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Serum vitamin A, zinc and visual function in children with moderate to severe persistent asthma

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ABSTRACT

Background: Asthma is a common childhood disorder with complex pathobiologic components that may include aspects of nutritional deficit. The contribution of vitamin deficiency, specifically vitamin A, as part of the disease complex has not been well studied, particularly among at risk children. In this study, we examined the prevalence of vitamin A as well as zinc deficiency in conjunction with visual function among an urban pediatric population sample with moderate-severe persistent asthma. **Methods:** A cross-sectional case-control assessment of serum vitamin A, zinc and visual function among urban children with and without asthma was undertaken. Inclusion criteria involved (1) well-controlled pediatric asthmatic patients between the ages of 8–18 with corrected vision of at least 20/25 in each eye and (2) chronic use of a combination beta agonist-steroid inhaler. Visual function was assessed by Snellen visual acuity and Peli Robson contrast sensitivity assessment. **Results:** Overall, 24 patients were enrolled for study with body mass index and age matched between asthmatic and control groups. Median serum vitamin A and zinc levels among control subjects was statistically higher compared to asthmatics ($p=0.0303$ and $p=0.0111$, respectively). Based on age-based reference levels there was no evidence of vitamin A or zinc deficiency among asthmatics or controls. Serum vitamin A and zinc were found to directly correlate with body mass index ($p=0.0074$ and $p=0.0474$, respectively), but not age or measures of visual function. Contrast sensitivity was however significantly reduced among asthmatic subjects ($p=0.0003$). **Conclusions:** Children with chronic asthma demonstrate reduced levels of vitamin A and zinc that may be related to disease pathobiology however, evidence of frank zinc or vitamin A deficiency was not demonstrated. Reduced contrast sensitivity found in the asthmatic group appears unrelated to serum vitamin A and/or zinc levels.

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Nutrition; vision; retinol; cataract; pediatric

Introduction

Vitamin A and zinc are essential nutrients required for a variety of physiologic functions including growth, reproduction, taste, and most notably, vision. Additional roles for vitamin A/retinoic acid have been recognized more recently. These include activation of synthesis of immune system proteins, enzyme synthesis relative to apoptosis and drug metabolism and protein synthesis related to neurotransmission, and reproduction [1]. These findings suggest that quantitative changes in levels of serum vitamin A may indeed relate to comorbidities associated with pathobiologic influences of disease occurrence.

The role of vitamin A in terms of immunity and respiratory function is intertwined with a complex of reciprocal interactions with other micronutrients. The

role of vitamin A in growth and development is highly dependent on levels of zinc, which acts synergistically with vitamin A to promote immune function [1]. Interestingly, prior studies have shown a relationship between vitamin A deficiency and mechanistic aspects of asthmatic responses related to autoimmune function [2–4]. Further, vitamin A deficiency has been reported to diminish the ability to fight infections, a finding of particular relevance to asthmatics who are at high risk for respiratory complications due to bronchial infection [5].

One of the most important roles of vitamin A as it exists in the form of retinol is in regard to human vision. Indeed, subtle deficit in visual function is one of the first signs of vitamin A deficiency, most notably related to impairment in dark adaptation.

In conjunction with retinol, zinc also plays a key role in retinal metabolism. The physiological functions for zinc have been studied predominantly in retina and retinal pigment epithelium where zinc is believed to have several functions in regard to retinal photochemistry. Zinc status also influences several aspects of vitamin A metabolism, including its absorption, transport, and utilization [6]. Prior study of the relationship between serum zinc and asthma has suggested that serum zinc levels are significantly reduced in adult asthmatic patients, which, interestingly, were found to rise to normal levels following corticosteroid therapy [7].

Current knowledge regarding vitamin A and zinc suggest these entities have an important role in both visual photochemistry as well as homeostasis related to autoimmunity and asthma pathobiology. However, it is unclear if a relationship exists between serum vitamin A, zinc status and clinical measures of visual function among pediatric patients with moderate-severe persistent asthma. Although other studies have identified a statistically reduced level of vitamin D in asthmatic children [8], there is little data describing vitamin A and zinc levels in this cohort.

The purpose of this study therefore was to elucidate the relationship between serum vitamin A, zinc and visual function among pediatric asthmatic patients.

Methods

We employed a cross-sectional case-control assessment of serum vitamin A and zinc among children with moderate to severe persistent asthma who presented for examination at the asthma and respiratory clinic of the Fantus Health Outpatient Clinic of the Cook County Hospital and Health System located in Chicago, IL. The Fantus outpatient clinic largely serves an urban population of Cook County, Illinois who are classified as either medically uninsured or underinsured. Patients who presented to the Fantus community asthma clinic with a history of moderate-severe persistent asthma based on review of their medical records with use of an inhaled steroid/beta agonist combination product and use of rescue inhaler from the period of January 1 to June 30 2015 were enrolled for study. All asthmatic cases were diagnosed by a Fantus Clinic staff physician. Written informed consent was obtained from a parent or guardian that accompanied each patient enrolled for study. Following documentation of consent, patients underwent a vision screening that included measurement of best-corrected visual acuity by use of a Snellen eye

chart [9]. Distance visual acuity was tested by setting a Snellen eye chart designed for use at a 10 feet distance. Proper illumination of the test chart was ascertained prior to testing. Subjects who had glasses were asked to wear their spectacles for testing. Subjects were seated and each eye was then tested separately using a paddle occluder. Subjects were requested to start reading the chart from the top (largest letters) and read each line of letters down to the smallest letter size recognizable. Subjects who missed the majority of letters in a single line (5/10 letters for the 20/40 line or better) were assigned the next largest line as their vision. Subjects who were unable to reach at least 20/25 in each eye with or without use of spectacles were not enrolled for study. Assessment of contrast sensitivity (CS) was performed using a Pelli-Robson contrast sensitivity chart. Following assurance of 20/25 vision in each eye as determined by Snellen testing, CS testing was commenced. Of note, Snellen vision measures spatial discrimination (small letters) at very high contrast. Contrast sensitivity is the visual ability to distinguish an object from its background; it is not the same as visual acuity. Contrast sensitivity tests can pick up losses that are not evident from measuring visual acuity. For example, contrast sensitivity tests may be sensitive to visual loss caused by cataracts, glaucoma, and multiple sclerosis (diseases in which impairment in contrast sensitivity is common), in subjects with little or no loss in visual acuity [10,11]. These people may fail to see large, low-contrast objects under conditions of poor visibility (such as fog) despite normal or near normal visual acuity.

CS testing was conducted with appropriate illumination at a test distance of 1 m from the patient. It was assumed the subjects had sufficient accommodative reserve for this test distance therefore an additional +0.75 dioptic lens was not utilized. An occluder paddle was held over each eye with spectacle correction if present and the patient was asked to identify each letter of each line of Peli Robson down to which level as to no further letters were discernable. The number of letters read correctly was then recorded for each eye [12].

Weight was measured as follows: the child's shoes, boots, jackets, bulky clothing, and hair ornaments that interfered with testing were removed. The subjects were asked to step on the scale and weight in pounds was recorded. This measurement was then transformed to kilograms. Height measurement was done on flooring that was not carpeted and with the subject standing against a flat surface such as a wall with no molding. Height was measured in feet and inches and

converted to centimeters. These metrics were then converted to a measure of body mass index (BMI). The BMI was then subsequently converted to a growth percentile based on the Centers for Disease Control reference norms [13]. BMI is a useful population-level measure of overweight and obesity and has been demonstrated to strongly correlate with percent body fat estimated by bioelectrical impedance [14].

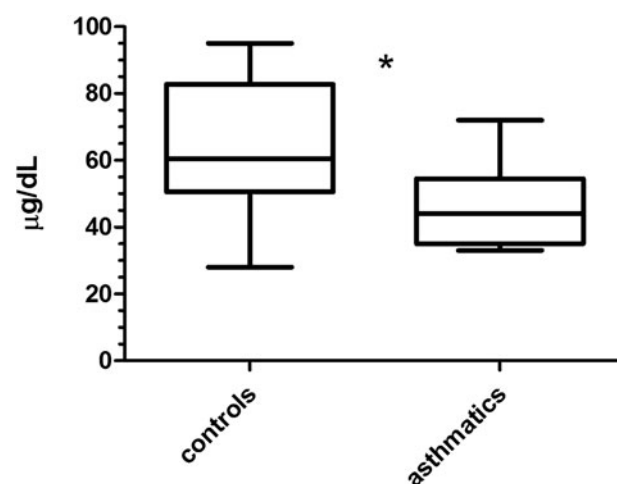
A control group was recruited from the Fantus pediatric clinic with similar age and weight/height characteristics of the asthmatic subjects who presented for annual physical examination and were otherwise healthy and did not require any form of medication. Controls were assessed using same Snellen and Pelli-Robson eye charts. Following the visual assessment, phlebotomy was performed for assessment of serum vitamin A and zinc levels.

Laboratory analysis was performed at Specialty Laboratories, Inc. (Santa Monica, CA) using standard commercial equipment. Age based reference levels for serum vitamin A and zinc was obtained using the Harriet Lane guidebook for pediatric house officers and published reference levels [15,16]. Descriptive statistics on both study and control groups were employed in conjunction with nonparametric univariate statistics (Mann-Whitney U test and Spearman correlation) due to the small sample size.

Results

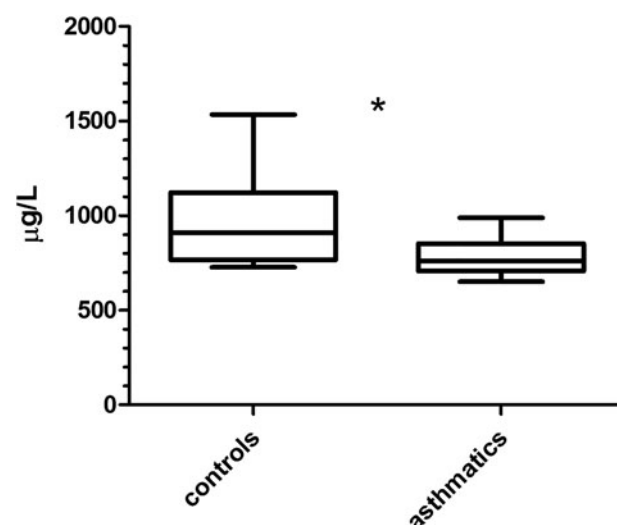
Demographics, contrast sensitivity, vitamin A and zinc levels in both asthmatic subjects and controls are described in Table 1, and Figures 1 and 2. The mean age was 14.08 (range of 8–18 years old) in asthmatic subjects and 13.9 (range of 10–18 years old) in control group. Mean body mass index (BMI) was 23.38 in asthmatic and 23.21 in controls. There was no statistically significant difference between study groups based on age and BMI.

Median and interquartile ranges for serum vitamin A, zinc, and contrast sensitivity measurements are shown in Figures 1, 2 and 3, respectively. Median serum vitamin A and zinc levels were significantly reduced among asthma patients, however neither result was abnormally low. Based on pediatric age-based serum vitamin A (retinol) reference levels, as well as reference serum zinc levels, no subject in either asthmatic or control group demonstrated vitamin A or zinc deficiency. Interestingly, 16.67% of the asthmatic subjects and 41.67% of control subjects demonstrated vitamin A levels above their normal age-based reference levels. While of clinical interest,



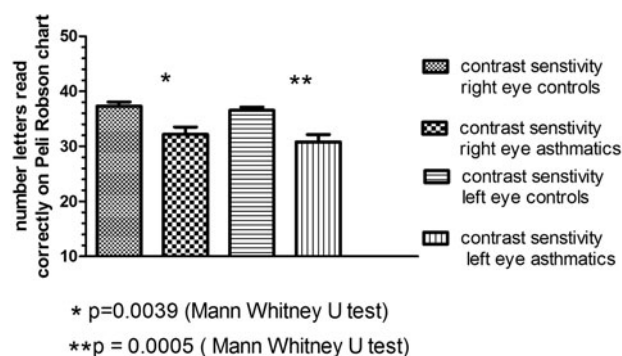
* $p = 0.0303$ (Mann Whitney U test)

Figure 1. Median and interquartile range for serum vitamin A; controls vs asthmatics.



* $p = 0.0111$ (Mann Whitney U test)

Figure 2. Median and interquartile range for serum zinc; controls vs asthmatics.



* $p = 0.0039$ (Mann Whitney U test)

** $p = 0.0005$ (Mann Whitney U test)

Figure 3. Peli Robson contrast sensitivity; controls vs asthmatics, right vs left eye.

Table 1. Description of study variables and significance.

	Asthmatics	Controls	<i>p</i> value ^a
Median age (range-years)	14.00 (8–18)	14.00 (10–18)	0.8004
Median body mass index (range)	23.50 (16.3–36.8)	20.80 (17.5–32.0)	0.6438
Median serum vitamin A (µg/dL) (range)	44.00 (38.82–53.85)	60.50 (49.4–75.8)	0.0303
Median serum zinc (µg/L) (range)	759.00 (723.5–838.9)	910.00 (835.0–1130.0)	0.0110
Contrast sensitivity (right eye, median and range, # letters correctly read)	32 24–42	38 30–42	0.0039
Contrast sensitivity (left eye, median and range, # letters correctly read)	32 21–36	37 30–40	0.0005

^aMann–Whitney U test, alpha =0.05.

Bolded findings = statistically significant.

Table 2. Correlation between serum vitamin A, zinc or Peli Robson contrast sensitivity (CS) and BMI.

	<i>R</i> (rho)	<i>p</i> value ^a
Vitamin A-BMI (controls)	0.7273	0.0074
Vitamin A-BMI (asthmatics)	0.8630	0.0006
Vitamin A-CS (both eyes-controls)	−0.2919	0.3545
Vitamin A-CS (both eyes-asthmatics)	−0.1319	0.7164
Zinc-BMI (controls)	0.1484	0.6286
Zinc-BMI (asthmatics)	0.5814	0.0474
Zinc-CS (both eyes-controls)	−0.4770	0.0993
Zinc-CS (both eyes-asthmatics)	0.5618	0.0910

^aSpearman rank correlation, alpha =0.05.

Bolded findings = statistically significant.

the difference was not statistically significant (two sided chi square test, $p=0.1779$). All subjects, both controls and asthmatics demonstrated serum zinc level within the normal reference range. Of note, contrast sensitivity levels in both the right and left eyes was found to be statistically reduced in asthmatic subjects (Table 1, Figure 3).

There was no correlation however between serum vitamin A or zinc and measure of visual function when analyzed for either the right or left eyes or with averaged CS levels between both eyes. However, serum vitamin A levels were found to be directly correlated to BMI in both controls and asthmatics. Serum zinc was found to directly correlate with BMI in the asthmatic group only (Table 2). Due the low sample size, nonparametric testing was applied. Multivariate statistical models were not applied as the data did not meet the assumptions required for this type of analysis. Based on the study sample size, the post-hoc study power to detect a significant difference between median vitamin A and zinc (alpha =0.05) was determined to be 74.4% and 80.7%, respectively.

Discussion

Our study identified a statistically significant reduction in vitamin A and zinc levels among children with chronic asthma, however no child was found to be vitamin A or zinc deficient based on age-based reference levels. The results also demonstrate reduced contrast sensitivity in subjects with asthma however the findings are not correlative to vitamin A and zinc serum levels.

Previous research on the role of vitamin A in immunity has explored a possible relationship between low vitamin A and asthma. Prior studies suggested that levels of vitamin A are reduced in children with persistent moderate–severe asthma, but once again levels were not abnormally low based on age based pediatric reference levels [4]. Further, it has been found that C-reactive protein (CRP) levels indirectly correlate with vitamin A thereby suggesting a relationship between the acute phase response and/or coinfection among asthmatic subjects with reduction in serum vitamin A [17]. Vitamin A deficiency is also thought to result in disrupted immune function and allergic response that may exacerbate asthmatic symptoms [18].

The role of zinc in promoting immunity has also been explored more in recent years. Zinc is thought to potentiate the effect of vitamin A and has been suggested to have a synergistic action with vitamin A in terms of retinal function [19]. Zinc, a trace element that influences cell metabolism through a variety of mechanisms, appears to play an integral role in maintaining normal ocular function. This element is present in high concentrations in ocular tissue, particularly in retina and choroid [20]. Zinc deficiency has been shown in a number of species to result in a variety of gross, ultrastructural, and electrophysiological ocular manifestations [20]. The physiological functions for zinc have been studied predominantly in retina and retinal pigment epithelium where zinc is believed to interact with taurine and vitamin A [20]. Zinc deficiency is thought to modify photoreceptor plasma membranes, regulate the light-rhodopsin reaction, modulate synaptic transmission and serve as an antioxidant. Suboptimal zinc status in North America may influence the development and progression of several chronic eye diseases including age related macular degeneration.

Zinc has been implicated in lung function by promoting integrity of the respiratory epithelium through its antioxidant effect and it has been shown to act as a stabilizer of microtubules and act as an antiapoptotic agent, growth cofactor, and anti-inflammatory

agent all of which are critical for appropriate lung function [21,22]. The proposed mechanisms of why serum levels of zinc is lower in asthmatics include serum zinc redistribution to hepatocytes during allergic reactions, increased demand of zinc to produce key immune proteins (phagocytes, natural killer cells, granulocytes) and increased oxidative stress which causes respiratory cells to deplete its zinc reserves [21]. Our study shows a statistically significant lower level of zinc measured in patients with asthma. Indeed, studies have demonstrated that supplementation with zinc to asthmatics may alter airway reactivity and serum IgE levels [22]. It has been proposed that zinc decreases NF- κ B by altering the levels of protein A20, a natural inhibitor of NF- κ B, and therefore decreases inflammation by reducing neutrophil infiltration and cytokines release [22].

In regards to the lower contrast sensitivity found in children with asthma, several hypotheses are explored. We believe this finding may be related to the chronic steroid use and subsequent subclinical loss of lens transparency known to impact contrast sensitivity function. Since vitamin A and zinc levels were found to be of normal age-based levels among both cases and controls, the most likely reason for reduced contrast function in asthmatic children studied in this report relates to alteration in lens transparency due to incipient cataract. Although data on prior medication use was not obtained in this study, children with asthma may have been exposed to systemic prednisone during asthmatic exacerbations that may have propagated cataract progression. Furthermore, chronic use of inhaled corticosteroids for treatment of asthma has been shown to result in cataracts in children. We cannot exclude the possibility that vitamin or nutrient deficiency aside from vitamin A and/or zinc may have influenced cataract formation in asthmatic subjects.

Prior studies have shown increased risk of both cortical and posterior subcapsular cataract among adult asthmatics that use corticosteroids [23]. Additional studies have substantiated the risk of cataract among adult asthmatics that use corticosteroids; however, the findings were less notable among children [24]. A longitudinal study in a cohort of older population in Australia reports that there is significant risk of cataract formation in patients with use of corticosteroids, mainly in those with combined inhaled and oral use [25]. To our knowledge, our findings are the first to report significant degradation in contrast sensitivity among children with moderate-severe persistent asthma who utilize inhaled corticosteroids. Although our patients did not undergo an ophthalmic

examination to identify cataract formation, it is known that contrast changes are a sensitive indicator of loss of crystalline lens transparency that may precede the formation of frank cataract [26].

The noted direct relationship between serum vitamin A, zinc, and BMI found in this study deserves comment. The findings of the present study are aligned with prior data presented by Ballew et al. who demonstrated a positive correlation between serum retinol, a child's age, serum lipids, and BMI [27]. Other studies have shown that retinol binding protein-4 (RBP4), which is key transport protein for vitamin A and is highly bound to vitamin A in the serum is directly correlated to BMI as well [28], however other studies have not supported this finding [29]. RBP4 is an adipokine secreted in adipose tissue and liver, it belongs to the lipocalin family and is the sole specific retinol (vitamin A) transporter in blood. Currently, is unclear if RBP4 is a marker for asthmatic disease, however prior studies have suggested an association [30].

The strengths of this study include tight control of demographics in terms of age and BMI between asthmatics and controls as well as case-control study design format. The inherent study limitations of the cross-sectional design strategy in terms of inability to determine causality is noted as well as the limited sample size. Furthermore, formal eye examinations were not conducted and data regarding the duration of the disease and comorbidities, drug history and dietary analysis were not obtained at the time of study enrollment. Increasing sample size and use of a prospectively designed study would improve the statistical as well as clinical relevance of the findings.

Conclusions

Parents of asthmatic children should be educated regarding the importance of adequate nutrition, particularly among children in vulnerable socioeconomic circumstances. Further, study findings point to the association between moderate-severe persistent asthma in children and reduced visual function as determined by contrast sensitivity measurements. The explanation for this observation is unclear, however the high sensitivity for CS as a measurement for abnormalities in the optical integrity of the eye such as cataract, suggests that crystalline lens alterations may be responsible.

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Declaration of interests

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that I no financial and/or business interests associated with this manuscript from a company that may be affected by the research reported in the enclosed paper.

References

1. Sempertegui F. Commentary: is vitamin a playing a hidden role in children's lung function? *Int J Epidemiol* 2001;30:465–466.
2. Mizuno Y, Furusho T, Yoshida A, Nakamura H, Matsuura T, Eto Y. Serum vitamin A concentrations in asthmatic children in Japan. *Pediatr Int* 2006;48: 261–264.
3. Arora P, Kumar V, Batra S. Vitamin A status in children with asthma. *Pediatr Allergy Immunol* 2002;13: 223–226.
4. Kassaye T, Becklake MR, Receveur O, Hanley JA, Johns T. Asociación between vitamin A status and lung function level in children aged 6–9 years in Wukro Wereda, Northern Ethiopia. *Int J Epidemiol* 2001;30:457–464.
5. Sommer A, Tarwotjo I, Djunaedi E, West Jr KP, Loeden AA, Tilden R, Mele L. Impact of vitamin A supplementation on childhood mortality: a randomised controlled community trial. *Lancet* 1986;1: 1169–1173.
6. Smith J, J C. The vitamin A-zinc connection: a review. *Ann NY Acad Sci* 1980;355:62–75.
7. Yousef AM, Ekramy E. Serum zinc level in bronchial asthma. *Egypt J Chest Dis Tuberc* 2017;66:1–4.
8. Freishtat RJ, Iqbal SF, Pillai DK, Klein CJ, Ryan LM, Benton AS, Teach S. High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC. *J Pediatr* 2010;156: 948–952. doi:10.1016/j.jpeds.2009.12.033.
9. Stevens S. Test distance vision using an eye chart. *Comm Eye Health J* 2007;20:52.
10. Regan D. Do letter charts measure contrast sensitivity? *Clin Vision Sci* 1991;6:401–408.
11. Regan D. Spatiotemporal abnormalities of vision in patients with multiple sclerosis. In: D. Regan, editor. *Vision and visual dysfunction*, volume 10: Spatial vision (pp. 239–247). London: MacMillan Press; 1991.
12. Mantyjarvi M, Laitinen T. Normal values for the Pelli Robson contrast sensitivity chart. *J Cataract Refract Surg* 2001;27:261–266.
13. https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html.
14. Ranasinghe C, Gamage P, Katulanda P, Andraweera N, Thilakarathne S, Tharanga P. Relationship between body mass index (BMI) and body fat percentage, estimated by bioelectrical impedance, in a group of Sri Lankan adults: a cross sectional study. *BMC Public Health* 2013;13:797.
15. Hughes H, Kahl L, editors. *The Harriet lane handbook: a manual for pediatric house officers*, 21st ed. New York: Elsevier; 2017.
16. Lin CN, Wilson A, Bella B, Church B, Ehman S, Roberts WL, McMillin G. Pediatric reference intervals for serum copper and zinc. *Clin Chim Acta* 2012;413: 612–615.
17. Stephensen CB, Gildengorin G. Serum retinol, the acute phase response, and the apparent misclassification of vitamin A status in the third national health and nutrition examination survey. *Am J Clin Nutr* 2000;72:1170.
18. Caram LMO, Amaral RAF, Ferrari R, Tanni SE, Correa CR, Paiva SAR, Gody I. Serum vitamin A and inflammatory markers in individuals with and without chronic obstructive pulmonary disease. *Med Inflamm* 2015;2015:1–6. Article ID 862086
19. Christian P, Khatry SK, Yamini S, Stallings R, LeClerq SC, Shrestha SR, Pradhan EK, West KP. Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *Am J Clin Nutr* 2001;73:1045–1051.
20. Grahn BH, Paterson PG, Gottschall-Pass KT, Zhang Z. Zinc and the eye. *J Am Coll Nutr* 2001;20:106
21. Truong-Tran A, Carter J, Ruffin R, Zalewski P. New insights into the role of zinc in the respiratory epithelium. *Immunol Cell Biol* 2001;79:170–177.
22. Morgan CI, Ledford JR, Zhou P, Page K. Zinc supplementation alters airway inflammation and airway hyper-responsiveness to a common allergen. *J Inflamm* 2011;8:36.
23. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8–14.
24. Jick SS, Vasilakis-Scaramozza C, Maier WC. The risk of cataract among users of inhaled steroids. *Epidemiology* 2001;12:229–234.
25. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. *Ophthalmology* 2009;116:652–657.
26. Williamson TH, Strong NP, Sparrow J, Aggarwal RK, Harrad R. Contrast sensitivity and glare in cataract using the Pelli-Robson chart. *Br J Ophthalmol* 1992; 76:719–722.
27. Ballew C, Bowman BA, Sowell A, Gillespie C. Serum retinol distributions in residents of the United States: third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 2001;73:586–593.
28. Qi Q, Yu Z, Ye X, Zhao F, Huang P, Hu FB, Franco O, et al. Elevated retinol-binding protein 4 levels are associated with metabolic syndrome in Chinese people. *J Clin Endocrinol Metabol* 2007;92:4827–4834.
29. Alkhouiri N, Lopez R, Berk M, Feldstein A. Serum retinol binding protein 4 (RBP4) levels in patients with non-alcoholic fatty liver disease. *J Clin Gastroenterol* 2009;43:985–989.
30. Yeo HP, Kim KW, Lee KE, Kim ES, Sohn MH, Kim KE. Clinical implications of serum retinol-binding protein 4 in asthmatic children. *J Korean Med Sci* 2009;24:1010–1014.