The Efficacy of Interventions Aimed at Reducing the Incidence of Upper Respiratory Tract Infections (URTI) In Athletes Following the Performance of Strenuous, Intense Prolonged Exercise – A Systematic Review

Mr Ethan J. Berndt (**BComm, Rhodes**)
Dr Candice J. Christie (**BSc (Med) (Hons) Biokinetics, UCT; PhD, Rhodes**)

Corresponding Author
Mr Ethan J. Berndt (BComm, Rhodes)
Department of Human Kinetics and Ergonomics
P.O. Box 94
Rhodes University
Grahamstown
6140
SOUTH AFRICA
Email: g10b1890@campus.ru.ac.za

Abstract

Endurance athletes appear to be at a higher risk of contracting upper respiratory tract infections (URTI) during periods of intense training and following major competition. Immunoglobulin A (IgA) has been found to provide major resistance to many pathogenic micro-organisms and therefore salivary IgA is currently considered the best indicator of mucosal immunity. This review aims to assess the status of the literature on the efficacy of interventions to reduce the incidence of URTI in athletes following the performance of strenuous, intense prolonged exercise. Medium evidence indicates that *Pelargonium sidoides* supplementation or a high carbohydrate diet significantly increased the concentration of salivary IgA, while chronic glutamine supplementation did not significantly increase salivary IgA concentration. Medium evidence also showed that the consumption of a high carbohydrate diet had a significant positive effect on the immunosuppressive stress hormone cortisol, while limited evidence showed that a high protein diet resulted in a reduced number of self-reported symptoms of URTI.

Key words: *upper respiratory tract infection, overtraining, Immunoglobulin A, mucosal immunity, intervention*

Introduction

Endurance athletes appear to be at a higher risk of contracting upper respiratory tract infections (URTI) during periods of intense training and following major competition (Mackinnon, Ginn and Seymour, 1993). It has been suggested that the amount of exercise and/or intensity is related to the incidence of URTI (Heath et al. 1991), with a “J-shaped” relationship having been presented by Nieman (1997) between the level of physical activity and the susceptibility to URTI, where a high training load is often related to an increased incidence of URTI. Epidemiological studies show that distance runners experience a greater incidence of URTI during the two weeks following competition compared to non-runners (Peters and Bateman 1983) or similarly trained runners who do not compete (Nieman, Johanssen,, Lee and Arabatzis, 1990). Strenuous long-term training has been associated with a chronic suppression of mucosal immunity lasting seven days or more (Bishop and Gleeson 2009), while it has been found that components of the immune system demonstrate an altered suppressed function for three to twelve hours following a single bout of strenuous, intense, prolonged endurance exercise (Nieman 1997). This resulted in the concept of the "open window" period, described as the period of depressed mucosal immunity, where athletes are more susceptible to URTI, which will in turn negatively affect training and performance (Costa, Jones, Lamb, Coleman and Williams, 2005).

The secretory immune system of mucosal tissues, such as in the upper respiratory tract, is the first barrier of defence against certain pathogens (Papacosta and Nassis 2011). Immunoglobulin A (IgA), the principle immunoglobulin in mucosal fluids, has been found to provide major resistance to many pathogenic micro-organisms (Mackinnon et al. 1993) and therefore salivary IgA is currently considered the best indicator of mucosal immunity (Papacosta and Nassis 2011). IgA has been shown to inhibit the attachment and the replication of certain pathogens, as well as being capable of neutralizing viruses and toxins (Mackinnon et al. 1993). It should also be noted that, with the exception of salivary IgA, there are no established biomarkers to predict URTI in athletes (Bishop and Gleeson 2009). An immediate decrease in IgA is apparent after an acute bout of prolonged, strenuous exercise, which usually recovers within twenty-four hours post-exercise (Costa et al. 2005; Papacosta and Nassis 2011). The decreased concentrations of salivary IgA have been observed as a result of reduced synthesis and the accelerated degradation of this immunoglobulin (Mackinnon and Hooper 1994) and this has been associated with the increased incidence of URTI in elite professional athletes (Papacosta and Nassis 2011). Research on possible interventions to decrease the incidence of URTI in athletes during intense training and following major completion is thus necessary.

This review aims to assess the status of the literature on the efficacy of interventions to reduce the incidence of URTI in athletes following the performance of strenuous, intense prolonged exercise. The effectiveness of interventions will be determined by measures of salivary IgA.

Method

Literature search

The ISI Web of Science, PubMed, Science Direct and the Cochrane Library were searched from inception to 24 May 2014. Studies evaluating the effects of possible interventions on the prevalence of the contraction of URTI following strenuous/intense prolonged exercise were identified by using the query "upper respiratory tract infection" AND "overtraining".

Inclusion/exclusion criteria for intervention studies

Inclusion into this review required that the study was an intervention study aimed at treating and/or preventing URTI following any form of excessive/intense exercise.

Patents, conference/congress proceedings, observational studies, magazines, books, government documents, reviews, theses, interventions performed on animals, editorials and non-English studies were excluded from this review.

Quality assessment

Study eligibility and quality were assessed by a single investigator and reviewed by another investigator. The Downs and Black's tool was used to evaluate the intervention study quality (Downs and Black 1998). Studies evaluating possible interventions associated with a decreased prevalence of URTI with a score over 20 were considered high quality, while studies with a score equal to or below 20 were considered low quality (Morton, Barton, Rice and Morrissey, 2013).

Data extraction and analysis

Outcome measures of studies were extracted, compared, contrasted and analysed for potential interventions associated with a decreased prevalence of URTI following strenuous/intense prolonged exercise. The investigator reviewed the full texts of the included articles and tabulated some of the characteristics of the studies. Definitions for levels of evidence were guided by recommendations made by van Tulder, Furlan, Bombardier and Bouter (2003). Strong evidence was defined as consistent findings among multiple high-quality studies; moderate evidence as consistent findings among multiple low-quality studies, or one high-quality study; limited evidence as findings from one low-quality study and conflicting evidence defined as inconsistent findings among multiple studies.

Results

Results of literature search

A total of 44 articles were identified during the literature search, of these, 15 duplicates and 11 articles which were unavailable were removed. The review process of the remaining 18 article abstracts against the inclusion and exclusion criteria excluded 14 of the articles. The four remaining articles were included in this review of possible intervention studies aimed at decreasing the prevalence of URTI following strenuous, intense prolonged exercise.

Quality assessment

The quality of all four studies was assessed by a single researcher and validated by another researcher. Only three of the four studies evaluating potential interventions aimed at decreasing the prevalence of URTI following strenuous, intense prolonged exercise, were considered high quality (scoring >20) and one was considered low quality.

Discussion

High quality research evaluating possible interventions aimed at decreasing the incidence of URTI in overtrained individuals is currently limited. Despite these limitations, the available research findings synthesised and critiqued in this review can be used to provide guidance to clinicians, trainers and athletes.

Both the *Pelargonium sidoides* (a medicinal plant native to South Africa) extract supplementation study (Luna et al. 2011) and the chronic glutamine supplementation study (Krieger, Crowe and Blank, 2004) incorporated a double blinded randomized non-repeated study design, while the high dietary protein study (Witard et al. 2013) used a single blinded randomized crossover study design and the high dietary carbohydrate study (Costa et al. 2005) used a randomized non-repeated study design. Three of the studies included in this review (*Pelargonium sidoides* extract, high carbohydrate diet and the high protein diet study) recruited only male athletes, while the study determining the effect of chronic glutamine supplementation on the concentration of salivary IgA included both male and female athletes. Further studies need to be performed on both sexes, in order to determine whether females and males respond separately.

The *Pelargonium sidoides* extract supplementation study was performed on relatively older marathon runners (40.4 ± 7.9 years), as well as for a relatively longer treatment period, which consisted of 28 consecutive days, after which a single bout of high-intensity running at approximately 85% of VO_{2max} was performed. The chronic glutamine supplementation study used runners of the ages 29.1 ± 2.8 years, where participants in the experimental group received 0.1 g/kg of L-glutamine four times daily for 14 days starting at the beginning of a nine day intense interval training program. The high carbohydrate study recruited 32 competitively trained triathletes (32.1 ± 9 years), where participants in the experimental group were provided with a daily programmed high carbohydrate diet to be consumed 24 hours prior to, and during the course of six days, where participants performed a one hour running exercise bout (70% of VO_{2max}). The high dietary protein crossover study included eight cyclists (27

± 8 years) whom undertook two separate weeks of high-intensity training (1-2 sessions a day for seven days) while consuming either a high protein diet (3g kg^{-1} protein BM^{-1} day^{-1}) or an energy and carbohydrate matched control diet (1.5 g kg^{-1} protein BM^{-1} day^{-1}). The high-intensity training weeks were preceded by a week of normal-intensity training under the control diet. Future research needs to determine whether the length of the intervention and whether starting the intervention prior to or following the training has an effect on the concentration of salivary IgA.

Medium evidence indicates that *Pelargonium sidoides* supplementation for 28 consecutive days before an acute bout of running, or a high carbohydrate diet 24 hours prior to and during the course of six days of high-intensity running, significantly increased the concentration of salivary IgA. While chronic glutamine supplementation for 14 days starting at the beginning of a nine day intense interval training program did not significantly increase salivary IgA concentration. Noteworthy however, the glutamine supplementation resulted in a significantly higher nasal IgA concentration. This is an important finding, as some pathogens (such as rhinovirus) only affect the nasal mucosa. Medium evidence also showed that the consumption of a high carbohydrate diet throughout a six day period of overtraining had a significant positive effect on the immunosuppressive stress hormone cortisol, while limited evidence showed that a high protein diet resulted in a reduced number of self-reported symptoms of URTI.

The *Pelargonium sidoides* intervention study measured the concentration of salivary IgA before the treatment period and 48 hours following the single bout of high intensity running, while the glutamine supplementation study measured the concentration of salivary IgA mid-training, post-training and five days following recovery and the high dietary carbohydrate study measured the concentration of salivary IgA pre-exercise, immediately post exercise and the morning post exercise on day one, day four and day six. These studies measured salivary IgA concentration at markedly different points in time, which may have affected the results. The timing of when the concentration of salivary IgA is to be measured needs to be standardized, in order for direct comparisons between the efficacies of interventions to be made.

The high dietary carbohydrate study provided evidence that a consistent and conscious high carbohydrate diet promotes a well maintained level of blood glucose, which allows blood glucose to be longer maintained during consecutive, strenuous training sessions, thereby, attenuating cortisol release, elevating salivary IgA response and decreasing the risk of any post-exercise or accumulative immunosuppressive effects. During the initial dietary assessment of the high dietary carbohydrate study, it was noted that both dietary groups consumed similar, but rather low energy and carbohydrate concentrations. This level of energy intake is not uncommon amongst endurance athletes and reflects a general lack of awareness of the nutritional requirements for their exercise demands. The high carbohydrate dietary group presented an expected large increase in total energy intake, which was solely due to the increased intake of carbohydrates. It may be that the enhancement in salivary IgA concentration and the decrease in cortisol levels in the high carbohydrate dietary group may have occurred owing to the increased energy intake and not that the extra energy intake was in the form of

carbohydrates. However, the high protein diet intervention study, which used an energy and carbohydrate-matched control diet, resulted in no effect on the epinephrine or cortisol response to exercise. So, it seems that a well maintained level of blood glucose which allows blood glucose to be longer maintained during consecutive strenuous training sessions and thereby attenuating cortisol release may in fact result in an elevation of salivary IgA release and lead to a decrease in the risk of any post-exercise or accumulative immunosuppressive effects.

Conclusion

Medium evidence indicates that *Pelargonium sidoides* supplementation, or a high carbohydrate diet, significantly increased the concentration of salivary IgA, while chronic glutamine supplementation did not significantly increase salivary IgA concentration. Medium evidence also showed that the consumption of a high carbohydrate diet had a significant positive effect on the immunosuppressive stress hormone cortisol, while limited evidence showed that a high protein diet resulted in a reduced number of self-reported symptoms of URTI. It seems that a well maintained level of blood glucose which allows blood glucose to be longer maintained during consecutive strenuous training sessions and thereby attenuating cortisol release may in fact result in an elevation of salivary IgA release and lead to a decrease in the risk of any post-exercise or accumulative immunosuppressive effects.

Recommendations

Future research needs to determine whether the length of the intervention and whether starting the intervention prior to or following the training has an effect on the concentration of salivary IgA. Although these studies looked at the change in immunological markers, they did not however look at the incidence of URTI occurring. This makes it difficult to conclusively determine whether the improvement in the immunological markers did in fact have a positive effect on the rate of incidence of UTRI. Further intervention research should include the incidence of URTI following the intervention, in order to determine whether altered immunological markers actually led to a change in the prevalence of URTI. These studies measured salivary IgA concentration at markedly different points in time, which may have affected the results. The timing of when the concentration of salivary IgA is to be measured needs to be standardized, in order for direct comparisons between the efficacies of interventions to be made.Further studies need to be performed on both sexes, in order to determine whether females and males respond separately.

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Appendix 1: Downs and Black's Tool (Downs and Black, 1998)

		Luna *et al.*, 2011	Krieger *et al.*, 2004	Costa *et al.*, 2005	Witard *et al.*, 2013
	Reporting				
1)	Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1
2)	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1
3)	Are the characteristics of the patients included in the study clearly described?	1	0	1	1
4)	Are the interventions of interest clearly described?	1	1	1	1
5)	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	0	0	0	1
6)	Are the main findings of the study clearly described?	1	1	1	1
7)	Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1
8)	Have all important adverse events that may be a consequence of the intervention been reported?	0	0	0	0
9)	Have the characteristics of patients lost to follow-up been described?	0	1	0	0
10)	Have actual probability values been reported for the main outcomes expect where the probability value is less than 0.001?	1	1	1	1
	External validity				
11)	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	1	1	1
12)	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	1	1	1
13)	Were the staff, places and facilities where the patients were treated, representative of the treatment the majority of patients receive?	1	1	1	1
	Internal Validity – bias				
14)	Was an attempt made to blind study subjects to the intervention they have received?	1	1	0	0
15)	Was an attempt made to blind those measuring the main outcomes of the intervention?	1	1	0	0

16)	If any of the results of the study were based on "data dredging", was this made clear?	1	1	1	1
17)	In trails and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	1	1	1	1
18)	Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1
19)	Was compliance with the intervention/s reliable?	1	1	1	1
20)	Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1
	Internal Validity - confounding (selection bias)				
21)	Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	1	1	1	1
22)	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	1	1	1
23)	Were the study subjects randomised to intervention groups?	1	1	1	0
24)	Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	0	0	0	0
25)	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	0	0	0
26)	Were the losses of patients to follow-up taken into account?	1	1	1	0
27)	Did the study have sufficient power to detect a clinically important effect where the probability value of the difference being due to chance is less than 5%?	1	1	1	1
		22	**22**	**20**	**19**

Appendix 2: Summary table of study characteristics

	Luna *et al.*, 2011	**Krieger *et al*., 2004**	**Costa *et al*., 2005**	**Witard *et al*., 2013**
number of subjects	25	13	32	8
sex	male	4 female, 9 male	male	male
sport	marathon	Runners	triathletes	cyclists
intervention	pelargonium sidoides	Glutamine	high carbohydrate diet	high dietary protein
salivary IgA	measured	Measured	measured	not measured
salivary IgA rate	not measured	Measured	not measured	not measured
cortisol	not measured	not measured	measured	measured
incidence of URTI	not measured	not measured	not measured	measured
age	40.4 ± 7.9	18-49	32.1 ± 9	27 ± 8
quality score	22	22	20	19
quality ranking	high	High	high	medium
length of intervention	28 days	14 days	6 days	7 days
study design	double blind randomised study	double blind randomised study	repeated study	non repeated study
results				
salivary IgA	significant increase	no significant difference	significant increase	-
salivary IgA rate		no significant difference	-	-
cortisol	-	-	significant decrease	no effect
incidence of URTI	-	-	-	significant decrease
p-value				
salivary IgA	p<0,001	p=0,41	p<0.01	-
salivary IgA rate	-	p=0,17	p<0.02	-
cortisol	-	-	-	not given
incidence of URTI	-	-	-	p<0.05