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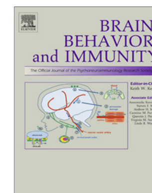

Effects of bovine colostrum supplementation on upper respiratory illness in active males

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A B S T R A C T

Bovine colostrum (COL) has been advocated as a nutritional countermeasure to exercise-induced immune dysfunction and increased risk of upper respiratory illness (URI) in athletic populations, however, the mechanisms remain unclear. During winter months, under double-blind procedures, 53 males (mean training load ± SD, 50.5 ± 28.9 MET-h week^{-1}) were randomized to daily supplementation of 20 g of COL ($N = 25$) or an isoenergetic/isomacronutrient placebo (PLA) ($N = 28$) for 12 weeks. Venous blood was collected at baseline and at 12 weeks and unstimulated saliva samples at 4 weeks intervals. There was a significantly lower proportion of URI days and number of URI episodes with COL compared to PLA over the 12 weeks ($p < 0.05$). There was no effect of COL on *in vitro* neutrophil oxidative burst, salivary secretory IgA or salivary antimicrobial peptides ($p > 0.05$), which does not support previously suggested mechanisms. In a subset of participants (COL = 14, PLA = 17), real-time quantitative PCR, targeting the 16S rRNA gene showed there was an increase in salivary bacterial load over the 12 weeks period with PLA ($p < 0.05$) which was not as evident with COL. Discriminant function analysis of outputs received from serum metabolomics showed changes across time but not between groups. This is the first study to demonstrate that COL limits the increased salivary bacterial load in physically active males during the winter months which may provide a novel mechanism of immune-modulation with COL and a relevant marker of *in vivo* (innate) immunity and risk of URI.

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1. Introduction

It is now well established that exercise of a strenuous and/or prolonged nature can lead to significant transient perturbations of immune function (commonly referred to as immunodepression) which includes, but is not limited to, decreases in both cell-mediated and mucosal parameters (Nieman, 2007). This may result in an 'open window' during which risk of illness is increased (Nieman, 2000). Hence, if such exercise is performed on a regular basis, as with endurance athletes, and particularly in combination with other life stressors (e.g. inadequate nutrition, psychological stress) the overall risk can be substantially higher (Gleeson, 2007). The increase in the frequency and severity of symptoms of upper respiratory illness (URI) in athletes (e.g. sore throat, runny nose) has been attributed to such periods of heavy exertion (Walsh et al., 2011).

Bovine colostrum (COL) may be effective at alleviating recurrent URI in situations of immune deficiency (Patel and Rana, 2006). Previous evidence has shown that 8–10 weeks of COL supplementation can reduce the incidence of URI in physically active populations but the mechanism(s) behind such effects remains unclear (Brinkworth and Buckley, 2003; Crooks et al., 2010). Animal and *in vitro* culture studies demonstrate that COL has a mediating effect on cell-mediated immunity by influencing the production of cytokines (Biswas et al., 2007; Boudry et al., 2007; Shing et al., 2009). Increasing concentrations of COL, *in vitro*, has been shown to modulate cytokine production in peripheral blood mononuclear cells from resting, healthy individuals, to promote a Th1 profile (cell-mediated immunity) (Shing et al., 2009), which may suppress the binding of pathogens (e.g. rhinovirus) (Sethi et al., 1997). Direct effects of COL on leukocyte capacity are also supported by evidence of an enhancement of phagocytosis and oxidative burst of polymorphonuclear cells (i.e. neutrophils) following short term culture with COL (Sugisawa et al., 2001, 2002, 2003). Sugisawa et al. (2003) proposed that in the presence of COL leukocytes become primed

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for subsequent activation by low-molecular weight substances (<10 kDa) such as protease peptones.

Given the aforementioned effects of COL within inflammatory *in vitro* culture conditions, it may be expected that COL can act as a nutritional countermeasure to exercise-induced immunodepression. Our previous work suggests that 4 weeks of COL (20 g day^{-1}) supplementation can limit the immunodepressive effects of an acute physical stressor (2 h of cycling) by enhancing neutrophil function (stimulated degranulation/elastase release) post-exercise (Davison and Diment, 2010). Within this study the modulatory effects of COL also extended to innate mucosal immunity by preventing the exercise-induced decrease of salivary lysozyme concentration and secretion.

Such findings may provide support to proposed mechanisms that some of the immune-modulatory effects of COL are due to bioactive components that become biologically available upon digestion of COL and prime leukocyte capacity (Davison, 2013). It is currently unclear whether longer term supplementation of COL and exposure to these priming agents also leads to changes in innate markers in athletes at rest. Crooks et al. (2006) demonstrated that longer periods of COL supplementation (i.e. 12 weeks) may be associated with significant increases in resting concentrations of salivary secretory IgA (sIgA), which is the only immune measure to date that has been consistently related to risk of URI in exercising populations (Walsh et al., 2011). Other studies have also seen improvements in resting sIgA concentrations with COL supplementation but have not monitored URI (Appukutty et al., 2010; Mero et al., 2002). To date, the majority of both longitudinal and cross-sectional exercise training studies have focused on changes in salivary sIgA (Walsh et al., 2011). Although the importance of other salivary antimicrobial peptides (AMPs) (e.g. lysozyme, lactoferrin) for host defense have been recognized, they have received limited attention (West et al., 2006).

In addition to the presence of inducible factors such as AMPs at mucosal surfaces, protection from invading microorganisms is also provided by the diverse community of commensal microbes which colonize the upper respiratory tract (Blaser and Falkow, 2009; Bosch et al., 2013). Subsequently, disturbance of this respiratory microbial community can contribute to acquisition of new pathogens which may result in respiratory illness, particularly if host immunity is compromised (Murphy et al., 2009). However, the effects of exercise and nutritional interventions on changes in the salivary microbiome have not previously been investigated.

The aims of this study were to investigate the effects of 12 weeks of COL supplementation on innate and mucosal immunity as well as the salivary microbiome in a population of males who engage in exercise training during the winter months. The study also aimed to determine whether any effects of COL on these parameters would also lead to a change in the incidence of URI. Given the potential involvement of a diverse array of biological pathways, we also undertook a metabolomic profiling approach on serum in an attempt to gain a more detailed understanding of any modulation of the immune system by COL.

2. Methods

2.1. Participants

Following both verbal and written details of the procedures, 57 male participants provided written informed consent for their inclusion within the study. The study was conducted in accordance with the Declaration of Helsinki principles and all procedures were approved by the Research Ethics Committee of Aberystwyth University. Participants were non-smokers, not taking medication or other supplements, free from any infectious illness for 4 weeks prior to the study and completing at least 3 h of moderate-vigorous endurance exercise per week. Participants were not limited in their use of mouthwash before and during the study period.

2.2. Supplementation

All 57 participants were randomly allocated into COL or placebo (PLA) groups with stratification by age and type of exercise training only. In a double blind manner, participants were asked to consume 20 g day^{-1} (10 g prior to morning and evening meal) of COL (Neovite UK, London) or an isoenergetic/isomacronutrient PLA (as used in Davison and Diment, 2010) for 12 weeks. Four participants (COL = 3, PLA = 1) were lost due to lack of compliance with the study protocol (e.g. lack of training or supplement consumption due to injury, family bereavement or air travel). All participants who successfully completed the study (COL group, $n = 25$, age: 30.5 ± 13.8 years, height: 179.9 ± 6.4 cm, body mass: 77.2 ± 8.9 kg); PLA group, $n = 28$, age: 31.5 ± 13.2 years, height 178.4 ± 6.6 cm, body mass 74.5 ± 8.7 kg) commenced the study between September and December.

2.3. Monitoring of upper respiratory illness and training volume

Participants completed a health questionnaire (Gleeson et al., 2011, 2012) on a daily basis. This involved participants indicating if they were suffering from any of the illness symptoms listed on the questionnaire: sore throat, catarrh in the throat, runny nose, cough, repetitive sneezing, fever, persistent muscle soreness, joint aches and pains, weakness, headache, and loss of sleep. Upon reporting of any of the above symptoms, participants were asked to provide a subjective rating of the severity of symptoms (light, moderate, severe). As used previously (Fricker et al., 2005; Gleeson et al., 2011, 2012), these ratings of light, moderate and severe were given numerical scores of 1, 2 and 3 respectively for data analysis. At any given point during the 12 weeks, a total symptom score of $\geqslant 12$ was used to indicate that an URI was present. Each week, participants were asked to complete a standard short-form International Physical Activity Questionnaire (http://www.ipaq.ki.se/downloads.htm) to provide quantitative data of training loads in metabolic-equivalent (MET)-h $week^{-1}$ (Craig et al., 2003). Participants were allowed unrestricted use of medication during episodes of URI but were asked to report such use and report how their training was affected by the URI (1 – training maintained, 2 – training reduced, 3 – training discontinued).

2.4. Blood sampling

Blood samples were drawn from an antecubital vein into 4 ml K_3EDTA (BD, Oxford, UK) and 6 ml plain (BD, Oxford, UK) vacutainers at baseline and 12 weeks following COL or PLA supplementation. All participants avoided strenuous exercise for 24 h prior to each visit and arrived at the laboratory following an overnight fast of at least 10 h. Blood collected in the K_3EDTA vacutainer was used for determination of total and differential leukocyte counts (Pentra 60C+, Horiba, Montpellier, France) and neutrophil function. Blood collected in the 6 mL plain vacutainers was allowed to clot at room temperature for 1 h 20 min. Following centrifugation (1300g for 10 min at 4 °C), serum was stored at −80 °C for later metabolomic analysis.

2.5. Neutrophil function

Whole blood from the EDTA vacutainers was stored at room temperature (no longer than 2 h) prior to measurement of *in vitro* stimulated neutrophil oxidative burst activity response to formyl-leucyl-methionyl-phenylalanine (fMLP) using a commercially

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