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Recovery of the immune system after exercise

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1 ABSTRACT

2 The notion that prolonged, intense exercise causes an 'open window' of
3 immunodepression during recovery after exercise is well accepted. Repeated exercise bouts
4 or intensified training without sufficient recovery may increase the risk of illness. However,
5 except for salivary IgA, clear and consistent markers of this immunodepression remain
6 elusive. Exercise increases circulating neutrophil and monocyte counts, and reduces
7 circulating lymphocyte count during recovery. This lymphopenia results from preferential
8 egress of lymphocyte subtypes with potent effector functions (e.g., NK cells, $\gamma\delta$ T cells and
9 CD8⁺ T cells). These lymphocytes most likely translocate to peripheral sites of potential
10 antigen encounter (e.g., lungs, gut). This redeployment of effector lymphocytes is an integral
11 part of the physiological stress response to exercise. Current knowledge about changes in
12 immune function during recovery from exercise is derived from assessment at the cell
13 population level of isolated cells ex vivo or in blood. This assessment can be biased by large
14 changes in the distribution of immune cells between blood and peripheral tissues during and
15 after exercise. Some evidence suggests that reduced immune cell function in vitro may
16 coincide with changes in vivo and rates of illness after exercise, but more work is required to
17 substantiate this notion. Among the various nutritional strategies and physical therapies that
18 athletes use to recover from exercise, carbohydrate supplementation is the most effective for
19 minimizing immune disturbances during exercise recovery. Sleep is an important aspect of
20 recovery, but more research is needed to determine how sleep disruption influences the
21 immune system of athletes.

22

23 **Keywords:** open window; repeated exercise bouts; immunodepression; overreaching; sleep

24 INTRODUCTION

25 The immune system is integral to the body's defense against infection. It also influences
26 other physiological systems and processes, including tissue repair, metabolism,
27 thermoregulation, sleep/fatigue, and mental health. Over the past 40 years, exercise
28 immunology has developed into its own discipline based on the recognition that the immune
29 system mediates many exercise effects and that stress responses mediated through the
30 nervous and endocrine systems play a key role in determining exercise-induced immune
31 changes (84). A classic paradigm in exercise immunology is that an 'open window' of
32 immunodepression can occur during recovery from intense exercise. In particular, this
33 paradigm proposes that after intense exercise, some immune variables (e.g., lymphocyte and
34 natural killer cell numbers, antibody production) transiently decrease below preexercise
35 levels. As a result of this immunodepression microbial agents, especially viruses, may invade
36 the host or reactivate from a latent state, leading to infection and illness (87). If exercise is
37 repeated again while the immune system is still depressed, this could lead to a greater degree
38 of immunodepression and potentially a longer window of opportunity for infection (87).

39 Exercise-induced fatigue exists on a continuum. Repeated bouts of intense exercise on the
40 same day or over several days may cause acute fatigue, as indicated by an inability to maintain
41 exercise workloads (64). An athlete who trains intensely for 1–2 weeks may experience a state
42 of 'functional overreaching', which is associated with a temporary performance decrement,
43 followed by improved performance. Intense training over an extended period without
44 sufficient balance between training and recovery may lead to 'nonfunctional overreaching'
45 (NFOR) (64). This condition is typically characterized by persistent fatigue, performance
46 decrement, muscle soreness, and psychological and hormonal disturbances that can last for

47 weeks or months. Depending on the time needed to recover from NFOR, an athlete may be
48 diagnosed (retrospectively) as experiencing 'overtraining syndrome' (64).

49 Recognition of the link between excessive training and risk of illness has stimulated
50 interest in nutritional supplements and physical therapies to counteract immunodepression
51 and to restore immune function after exercise training. In this mini-review, we update the
52 current state of knowledge about the temporal changes in the immune system following
53 exercise; how repeated bouts of exercise on the same day, extended periods of intense
54 training, and sleep disruption influence the immune system; and the efficacy of various
55 strategies for restoring immune function after exercise.

56

57 **LEUKOCYTE REDEPLOYMENT DURING EXERCISE AND RECOVERY**

58 A single exercise bout causes profound changes in the number and composition of blood
59 leukocytes that may persist long into exercise recovery. All major leukocyte subpopulations
60 tend to increase in number during exercise as a result of hemodynamic shear stress and/or
61 catecholamines acting on leukocyte β_2 adrenergic receptors (126). The postexercise recovery
62 period is marked by opposite effects on blood neutrophil and lymphocyte numbers.
63 Neutrophil number (and, consequently, the total leukocyte count) often continues to increase
64 long into the recovery period (up to 6 h after exercise cessation), particularly if the exercise
65 bout is prolonged (>2 h) (86). This sustained 'neutrophilia' is characterized by an increased
66 presence of immature, less differentiated, precursor neutrophils in the blood (117), most
67 likely in response to the increased plasma levels of soluble agents including glucocorticoids,
68 growth hormone, and cytokines such as IL-6 and granulocyte colony-stimulating factor, which

69 mobilize myeloid cells from the bone marrow (117). Although this neutrophilia following
70 prolonged exercise is akin to that observed during bacterial infection ($>7.0 \times 10^6/\text{ml}$), 24 h of
71 recovery is usually sufficient for neutrophil number to return to normal (126). A delayed
72 monocytosis is sometimes observed within 1–2 h after very prolonged exercise, but monocyte
73 number typically returns to the resting level within 6 h after exercise cessation (126).

74 By contrast, lymphocyte number decreases rapidly after exercise. Following prolonged
75 and/or high-intensity exercise in particular, lymphocyte number commonly decreases to
76 below the preexercise value within as little as 30 min (126). This 'lymphopenia' can often
77 reach levels typical of clinical lymphopenia ($<1.0 \times 10^6/\text{ml}$) but the lymphocyte count is usually
78 restored to both the resting and clinically normal level within 4–6 h of recovery (126). After
79 prolonged bouts of exercise (e.g., 2 h cycling), natural killer (NK) cells (which account for most
80 of the exercise-induced lymphocytosis) may be ~40% lower than the baseline value for up to
81 7 d after exercise (104). Exercise-induced lymphopenia reflects the preferential movement of
82 lymphocyte subtypes with potent effector functions (e.g., NK cells, $\gamma\delta$ T cells, and CD8^+ T cells)
83 out of the blood. Even within these subsets, there is a preferential egress of discrete subtypes
84 of highly differentiated NK-cells, $\gamma\delta$ T cells, and CD8^+ T cells with phenotypes associated with
85 tissue-migrating potential, and effector capabilities (107).

86 The rapid lymphopenia observed during the early stage of exercise recovery was initially
87 of concern, particularly because early studies reported large rates of lymphocyte apoptosis
88 (programmed cell death) after exhaustive exercise (62). However, these findings have not
89 been substantiated. Subsequent studies have reported lymphocyte apoptosis in the order of
90 0–2% after exercise, even though the blood lymphocyte count was up to 30–40% lower than
91 at rest (66, 105). Lymphocytes and monocytes leave the blood in large numbers during

92 exercise recovery under the influence of glucocorticoids. Lymphocyte subtypes that
93 preferentially egress the peripheral blood during exercise recovery also have phenotypes
94 consistent with tissue migration (e.g., expression of surface adhesion molecules, chemokine
95 receptors) (108). These lymphocytes most likely translocate to peripheral sites of potential
96 antigen encounter, such as the lungs or the gut (48).

97 The skin has long been considered a likely destination for effector lymphocytes in
98 response to exercise and stress in general (24). However, recent evidence indicates that CD8⁺
99 T cells and NK cells mobilized by exercise do not express cutaneous homing receptors on their
100 surface (121). Exercise appears to 'prime' effector T cells, thereby allow them to transmigrate
101 to the peripheral tissues that require enhanced immune surveillance following physical stress
102 (54). Compared to the resting condition, the percentage of circulating lymphocytes expressing
103 effector cytokines is lower following prolonged exercise (115), but it is unknown whether this
104 decline reflects impairment at the individual cell level or preferential movement of effector T
105 cells into peripheral tissues (e.g., lungs, gut). Recent evidence showing that exercise redeploys
106 T cells that are specific to latent herpesviruses such as cytomegalovirus (CMV) and Epstein–
107 Barr virus (EBV) (111, 112) suggests that this response may be a countermeasure against
108 stress-induced viral reactivation (107). Exercise may also mobilize 'older' functionally
109 exhausted/senescent lymphocytes to undergo apoptosis in the tissues and allow new
110 'recruits' to take their place (106, 107).

111 Monocytes mobilized by exercise are likely to infiltrate skeletal muscle and differentiate
112 into tissue-resident macrophages that facilitate repair and regeneration, particular following
113 arduous bouts of exercise that cause significant skeletal muscle damage (85). Monocytes with
114 effector phenotypes are also preferentially redeployed after exercise. The CD14⁺/CD16⁺

115 'proinflammatory' monocytes are preferentially mobilized over their CD14⁺/CD16⁻
116 counterparts (109). Monocyte expression of pathogen recognition receptors (e.g., toll-like
117 receptors [TLRs]) tends to decrease in response to moderate-intensity exercise (109).
118 Conversely, prolonged, intense exercise (60 km cycling time trial) increases TLR2 and TLR4
119 expression on monocytes, which may indicate a heightened proinflammatory state (11). A
120 recent study showed that acute exercise mobilizes angiogenic T cells, which may facilitate
121 vascular remodeling during exercise recovery (53). Exercise is also known to mobilize
122 hematopoietic stem cells, which may participate in skeletal muscle repair and regeneration
123 after exercise (25, 49). It has been suggested that exercise may have a role as an adjuvant to
124 mobilize stem cells in donors for hematopoietic stem cell transplantation (25).

125 In addition to cellular redeployment, the recovery phase of exercise, especially following
126 very prolonged bouts of endurance-based exercise, is marked by striking alterations in the
127 functional capacity of several blood leukocyte populations. Neutrophil bactericidal activity is
128 greatly influenced by the intensity and duration of exercise. For example, after 1 h of cycling
129 at 50% and 80% of $\dot{V}O_{2max}$ increases and reduces neutrophil oxidative burst activity,
130 respectively (94). During the early stages of recovery after exercise, neutrophil bactericidal
131 activity continues to increase after 40 min to 1 h of moderate intensity exercise, whereas it
132 remains impaired after exhaustive or prolonged exercise (86). NK cell cytotoxicity after
133 exercise bouts of relatively short duration tends to remain unchanged on a per cell basis
134 during recovery (81) but may decline after very prolonged bouts (33). T-cell proliferation in
135 response to mitogen stimulation typically decreases both during and after exercise, regardless
136 of exercise modality, intensity, or duration (126). Prolonged exercise may also reduce T-cell
137 homing and migration (8), LPS-induced cytokine secretion by monocytes (113), and the

138 percentage of T cells producing effector cytokines in response to mitogen stimulation (115).
139 Thus, the general trend during exercise recovery is that short bouts of moderate-intensity
140 exercise have little effect (or might even enhance) cellular immune function, whereas
141 prolonged bouts (>1.5 h) of heavy exertion appear to reduce the normal functioning of all
142 major immune cell subtypes. These effects may leave athletes susceptible to illness during
143 recovery from competition or heavy training (87).

144

145 **REPEATED EXERCISE BOUTS AND EXTENDED PERIODS OF INTENSE TRAINING**

146 The repeated bout paradigm (87) proposes that, compared with a single bout of exercise,
147 repeated exercise bouts on the same day (27, 73, 96, 102) or over several days (43) cause
148 different changes in circulating cell counts, lymphocyte proliferation, and NK cytotoxicity.
149 Subsequent research has investigated changes in other immune responses to repeated
150 exercise bouts on the same day with short versus long recovery and intensified training over
151 weeks or months. Table 1 summarizes the evidence for changes in the immune system after
152 repeated exercise bouts and days to months of intense training.

153 *One Versus Two Bouts of Exercise per Day*

154 Studies on the effects of one versus two bouts of exercise on a single day have included
155 physically active (56-58, 63, 96, 102), highly trained (23, 88), or elite (12, 73, 98, 99)
156 participants. The exercises involved cycling (12, 27, 56-58, 63, 96, 98, 99, 102), running (23,
157 88), or rowing (73). The duration and intensity ranged from <15 min at maximal intensity (27,
158 73) up to 2 h at medium–high intensity (i.e., 60–75% $\dot{V}O_{2max}$) (56, 96). The recovery period
159 between exercise bouts was most commonly 3–4 h but ranged from 45 min (102) to 12 h (88).

160 Compared with the initial bout of exercise, typically either show a greater relative change or
161 a higher absolute value after a second bout of exercise for the following immune variables:
162 total leukocyte count (57, 63, 99, 102), neutrophil count (23, 73, 96, 99, 102), oxidative burst
163 (per neutrophil) (12), elastase release (per neutrophil) (57), CD4⁺ T-cell count (73, 99, 102),
164 whole-blood IL-8 production (23), and NK cell activation (represented by CD69 expression)
165 (99). Conversely, lymphocyte proliferation (96, 102) and whole-blood IL-6 production (23) are
166 typically lower following a second bout compared with the first bout of exercise.

167 *Short Versus Long Recovery*

168 Three studies on the effects of recovery duration between two bouts of exercise included
169 highly trained or elite athletes who cycled for 65 min at 75% $\dot{V}O_{2max}$, twice each day, with
170 either 3 or 6 h between the exercise bouts (12, 97, 98). A short recovery period (i.e., 3 h)
171 induces either a greater relative increase or higher absolute values for neutrophil count (12,
172 97), oxidative burst activity per neutrophil (12), and CD8⁺ T-cell and NK-cell counts (97) after
173 the second bout of exercise. Exercise-induced changes in lymphocyte (97), monocyte, and
174 eosinophil (12) counts; absolute oxidative burst activity (12); NK cytotoxicity (97); and plasma
175 concentrations of IL-6 and IL-1ra (98) do not differ after a short versus long recovery period.

176 *Consecutive or Multiple Days of Exercise*

177 Studies detailing how the immune system responds to exercise repeated on consecutive
178 days or every second day have included untrained or physically active participants (43, 116,
179 118) or well-trained or elite athletes (60, 73, 77, 79). Exercise included 3 × 6 min maximal
180 rowing, repeated twice over 2 d (73), 1–3 h cycling (77, 79, 118) or running (60) at 50–70%
181 $\dot{V}O_{2max}$ repeated over 3 d, every second day for 3 d (43), or daily for 7 d (116). Exercise-induced
182 changes in plasma cytokine and elastase concentrations and cytokine mRNA expression in

183 leukocytes and muscle diminish over consecutive days (77, 118). By contrast, changes in total
184 leukocyte, neutrophil, and monocyte counts (73, 116, 118), lymphocyte proliferation (79),
185 neutrophil chemotaxis (116), leukocyte IL-1ra mRNA expression (77), plasma
186 myeloperoxidase concentration, and salivary IgA secretion rate (79) do not change over time.
187 Changes in lymphocyte subsets (43, 73), oxidative burst activity (79, 116, 118), salivary IgA
188 secretion rate (60, 77), and NK-cell count and cytotoxicity (73, 79) over consecutive days are
189 more variable.

190 *Immune Changes Associated with Overreaching and Overtraining*

191 Studies on short periods (2–4 weeks) of functional overreaching have reported decreases
192 in resting neutrophil degranulation (95), lymphocyte proliferation, and antibody production
193 (124). Neutrophil count, plasma cytokine concentrations, CD4:CD8 T-cell ratio, and salivary
194 IgA concentration are more variable (or do not change) in response to functional overreaching
195 (39, 95, 124). Athletes who exhibit signs of nonfunctional overreaching and/or frequent upper
196 respiratory illness present with lower salivary IgA concentration (26, 35, 60); lower cytokine
197 production by monocytes, neutrophils and dendritic cells (67); and a greater number of
198 activated (CD25⁺) lymphocytes (29). Changes in differential blood cell counts, lymphocyte
199 subsets, and NK-cell count following extended periods of intensified training are variable (29,
200 35, 61). Studies of athletes exhibiting the hallmarks of overtraining syndrome—including
201 illness—have not revealed any consistent or characteristic immune profile (30, 101).

202

203 SLEEP DISTURBANCE AND IMMUNE FUNCTION

204 Sleep disturbances influence immunity via activation of the hypothalamic–pituitary–
205 adrenal axis and the sympathetic nervous-system (46). Chronic sleep disturbance and
206 disruption to the normal circadian rhythm are associated with inflammation and
207 desynchronization of rhythmic immune variables. These responses likely contribute to
208 increased risk of infection, cardiovascular disease, and cancer in shift workers (21, 68).
209 Despite evidence that athletes experience poor sleep patterns compared with nonathletes
210 (16, 55), surprisingly little is known about how sleep disturbance influences the immune
211 responses to exercise. Compared with normal sleep, a disrupted night’s sleep appears to
212 prime the immune system and enhance immunosurveillance by stimulating total
213 lymphocytes, CD8⁺ T cells, NK cells, and $\gamma\delta$ T cells to leave the blood and migrate to potential
214 sites of infection during the early recovery period after exercise (45). By contrast, other
215 studies indicate that a night without sleep does not influence leukocyte trafficking, neutrophil
216 degranulation, or mucosal immunity at rest or after exercise (31, 93). Subtle immune changes
217 have been observed after a night without sleep, including a shift toward a T helper 2 cytokine
218 profile (46).

219 It is uncertain whether these subtle immune modifications with acute sleep loss are
220 clinically meaningful. When considering the potential effects of poor sleep on immunity in
221 athletes, it is important to distinguish between acute and chronic sleep disturbance. Chronic
222 sleep disturbance (12 nights, 50% sleep loss) increases the plasma inflammation markers C-
223 reactive protein and IL-6 (38). However, intervening daytime naps can counter this apparent
224 inflammatory response (103). Short sleep duration (<7 h/night for 7 d) decreases the response
225 to hepatitis B vaccination and the likelihood of clinical protection (90). Similarly, a night of

226 wakefulness after hepatitis A vaccination decreases the specific antibody response 2–4
227 months later (52). People who experience poor quality sleep and/or regular sleep deprivation
228 also have a 4–5-times greater risk of developing the common cold (16, 91). Continued
229 research efforts should be directed toward monitoring and improving sleep in athletes and
230 understanding the implications for immune health.

231

232 **NUTRITIONAL INTERVENTIONS FOR RESTORING IMMUNE FUNCTION AFTER EXERCISE**

233 Research over the last 30 years has investigated whether nutritional strategies counteract
234 exercise-induced immunodepression and systemic inflammation (32, 125). A comprehensive
235 review of the literature on these is beyond the scope of this mini-review; other more detailed
236 reviews on this topic are available (e.g., (32, 125). Here, we focus on the most effective
237 nutritional strategies—primarily carbohydrate ingestion—for restoring systemic immune
238 function in the first few hours after exercise (9, 10, 19, 51, 65, 76, 78, 82, 83) and over
239 consecutive days (7). We also assess whether the timing of nutritional interventions (i.e.,
240 before, during or after exercise) influence their effectiveness (50, 59).

241 *Carbohydrate Supplementation before and/or during Exercise*

242 Carbohydrate supplementation during prolonged, intense exercise consistently attenuates
243 exercise-induced increases in circulating cytokines (74, 125), and the re-distribution of
244 neutrophils (74, 76, 78), monocytes (76, 82), natural killer cells (78), and lymphocytes (51).
245 The immunomodulatory effects of carbohydrates arise from better maintenance of blood
246 glucose concentrations and blunted release of stress hormones such as catecholamines and
247 glucocorticoids during and after exercise (51, 76, 78, 82, 83). Although the systemic release

248 of IL-6 during exercise is related to muscle glycogen depletion (114), the precise mechanism
249 by which carbohydrate supplementation reduces systemic IL-6 release from contracting
250 muscle during exercise is not clear, because carbohydrate supplementation does not alter
251 muscle glycogen content (75).

252 In several studies, the immunomodulatory effects of carbohydrate supplementation
253 were observed to 'carry over' into the recovery period (i.e., ≥ 2 h post-exercise) (51, 76, 78,
254 82, 83). Nieman et al reported that carbohydrate supplementation during 2.5 h high-intensity
255 running reduces the number of neutrophils (immediately and 1.5 h post-exercise), monocytes
256 (immediately and 6 h post-exercise) and lymphocytes (immediately and 3 h post-exercise)
257 (76, 78). Extending carbohydrate ingestion to the post-exercise recovery period also reduces
258 neutrophil count (74), blood granulocyte and monocyte phagocytosis 6 h post-exercise (82).
259 Lancaster et al showed that carbohydrate consumption (30 and 60 g per hour) during 2.5 h
260 cycling minimized the suppression of CD4⁺ and CD8⁺ T lymphocyte that express and produce
261 IFN- γ during the 2 h following exercise (51).

262 Considering that exercise-induced responses of the adaptive immune system are relatively
263 slow (125), it is important to assess whether these effects are maintained over consecutive
264 days of exercise. Carbohydrate ingestion before, during and after two exercise bouts on two
265 consecutive days attenuated the decrease in antigen-stimulated proliferative lymphocyte
266 responses before exercise on the second day (7). Carbohydrate ingestion also enhanced
267 lymphocyte proliferative responses to mitogen stimulation post-exercise on the second day
268 (7). These findings suggest that carbohydrates may help to diminish potential cumulative
269 immunodepression over consecutive days of exercise.

270 The immunomodulatory effects of carbohydrate may depend on the timing of

271 carbohydrate intake. The ingestion of a glucose solution 15 min—but not 75 min—before 1 h
272 high-intensity cycling prevented immunoendocrine perturbations (50). The lack of an effect
273 of carbohydrates ingested 75 min pre-exercise was potentially associated with an insulin-
274 induced decrease in the plasma glucose concentration prior to exercise, which in turn might
275 have enhanced immunoendocrine responses (50). Carbohydrate ingestion during either the
276 first or the second of two 90-min bouts of cycling on the same day better maintained plasma
277 glucose and attenuated plasma stress hormone responses to the second bout (59). By
278 contrast, carbohydrate ingestion during the 2 h recovery period between these exercise bouts
279 had no such effects (59). These findings suggest beneficial effects of a timely carbohydrate
280 supplementation (i.e., shortly before and/or during exercise) on immune responses to
281 exercise. This may be particularly relevant with more prolonged and/or intense exercise
282 protocols, and when the recovery duration between two consecutive exercise bouts is short.

283 Carbohydrate ingestion does not influence all aspects of the immune system. For example,
284 carbohydrate supplementation does not alter the exercise-induced suppression of natural
285 killer cell function (78) or salivary IgA secretion (18). Importantly, it remains unclear whether
286 the immunomodulatory effects of carbohydrates have clinical relevance for resistance to
287 illness or adaptation of the immune system to regular exercise stress (32, 125). Recent
288 evidence indicates that carbohydrate supplementation during prolonged exercise blunts
289 exercise-induced immune-endocrine perturbations, but does not prevent the suppression of
290 in vivo immunity (22). More research is required to examine the effects of carbohydrates (or
291 other nutritional strategies) on in vivo immune function in response to acute and chronic
292 exercise.

293 *Dietary Carbohydrate Intake after Glycogen-Depletion*

294 Some studies have investigated the effects of dietary carbohydrate intake on immune
295 responses to consecutive days of exercise intended to deplete muscle glycogen (9, 10, 34, 65).
296 A higher carbohydrate intake consistently attenuated certain components of
297 immunodepression well into the recovery period (i.e., ≥ 2 hours post-exercise) after the
298 second exercise session (10, 34, 65). Athletic training often involves conditions of low
299 carbohydrate availability e.g., due to abbreviated recovery periods and/or as part of 'train
300 low-compete high' training regime (41, 42). These investigations therefore have particular
301 practical implications. Compared with a higher carbohydrate intake (8 g/kg/d), very low
302 carbohydrate intake (0.5 g/kg/d) leads to greater perturbation in leukocyte subsets during
303 recovery from exercise (65). These effects may be related to sustained elevation of plasma
304 cortisol concentration (65). Bishop et al observed that compared with a low-carbohydrate
305 diet (1.1 g/kg/d), a high- (8.4 g/kg/d) for 3 d after glycogen-lowering cycling attenuated
306 plasma cortisol and cytokine concentrations, circulating total leukocyte and neutrophil counts
307 following subsequent exercise (10).

308 Consuming a high carbohydrate diet (8.5 g/kg/d) also reduces overreaching symptoms
309 during 11 d of intense training, compared with moderate carbohydrate consumption (5.5
310 g/kg/d) (1). The periodic implementation of 'train-low' strategies (e.g., by commencing
311 training with low muscle glycogen stores) may further amplify metabolic adaptations in
312 skeletal muscle (41, 42). When considering their dietary carbohydrate intake, athletes should
313 aim to achieve a balance between minimizing immunodepression and maximizing metabolic
314 adaptations in skeletal muscle. In view of the detrimental effects of low carbohydrate
315 availability on the immune system, *chronic* carbohydrate restriction should be avoided during
316 intense periods of training (32, 41). Additional research is warranted to better understand the
317 effect of long-term training consisting of intermittent 'train-low' sessions on immune function

318 and susceptibility to illness.

319 *Dietary Protein Intake and Post-Exercise Protein Supplementation*

320 Recognizing the importance of protein for immunocompetence (15), there are benefits of
321 post-exercise protein ingestion (18, 19, 69) or a diet high in protein (128) on immune
322 responses to exercise. Based on previous results indicating that the exercise-induced
323 lymphocyte trafficking was impaired during high-intensity training, Witard et al examined
324 whether a high protein diet can restore these impaired immune responses (128). Consuming
325 a high protein diet (3 g/kg/d) helped to minimize exercise-induced changes in lymphocyte
326 distribution during a period of intense training (128). Interestingly, an energy- and
327 carbohydrate-matched normal protein diet (1.5 g/kg/d) failed to provide the same benefit
328 (128). The high-protein diet was also associated with fewer self-reported upper-respiratory
329 illnesses (128). Another study demonstrated that protein and leucine supplementation for 1–
330 3 h post-exercise during 6 d of high-intensity training enhanced neutrophil respiratory burst
331 activity after the last exercise session (69). Consuming a carbohydrate-protein solution
332 immediately—but not 1 h—after exercise prevents a decrease in neutrophil degranulation
333 during the post-exercise recovery period (19).

334 Recent research has shown that the timing, distribution and amount of post-exercise
335 protein intake modulate the blood and tissue availability of protein/amino acids and adaptive
336 responses of skeletal muscle (3, 42). Notably, amino acid-sensitive mammalian target of
337 rapamycin (mTOR) signaling is also a key mechanism underlying leukocyte trafficking (110).
338 More studies are therefore needed to examine whether different post-exercise protein
339 feeding patterns influence immune function during recovery from exercise.

340 *Antioxidants and Phytochemicals*

341 Except for carbohydrate supplementation, evidence for effective nutritional
342 countermeasures to exercise-induced immune alterations is limited (32, 125). Among other
343 types of nutritional supplements (e.g., probiotics and vitamin D (for reviews see (32, 125)),
344 antioxidants and phytochemicals such as quercetin have been studied for their potential
345 capacity to minimize immune perturbations—particularly during exercise recovery (75, 77,
346 79, 80). Some data point toward beneficial effects of quercetin supplementation on immune
347 health after intense exercise (77, 79). Other findings suggest an increased need for nutritional
348 antioxidants during the first 24 h of recovery from intense exercise lasting several hours such
349 as an Ironman triathlon (71). However, taken together, the present literature is not
350 sufficiently robust to recommend supplementation with phytochemicals or antioxidants to
351 prevent immune suppression and illness in athletes and exercising individuals. Athletes often
352 take high doses of antioxidant/phytochemical supplements in the belief that this will reduce
353 their risk of illness (47). However, high doses of antioxidant/phytochemical supplements can
354 interfere with training adaptations (42, 72). A natural diet rich in fruits, vegetables, whole
355 grains and nuts delivers antioxidants and phytochemicals in physiologically effective amounts
356 that are most likely sufficient to help maintain immune function following exercise and during
357 exercise training (32, 72, 125).

358

359 **OTHER STRATEGIES FOR RESTORING IMMUNE FUNCTION AFTER EXERCISE**

360 In addition to nutritional interventions, other research has examined the efficacy of
361 nonsteroidal anti-inflammatory drugs (NSAIDs) and various physical therapies for restoring
362 immune function after exercise. Some studies (13, 20, 70, 89, 120, 127) have shown effects
363 of NSAIDs, but other human studies have failed to demonstrate any effects of NSAIDs (122,

364 123), cryotherapy (44), compression garments (5, 37, 92), active recovery (2, 119), or other
365 physical therapies (28) on immune responses during recovery from exercise (Fig. 2). Despite
366 this lack of empirical evidence for the benefits of NSAIDs and physical therapies for restoring
367 immune function after exercise, some of these treatments are associated with positive
368 psychological outcomes and other effects not related to immune function after exercise (4,
369 17). Therefore, although the physiological effects of these physical treatments are not
370 understood fully at the present time, they may confer some important benefits for athletes,
371 which may involve the immune system—perhaps indirectly.

372

373 **THEORETICAL AND PRACTICAL CONSIDERATIONS**

374 The redeployment of effector lymphocytes from blood to peripheral tissues is seen as an
375 integral part of the physiological stress response and the immune system's response to
376 prepare the body for potential injury by mobilizing its 'troops' (cells) to increase
377 immunosurveillance (24). Therefore, immune integrity during exercise recovery may be
378 characterized by the host's ability to redeploy effector lymphocytes effectively to the
379 peripheral tissues. Lymphocyte redeployment may be impaired following very prolonged
380 bouts of exercise or in athletes who are overreaching. The redeployment of CD8⁺T cells both
381 during and after exercise is significantly reduced after 1 wk of high-intensity training
382 compared with normal training (129). Specifically, the egress of CD8⁺T cells was 1.4-fold
383 higher after normal compared with high-intensity training.

384 Considering other evidence that stress-induced leukocyte redeployment is linked to poor
385 clinical outcomes following surgery (100), immune cell redistribution and infection risk after

386 exercise warrants further investigation. High-volume exercise training may impair the
387 redeployment of viral-specific T cells and NK cells, thereby reducing antiviral 'patrolling'
388 during exercise recovery (Fig. 1). Herpes viruses such as EBV and CMV are highly prevalent in
389 the population, and reactivation of these viruses from a latent state is indicative of systemic
390 immunodepression (107). EBV viral DNA is present in saliva from athletes after even short
391 periods of high-intensity training (36), but it is unknown whether this reflects training-induced
392 impairment in the trafficking of virus-fighting lymphocytes.

393 Cellular immune function in response to exercise is typically assessed in isolated cells ex
394 vivo, or at the cell population level in the blood compartment. This approach can make it
395 difficult to interpret changes in immune cell function after exercise because of the massive
396 alterations in the cellular composition of discrete leukocyte subtypes. On the one hand, it
397 seems intuitive to interpret lower immune cell function measured in blood during the early
398 stages of exercise recovery as indicative of immunodepression. On the other hand, it is equally
399 possible that, after exercise, the most functional immune cells (i.e., those with effector
400 phenotypes and high tissue-migrating potential) are redeployed to other areas of the body
401 where they are needed. If true, this suggests that systemic immunosurveillance may be
402 enhanced during exercise recovery, despite an apparent depressed profile in the blood
403 compartment.

404 It is difficult to determine the biological significance of exercise-induced changes in
405 immune cell function when assessed *in vitro*. This is because cell function is typically assessed
406 relative to the total cell population (e.g., percentage of T cells responding to mitogen
407 stimulation, number of target cells killed per NK-cell, oxidative burst activity per neutrophil,
408 etc.) without accounting for exercise-induced changes in the subset composition of these cell

409 populations. For example, the proportion of NK cells expressing the activating receptor,
410 NKG2C, is markedly elevated during exercise recovery (6). As a result, NK-cell cytotoxic activity
411 for the total NK-cell population increases markedly when an NKG2C-sensitive target cell is
412 used to assess NK-cell function (6). Conversely, when an NKG2C-insensitive target cell line
413 (K562) is used, NK-cell killing is not affected by exercise (6). Therefore, the proportional shifts
414 in the composition of cell subtypes should be considered when interpreting exercise-induced
415 changes in immune cell function at the total cell population level in vitro. Moreover,
416 assessment of in vitro immune cell function using venous blood samples does not account for
417 the complex interactions among immune cells and soluble factors within tissues (e.g., gut,
418 lungs, skin). However, some evidence suggests that reduced immune cell function in vitro may
419 coincide with changes in vivo and rates of illness (14, 40).

420 The validity of the original paradigm of cumulative immunodepression with repeated
421 bouts of exercise (87) is somewhat difficult to assess. Months of intense training increase the
422 incidence of illness in elite athletes (26, 30, 35). However, based on these studies, we can only
423 assume—but not assert—that increased incidence of illness results from an imbalance
424 between training and recovery. Research that has systematically manipulated the balance
425 between training and recovery has not identified any immune variables that are consistently
426 depressed as a result of insufficient recovery after exercise. However, with one exception
427 (79), these studies have not tracked the incidence of illness after repeated bouts of exercise.

428 Reduced salivary IgA concentration and secretion rate (amount of IgA secreted over a
429 fixed period) may predispose athletes to illness in the long term (26, 35). IgA binds micro-
430 organisms such as bacteria and viruses in the mucosa so that they can be destroyed by
431 immune cells. However, short-term changes in salivary IgA concentration and secretion rate

432 after repeated bouts of exercise are variable (56, 58, 60, 79). Salivary IgA concentration and
433 secretion rate may decrease incrementally over longer periods. The repeated exercise models
434 used in many of the studies described above induce only acute fatigue (64). Accordingly,
435 smaller exercise-induced changes in immune variables following repeated bouts of exercise
436 may actually represent positive adaptation of the immune system—as opposed to depression
437 of immunity that may lead to illness.

438 Pedersen et al (87) suggested that there is a critical threshold for exercise intensity and
439 duration that determines the risk of immunodepression after repeated bouts of exercise.
440 However, no studies have systematically determined the effects of repeated exercise bouts
441 of different intensity and duration. There are also no data on the effects of repeated bouts of
442 anaerobic or resistance/strength exercise, or a combination of different types of exercise on
443 the same day. The large gaps in Table 1 show that much remains to be learned about the
444 effects of repeated bouts of exercise on the immune system.

445 Among various nutritional interventions that have been studied to counteract
446 immunodepression during exercise recovery, carbohydrate supplementation has proven the
447 most effective. A balanced and well-diversified diet that meets the energy demands in
448 athletes and exercising individuals is certainly a key component to maintain immune function
449 in response to strenuous exercise and intense periods of training. Additional research is
450 warranted to investigate how the timing and pattern in the ingestion of nutrients—
451 particularly carbohydrates and protein/amino acids—influence recovery of the immune
452 system after exercise.

453 Sleep disturbances can depress immunity, increase inflammation, and promote adverse
454 health outcomes in the general population. However, the limited data available on how sleep

455 disturbances influence immune responses to exercise are inconsistent. Physical treatments
456 that are used after exercise (e.g., hydrotherapy and massage) may enhance the athlete's
457 sense of well-being, and should be considered as adjunct therapies for maintaining immune
458 health.

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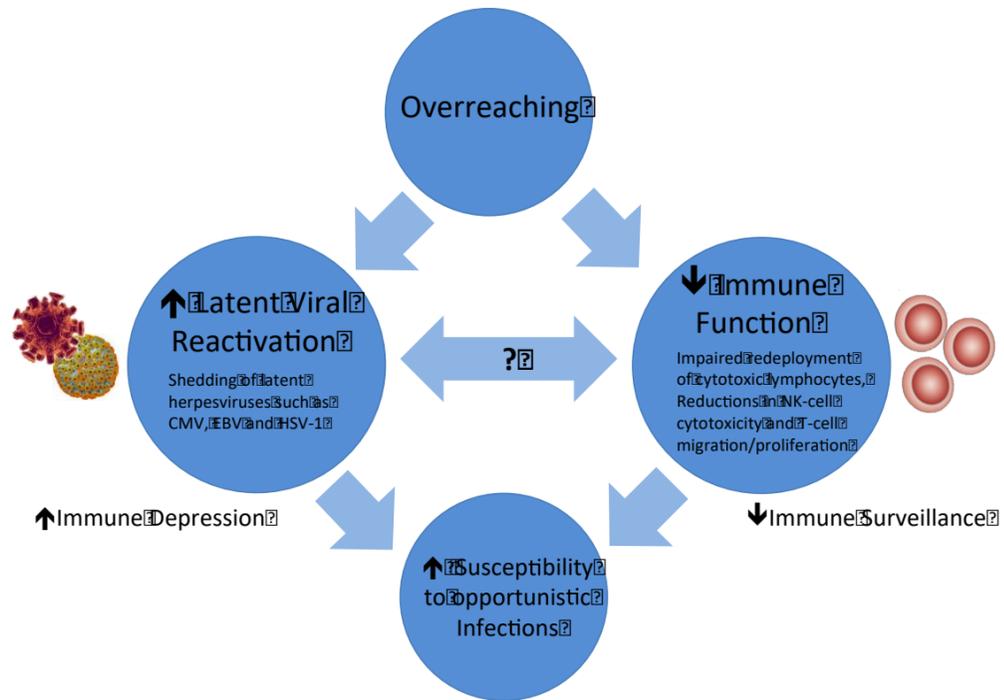
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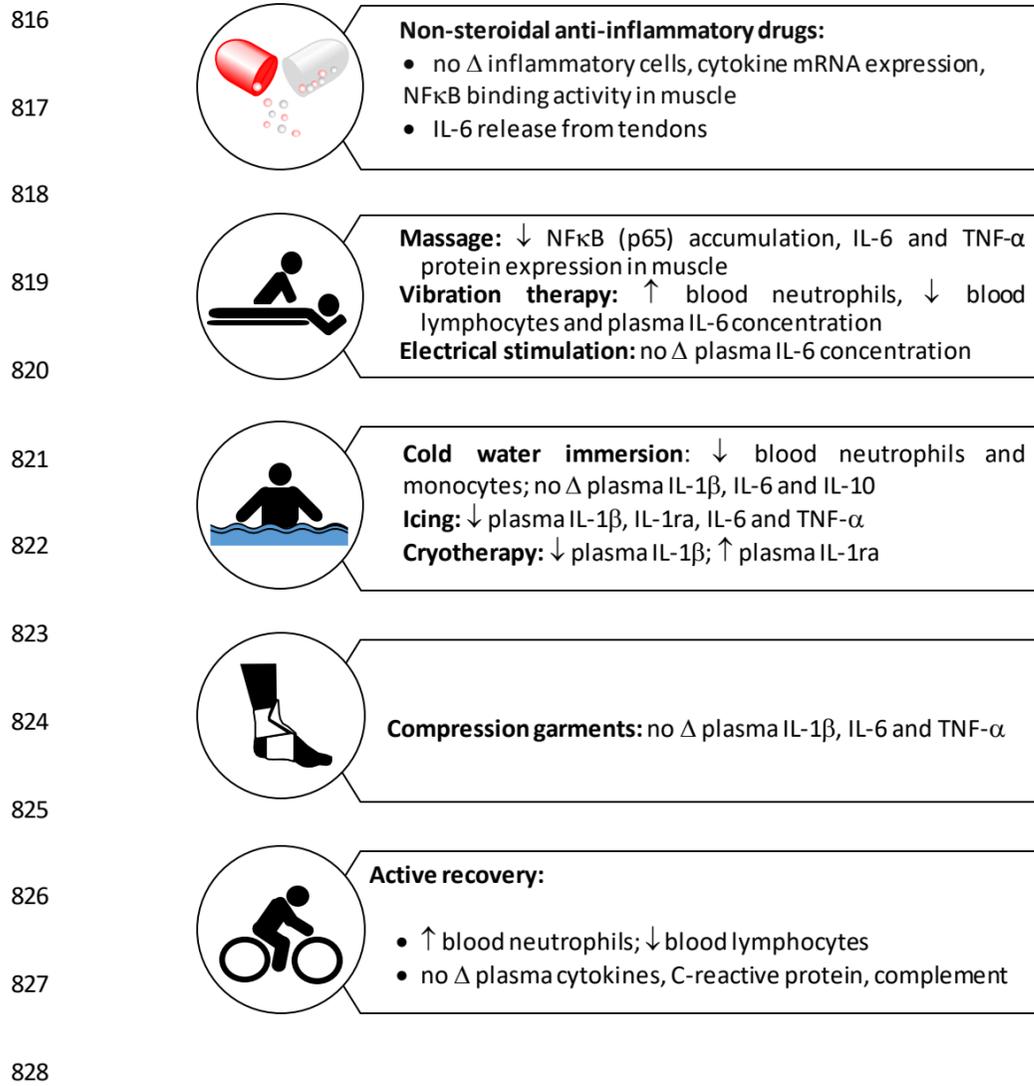
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809 **Figure 1.** Overreaching or heavy training is associated with impaired cellular immune function
 810 and latent viral reactivation. Reduction in lymphocyte trafficking and function during exercise
 811 recovery impairs immune surveillance, which may increase susceptibility to opportunistic
 812 infection. Lowered immunity may also allow previously acquired viruses to reactivate from a
 813 latent state, which may cause further immunodepression and increase susceptibility to
 814 infection.

815



829 **Figure 2.** Summary of the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and
 830 physical therapies on immune changes during recovery from exercise.

Table 1. Evidence heatmap comparing differences in immune responses to two versus one exercise bout on the same day (A), short vs long recovery between bouts on the same day (B), consecutive days of exercise (C), and weeks (D) or months (E) of intensified training.

	A	B	C	D	E		
Leukocyte cell count	5	3		2	1	2	
Neutrophil cell count	8	3	2	2	1	2	
Monocyte cell count	3	2	1		2	2	1
Lymphocyte cell count	4	3	2	1	1	2	2
Eosinophil cell count		1	1				1
Oxidative burst activity		1	1	1	2		
Oxidative burst activity/neutrophil	1		1				
Plasma ELA concentration				1			
Plasma MPO concentration			1				
LPS-induced ELA release		1			1		
LPS-induced ELA release/neutrophil	1						
CD3 ⁺ T cell count	1	1		1			2
CD4 ⁺ T cell count	4	2	1				2
CD8 ⁺ T cell count	4	1	1	1			2
CD4:CD8 ratio					1	1	
CD19 ⁺ B cell count	1	1					2
CD4 ⁺ /CD69 ⁺ T cell count		1	1				
CD8 ⁺ /CD69 ⁺ T cell count		1	1				
Lymphocyte proliferation		2		1		1	
Antibody production		1				1	
Saliva IgA concentration	1	1			2		5
Saliva IgA secretion rate	1	1		1	1		1
CD16 ⁺ or CD56 ⁺ NK cell count	2	2	1		1	1	2
CD56 ⁺ /CD69 ⁺ NK cell count	1		1				
NK cell cytotoxicity		1	1		1		
LPS-induced IL-6 production		1					
LPS-induced IL-8 production	1						
Leukocyte IL-8 mRNA					1		
Leukocyte IL-10 mRNA					1		
Leukocyte IL-1ra mRNA				1			
Plasma IL-6 concentration			1	2	1	1	
Plasma IL-1ra concentration			1	1			
Plasma IL-8 concentration				1			
Plasma IL-10 concentration				1			
Plasma TNF-α concentration				1		1	
Plasma MCP-1 concentration				1			
Muscle IL-6 mRNA expression				1			
Muscle IL-8 mRNA expression				1			
Muscle IL-1β mRNA expression				1			
Muscle TNF-α mRNA expression				1			

Numbers represent the number of studies demonstrating an increase/greater change (red), no difference (green), or decrease/smaller change (blue) compared with the first bout of exercise, long recovery, before training, or healthy athletes (refer to text). Abbreviations: ELA, elastase; MPO, myeloperoxidase; NK, natural killer; MCP-1, monocyte chemoattractant protein 1

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