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EFFECT OF ZINC AND VITAMIN A SUPPLEMENTATION ALONG WITH INTER-TUBERCULAR TREATMENT IN PULMONARY TUBERCULOSIS IN NORTH INDIAN PATIENTS

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ABSTRACT: Tuberculosis is the major public health problem in throughout the world caused by *Mycobacterium tuberculosis*. Result indicates that micronutrient deficiency is common in patients with tuberculosis. As per in this study patients with newly diagnosed tuberculosis patients were divided into four groups. One group (n=41) received a placebo, second group (n=47) received 5000 IU vitamin A as retinyl acetate, third group (n=49) received 15 mg zinc as zinc sulphate and fourth group (n=41) received both 5000 IU vitamin A as retinyl acetate & 15 mg zinc as zinc sulphate. All groups received the same antituberculosis treatment (ATT). Results there were no significant differences in biochemical status amongst groups at baseline. After 2 months, the number of patients with sputum smears negative for tubercle bacilli was almost equal in all the groups (Group A-90.6%, Group B-90.3%, Group C-91.4% and Group D=93.1%). After 2 and 6 months of ATT, the increase in hemoglobin, serum albumin, vitamin A and zinc concentrations were significantly higher in the micronutrient group than in the placebo group. By which we can depict that the supplementation of micronutrient improved the effectiveness of antituberculosis drugs in the first 2 and 6 month. It may be possible to reduce the antituberculosis drugs in the first and second phase of treatment or to introduce a shorter regimen. Such a shorter regimen would lead to a higher completion rate, fewer drugs adverse effect and lower cost of ATT.

INTRODUCTION: Tuberculosis remains a major public health problem throughout the world. Vitamin A deficiency has been found to be associated with many infectious diseases. A high prevalence of vitamin A deficiency has been observed in patient with pulmonary tuberculosis, which is more pronounced in those co-infected with HIV and this indicates an association between vitamin A deficiency and tuberculosis [1].

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Hanekom *et al* found a low plasma Vitamin A levels to be associated with more extensive or severe disease, and low levels of retinol binding protein, prealbumin and albumin [2]. Ramachandran *et al* also found a lower serum vitamin A level in patient with pulmonary tuberculosis [3]. The levels increased following ATT even without Vitamin A supplementation. Koyanagi *et al* found a lower serum concentration of retinol and zinc in patients with pulmonary tuberculosis as compared with healthy volunteers [4].

These studies have shown that in developing countries patients with tuberculosis have low serum Vitamin A levels. This could be because patients with Vitamin A deficiency have an increased risk of developing tuberculosis or because of

development of active tuberculosis which may decrease the plasma Vitamin A levels [5].

Vitamin A supplementation alone fails to revert this vitamin A deficiency. After the animals are given either zinc supplements or zinc-containing diets, however, their serum retinol concentrations improve, suggesting that the low serum retinol concentrations are related to zinc deficiency [6, 7]. The association of zinc deficiency and vitamin A metabolism is further supported by the simultaneous reduction in retinol and retinol binding protein (RBP) in zinc deficient rats [8], which suggests that the low plasma retinol concentrations in zinc deficiency might be caused by an impaired ability of the deficient animals to mobilize hepatic retinol.

Data on the interaction between zinc and vitamin A in humans are more limited and the results of such studies are inconclusive. Most studies of the interaction have been conducted in individuals with severe disease conditions, such as cystic fibrosis [9] and cirrhosis of the liver [10-14]. Some studies showed an association between low zinc status and reduced retinol concentrations [15-17] and others did not [18-19].

Zinc is known to be essential for growth and development of all organisms [20-23]. It is important for enzymes of all six classes as well as transcription and replication factors [24, 25]. It is necessary for the normal function of the immune system [26]. Zinc supplementation results in increased numbers of T and NK cells and elevated production of IL-2 and sIL-2R. Furthermore, lymphocyte response to phytohemagglutinin stimulation as well as NK cell activity improves significantly compared to the placebo group [27].

In vivo, natural killer (NK)3 cell activity, phagocytosis of macrophages and neutrophils and generation of the oxidative burst are impaired by decreased zinc levels [28, 29]. The number of granulocytes is shown to be decreased during zinc deficiency [30]. Vitamin A deficiency is associated with diminished phagocytic and oxidative burst activity of macrophages activated during inflammation [31] and a reduced number and activity of natural killer (NK) cells [32]. The increased production of IL- 12 (promoting T cell growth) and pro-inflammatory TNF-α (activating microbicidal action of macrophages) in a vitamin A deficient state may promote an excessive inflammatory response, but supplementation with vitamin A can reverse these effects [33]. Lymphocyte proliferation is caused by activation of retinoic acid receptors and therefore vitamin A is playing an essential role in the development and differentiation of Th1 and Th2 lymphocyte subsets [34].

Vitamin A maintains the normal antibody mediated Th2 response by suppressing IL- 12, TNF-α and IFN-γ production of Th1 lymphocytes. As a consequence, in vitamin A deficiency there is an impaired ability to defend against extracellular pathogens [35]. Antibody mediated immunity is strongly impaired in vitamin A deficiency [36]. Oral vitamin A supplementation increases delayed type hypersensitivity (DTH) in infants which may reflect vitamin A-related up-regulation of lymphocyte function [37]. In humans, vitamin A supplementation has been shown to improve antibody titre response to various vaccines [38, 39].

It is not known whether zinc and vitamin A supplements given together with antituberculosis drugs would increase the efficacy of the ATT in North India. Therefore, we investigated the effect of zinc and vitamin A supplementation on tuberculosis treatment among North Indian patients with pulmonary tuberculosis and assessed the following biochemical indexes and conversion of sputum smears to negative.

METHODS:

Study population: The study has been carried out on Cat-1 pulmonary tuberculosis patients attending the DOTS centre.

Study design, Randomization and Supplementation: This was a randomized, double-blind, placebo-controlled trial. Patients were randomly assigned to receive either placebo (A group) or vitamin A (B group) or zinc (C group), or vitamin & zinc both (D group). Each micronutrient capsule contained 1500 retinol equivalents (5000 IU) vitamin A (as retinyl acetate) and 15 mg Zn (as zinc sulfate). The placebo consisted of lactose alone. Supplement and placebo capsules were indistinguishable in appearance both externally and internally. Dosage was based on the recommendation of the World Health Organization [40].

Supplements or placebo has been given to the patients with the antituberculosis drugs on DOTS day. At least one family member or neighbour was asked to help in monitoring patient compliance. This is in line with the directly observed treatment short-course (DOTS) strategy recommended by the World Health Organization [41].

Patients, who did not take their medication regularly, missing even one dose in the first 2 month, were dropped from the study. Patients who had severe adverse drug effects were excluded from the study and received further treatment under the guidance of clinicians in each participating clinic.

Patients with strains of *Mycobacterium tuberculosis* resistant to one or more drugs after 2 month of ATT were placed on a modified drug regimen and their data were excluded from the study.

Sample size: A total of 178 Cat.1 TB patients were randomly assigned to four treatment group (Placebo-41, Vit.A-47, Zinc-49 and Vit A & Zinc-41). Out of these, a total of 127 patients (Placebo-32, Vit.A-31, Zinc-35 and Vit A & Zinc-29) completed the study.

Collection of Blood Samples: Blood samples (5 ml) were collected from enrolled patients via venipuncture at the start of the treatment, after 2 month and after 6 month of the treatment. 2 ml blood were kept in EDTA vial to determine haemoglobin, white blood cell count, erythrocyte sedimentation rate (ESR) and remain in the venipuncture. In the laboratory, the serum was separated and stored at -20ºC. The serum samples were later analyzed for albumin, retinol and zinc concentration.

Biochemical Analysis: Haemoglobin concentration and white blood cells were measured directly using an automatic analyzer (Sysmex Microdilutor F-800, Kobe, Japan). ESR was determined directly using the Westergreen technique [42]. Albumin was determined by the bromcresol green method [43]. Serum retinol was measured using RBP4 (human) ELISA Kit (Cat. No. AG-45A-0011EK-KI01) and zinc concentration was measured using simple colorimetric method [44].

Ethical considerations: The study has been approved by the Institutional Ethics Committee of CSM Medical University UP, Lucknow, India. Informed consent was obtained from each subject before the start of the study.

Statistical analysis: The data collected was entered in Microsoft Excel program and was checked for any inconsistency. A one sample Kolmogorov-Smirnov test was used to investigate whether the variables were normally distributed. The One Way Analysis of Variance (ANOVA) was used to investigate the differences at the baseline values amongst 4 groups. The differences in treatment effects within groups and between the micronutrient and placebo groups were tested by a multivariate analysis of variance repeated-measures design with supplement type as a between subject factor (4 groups) and treatment effect (baseline compared with 2 and 6 months) as a within subject factor.

A significant p-value for the treatment effect indicated a change over time in the combined values of the 4 groups and was further investigated by using a paired t-test for each individual group. Boneferroni corrections were done to adjust for multiple comparisons. Bewteen-group differences in treatment effect were indicated by significant interactions between treatment effect and supplement type. The statistical significance was accepted at a probability level of 0.05. Analyses were performed by using SPSS software package (WINDOWS version 15.0: SPSS Inc. Chicago).

RESULTS: A total of 95 patients in the micronutrient group (B, C and D) and 32 in the placebo group (Group A) completed the study. There were no significant differences in biochemical status amongst groups at baseline. All the patients in all the groups had smear positive. Micronutrient supplementation resulted in an earlier elimination of tubercle bacilli from sputum. After 2 months, the number of patients with sputum smears negative for tubercle bacilli was almost equal in all the groups (Group A-90.6%, Group B-90.3%, Group C-91.4% and Group D=93.1%). After 2 and 6 months of ATT, there were significant increases in hemoglobin, serum albumin, vitamin A and zinc concentrations as well as decreases in WBC count & ESR in all the groups.

After 2 and 6 months of ATT, the increase in hemoglobin, serum albumin, vitamin A and zinc concentrations were significantly higher in the micronutrient group than in the placebo group (**Table 1**).

TABLE 1: MICRONUTRIENT CONCENTRATIONS IN PATIENTS WITH PULMONARY TUBERCULOSIS AT 0, 2 AND 6 MONTHS OF VIT. A AND ZINC SUPPLEMENTATION[1]

	Vit. A (Group B) (n=31)	Zinc (Group C) (n=35)	Vit. A and Zinc (Group D) (n=29)	Placebo (Group A) (n=32)
Fig. 1: [Hemoglobin] Average percent increase in Hb level from Baseline to 2 and 6 months				
0 month	10.32±1.58	10.11±1.25	10.08±1.17	10.55±1.38
2 month	11.64±0.89[2,3]	11.36±0.81[2,3]	11.20±0.73[2,3]	11.16±1.16[2,3]
6 month	12.33±0.82[2]	12.18±0.90[2]	12.34±0.77[2]	11.82±0.82[2]
Fig. 2: [WBC count] Average percent decrease in WBC count from Baseline to 2 and 6 months				
0 month	8926.13±2468.22	9657.14±1568.87	10220.69±2468.28	9528.13±1478.72
2 month	8954.84±1160.41[2,3]	9048.57±1159.20[2,3]	9748.28±1466.93[2,3]	8962.50±1344.94[2,3]
6 month	8377.42±1047.13[2]	7931.43±820.61[2]	8531.03±1028.56[2]	7943.75±1096.02[2]
Fig. 3: [**ESR]** Average percent decrease in ESR from Baseline to 2 and 6 months				
0 month	12.97±2.39	13.83±3.71	15.00±3.27	14.25±3.20
2 month	11.55±2.06[2,4]	11.71±2.69[2]	13.66±2.81[2,4]	12.47±2.36[2]
6 month	9.39±1.87[2,4]	9.31±1.84[2]	10.48±2.76[2,4]	10.00±1.97[2]
Fig. 4: [Serum albumin] Average percent increase in Serum Albumin from Baseline to 2 and 6 months				
0 month	3.46±0.33	3.14±0.97	3.40±0.33	3.43±0.37
2 month	3.93±0.28[2]	3.75±0.40[2]	3.61±0.29[2]	3.85±0.35[2]
6 month	4.38±0.31[2]	4.28±0.33[2]	4.08±0.26[2]	4.23±0.28[2]
Fig. 5: [Vit. A] Average percent increase in Vit. A level from Baseline to 2 and 6 months				
0 month	0.77±0.21	0.77±0.32	0.78±0.23	0.82±0.29
2 month	1.20±0.27[2,5]	1.18±0.30[2,5]	1.14±0.25[2,5]	1.13±0.34[2,5]
6 month	1.67±0.29[2,5]	1.66±0.31[2,5]	1.62±0.23[2,5]	1.59±0.33[2,5]
Fig. 6: [Zinc] Average percent increase in Zinc level from Baseline to 2 and 6 months				
0 month	9.86±0.86	9.86±0.87	9.56±0.77	9.88±1.40
2 month	11.51±0.98[2]	12.23±1.12[2,6]	11.17±0.86[2,6]	11.23±1.34[2,6]
6 month	13.63±1.01[2]	13.97±0.80[2,6]	13.34±1.20[2,6]	12.85±1.03[2,6]

[1]Mean±sd, [2-3]Significantly different from baseline within the same group , [2]p<0.0001, [3]p<0.01
[4]Significantly different between Group B and D, [4]p<0.05
[5]Significantly different between Group A and C, B and C, C and D, [5]p<0.05
[6]Significantly different between Group A and C, C and D, [6]p<0.05

Before antituberculosis treatment, the prevalence of anemia (hemoglobin < 12 g/dl), low serum albumin (<3.4 g/dl), low vitamin A (<0.7 µmol/l) and zinc concentrations (9.2<µmol/l) in all the patients were 85.8%, 44.9%, 37%, and 31.5%, respectively. The patients with anemia, low serum albumin, low vitamin A and zinc concentrations, most of them became normal after 2 and 6 months of ATT (Data not shown).

DISCUSSION: All the concentrations were lower in Cat-1 TB patients at the baseline [4]. The prevalence of anemia was 85.8% at the baseline. The results of the present study showed that zinc, vitamin A and combined zinc and vitamin A supplementation successfully reverted the deficiency in vitamin A–deficient TB patients.

This finding indicates that there is a synergistic effect of zinc and vitamin A on vitamin A status. In our study, the vitamin A and zinc are significantly correlated at 6 months (r=0.60, p<0.0001) [6, 7]. Thus, vitamin A status improved significantly in patients who received zinc and vitamin A as well as vitamin A and zinc separately.

Other than its essential role in vitamin A transport, zinc aids in the absorption of vitamin A in the intestine [45, 46]. In adult male rats with experimentally induced zinc deficiency, retinol absorption is markedly reduced; in contrast, essential fatty acid deficiency exerts only a mild effect on the absorption of retinol [45]. Compared with the essential fatty acids, dietary zinc has a more pronounced effect on phospholipids, which are necessary for the absorption of vitamin A [45, 46].

In our findings, the ESR was negatively correlated with plasma zinc concentration at the baseline in all patients ($r = -0.66$, $p<0.0001$) which maintained till six months of follow-ups.

The supplementation improved the effectiveness of the antituberculosis drugs in the first 2 and 6 months. During this period, the ATT aims at killing active bacilli; the subsequent treatment aims at killing dormant bacilli. The use of the DOTS strategy in monitoring treatment compliance and variations in drug absorption may have contributed to the changes observed in sputum positivity and other clinical outcomes. The improved outcome in the micronutrient group was indicated by the higher number of patients with sputum negative for bacilli. This improvement was associated with higher mean plasma retinol concentrations.

A previous study in India showed that a 4-drug tuberculosis regimen for 3 months in patients with smear-positive tuberculosis resulted in unacceptably high relapses rates [47].

We did not assess the relapse rate in our patients; however, micronutrient supplementation showed an effect on clinical outcome in the first 2 months (data not shown). The results of our study suggest that it would be useful to adapt current tuberculosis treatment regimens by including micronutrient supplements.

It may be possible to reduce the dosage of antituberculosis drugs either in the first or second phase of treatment or to introduce a shorter regimen. Such a shorter regimen would lead to a higher completion rate, fewer adverse drug affects, and a lower cost of ATT. The major benefit of faster sputum conversion would be seen at the community level, because it would reduce the risk of tuberculosis transmission: a person with active tuberculosis will infect an average of 20–28 other persons before recovering from the disease or dying [48].

This present study showed that the effectiveness of ATT was improved during the first 2 and 6 months by vitamin A & zinc supplementation and both.

The conclusions drawn from this study should now be tested in larger trials.

REFERENCES:

1. Wiid I, Seaman T, Hoal EG, Benade AJ Van helden PD: Total antioxidant levels are low during active TB and rise with anti-tuberculosis therapy. IUBMB Life 2004; 56:101-6.
2. Hanekom WA, Potgieter S. Hughes EJ. Malan H. Kessow G. Hussey GD: Vitamin A status and theraphy in childhood pulmonary tuberculosis. J Pediater 1997; 131:1130-3.
3. Ramachandran G, Santha T, Garg R. Baskaran D, lliayas SA, Venkatesan P. et al : Vitamin A levels in sputum-positive pulmonary tuberculosis patients in comparison with household contacts and healthy 'normals'. Int J Tuberc Lung Dis 2004; 8:1130-3.
4. Koyanagi A, Kuffo D. Gresely L. Shenkin A. Cuevas LE: Relationships between serum concentrations of C-reactive protein and micronutrients, in patients with tuberculosis. Ann Trop Med Parasitol 2004; 98:391-9.
5. Getz HR, Long ER, Hendrson HJ: A study of the relation of nutrition to the development of tuberculosis: Influence of ascorbic acid and vitamin A. Am Rev tuberc 1951; 64:381-93.
6. Smith JC Jr, McDaniel EG, Fan FF, Halsted JA: Zinc- a trace element essential in vitamin A metabolism. Science 1973; 181: 954–5.
7. Brown ED, Chan W, Smith JC Jr: Vitamin A metabolism during the repletion of zinc deficient rats. J Nutr 1976; 106:563–8.
8. Smith JE, Brown ED, Smith JC Jr: The effect of zinc deficiency on the metabolism of retinol-binding protein in the rat. J Lab Clin Med 1974;84:692–7.
9. Jacob RA, Sandstead HH, Solomons NW, Rieger C, Rothberg R: Zinc status and vitamin A transport in cystic fibrosis. Am J Clin Nutr 1978; 31:638–44.
10. Patek AJ Jr, Haig C: The occurrence of abnormal dark adaptation and its relation to vitamin A metabolism in patients with cirrhosis of the liver. J Clin Invest 1939; 18:609–16.
11. Vallee BL, Hoch FL: Zinc in horse liver alcohol dehydrogenase. J Biol Chem 1957; 225:185–95.
12. Halsted JA, Hackley B, Rudzki C, Smith JC Jr: Plasma zinc concentration in liver diseases. Comparison with normal controls and certain other chronic diseases. Gastroenterology 1968; 54: 1098–105.
13. Russell RM, Morrison SA, Smith FR, Oaks EV, Carney EA: Vitamin-A reversal of abnormal dark adaptation in cirrhosis. Study of effects on the plasma retinol transport system. Ann Intern Med 1978; 88:622–6.
14. Morrison SA, Russell RM, Carney EA, Oaks EV: Zinc deficiency- a cause of abnormal dark adaptation in cirrhotics. Am J Clin Nutr 1978; 31:276–81.
15. Kozlowski BW, Taylor ML, Baer MT, Blyler EM, Trahms C: Anticonvulsant medication use and circulating levels of total thyroxine, retinol binding protein, and vitamin A in children with delayed cognitive development. Am J Clin Nutr 1987; 46:360–8.
16. Coutsoudis A, Coovadia HM, Broughton M, Salisbury RT, Elson I. Micronutrient utilisation during measles treated with vitamin A or placebo. Int J Vitam Nutr Res 1991; 61:199–204.
17. Ahmed F, Barua S, Mohiduzzaman M, et al: Interactions between growth and nutrient status in school-age children of urban Bangladesh. Am J Clin Nutr 1993; 58:334–8.
18. Chase HP, Hambidge KM, Barnett SE, Houts-Jacobs MJ, Lenz K, Gillespie J: Low vitamin A and zinc concentrations in Mexican- American migrant children with growth retardation. Am J Clin Nutr 1980; 33:2346–9.

19. Dorea JG, De Araujo MO: Zinc and vitamin A in liver of foetuses and infants. Acta Paediatr Scand 1988; 77:85–8.
20. Raulin, J. (1869) Etudes Chimique sur al vegetation (Chemical studies on plants). Annales des Sciences Naturelles Botanique et Biologie Vegetale 11: 293–299.
21. Todd, W. K., Evelym, A. & Hart, E. B. (1934) Zinc in the nutrition of the rat. Am. J. Physiol. 107: 146–156.
22. Prasad, A. S., Miaie, A., JR., Farid, Z., Schulert, A. & Sandsteadt: H. H. (1963) Zinc metabolism in patients with the syndrome of iron deficiency, hypogonadism and dwarfism. J. Lab. Clin. Med. 83: 537–549.
23. Neldner, K. H. & Hambidge, K. M: (1975) Zinc therapy in acroderamtitis enteropathica. N. Engl. J. Med. 292: 879–882.
24. Auld, D. S. Zinc coordination sphere in biochemial zinc sites. Biometals 2001; 14: 271–313.
25. Rink, L. & Gabriel, P. Zinc and the immune system. Proc. Nutr. Soc. 2000; 59: 541–552.
26. Rink, L. & Gabriel, P. Extracellular and immunological actions of zinc. Biometals 2001; 14: 367–383.
27. Chandra, R. K. Effects of vitamin and trace-element supplementation on immune responses and infections in the elderly. Lancet 1992; 340: 1124-1137.
28. Allen, J. L., Perri, R. T., McClain, C. J. & Kay, N. E. Alterations in human natural killer cell activity and monocyte cytotoxicity induced by zinc deficiency. J. Lab. Clin. Med. 1983; 102: 577–589.
29. Keen, C. L. & Gershwin, M. E. Zinc deficiency and immune function. Annu. Rev. Nutr. 1990; 10: 415–431.
30. Prasad, A. S. Effects of zinc deficiency on immune functions. J. Trace Elem. Exp. Med. 2000; 13: 1–20.
31. Ramakrishnan U, Web AL & Ologoudou K. Infection, immunity, and vitamins. In Handbook of Nutrition and Immunity, 2004; 93–115 [NE Gershwin, P Nestel and CL Keen, editors]. Totoja, NJ: Humana Press.
32. Dawson HD, Li NQ, Deciccio KL, Nibert JA & Ross AC. Chronic marginal vitamin A status reduces natural killer cell number and activity and function in aging Lewis rats. J Nutr 1999; 129, 1510–1517.
33. Aukrust P, Mueller F, Ueland T, Svardal A, Berge R & Froland SS. Decreased vitamin A levels in common variable immunodeficiency: vitamin A supplementation in vivo enhances immunoglobulin production and downregulates inflammatory responses. Eur J Clin Invest 2000; 30: 252–259.
34. Halevy O, Arazi Y, Melamed D, Friedman A & Sklan D. Retinoic acid receptor-alpha gene expression is modulated by dietary vitamin A and by retinoic acid in chicken T lymphocytes. J Nutr 1994; 124: 2139–2146.
35. Cantorna MT, Nashold FE & Hayes C. In vitamin A deficiency multiple mechanisms establish a regulatory T helper cell imbalance with excess Th1 and insufficient Th2 function. J Immunol 1994; 152: 1515–1522.
36. Long KZ & Santos JL. Vitamins and the regulation of the immune response. Ped Inf Dis J 1999; 18: 283–290.
37. Rahman MM, Mahalanabis D, Alvarez JO, Wahed MA, Islam MA & Habte D. Effect of early vitamin A supplementation on cell-mediated immunity in infants younger than 6 months. Am J Clin Nutr 1997; 65: 144–148.
38. Semba RD. Vitamin A as "anti-infective" therapy. J Nutr 1999; 129: 783–791.
39. Semba RD. Vitamin A, infection and immune function. In Nutrition and Immune Function 2002; (Frontiers in Nutritional Science, No. 1) chapter 8, 151–170 [PC Calder, CJ Field and HS Gill, editors]. Oxford: CABI Publishing.
40. World Health Organization. Treatment of tuberculosis. Guidelines for national programmes. Geneva: WHO, 1993.
41. World Health Organization. What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS. Geneva: WHO, 1999.
42. Kohli RN, Singh S, Singh M. Studies on erythrocyte sedimentation rate in buffaloes. I. Evaluation of various techniques. Indian Vet J 1975; 52:12, 915–8.
43. Dumas BT, Watson WA, Biggs HG. Albumin standards and the measurement of serum albumin with bromcresol green. 1971. Clin Chim Acta 1997; 258:21–30.
44. Fuentes J, Miro J, Riera J. (1982) Simple colorimetric method for seminal plasma zinc assay. Andrologia. 14(4): 322-327.
45. Ahn J, Koo SI. Effects of zinc and essential fatty acid deficiencies on the lymphatic absorption of vitamin A and secretion of phospholipids. J Nutr Biochem 1995; 6:595–603.
46. Ahn J, Koo SI. Intraduodenal phosphatidycholine infusion restores the lymphatic absorption of vitamin A and oleic acid in zinc-deficient rats. J Nutr Biochem 1995; 6:604–12.
47. Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Am Rev Respir Dis 1986; 134:27–33.
48. Appropriate Health Resources and Technologies Action group (AHRTAG). Tuberculosis and children: the missing diagnosis. Nottingham, United Kingdom: Russell Press, 1996.

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