

# Influence of Carbohydrate Delivery on the Immune Response During Exercise and Recovery From Exercise

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Acute, sustained, moderate- to high-intensity exercise has been shown to induce significant alterations in the distribution and function of leukocytes during recovery. In many instances, these changes have been found to reflect a transient impairment of immune function in vitro during recovery from such exercise. Carbohydrate supplementation during exercise has been associated with an attenuation of cortisol production. Because cortisol has been linked to immunosuppression, a growing body of research has examined the influence of carbohydrate supplementation on immune function in response to exercise. New areas along this line of inquiry involve examination of the cytokine response to exercise and the role that carbohydrate may play in regulating the production of proinflammatory cytokines. Inter-relations among the immune response, production of specific cytokines, and cortisol are also examined. The clinical significance of an attenuated immune response when exercising as a result of the administration of supplemental carbohydrate is yet to be determined. *Nutrition* 2004;20:645–650. ©Elsevier Inc. 2004

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## INTRODUCTION

The body of literature on exercise immunology has largely focused on the immune response to an acute exercise challenge or the influence of chronic training on immunosurveillance and how host defense and infection incidence might be affected. An extensive volume of work has been published in these two broad areas,<sup>1–18</sup> yet many questions remain. Due to the strong evidence for enhancement of endurance performance and an attenuated stress hormone response via carbohydrate (CHO) supplementation, it is logical that a growing body of research has focused on the relations between CHO supplementation and immune function. The rationale for pursuing CHO influence on host defense is likely related to the observation that acute exercise has been associated with transient suppression of immune function, potentially adverse effects on cellular distribution of immune cells, and elevation in the production of cytokines that exert proinflammatory effects. Due to the intricate nature of the immune system, much of the exercise-related literature has been descriptive, as investigators have sought to define immune response to short- and long-term exercise. The immune system is highly complex and this presents much of the challenge of not only characterizing how it responds to an exercise stimulus but also of gauging whether exercise-caused perturbations in immunity are meaningful. That is, if immune function or cellular distributions are adversely affected transiently by exercise, is the suppressive effect great enough to place the host at risk? Further, the immune system has considerable redundancy, which makes it difficult to determine whether sup-

pression in one area might be balanced by enhanced function in another.

One area of research that has gained attention is the interaction between glutamine and the immune system. Glutamine serves as a primary substrate for many leukocytes and is necessary for lymphocyte proliferative response to a mitogen.<sup>19–21</sup> Glucose is also recognized as an important substrate for leukocytes.<sup>22</sup> As a consequence, CHO supplementation may enhance immune function during and in response to exercise by conserving glutamine and by maintaining glucose availability for leukocytes. Several reviews have been written on the role that glutamine plays in immune function and the reader is referred to these for further information on this area of research.<sup>19,20,23–25</sup> It is also well established that provision of exogenous CHO reduces the cortisol response to exercise. Cortisol has been implicated in immunosuppression and is notable for stimulating neutrophilia, which is commonly found during recovery from vigorous exercise. Therefore, the question must be raised as to whether CHO supplementation might be beneficial for sustaining immune function in response to acute, intense exercise.

Several investigators have proposed associations between acute and long-term exercise and risk of infection such as the “open window” theory<sup>26</sup> and the “J-shaped”<sup>27</sup> and “inverted J-shaped”<sup>28</sup> curves. These “models” have become widely accepted and are suggestive of impaired host defense when exercise stress is excessive. Based on such relations, a rationale was developed to examine whether CHO supplements may offset these adverse effects and manage to promote host defense. This review examines and summarizes literature on this rapidly growing area of research and examines the effects of CHO supplementation on immune cell distribution and function and cytokine production during and after acute, moderate- to high-intensity exercise. Specifically, the effects of CHO supplementation on factors including lymphocyte proliferation, natural

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cell-mediated cytotoxicity, and distribution of selected cytokine populations are discussed.

## BACKGROUND: ACUTE EXERCISE AND IMMUNE RESPONSE

There appears to be a threshold stimulus that is required to induce changes in immunity or cellular distribution. It has commonly been found that, to induce suppressive effects on immune function and/or cellular distribution, that the exercise must be of moderate intensity (~65% maximum oxygen capacity [ $\text{VO}_{2\text{max}}$ ]) or greater or of a prolonged duration (>1 h). Resistance exercise has also been found to result in significant alterations in the immune response when rigorous, sustained work is performed.<sup>11,29</sup> If the exercise stress is sufficient, it may cause transient suppression of natural killer (NK) activity and lymphocyte proliferative response to mitogen, transient reduction in the T-helper:T-cytotoxic ratio, and a reduction in circulating NK cells. These alterations in cellular immunity have, in large part, led to the open window theory proposed by Pedersen et al.<sup>26</sup> Because NK cells play an important role as a component of the host's first line of defense against an antigen, attention has been given to determining whether the exercise-induced reduction in NK activity is simply due to numerical redistribution of NK cells or whether it reflects a true diminution of NK cytotoxicity on a per-cell basis.<sup>30–33</sup> Whereas some evidence has implicated increased postexercise prostaglandin synthesis in the downregulation of NK activity,<sup>32,33</sup> other investigators have failed to report a strong association between prostaglandin synthesis and impaired NK activity.<sup>30,31</sup> However, it should be considered that, even if the suppression of NK activity is related to a redistribution effect, the blood-borne prowess of this innate defense mechanism may still be reduced. In contrast, migration of NK cells from the circulation during recovery from exercise may be reflective of a functional need for these cells in tissue.

During acute exercise, the intensity of the work bout appears to be a critical factor in causing changes in leukocyte distribution. In general, the greater the exercise intensity, the greater the perturbation will be. For example, in comparing work performed at 25%, 50%, and 75%  $\text{VO}_{2\text{max}}$ , Tvede et al.<sup>34</sup> observed increases in blood leukocyte concentration of approximately 20%, 45%, and 95%, respectively, above resting values. The lymphocyte distribution mirrored this pattern during exercise.<sup>34</sup> Similar findings were observed by Nieman et al.<sup>35</sup> when comparing treadmill exercise performed at 50% and 80% of  $\text{VO}_{2\text{max}}$ . The higher intensity exercise resulted in a greater postexercise leukocytosis and lymphocytosis. The lymphocytosis was largely accounted for by increases in T- and NK-cell populations. In contrast, Bury et al.<sup>36</sup> noted significant increases in leukocyte and lymphocyte cell counts in response to different exercise intensities (45%, 60%, and 75%  $\text{VO}_{2\text{max}}$ ), but the magnitude of alteration during recovery was not clearly related to the preceding exercise intensity. Many other investigators have also shown significant alterations in leukocyte concentration and distribution during or immediately after completing moderate to high intensity exercise.<sup>2–5,10,11,30,37–45,74</sup>

During recovery (1 to 4 h after exercise) from moderate to intense exercise, neutrophilia has been commonly observed. The persistent neutrophilia tends to be the primary driving force for a sustained leukocytosis during recovery.<sup>10,29–31,35,44–47</sup> During this time, lymphopenia is often present<sup>10,11,29,35</sup> and this results primarily from large reductions in NK cells and T cells.<sup>10,11,30,35,41</sup> It is not uncommon during recovery from exercise for NK-cell concentration to fall by approximately 50% or more below that of a pre-exercise measure.<sup>4,35,44,48,49</sup> Although such changes likely represent alterations in cell trafficking, it seems feasible that, with such a large exodus of lymphocytes and NK cells from the circulation, it may be easier for a bacterium or virally infected cell to achieve a foothold during this time. As a result, infection risk may

be heightened during recovery from intense exercise due to induction of transient immunosuppression.<sup>26,75</sup> However, the clinical significance of exercise-induced transient immunosuppression has yet to be firmly established.

## CARBOHYDRATE SUPPLEMENTATION AND LEUKOCYTE DISTRIBUTION AND PROLIFERATION

CHO supplementation and dietary modification have been shown to influence cell distribution and in some cases cell responsiveness upon completion and during recovery from exercise. Leukocyte concentration has been reported to be lower upon completion of exercise when CHO has been administered and this effect often persists into recovery.<sup>41,46,47,50</sup> In most instances, the greater leukocytosis observed with the control (low CHO or placebo) conditions have been related to a greater neutrophilia and this effect has commonly been attributed to higher cortisol concentrations. CHO supplementation has been shown to attenuate the cortisol response to exercise, resulting in a smaller induction of neutrophils.<sup>37,42,43</sup> Henson et al.<sup>51</sup> noted significantly lower monocyte and NK-cell concentration upon completion of a 2.5-h run compared with a placebo condition. Green et al.<sup>47</sup> examined the influence of CHO supplementation on immune function in response to 2.5 h of cycle ergometry and observed a significantly lower neutrophil concentration upon completion of exercise and during recovery with the CHO condition. Bishop et al.<sup>37</sup> also observed a substantially smaller neutrophilia upon completion of, and during recovery from, intense, intermittent exercise when CHO was administered. In addition, CHO feedings have been associated with a reduced lymphocyte cell death rate *in vitro*.<sup>47</sup> Total leukocyte count was also significantly lower at these time points. No other cell parameters were found to be different.<sup>47</sup> Several of these studies are summarized in Table I.

NK cells and neutrophils represent one of the body's first lines of defense against invading microorganisms or pathogens. As a consequence, the distribution and function of these cells in response to exercise challenge has been well documented.<sup>3,5,17,30–33,48</sup> The influence of CHO supplementation on NK-cell distribution has not yet been confirmed. McFarlin et al.<sup>52</sup> reported that NK distribution was unaffected by CHO supplementation during 1 h of intense cycling (~77%  $\text{VO}_{2\text{max}}$ ) and over 4 h of recovery. In contrast, Nieman et al.<sup>53</sup> reported that CHO administration during a 2.5-h run was associated with a significantly lower NK-cell concentration upon completion of the run compared with a placebo condition. The distribution of NK cells during 6 h of recovery was not different between conditions. Similarly, Henson et al.<sup>51</sup> found a significantly lower concentration of NK cells upon completion of a 2.5-h run when CHO was administered. NK distribution was not different during recovery from exercise.

Few studies have been conducted to examine the effects of CHO availability on immune response to resistance exercise. Koch et al.<sup>29</sup> provided a CHO supplement (1.0 g/kg mass) 10 min before and 10 min after a bout of squat exercise. The CHO condition was not associated with any significant treatment effects on cell distribution in response to exercise or during a 4-h recovery period. Nieman et al.<sup>54</sup> examined the effects of CHO supplementation on immune response to 2 h of resistance exercise. The CHO condition resulted in a significantly lower leukocyte change upon completion and at 1 h after exercise relative to the baseline measure. However, the response could not be attributed to a specific measured cell population because there were no differences in distribution of neutrophils, lymphocytes, or monocytes.<sup>54</sup>

There is also limited available research findings on the effects of CHO supplementation on lymphocyte proliferative response to exercise. Bacurau et al.<sup>55</sup> reported that CHO supplementation during repeated bouts of cycle ergometry "overcame" a significant drop in proliferative response that was demonstrated with the

TABLE I.  
EFFECTS OF CARBOHYDRATE SUPPLEMENTATION ON SELECTED IMMUNE RESPONSES TO ACUTE EXERCISE RELATIVE TO CONTROL

Reference	Mode	Intensity	CHO dose	leukocyte	lymphocytes	neutrophils	NK cells	LP
Bishop et al. <sup>46</sup>	90-min soccer drills	—	6% varied volume	↓ After, ↓ 1 h after	ND	ND (↓ trend, <i>P</i> = 0.06)	—	—
Green et al. <sup>47</sup>	1-h cycle	85% VT	3.2 g/kg*	↓ After, ↓ 1 h after	ND	↓ After, ↓ 1 h after	—	↑, Less cell death
Koch et al. <sup>29</sup>	20-min RT	40–85% 1-RM	1 g/kg before, 1 g/kg after	ND	ND	ND	—	Sig IA
McFarlin et al. <sup>52</sup>	1-h cycle	77% VO <sub>2peak</sub>	60 g	ND	—	—	ND	—
Nieman et al. <sup>42</sup>	marathon run	—	60 g/h	—	ND	↓ After, ↓ 1.5 h after	—	—
Nieman et al. <sup>53</sup>	2.5-h run	77% VO <sub>2peak</sub>	60 g/h	—	↓ post, ↑ 3 h post	↓ After	↓ After, ↑ 3 h after	—
Scharhag et al. <sup>50</sup>	4-h cycle	70% AT	50 mL/kg* 6%, 12%	↓ After, ↓ 1 h after	—	↓ After, ↓ 1 h after	—	—

\* Distributed over time.

AT, anaerobic threshold; CHO, carbohydrate; LP, lymphocyte proliferation; ND, not different versus control; NK, natural killer; RM, repetition maximum; RT, resistance training exercise; Sig IA, significant interaction (appeared higher with CHO); VO<sub>2peak</sub>, peak oxygen capacity; VT, ventilatory threshold

control condition. Unfortunately, data were not collected during recovery from exercise, so it is not known whether the supplementation helped to offset the commonly observed decline in lymphocyte proliferation during recovery. The concentration of glutamine, which serves as a fuel for various leukocytes, was sustained by CHO feedings and fell significantly under the control condition.<sup>55</sup> Therefore, proliferative response during recovery may have been less likely to be diminished. Henson et al.<sup>39</sup> found that CHO supplementation during 2.5 h of intense running had no effect on concanavalin A-, phytohemagglutinin (PHA)-, or pokeweed mitogen (PWM)-stimulated lymphocyte cultures. However, when PHA-stimulated proliferative response was expressed per T cell, the CHO condition was associated with a significantly better maintenance of proliferation upon completion of exercise. Recovery responses were not different between treatments.<sup>39</sup> Green et al.<sup>47</sup> found that CHO supplementation during 2.5 h of cycling (85% ventilatory threshold) prevented the decline in lymphocyte expansion that was experienced during the control condition for CD4 (T helper) and CD8 (T cytotoxic) cells. Similar effects were reported by McFarlin et al.<sup>40</sup> in response to 1 h of intense cycling. Although more research is needed to confirm the effects of exogenous CHO on lymphocyte proliferative response to exercise, there is limited evidence that CHO supplementation may help to offset exercise-induced reductions in this measure. Whether such effects would help to sustain immune responsiveness during recovery from rigorous exercise is yet to be confirmed.

### CARBOHYDRATE SUPPLEMENTATION AND NK ACTIVITY

Despite a large body of research on the influence of exercise on NK activity, surprisingly few studies have been conducted to examine the effects of CHO supplementation on this indicator of innate immune function. McFarlin et al.<sup>52</sup> investigated the effects of CHO supplementation on in vitro interleukin (IL)-2 stimulation of NK cells during and after endurance cycling exercise. IL-2-mediated stimulation of NK cells was greater upon completion of exercise and during recovery from exercise in comparison with a placebo condition. However, unstimulated NK activity was not affected by CHO supplementation. As a result, the investigators suggested that CHO delivery may have optimized function of a distinct branch of NK cells (type I NK cells). Based on these findings, it appears that the potential for exogenous CHO to benefit NK activity is partly dependent on the presence of IL-2, which is released from activated T cells, but may also be specific to type I NK cells. Nieman et al.<sup>53</sup> did not observe an enhancement of NK activity when CHO was administered during 2.5 h of running.

### CARBOHYDRATE SUPPLEMENTATION AND CYTOKINE PRODUCTION

The literature on cytokine response to exercise is rapidly developing. It is recognized that cytokines play important roles in communication between cells and in cell signaling in response to infection and tissue injury. Commonly, the cytokines that have been investigated include constituents of the IL family. ILs are secreted primarily from macrophages and lymphocytes and they are involved in induction or regulation of the inflammatory response, although they may also influence other biological processes, including substrate regulation.<sup>56,57</sup> Acute exercise has been shown to stimulate production of a variety of cytokines, including IL-2, IL-6, and tumor necrosis factor- $\alpha$ , which exert proinflammatory effects, and IL-1 receptor antagonist (IL-1ra) and IL-10, which counter-regulate the inflammatory response.<sup>58,59</sup> Due to the complex interactions among immune cells, their secretory factors, and targets for these factors, research on cytokine production and function is highly intricate and there is much that has to be established.

TABLE II.

CARBOHYDRATE INFLUENCE ON CYTOKINE RESPONSE TO ACUTE EXERCISE (RELATIVE TO PLACEBO OR CONTROL CONDITION)									
Reference	Year	Mode	Intensity	Duration	Cytokines	After exercise	Recovery	Treatment	
Bacurau et al. <sup>55</sup>	2002	Cycling	90% AT	2 h	IL-1	↑	NA	Feedings	
					IL-2	↑	NA		
					IL-4	↑	NA		
					IL-6	↑	NA		
					TNF- $\alpha$	↑	NA		
Bishop et al. <sup>46</sup>	2002	Soccer drills	—	90 min	TNF- $\alpha$	ND	ND	Feedings	
					IL-6	ND	↓		
Bishop et al. <sup>38</sup>	2001	Cycling	60% $W_{max}$ and time trial	~90 min	IL-6	ND	↓	Control diet	
					IL-1ra	ND	↓		
					IL-10	ND	↓		
Nehlsen-Cannarella et al. <sup>61</sup>	1997	Running	70%	2.5 h	Total IL-6	↓	↓	Feedings	
					Biological IL-6	↑	ND		
Nieman et al. <sup>43</sup>	1998	Running, cycling	75%	2.5 h	IL-6	↓	↓	Feedings	
					IL-1ra	↓	↓		
Nieman et al. <sup>42</sup>	2001	Marathon	—	Varied	IL-6	ND	ND	Feedings	
					IL-1ra	↓	↓		
					IL-8	ND	↑		
					IL-10	↓	↓		
					TNF- $\alpha$	ND	ND		
Nieman et al. <sup>54</sup>	2003	Resistance training	—	2 h	IL-6	ND	NA	Feedings	
					IL-8	ND	NA		
					IL-10	ND	NA		
					IL-1ra	ND	NA		

AT, anaerobic threshold; IL, interleukin; NA, not available; ND, not different versus control; ra, receptor antagonist; TNF, tumor necrosis factor,  $W_{max}$ , maximal power output in watts

Many investigators have studied the effects of CHO supplementation and dietary control on the cytokine response to exercise. Bishop et al.<sup>60</sup> examined the effects of a low versus a high CHO diet regimen on cytokine response to cycle ergometric performance. IL-6, which is associated with activation of inflammation, was found to be significantly higher in a low-CHO state. Similar effects were found with IL-10 and IL-1ra, which are reported to be counter-regulatory cytokines that produce anti-inflammatory effects.<sup>60</sup> The higher-CHO dietary intake regimen tended to diminish the cytokine response to exercise. These findings were supported in a study by the same investigators who examined cytokine response to CHO supplementation during intermittent, intense exercise.<sup>37</sup> Plasma IL-6 concentration was significantly higher during recovery in the placebo condition. Similar effects were observed by Nehlsen-Cannarella et al.<sup>61</sup> who noted significantly higher total IL-6 in a placebo condition versus a CHO-supplemented condition during recovery from a 2.5-h run in marathoners. IL-1ra was also found to be higher during recovery in the placebo condition. Nieman et al.<sup>43</sup> reported comparable effects in response to 2.5 h of cycling and running in triathletes. Running resulted in higher postexercise concentrations of IL-6. These differences may be related to the higher eccentric demand of running because Bruunsgaard<sup>62</sup> associated higher IL-6 with eccentric work. Within exercise mode, IL-6 and IL-1ra were significantly higher in the placebo condition during recovery.<sup>43</sup> Based on these findings, it is possible that CHO supplementation or a high-CHO diet aids in limiting the production of proinflammatory cytokines (Table II). A blunted production of anti-inflammatory cytokines (IL-1ra and IL-10) may be secondary to this effect. These findings may be important, particularly when exercise involves heavy eccentric loading, because it has been proposed that a hyperinflammatory response (as may occur with infection and heavy eccentric exercise) may lead to delayed immunosuppression.<sup>59,63</sup>

In response to strenuous exercise and/or exercise in which muscle damage results, proinflammatory cytokines are believed to induce anti-inflammatory cytokine production as part of a counter-regulatory mechanism.<sup>36,62,64,65</sup> Nehlsen-Cannarella et al.<sup>61</sup> and Bishop et al.<sup>37</sup> indicated that IL-6 induces acute-phase proteins but also activates the hypothalamic-pituitary-adrenal axis and stimulates IL-1ra release, both of which serve as counter-regulatory factors against the inflammatory response. In addition, low blood glucose level results in stimulation of the hypothalamic-pituitary-adrenal axis, leading to heightened cortisol release.<sup>42,61,66</sup> Therefore, by providing exogenous CHO during prolonged, hard exercise, the influence of cortisol on the immune system may be lessened. Bacurau et al.<sup>55</sup> found that significant reductions in cytokine production (IL-1, IL-2, and tumor necrosis factor- $\alpha$ ) during repeated cycling bouts were inhibited when CHO was provided. These findings support the notion that CHO serves to downregulate the proinflammatory response to exercise, and that there is a concomitant reduction in anti-inflammatory cytokine secretion. Although the mechanisms are not yet established, it is possible that factors such as glutamine preservation and cortisol response influence the production of cytokines under exercise conditions.

## THE IMMUNE SUBSTRATE LINK

There is evidence that the elevation in IL-6 observed in response to intense exercise is in part caused by muscle production of this cytokine.<sup>56,57,67-69</sup> It has been shown that myocytes produce IL-6 in response to muscle contraction,<sup>56,57</sup> and it has been proposed that the cytokine plays a role in substrate mobilization and/or regulation.<sup>37,56,57</sup> Pedersen et al.<sup>56</sup> also reported that physiologic concentrations of IL-6 induce lipolysis. As a consequence, it might be implied that the blunted IL-6 production that commonly occurs during exercise in which CHO is provided is a result of substrate





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