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Use of zinc supplements to reduce upper respiratory infections in United States Air Force Academy Cadets

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ABSTRACT

Although known primarily for its antioxidant function, zinc appears to be an important modulator for the production of immune cells as well as ensuring the proper action of various leukocytes such as neutrophils, monocytes, macrophages, B and T lymphocytes. The primary study objective was to compare URI incidence between supplemented (zinc gluconate 15 mg/day capsules) and non-supplemented (corn-starch placebo) groups. This study was a seven month randomized, double blind, placebo-controlled trial involving 40 cadets to evaluate zinc's effectiveness in reducing the risk of upper respiratory infections (URIs). Self-reported symptoms as recorded by a weekly web site survey revealed that supplemented participants experienced significantly more symptom free episodes than those in the placebo group ($p = 0.01$). No significant differences were found between groups in terms of physician diagnosed cases ($p = 0.99$). Higher zinc dosage may be warranted to confer a protective effect under more challenging immunological conditions.

Zinc is considered to be one of the essential micronutrients used by the human body. Although zinc fulfills a number of metabolic and physiological roles, interest concerning its action within the immune system has grown considerably in recent years. Specifically, zinc is critical for both aspects of innate as well as acquired immunity for host defense. This includes proper maturation and function of neutrophils, macrophages and natural killer cells requisite for the signaling pathways of nonspecific responses. Additionally, zinc is important for the initiation of both T and B lymphocytes via signaling mediators which incorporate this important mineral as part of specific immune system pathways.[1] Some studies have indicated that a deficiency in zinc predisposes individuals to increased risk of infectious diseases.[1] Marginal zinc deficiencies present with problems of impaired taste and smell, night blindness, memory decrement, and immune impairment. Greater degrees of deficiency result in more severe symptoms such as diarrhea, pustular dermatitis, mental disturbances, alopecia, and frequent infections as a result of an even more compromised immune system.[2] Studies involving animal models have also reported growth and immune deficiencies as a result of low zinc diets.[3–5]

More recently research has focused on the use of zinc supplements in reducing the risk or ameliorating the effects of upper respiratory infections (URIs) such as the common cold or flu. "The common cold is an acute, usually afebrile, self-reported viral infection involving upper respiratory symptoms, such as rhinorrhea, cough, and sore throat."[6] (p. 1595). Observing the results of trials from zinc deficient diets (and the concomitant improvements in immunocompetence when fed zinc replete diets), medical researchers are interested in determining appropriate zinc levels to preclude the infectious state. Mossad et al.[7] found the provision of zinc (in the form of zinc gluconate lozenges) to subjects experiencing the onset of cold symptoms significantly reduced the duration of illness by nearly half. A more recent meta-analysis of studies involving zinc supplementation and colds did not, however, find any significant reductions in cold symptom duration.[8] The discrepancy in findings may be in the manner in which supplementation is used. Zinc may have its best efficacy when used in a preventive fashion as opposed to using it to ameliorate cold and flu symptoms. According to Prasad et al.[9] it may be more important

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to establish a higher level of circulating plasma zinc prior to an infectious state for best results. Prasad's group used elderly subjects who typically have lower circulating plasma zinc levels and divided them into placebo and test groups over a specified period of time. After one year, the test group had significantly lowered incidence of infectious upper respiratory cases over the placebo group. Interestingly, the test group also had significantly lower oxidative stress and inflammatory cytokine levels; both are known as key contributors to a number of degenerative disorders such as cardiovascular disease, cancer, immunological compromises and atherosclerosis. Among zinc's myriad of important roles is its function as an antioxidant. It may be plausible that zinc is working in a number of ways in which to exert its protective effects in the body.

Although aging results in lowered zinc intakes through the diet, it is possible that physical or psychological stress can also lower plasma zinc levels. Perceived mental stress or incurred physical stressors usually result in an acute phase response which predictably drive physiological changes in the body. According to some, these changes are nothing more than bodily compensations' driving adaptations which allow for cellular repair and immune response.[10] Yet the results of these stressors are sufficient to cause lowered zinc in the circulating plasma. Singh et al.[11] reported significantly lowered zinc concentrations in men training as part of the United States Special Forces unit. Researchers examined blood samples before and after a particular extreme bout of mental and physical training and observed a 33% reduction in zinc levels. Although some of the loss was attributed to sweat and urinary routes, investigators suggested that a considerable amount of zinc was sequestered by organs and tissues for use in mounting an immune response. Taking the aforementioned in consideration, it may be helpful for individuals to take zinc supplements in advance of anticipated circumstances which cause an inordinate lowering of zinc levels during critical immunological challenges. At the United States Air Force Academy (USAFA), cadets are exposed to a number of stressful situations which could probably deplete zinc stores to less than optimal levels – from the first day that the cadets arrive they experience the stresses of military in processing and rigorous basic training then later they must adjust to military academy life, which involve continuous military bearing and a full-time college course load.

Although a cause and effect relationship has not been established, it is interesting that cadets present with more than the usual number of URI cases during these stressful episodes. According to data provided by the USAFA hospital,[12] there appears to be an increased incidence of URIs during certain times of the academic year. Specifically, there is a double or triple increase in URI cases diagnosed starting in the beginning of the cold and flu season (fall through spring) and another several fold increase in diagnosed cases during Basic Cadet Training in the summer. Based on the limited data regarding the aforementioned and the need to understand and develop potential public health countermeasures during times of increased risk for URIs, this study evaluated whether or not the zinc supplemented condition results in measurable decreases in reported URI cases. Assuming that appropriate biomarkers (plasma zinc and copper) are adequately detected and measured, this study will provide insight into the role of zinc supplementation as a nutraceutical (as opposed to a dietary essential) towards maximizing individual health.

1. Materials and methods

This study used a randomized, double blind, placebo-controlled design. The purpose was to compare URI infection rates in 17 zinc supplemented vs 17 non-supplemented cadets. A total sample size of 34 was derived based on a 25% reduction in URI incidence rates detected in the zinc supplemented group with a 2 sided p value of 0.05 and an approximate power of $\geq$80%.[13] However, in consideration of drop-out rates as experienced in previous studies similar to this work, 40 subjects were recruited in order to retain power for detecting differences. This study was approved by the United States Air Force Academy Institutional Review Board before subject recruitment began.

This study included both male and female cadets. Exclusionary criteria included any chronic illness (Crohn's Disease, Irritable Bowel Syndrome, Acrodermatitis Enteropathica or Congenital Zinc Deficiency) or being under medical supervision for any condition, individuals currently self-supplementing with zinc or a multivitamin. During the recruitment phase, potential subjects were screened for study inclusion using a survey. From a participant pool of 1422 individuals, 96 basic cadets volunteered to join the study. Randomization was accomplished by using the last number of each cadet's social security in an odd/even fashion (even were assigned to the zinc group, odd were assigned to the placebo). Those with a social security number ending in zero were assigned based on the second to last odd/even number. Practitioners or individuals involved in drawing blood or running laboratory analyses were also blinded to the assignment. All subjects were volunteers from the general cadet population and approximately mirrored the general health status within this population (in terms of recorded illnesses).

In the fall of 2007, before the start of the cold and flu season, subjects ingested one capsule (either zinc or placebo) each day in the morning, taken first thing before eating breakfast for a period of seven months (through 30 April, projected end of the cold and flu season). Both zinc (15 mg per capsule) and placebo capsules (same capsule type as used for the zinc except filled with cornstarch or gelatin) were provided in a 30-day supply container through an FDA licensed clinical specialty pharmacy (FL, USA). The zinc supplement also underwent an independent lab analysis (MO, USA) to certify the content and quantity of zinc within the supplement capsules. Air Force research funds were used to fund supplement purchase.

While there is a minor risk associated with taking a zinc supplement over and above dietary intake, the risk was considered minimal due to total zinc intake (supplement and dietary intake) per day was estimated to be below recommended upper limit thresholds. According to the Institutes of Medicine,[14] Dietary References Intake Report, the upper limit (UL) threshold for zinc intake should not exceed 40 mg/day for both men and women. The Recommended Dietary Allowance (RDA) for zinc is 8 mg/day for women and 11 mg/day for men. Median zinc intakes from food in the United States are approximately 9 mg/day for females and for males, it is 14 mg/day. The zinc supplement capsules will provide 15 mg of zinc per day which will provide daily zinc levels beyond RDA levels but below the tolerable upper limits as directed by the IOM. Zinc is relatively nontoxic and only causes problems in terms of copper deficiency at levels exceeding 50 mg/day for periods of time exceeding 3 months or longer.[15] In fact, one study recently completed fed subjects 45 mg zinc per day for a one-year period without any ill effects reported.[9]

All subjects provided blood samples (from the forearm, samples obtained by trained laboratory personnel in the USAFA Cadet Clinic) at baseline (Sep 07) and end of study (May 08) time points for analyses of plasma zinc and copper. While our primary objective for the study was URI infection rate, we also tracked the results of the laboratory analyses for plasma zinc and plasma copper levels. Plasma biomarkers were required to validate subject compliance as well as ensure that zinc does not interfere with copper absorption. Subjects observed regular procedures whenever ill in seeking medical intervention and only had their diagnosed URI cases tracked by a database. Although subjects were given zinc