creatine kinase and reduced training adaptation compared with a control (Malm, Svensson, Ekblom, & Sjödin, 1997; Malm, Svensson, Sjöberg, Ekblom, & Sjödin, 1996).

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The major limitation at middle distance is likely to be that of decreasing pH of the muscle when the intensity remains high but the duration extends beyond 2–3 min. Although glycogen utilization in general is not considered to be limiting in this type of exercise, an inadequate supply at the onset of any race may be limiting. However, it cannot be ruled out that single muscle fibres may be glycogen depleted, especially if lactate is produced, and thus may adversely affect performance. Classically, it was believed that increased lactate (and decrease in pH) was the cause of metabolic acidosis, but this has been challenged recently and although the two factors may correlate increasingly, it is believed that they are not causal. Metabolic acidosis is more accurately caused by an increased reliance on non-mitochondrial ATP turnover and the production of ADP, P_i, and H^+. Adenosine diphosphate and P_i are ultimately recycled via glycolysis to form ATP, leaving H^+ to accumulate in the cytosol (Robergs, Ghiasvand, & Parker, 2004). Any transient increase in P_i is believed to reduce the amount of calcium released from the sarcoplasmic reticulum and thus reduces the excitation–contraction coupling of the muscle fibres (Dahlstedt & Westerblad, 2001), while re-uptake of calcium into the sarcoplasmic reticulum is negatively affected by reduced pH (Holloszy, 1967). Elevations in magnesium can also impair calcium release (Allen, Westerblad, Lee, & Lannergren, 1992), and magnesium elevations are a consequence of reduced ATP and pH. Strategies to offset decreases in pH include β-alanine as an intracellular buffer and bicarbonate or citrate in the extravascular space. The relevance of these supplements to improve performance are discussed in the reviews by Tipton *et al.* (2007), Stellingwerff *et al.* (2007), and Maughan *et al.* (2007).

During events lasting more than 30 min, blood glucose is also used as a fuel with its utilization peaking around 90 min (Maughan & Gleeson, 2004). Circulating blood glucose may be replenished through gluconeogenesis using alanine, lactate, and glycerol as liver substrates, although within the duration of most races the time scale of this source makes the contribution minimal. There is considerable evidence to suggest that the release of glucose from the liver is hormonally controlled, essentially by the glucagons–insulin ratio (Coker, Simonsen, Bulow, Wasserman, & Kjaer, 2001), as well as cortisol (Cryer, 1993), epinephrine (Howlett, Febbraio, & Hargreaves, 1999), and adrenergic neural stimulation (Sigal *et al.*, 1994). However, the case has been made (Febbraio & Pedersen, 2002) that these mechanisms simply cannot account for the rapid increase in hepatic extracellular glucose production (EGP) required during exercise. The possibility of a cytokine interleukin-6 (IL-6), which can increase up to 60-fold at the end of a marathon (Ostrowski, Rhode, Zacho, Asp, & Pedersen, 1998), being a humoral ''exercise factor'' has been supported by experiments indicating that when IL-6 infusion is combined with exercise at 40% maximal oxygen uptake ($\dot{V}O_{2max}$), EGP glucose kinetics were similar to those at 70% $\dot{V}O_{2max}$ (Febbraio *et al.*, 2004a, 2004b). This suggests that, at intensities of 40% $\dot{V}O_{2max}$ or above, IL-6, without any change in the glucoregulatory hormones identified earlier, can potentiate extracellular glucose production.

Although lipolysis starts relatively early in exercise, beyond 90 min –when the supply of glucose is virtually depleted – the rate of ATP production is reduced and the pace of performance must drop, as fat can only maintain exercise at intensities less than 50–60% $\dot{V}O_{2max}$. Nutritional manipulations to maintain an adequate supply of carbohydrate are discussed in detail by Stellingwerth *et al.* (2007) and Burke *et al.* (2007); however, athletes must still learn to pace appropriately to avoid depleting their carbohydrate sources. Noakes and colleagues (Noakes, St. Clair Gibson, & Lambert, 2005) have proposed a theory to suggest that pacing strategies are centrally governed and not peripherally dictated. In this model, the term ''fatigue'' is considered to be a sensory perception that is regulated centrally. The concept is attractive and would suggest that fatigue can be overridden by conscious effort.

Low glycogen before exercise, even when blood glucose is maintained, elevates IL-6 concentrations (Steensberg *et al.*, 2002), and when a dose of rhIL-6 was given to athletes before a 10-km time-trial, the participants reported an increased sensation of psychological and physical fatigue resulting in a reduced performance time (Robson, de Milander, Collins, & Noakes, 2004). Theoretically, this links to the theory of Noakes *et al.* (2005), whereby afferent ''energy-sensing signals'' (IL-6 levels) inform the brain of impending fuel depletion. Clearly, therefore, even before the glucose supply becomes limiting, elevated levels of IL-6 could lead to fatigue through central mechanisms. In addition, supplementation with glucose during exercise inhibits the exercise-induced increase of plasma IL-6 (Febbraio *et al.*, 2003).

An alternative central fatigue theory is associated with the increased utilization of non-esterified fatty acids during distance events. As exercise progresses, there is an increased utilization of non-esterified fatty acids, which requires albumin to circulate in the blood. In binding with the albumin, non-esterified fatty acids may displace tryptophan, thus increasing the free levels of tryptophan. Simultaneously, and in particular at longer distances, branched-chain amino acids are extracted from the blood and used as a fuel. Tryptophan and branched-chain amino acids

compete for transport into the brain and a reduction in branched-chain amino acids, together with elevated free tryptophan, can cause increased tryptophan transport into the brain. Tryptophan is a precursor of serotonin and is known to cause central fatigue (Sahlin, 2006). The possibility of supplementation with branched-chain amino acids to attenuate this form of fatigue is considered further by Maughan *et al.* (2007).

Finally, current research is investigating the effect of caffeine on central mechanisms and this is discussed in Maughan *et al.* (2007) elsewhere in this issue.

Immune system disturbances

At certain times, particularly after hard training, athletes are especially vulnerable to infectious agents. The physical barriers (e.g. skin, mucous membranes) and a sub-group of the white blood cells/leukocytes, including neutrophils and activated monocytes, engulf, ingest, and digest foreign material. This first line of defence is referred to as the ''innate immune system''. Acute bouts of high-intensity exercise are associated with a depression of immune function that may last up to 72 h (Nieman, 2000), and this period has been compared recently with trauma-induced systemic inflammatory response (Fehrenbach & Scheider, 2006). Leukocyte and lymphocyte numbers increase in response to exercise predominantly through the increase in catecholamines and cardiac output, and the resultant mechanical shear stress on the blood vessels. However, it is elevated cortisol that causes a delayed neutrophilia (Fehr & Grossman, 1979) and a suppression of the number of lymphocytes (Nielsen, Secher, Kappel, & Pedersen, 1998) at the end of exercise, which can last for 2–3 h. The response of the neutrophils to heavy exercise is diverse, although commonly there is a slight degranulation, which is a process that occurs following phagocytosis whereby the neutrophils digest micro-organisms and reactive oxygen species. This early degranulation may contribute to the attenuated degranulation on exposure to bacterial stimulation and the reduced immune response of an athlete. Following prolonged exercise, the majority of the evidence also suggests a fall in the production of immunoglobulins (Gleeson & Pyne, 2000), again exposing the athlete to a higher risk of infection. Ekblom (2002) has reported links between energy deficiency, lowered testosterone levels, and a reduced immune response in young football players when two competitive matches were played within 20 h. The reduced immune response and lowered testosterone were still evident 72 h after the final game. In addition, increases in adhesion and signalling molecules within the lymphocytes and monocytes were higher in those players with a lower $\dot{V}O_{2max}$ (Malm, Ekblom, & Ekblom, 2004), indicating that these less aerobically fit players were more vulnerable to immunosuppression. Although there is no direct evidence to link this immunosuppression with upper respiratory tract syndrome and exercise volume (Nieman, 1994), it is logical to assume that the two observations are linked. The most robust evidence for this speculation is provided by a study of Bruunsgaard *et al.* (1997), where several antigens were injected into the skin of tri-athletes who had just completed exercise and another group who were rested. The exercised group showed a weaker response to the injection, suggesting that their immune response was lowered. Clearly, athletes are continually exposing themselves to heavy exercise regimens and potentially are always vulnerable.

If the initial innate protection fails, the acquired immune system comes into play. The cells of this system are lymphocytes. The lymphocytes are responsible for the athlete's memory of previous infections, enabling him or her to respond more rapidly to a previous invader with a specific and targeted response.

The transition from innate to acquired immunity requires an initial infiltration of neutrophils, followed by their clearance and replacement by monocytes (Figure 1). Differential control of this leucocyte recruitment, activation, and apoptosis is linked to the activity of the cytokine IL-6 and its receptors (Jones, 2005). At rest, IL-6 is mainly released from monocytes/macrophages, fibroblasts, and endothelial cells (Akira, Taga, & Kishimoto, 1993). Adipose tissue also contributes about 30% of the circulating IL-6 at rest (Mohamed-Ali *et al.*, 1997). However, IL-6 is only biologically active when it interacts with two receptors, IL-6R and gp130 (Figure 2). During an

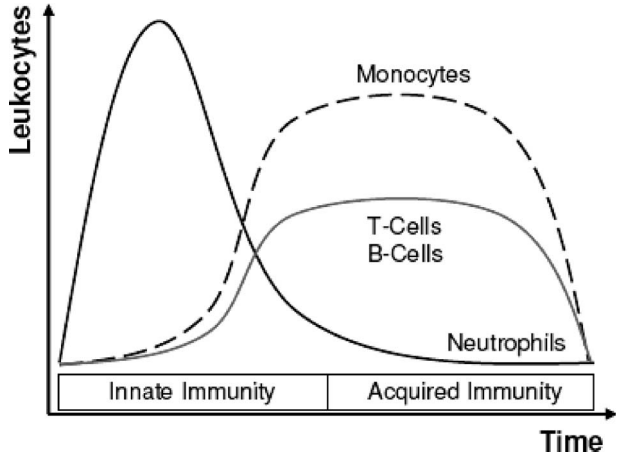

Figure 1. Schematic representation of the optimal profile of leukocyte recruitment observed as part of innate and acquired immunity, following inflammatory activation against disease, infection or injury.

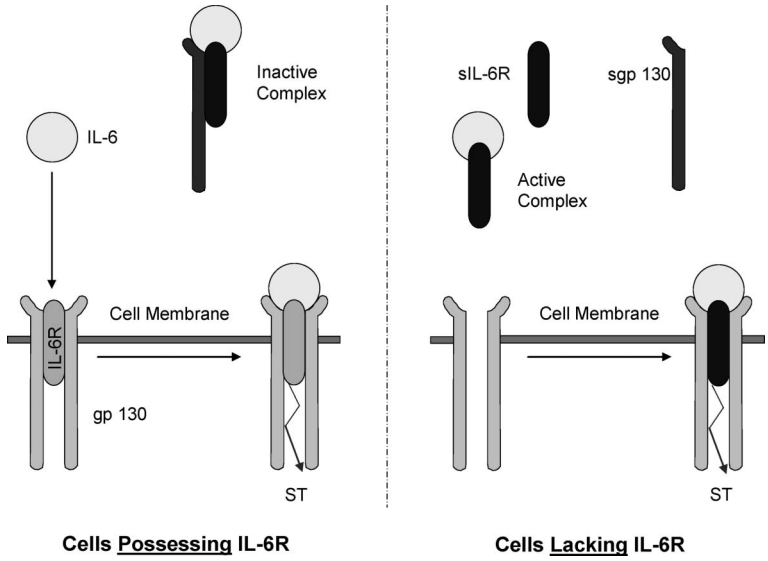

Figure 2. Schematic representation of IL-6 signalling. Iinterleukin-6 signalling upon cells possessing membrane-bound IL-6R; IL-6/sIL-6R trans-signalling in cells that do not possess IL-6R; and IL-6/sIL-6R trans-signalling blocked by the antagonist sgp130. *Abbreviations*: IL, interleukin; R, receptor; gp, glycoprotein; ST, signal transduction.

inflammatory event, IL-6 combines with sIL-6R and then with two membrane-bound gp130 receptors, and through a process called trans-signalling initiates gene transcription and the release of a number of other anti-inflammatory cytokines. Because of this pattern of activity, IL-6 may be considered as initiating a broad anti-inflammatory response (Figure 3).

Studies are consistent in reporting that during heavy exercise, such as a marathon, there is up to a 60-fold increase in plasma levels of IL-6 (Ostrowski *et al.*, 1998) with the duration of the event explaining more than 50% of the variation (Fischer, 2006). Although other cytokines increase with exercise, the IL-6 increase precedes that of any other cytokine and its increase is the most significant (e.g. Northoff & Berg, 1991; Ostrowski *et al.*, 1998), and muscle damage is not a necessary prerequisite (Ostrowski *et al.*, 1998). Other sources of IL-6 during exercise are the Achilles' tendon (Langberg, Olesen, Gemmer, & Kjaer, 2002) and the brain (Nybo, Nielsen, Pedersen, Moller, & Secher, 2002) but the contribution from these sources is relatively small compared with that of skeletal muscle. Considering the pivotal role that IL-6 and its receptors play in successfully resolving acute inflammation and in initiating a general anti-inflammatory response, the consequences of dramatically altering its concentration must be considered in the context of immune disturbances and illness in athletes.

General energy restriction can cause a reduction in cells of the acquired immune system with the consequence of a slower response to a previously

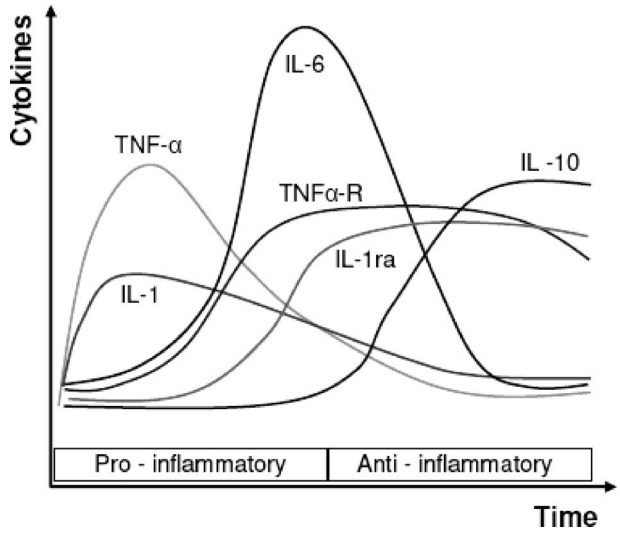

Figure 3. Schematic representation of the pro- and anti-inflammatory cytokine profiles coordinated as part of innate and acquired immunity, respectively. *Abbreviations*: TNF-α, tumour necrosis factor-alpha; IL, interleukin; R, receptor; ra, receptor antagonist.

encountered antigen (Mustafa, Ward, Treasure, & Peakman, 1997). Although this evidence arises from studies on fasting individuals and anorexia nervosa patients, anorexia athletica has also been associated with an increased susceptibility to infection (Beals & Manore, 1994). Specific nutrient availability also has the potential to affect all aspects of the immune system both directly and indirectly, with even a mild deficiency causing an altered immune response (Gleeson, Niemen, & Pedersen, 2004).

It would appear that elevated fatty acid availability may decrease immune function through increasing the amount of prostaglandin production (in particular prostaglandin E_2). Although it is known that omega-3 polyunsaturated fatty acids may alter the presentation of prostaglandin E_2 to the less potent prostaglandin E_3, supplementation is not advised as this prostaglandin is also immunosuppressive. Similarly, too low a diet in fat (<15% daily energy intake as fat) could also suppress immune function, thought to be through the loss of micronutrients (Venkatraman, Feng, & Pendergast, 2001).

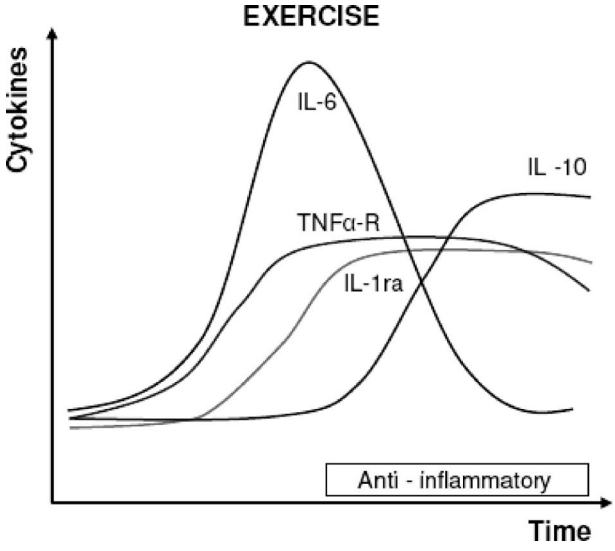

Figure 4. Schematic representation of the anti-inflammatory cytokine profile that occurs in response to exercise. *Abbreviations*: TNF-α, tumour necrosis factor-alpha; IL, interleukin; R, receptor; ra, receptor antagonist.

Dehydration will elevate catecholamines (Gonzalez-Alonso, Mora-Rodriguez, Below, & Coyle, 1995) and cortisol (Bishop, Scanlon, Walsh, McCallum, & Walker, 2004), which will almost certainly lead to immunosuppression. In addition, fluid replacement attenuates the decrease in saliva flow rate normally associated with dehydration (Walsh, Montague, Callow, & Rowlands, 2004), thus maintaining the supply of several proteins (IgA, lysozyme, and α-amylase) that have known microbial properties (Bishop, Blannin, Armstrong, Rickman, & Gleeson, 2000).

For some time the ''glutamine hypothesis'' (Parry-Billings, Evans, Calder, & Newsholme, 1990) suggested that plasma concentrations below $\sim 600\ \mu mol \cdot l^{-1}$ will have deleterious effects on immune function because of the restriction placed on the uptake by leukocytes. Until about 2000, there was therefore a recommendation for athletes to supplement with glutamine for this reason. However, these cells have been shown to function equally well at $300-400\ \mu mol \cdot l^{-1}$ and that concentrations of $100\ \mu mol \cdot l^{-1}$ would be required to affect these cells' functionality (Hiscock & Pedersen, 2002). As catabolic conditions only ever reduce glutamine to $200\ \mu mol \cdot l^{-1}$, the hypothesis therefore falls. However, there may be other indirect benefits, as yet

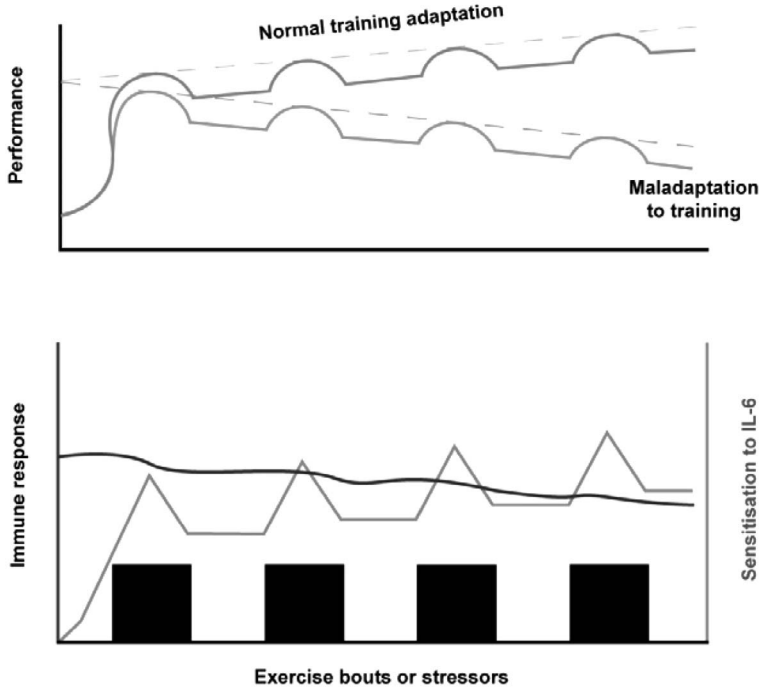

Figure 5. Diagrammatic representation of the current understanding of overtraining syndrome.

untested, that would benefit athletes, such as maintenance of gut barrier function (Walsh, 2006).

Pre-treatment with the antioxidants vitamin C and E significantly reduces the IL-6 release from the muscle bed (Fischer *et al.*, 2004). Fischer's group (Fischer *et al.*, 2006) showed a reduction in serum Hsp72 release if vitamin C was administered in combination with vitamin E in the γ- and α-tocopherol form. No such attenuation was found if only the α-tocopherol form was administered with vitamin C. Although a recent meta-analysis (Moriera *et al.*, 2007) supports the conclusion of vitamin C supplementation modulating the immunosuppression with exercise, there is no support for the administration of vitamin E supplementation in view of links to heart failure (Lonn *et al.*, 2005).

Worthy of further investigation is the herbal preparation *Echinacea purpuea*. A study conducted on tri-athletes was able to show a significant fall in illness in the treated group compared with control triathletes (Berg, Northoff, & Konig, 1998). Similarly, there is some evidence to suggest a beneficial effect of probiotics (Pujol *et al.*, 2000). However, both of these supplements require further study before they can be recommended to athletes.

Chronic exercise and overtraining/ underperformance

The process of overreaching is standard training practice whereby an intensified training period is built into a periodized cycle of training, allowing sufficient recovery to refuel and repair. After the overreaching period, it is common to have a supercompensation affect whereby an enhanced performance is exhibited. Although this appears a simple concept, in practice the coach has to manage the intensity, volume, and duration of each cycle plus any additional psychosocial aspects without very much sound scientific guidance. The consequence of getting this balance wrong is dramatic. Either insufficient training leads to a lack of performance progress or, alternatively, too much training or insufficient recovery can lead to overtraining. Overtraining is defined as an accumulation of training or non-training stress, which results in a long-term (weeks or months) decrement in performance. Overtraining also relates to an increased incidence of infections, persistent sore muscles, and general malaise and disturbed sleep. As identified in the definition, these symptoms can arise not only from excess training but may also be caused by psychological stress. For this reason, Robson (2003) has used the word ''underperformance'' rather than overtraining. However, most coaches will be familiar with the term overtraining and that is therefore the term used here. The aetiology of the syndrome is complex and some have challenged its existence (Halson & Jeukendrup, 2004), although other reports suggest that the incidence of overtraining syndrome is higher in athletes than the general population and it is also higher in individual competitor sports (48%) than team sports (30%) (Kentta, Hassmen, & Raglin, 2001). The major difficulty is the diagnosis of the syndrome, as there are no universally agreed diagnostic criteria.

Some progress is being made with reference to the mechanism by which the immune response is altered in athletes and again it lies around the cytokines. It is known that exercise will elevate not only IL-6, but also heat shock proteins (Hsp). Intracellular concentrations of heat shock proteins act as a chaperone to other proteins and protect them from stress. Progressively with exercise, mRNA Hsp72 in skeletal muscles will increase (Febbraio & Koukoulas, 2000) and Hsp 70 has been shown to increase in the skeletal muscles with training (Liu *et al.*, 1999). This would suggest that athletes build up a ''store'' of these proteins to help protect them from subsequent stress. However, it is perhaps the circulating or extracellular eHsp72 that has the most relevance to overtraining, and the major source of the increase in circulating eHsp72 is the hepato-splanchnic bed (Febbraio *et al.*, 2002), not the muscle. Increases in eHsp72 following a single bout of exercise (Lancaster *et al.*, 2004; Marshall, Ferguson, & Nimmo, 2006; Walsh *et al.*, 2004; Whitham *et al.*, 2004) act as ''danger signals'' and stimulate monocytes to release IL-6 and the subsequent cytokine cascade (Asea *et al.*, 2000; Campisi, Leem, & Fleshner, 2003). As discussed earlier, as leukocyte release of IL-6 does not appear to contribute to the circulating levels of IL-6 during or at the end of acute exercise, the timing of this effect on the monocytes and the effect of repeated exercise require more investigation. One theory relating chronic elevations of IL-6 to overtraining syndrome (Smith, 2003) suggests that this causes T-helper lymphocytes, which have a crucial role in acquired immune function, to alter. T-helper lymphocytes represent two subsets of cells: T(H)1 are associated with cell-mediated immunity and the killing of intracellular pathogens; T(H)2 lymphocytes are associated with humoral immunity and antibody production. As noted earlier, with sustained heavy exercise and possible tissue trauma, there will be an elevation of cytokines, particularly IL-6. This elevation in cytokines causes the T(H)2 cell type to predominate, resulting in a reduction in cell-mediated immunity and thus exposing the athlete to infection. Simultaneously, increased levels of stress hormones as well as prostaglandin E_2 support the up-regulation of T(H)2 lymphocytes. Smith (2003) therefore suggests that overtraining reflects a redirecton of the immune system to one of humoral

immunity rather than cell-mediated immunity. This theory may explain immune suppression in athletes who are more susceptible to viral infections but does not explain the increased incidence of upper respiratory tract infection, as the latter is a bacterial infection.

As it has become clear that tissue trauma is not required to increase circulating cytokines, the hypothesis has been refined to suggest that overtraining syndrome is a result of elevated cytokines predominantly based on the effect IL-6 has on the brain (Robson, 2003). As noted earlier, infusion of rhIL-6 into athletes before a 10-km time-trial resulted in a reduced performance (Robson *et al.*, 2004), and elevated cytokines have also been noted after an intensified acute training period (Robson-Ansley, Blannin, & Gleeson, 2007). An alternative hypothesis relates to the response to elevated IL-6. Both patients and athletes are often able to identify a particular stress (e.g. severe psychological stress or severe infection) just before the onset of symptoms. This initial exposure could sensitize the athlete to subsequent releases of IL-6 when exposed to a subsequent exercise bout or infection, potentially causing early fatigue.

It is clear that although some mechanisms are being proposed, there is no clear guidance as yet for coaches and athletes on the cause, the identification of, or remedy for overtraining syndrome. Alternative avenues for investigation may lie in the response of receptors in light of the increasing literature associated with sIL-6R's role in orchestrating the transition from innate to acquired immunity.

Iron deficiency

It has always been recognized that there is a susceptibility of female endurance runners to iron deficiency, particularly if they are vegetarian. In the majority of the athletic population, the most common finding is a dilutional pseudonaemia that is caused by a plasma volume expansion, rather than an actual blood loss. However, blood losses can occur and an evaluation should consider lowered blood counts due to foot strike haemolysis or iron losses through heavy sweating, gastrointestinal symptoms or poor nutrition. Clinical evaluation is normally through measurement of serum ferritin. There is still considerable controversy about the optimal haematological parameters for an athlete, but clearly low ferritin is an indication of low iron stores. Low iron stores do not directly reduce maximal oxygen uptake, physical endurance or important muscle components (Celsing, Blomstrand, Werner, Pihlstedt, & Ekblom, 1986; Celsing, Ekblom, Werner, Sylvén, & Åstrand, 1988); however, the margins for negative effects on performance are narrow. However, low iron stores may affect central nervous system functions and also compromise the body's anti-oxidant capacity by lowering catalase activity in cells (Halliwell & Gutteridge, 1999). Reconstitution of the iron stores can be managed through a balanced food intake or supplementation. Self-medications must be discouraged, not only because of other drug interactions but because excesses can impair immune function and increase susceptibility to infection (Sherman, 1992). Further discussion of iron requirements can be found in Burke *et al.* (2007).

Gastrointestinal problems and running

The most common gastrointestinal complaints in athletes relate to bowel urgency and diarrhoea (Kyriakos, Siewert, Kato, Sosna, & Kruskal, 2006), and are associated with problems of the lower gastrointestinal tract. The symptoms arise from alterations in permeability of the small intestine and possible transient ischaemia (Oktedalen, Lunde, Opstad, Aabakken, & Kvernebo, 1992). A common clinical finding is thickening of the caecal wall (Kyriakos *et al.*, 2006). The effect is normally transient and resolves itself with a lower mileage regimen and some dietary manipulation to reduce motility agents. If persistent, athletes may be treated with histamine H2-receptor antagonists (Butcher, 1993) and there may be a role for blockade of IL-6 trans-signalling (Atreya *et al.*, 2000), although the latter requires further exploration. Data gathered from the Chicago marathon in 1996 (Smetanka *et al.*, 1999) concluded that ibuprofen but not aspirin may aggravate gastrointestinal problems but the problems can arise with prolonged exercise alone.

In addition to its role in digestion, the small intestinal epithelia also act as a barrier between the external and internal environment (e.g. Travis & Menzies, 1992). Compromised barrier function may produce an inflammatory response and initiate a cytokine cascade that could contribute to gastrointestinal distress during and after running (Oktedalen *et al.*, 1992). One study reported that 81% of athletes racing over 81.4 km had elevated concentrations of plasma endotoxin with 2% at a level that would be considered lethal (Brock-Utne, *et al.*, 1988). A more recent study of triathletes undertaking a long-distance race noted mild endotoxaemia in 68% of athletes (Jeukendrup *et al.*, 2000). It should be noted, however, that these reports are from extremely demanding physical exertion for a prolonged time and that the incidence in well-managed training programmes would be substantially less, as evidenced by the fact that in the study by Brock-Utne *et al.* (1998), the most severe toxaemia was observed in the least fit individuals.

Upper gastrointestinal problems have been reported but are less common. They include reflux, nausea, vomiting, and gastritis, and may be due to altered oesophageal motility. Again, if persistent, H2-blockers have been found to be helpful for reflux and nausea (Simons & Kennedy, 2004).

Summary of guidelines for fatigue and illness

Consensus for:

- Maintenance of a diet to ensure sufficient calories to meet the energy expenditure demand.
- High pre-exercise glycogen stores and glucose feeding during exercise.
- Use of vitamin C to offset immunosuppression.
- Use of fluid replacement strategies to ensure euhydration.
- Holistic monitoring of athlete stress.

Consensus against:

- Abrupt increases in training load.
- Diets that are too high or too low in fat.

Issues that are equivocal:

- Accurate biomarkers for overtraining.
- Accurate diagnostic criteria for overtraining syndrome.
- The role of IL-6 and IL-6R in overtraining syndrome and immunosuppression.

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