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Title:

Bovine colostrum and immune function after exercise

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Abstract

Strenuous and/or prolonged exercise causes transient perturbations in immune function. It is well accepted that this is one mechanism contributing to the higher occurrence of infection (e.g. upper respiratory tract infection, URTI) in athletes, especially endurance athletes. URTI or URT symptoms can negatively affect training and competition performance but athletes must train intensively to be successful. Therefore, interventions that can legitimately enhance immune function and reduce URTI risk can be of benefit to athletes. Bovine colostrum supplementation has been investigated as a possible nutritional countermeasure to enhance (or maintain) immune function, and reduce URTI risk, following strenuous or prolonged exercise and during intensive training periods. There is convincing evidence that daily supplementation with bovine colostrum, for a number of weeks (and preliminary evidence for acute effects after a single dose), can maintain intestinal barrier integrity, immune function and reduce the chances of suffering URTI or URT symptoms in athletes or those undertaking heavy training. The mechanisms are not fully understood at present but there is preliminary evidence suggesting that the effects on immune function are attributable, at least in part, to small bioactive components that survive digestion and are biologically available after consumption but further work is required. In summary, the balance of existing evidence does support the notion that bovine colostrum is beneficial for certain groups of athletes, such as those involved in strenuous training (e.g. endurance athletes), in terms of immunity and resistance to infection.

Exercise, Immune Function and Infection Symptoms

It is generally accepted that moderate amounts of exercise improve immune system functions and hence reduce the risk of infection. However, there is now strong scientific support for the notion that athletes engaged in regular prolonged and/or strenuous exercise (e.g. endurance athletes such as cyclists, runners, swimmers, triathletes) have a higher than 'normal' incidence of minor infections, especially of the upper respiratory tract (URT) [1, 2, 3, 4]. Overtraining, or training with insufficient recovery can further exacerbate these effects.

Exercise Immunology research has clearly and consistently demonstrated that many components of the immune system are temporarily reduced (immunodepression) after strenuous and/or prolonged bouts of exercise [3, 4]. This exercise-induced immunodepresison may persist for as little as a few hours or a long as a few days. This depends largely on the nature of the exercise (in terms of intensity and duration). However, another key component is the frequency of exercise and/or recovery between bouts. For example, if subsequent bouts are commenced too soon, before the immune system has fully recovered, then a progressive accumulation of immunodepression may ensue resulting in chronically low immunity and increased infection risk. Periods of depressed immunity, whether small periods after individual sessions or more chronic periods, have been termed as "*Open Windows*" during which athletes are more susceptible to picking up an infection. If an athlete should pick up an infection then this will undoubtedly have effects on performance: either by reducing performance, preventing an athlete from competing altogether and/or interfering with training. Obviously, this is detrimental and may cause considerable set-backs for athletes wishing to maintain a high level of performance and/or 'peak' for a specific competition. Although an appropriately structured and periodised training programme can go some way to minimising the risks, endurance athletes must train intensively if they are to be successful, and are consequently at an increased risk (compared to non-athletes) for considerable periods of time. In addition to the direct effects of exercise, other factors like psychological stress of competition, personal or life stresses, inadequate diet, lack of sleep, travel for competition etc, may have further negative effects on the immune system and thus resistance to infection. Therefore, taking measures to maximise the immune system (and minimise risk and exposure to infection) will be particularly beneficial to such athletes. It is worthy of further note at this point that whilst depressed immune function may increase the chances of picking up an infection, whether or not an athlete picks up an infection is also dependent on their exposure to pathogens, which may be beyond their control. Factors like having contact with lots of other people (e.g. crowded

places, work, travel); increased ventilation during exercise; skin abrasions; environmental factors etc. may also increase the exposure to or entry of pathogens into the body [3].

Bovine colostrum

Bovine colostrum ('early milk') is the initial milk produced by cows, usually obtained within the first 48 hours postpartum. Like 'normal' milk, it contains a rich source of nutrition, both in terms of macronutrients and micronutrients but is also abundant in bioactive components including immune, growth and antimicrobial factors [5]. Bovine colostrum has received considerable attention within the *Sports Nutrition* and *Exercise Immunology* fields in recent years and has been suggested to confer immune, health and recovery benefits. A considerable amount of recent research has been conducted to investigate these claims. It is important to note here that all of the studies on (and reference to) bovine colostrum in this review refer to 'normal' bovine colostrum, from 'normal' dairy cows and **not** hyperimmune colostrum. For information only, hyperimmune bovine colostrum is obtained from cows that have been inoculated with or vaccinated against specific pathogens, meaning that the colostrum contains high concentrations of antibodies to a specific pathogen (or pathogens), usually for medical use. Hyperimmune colostrum is **not** considered here in relation to healthy athletes and active individuals. A number of studies have sought to determine whether daily supplementation with bovine colostrum, normally for periods of between 1 and 12 weeks, has a beneficial effect on immune function in athletes or individuals subjected to strenuous physical activity or intensive training regimes.

Bovine colostrum supplementation and intestinal barrier integrity

Many stressors, such as heat stress, certain types of medication, and oxidative stress are known to cause disturbance to gut function and integrity. A number of these stressors may be induced by strenuous exercise (e.g. heat stress, oxidative stress), which has been shown to increase intestinal permeability. This increases permeability to luminal toxins and bacteria, allowing them into the systemic circulation (endotoxaemia). This may place additional stress

on the immune system, which has to then deal with these bacteria and/or toxins, and this may be one factor contributing to exercise-induced immunodepression. However, increased intestinal permeability may also contribute to increased incidences of some acute gastrointestinal complaints and symptoms in athletes, such as stomach cramps, nausea and dizziness, and diarrhoea [6]. A high prevalence of such symptoms have been noted in some groups of athletes after strenuous competitive events (e.g. up to 50% incidence after marathon and ultra-endurance events or even > 90% incidence during and after a very strenuous ultra-endurance event, an Ironman Triathlon [6]). Such symptoms have potentially negative effects on performance if incurred during an event, or subsequent recovery, dietary intake, training or performance if they develop afterwards. Under extreme circumstances (e.g. exhaustive exercise in a hot and humid environment) this can cause severe endotoxaemia, leading to acute inflammation, sepsis, shock and organ failure, which can be fatal in extreme situations (although this is rare). Indeed, it has been suggested that damage to the gut can be a contributing factor in exertional heat stroke [7]. Supplementation with bovine colostrum has been shown to be beneficial in maintaining intestinal integrity. For example, Marchbank et al. [8] conducted a placebo-controlled, counterbalanced crossover study to determine the effects of bovine colostrum supplementation on exercise-induced changes in intestinal permeability. Subjects were required to run on a treadmill for 20 minutes (which caused core body temperature to increase by between 1 and 2℃) after 2 weeks of daily supplementation with 20 g per day of bovine colostrum or a protein and energy-matched placebo. Running caused a significant increase in intestinal permeability in the placebo trial but this was almost completely blunted in the colostrum trial. Similar beneficial effects of colostrum have been observed in human, animal and *in vitro* studies with cultured epithelial and gut cell lines (subjected to physical, chemical or thermal stressors). In summary, bovine colostrum supplementation may be beneficial in preventing exercise-induced increases in intestinal permeability and there is some preliminary evidence that this may be beneficial to athletes (e.g. by indirectly impacting upon training and

performance), especially in those required to exercise or compete in hot (or unfamiliar) environments.

Bovine colostrum and immune function

Bovine colostrum is of obvious importance for protection against infection in newborn calves and there is growing interest in this dairy product as a potential dietary supplement to counteract immunodepression in athletes. It should be noted, however, the mechanisms will be quite different in adult humans consuming bovine colostrum (as discussed in more detail below). That is, it is unlikely that there will be any passive transfer or that antibodies etc from colostrum will survive digestion in the human gut. A more likely explanation is that small bioactive constituents (or their metabolites) appear after consumption, digestion and absorption and that these have direct effects on immune function (see below). Indeed, it has been demonstrated that bovine colostrum can enhance a number of human immune functions, from the functioning of peripheral blood leukocytes assessed *in vitro* [9, 10, 11, 12], to *in vivo* immune functions such as the humoral immune response to an orally administered vaccine [13]. As discussed above, athletes may be at increased risk of infection during periods of strenuous training and stress and this may be detrimental to training and performance. Hence, there have been a number of recent studies that have investigated whether bovine colostrum is able to enhance immunity and/or reduce infections in athletes.

Mero et al. [14] observed a 33% increase in resting saliva secretary IgA (s-IgA) concentration after only 2 weeks of supplementation with 20 g per day bovine colostrum. Crooks et al. [15] recently demonstrated that a 12-week period of daily supplementation with a commercial chocolate drink powder (26 g per day) containing bovine colostrum (equivalent to ~ 12 g per day), in a group of distance runners, resulted in a 79% increase in resting saliva s-IgA concentration. The concentration and/or secretion of salivary s-IgA has been shown to be a good predictor of upper respiratory tract illness (or infection) risk in athletes,

so it has been proposed that the increases observed with bovine colostrum may be beneficial and confer protection in athletes. Indeed, Brinkworth and Buckley [16] demonstrated a lower incidence of self-reported (with illness logs) URT illness symptoms in a group of men taking daily (60 g per day for 8 weeks) bovine colostrum compared to a placebo group. Other studies have shown that bovine colostrum supplementation improves other markers of immune function and/or prevents the magnitude of decrease following strenuous exercise (i.e. exercise-induced immunodepression), which may contribute to the protective effects in athletes. For example, Davison and Diment [17] observed that 4 weeks of daily bovine colostrum supplementation (20 g per day) prevented the prolonged-exercise induced decrease of salivary lysozyme concentration and secretion. They also assessed neutrophil degranulation capacity (stimulated degranulation) and although similar decreases in this marker of neutrophil function were seen immediately post-exercise (which was 2 h at ~64% of maximal oxygen uptake), by 1 hour of recovery values were significantly higher in the colostrum group which could represent a more rapid closing of the "*Open Window*". These mechanisms may also contribute to the protective effects against illness in athletes. However, not all studies have observed beneficial effects on all measures and markers of immunity. For example, a recent study by Carol et al. [18] reported that bovine colostrum supplementation (25 g per day for 10 days) had no effect on 'immune variables' during a period of intensified training. However, the "immune variables" measured in this study were limited to circulating concentrations of selected cytokines, hormones, blood cell counts and immunoglobulins (furthermore, none of the immunoglobulin concentrations changed as a result of the exercise). These measures are recognised as having relatively limited value as markers of human immune modulation [19] and functional measures (e.g. immune cell function rather than just counts) may be more valuable. Indeed, the work of Davison & Diment [17] found no effect on markers such as total or subset counts of blood leukocytes and cortisol concentration (in agreement with reference number 18) but that the functional measures (stimulated neutrophil degranulation) were enhanced post-exercise in the colostrum compared to placebo group. Furthermore, Shing et al. [20] investigated the effects

of bovine colostrum supplementation on salivary s-IgA in addition to some components of innate immunity. They observed some beneficial effects on some immune measures but not salivary s-IgA. Likewise, in the study of Davison & Diment [17] salivary s-IgA was not affected, in contrast to some of the previous studies showing enhanced s-IgA. Such findings highlight the fact that variations in research design, dosage (and perhaps quality of supplements) and duration of supplementation, type of exercise (e.g. does it even cause notable immunodepression in the first place), as well as variations between different individuals (e.g. type of athlete, possible non-responders) may have a large effect on the nature of any benefits provided by bovine colostrum for athletes [5] and these are factors requiring further attention in future research.

Mechanisms

In conjunction with their *in vivo* study, Marchbank et al. [8] used *in vitro* investigations with gut epithelial cells to demonstrate that bovine colostrum's effects on maintaining intestinal barrier integrity were attributable to a number of mechanisms that can ultimately result in better maintenance of tight junctions under thermal, and possibly oxidative, stresses. The observed a reduction of heat-induced apoptosis in these cells, was shown to be partly attributed to epidermal growth factor (EGF) present in the colostrum, confirmed by incubation with anti-EGF antibodies, although some of the anti-apoptotic processes were unaltered by anti-EGF, showing that other factors must also contribute. Marchbank et al. [8] also showed that bovine colostrum enhanced heat shock proteins (HSPs) induction under basal and heat stress conditions. This is another possible mechanism to explain the beneficial effects of colostrum as HSPs provide cellular protection against numerous insults, including heat and oxidative stresses, and it is likely that this also contributed to the truncated exercise-induced rise in intestinal permeability seen in this study.

The underlying mechanism responsible for the effect of bovine colostrum on human immune parameters remains unclear. One possible, indirect, mechanism is by reducing the exercise-

induced increase in intestinal permeability as discussed above. For example, increased intestinal permeability allows the translocation of luminal bacteria (or toxins) into the systemic circulation, which may place additional stress on the immune system and/or may present an additional point of entry for infection causing pathogens. Therefore, the effects of bovine colostrum on maintaining intestinal integrity may contribute to the effects on immune function after strenuous exercise. In addition, evidence from *in vitro* cell culture studies suggests that bioactive, low molecular weight (≤ 10 kDa) components (such as the proteose peptones) may enhance leukocyte capacity by a direct effect [11, 12]. However, if this is the case, then it would be expected that the effects would be apparent after acute supplementation (immediately after the absorption of these components). To test this hypothesis we carried out a number of studies [21, 22] to assess the effects of acute ingestion. In the first study [21] we observed an increase of between 25 and 35% in neutrophil stimulated-oxidative burst capacity with colostrum compared to placebo ingestion (30 g) at rest, and this persisted for at least 3 hours. We also demonstrated that acute supplementation had some beneficial effects on the exercise-induced decrease in neutrophil stimulated-oxidative burst subsequent to prolonged (2.5 h) cycling exercise [22]. Taken together with the *in vitro* work previously mentioned [10, 11, 12] this does provide evidence in support of the idea that the mechanisms are associated with bioactive components that are biologically available to effect immune functions after ingestion of bovine colostrum by humans. Furthermore, when plasma was isolated from a subject who had consumed bovine colostrum or placebo (1 h and 3 h post-consumption) the addition of that plasma to pre and post-exercise blood samples in the same subject (but on a subsequent occasion) also enhanced neutrophil stimulated-oxidative burst and reduced the exercise-induced decrease [21]. This provides further evidence that biologically available constituents, after ingestion, are at least partly responsible for the effects on these immune functional measures in exercising subjects. However, somewhat surprisingly, the effects observed in the acute ingestion studies do not appear to be as great as those observed with longer-term supplementation [17] meaning that there is likely to be some other mechanisms contributing

to the greater effects seen in such studies (i.e. > 2 weeks supplementation periods). However, these mechanisms remain elusive at present and further research is required before we can fully determine all mechanisms involved. Despite this, the existing evidence does support the notion that bovine colostrum is beneficial for athletes involved in strenuous training (e.g. endurance athletes) in terms of immunity and resistance to infection, which may ultimately be beneficial to performance.

Conclusion

To conclude, it is well know that strenuous and/or prolonged exercise causes transient perturbations in immune function. However, athletes must train intensively if they are to be successful, and consequently are at an increased risk (compared to non-athletes) of picking up infections for considerable periods of time and taking measures to maximise the immune system will be particularly beneficial to such athletes. Bovine colostrum supplementation has been investigated as a possible nutritional countermeasures to enhance (or maintain) immune function following strenuous or prolonged exercise or during intensive training periods. There is convincing evidence that daily supplementation with bovine colostrum, for a number of weeks (and preliminary evidence for acute effects after a single dose), can maintain intestinal barrier integrity, immune function and reduce the chances suffering upper respiratory tract infections or symptoms in athletes or those undertaking heavy training. Preliminary work suggests that the beneficial effects on immune function are attributable, at least in part, to small bioactive components that survive digestion and are biologically available after consumption. However, further work is required to determine all of the mechanisms.

Conflict of interest: None

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