A Study of Malnutrition in Iranian Patients with Primary Antibody Deficiency

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ABSTRACT

Nutrition is an important factor that influences immunity, and nutritional deficiencies can impair resistance to infections. Malnutrition is the most common cause of immunodeficiency worldwide. Trace elements such as zinc, selenium, iron, and copper can influence several components of immunity. Primary antibody deficiency disorders are a group of disorders characterized by an unusual susceptibility to infections and malnutrition. Impaired nutritional status has been reported in immunodeficient patients. The aim of this study was to determine anthropometric indices and trace elements status in these patients. Thirty-eight children (28 males, 10 females, aged 2-18 years) with primary antibody deficiency referring to Children's Medical Center of Tehran University of Medical Science were enrolled in this research. Primary immunodeficiency disorders consisting of CVID, XLA, IgA deficiency, IgG subclass deficiency, and hyper IgM were assessed. Anthropometric indices, comprised of height, weight that were measured and body mass index (BMI) was calculated. Height-for-age (HAZ), weight-for-height (WHZ) and weight-for-age (WAZ) were determined according to Z-score to study mild, moderate and severe malnutrition. Serum copper, zinc, selenium and iron levels were measured by an atomic absorption spectrometer. The most common disorders were CVID 52.5% and X-linked agammaglobulinaemia 27.5%. Based on BMI measurements 21.1% of patients had malnutrition. According to HAZ, 13.2%, 13.2% and 36.8% had severe, moderate and mild malnutrition, respectively. According to WAZ, 10.5%, 18.4% and 28.6% had severe, moderate and mild malnutrition, respectively. Regarding to WHZ, 14.3% and 28.6% had moderate and mild malnutrition, respectively. Low selenium levels and high copper levels were observed in 37.5% and 70.3%, respectively. Anthropometric data showed that the frequency of malnutrition in these patients was higher than the CDC standard. Low serum selenium levels and high serum copper levels were observed, suggesting further research is needed on these parameters. Most of the patients had serum zinc and iron levels within the normal range. It is recommeded that clinical immunologists and nutritionists should make a collective effort to provide these patients with standard or specialized diets so as to decrease the risk of infection.

Keywords: Anthropometry; Antibody Deficiency Syndrome; Copper; Malnutrition; Iron; Selenium; Zinc

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INTRODUCTION

The importance of proper nutrition for sound health has been long appreciated in most societies.[1] Nutrition is an important factor that influences host defense against infection.[2] Nutrient deficiency can impair resistance to infections. Infections also have adverse effects on nutritional status. The significance of these effects depends on the previous nutritional status of the individual, the nature and duration of the infection and the diet during the recovery period.[3] In 1968, for the first time WHO's monograph, entitled *Interactions of Nutrition and Infection,* suggested that the relation between infection and malnutrition was synergistic.[4]

The relationship between nutritional status and the immune system was a topic of study for much of the 20th century.[5] Nutrition is a critical determinant of immune responses, and malnutrition is the most common cause of immunodeficiency worldwide. Protein-energy malnutrition (PEM) is associated with a significant impairment of immune system. Deficiency of single nutrient also results in altered immune responses. Of the micronutrients, zinc; selenium; iron; copper; and vitamins have important influences on immune responses.[6,7]

Primary immunodeficiency disorders are a group of diseases characterized by an unusual susceptibility to infections.[8,9] Antibodies have a crucial role in protecting against infections, and antibody deficiencies are the most common primary and secondary immunodeficiencies. Antibody deficiencies may be the only abnormality present in a patient, or they may be present and aggravate the symptoms of other conditions.[10] Patients with primary disorders of B lymphocytes and immunoglobulins usually display an increased susceptibility to bacterial infections; moreover, atopic, autoimmune and malignant disorders are also more common in these patients.[11,12] Most patients are recognized by the recurrent infections with high-grade extracellular encapsulated bacterial pathogens.[13] Consequently, these patients are susceptible to infections and malnutrition.

Impaired nutritional status has been reported in common variable immunodeficiency (CVID) patients, and anthropometric measurements have revealed an increased rate of malnutrition in CVID patients. In these patients, infections, persistent diarrhoea and malabsorption may result in malnutrition, which may in turn contribute to increased morbidity.[14] Micronutients disturbances have also been observed in these patients.[15]

Anthropometrics indices, comprised of weight; height; body mass index (BMI); height-for-age (HAZ); weight-for-height (WHZ); and weight-for-age (WAZ) are important indicators of development and nutritional inadequacy in children and adolescents can, also, have a great impact on the prevalence of malnutrition.

The aim of this study was to determine the frequency of malnutrition, anthropometric indices and serum levels of selenium, zinc, copper and iron in Iranian patients with primary antibody deficiencies.

MATERIALS AND METHODS

Thirty-eight patients (28 males, 10 females, aged 2-18 years) with definite diagnosis of primary antibody deficiency were enrolled in this study. The diagnosis of patients was made by the standard criteria of The World Health Organization.[8-16] The patients routinely underwent IVIG therapy at the Children's Medical Center of Tehran University of Medical Sciences. This study was approved by the Research Committee of Tehran University. All the patients were studied in the morning before the IVIG infusion. Questionnaires were filled by the patients or/and with their parents' help. All the patients who referring to Children Medical Center during one-year period (2003-2004) and who had the inclusion criteria were enrolled, and patients with liver or renal failure, malabsorption, chronic diarrhoea, malignancy and mineral or vitamin usage were excluded. The patients underwent anthropometrc assessment. Standing height was measured with a meter stick installed on the wall and a set-square. In the standard manner, the child stood in stockings feet with feet together and back and heels against an upright wall. The children's weights were taken wearing no shoes and a layer of indoor clothing, and the weights of clothing was estimated to correct the measurement. Then the body mass index. [BMI: BW (kg)/ height^2 (m^2)] was calculated, and BMI percentile was used according to the CDC 2000 age and sex percentiles (Center for Disease Control).[17] Having a BMI less than 5th, 5-85th, 85-95th and above 95th percentile were considered as underweight, normal, overweight and obese, respectively.

The children's weight and height were compared against weight-for-age (WA), height-for-age (HA) and weight-for-height (WH) CDC 2000 Z-Scores to show present, past and past-present malnutrition. Mild, moderate and severe cases of malnutrition were determined according to Z-Score (Z<-3 severe malnutition, -3<Z<-2 moderate malnutition, -2< Z<-1 mild malnutition and -1<Z<+1 normal, respectively).[18]

Low weight-for-age index identifies the condition of being underweight and reflects both past- present or chronic-acute undernutrition.Low height-for-age index identifies past undernutrition or chronic malnutrition or stunting. Low weight-for-height helps to identify children suffering from current or acute undernutrition or wasting.

Blood samples were collected in fasting state at 7-9 A.M. for the evaluation of serum micronutrients (including zinc, iron, selenium and copper), and the results were compared with standards. Normal ranges of micronutrients were considered 70-150mg/dl (<70 low, >150 high) for zinc; 50-175 µg/dl (<50 low, >175 high) for iron; 80-150 µg/dl (1-9 years) (<80 low, >150 high); 80-121 µg/dl (10-14years) (<80 low, >121 high); and 64-160 µg/dl (15-19 years) (<64 low, >160 high) for copper.[19,20] Normal serum selenium levels were evaluated according to a pilot study performed in 60 Iranian normal children and were considered 80-160 ng/ml. Serum trace elements levels were established by atomic absorption spectrophotometry.

Statistical evaluation was performed by Spss 10 software. The results were analysis by Chi-sqaure and P.value <0.05 was significant

RESULTS

Thirty-eight patients with primary antibody deficiency were studied. The most common disorders were CVID 52.5%, X-linked aggamaglobulinaemia (XLA) 27.5%, IgA deficiency 7.5%, IgG subclass deficiency 7.5%, and Hyper IgM 5%, respectively.

Body Mass Index (BMI)

The frequencies of underweight, normal, over-weight and obesity according to BMI percentiles are shown in table 1. There were no significant differences between both sexes (P=0.221).

There was a significant difference between the malnourished patients and the CDC standard (P=0.01).

Height-for-Age Z-Score (HAZ)

The frequencies of severe, moderate and mild malnutrition and normal dietary status according to HAZ are shown in table 2. There were no significant differences between both sexes (P=0.201).

Table 1. Children's nutritional status according to Body Mass Index (BMI).

Body Mass Index	Male		Female		Total	
	Number	Percent	Number	Percent	Number	Percent
BMI <5 (under weight)	6	21.4	2	20.0	8	21.1
BMI 5-85 (normal)	20	71.4	6	60.0	26	68.4
BMI 85-95 (over weight)	1	3.6	2	20.0	3	7.9
BMI >95 (obese)	1	3.6	0	0.0	1	2.6
Total	28	100.0	10	100.0	38	100.0

No significant differences between boys and girls (P=0.221)

Table 2. Children's nutritional status according to Height-for-Age Z-Score (HAZ).

Nutritional Status	Male		Female		Total	
	Number	Percent	Number	Percent	Number	Percent
Severe malnutition (HAZ<-3)	3	10.7	2	20.0	5	13.2
Moderate malnutition (-3<HAZ<-2)	2	7.1	3	30.0	5	13.2
Mild malnutition (-2<HAZ<-1)	12	42.9	2	20.0	14	36.8
Normal (-1<HAZ<+1)	11	39.3	3	30.0	14	36.8
Total	28	100.0	10	100.0	38	100.0

No significant differences between boys and girls (P=0.201)

Table 3. Children's nutritional status according to Weight-for-Age Z-Score (WAZ).

Nutritional Status	Male		Female		Total	
	Number	Percent	Number	Percent	Number	Percent
Severe malnutition (WAZ<-3)	3	10.7	1	10.0	4	10.5
Moderate malnutition (-3<WAZ<-2)	5	17.9	2	20.0	7	18.4
Mild malnutition (-2<WAZ<-1)	8	28.6	0	0.0	8	28.6
Normal (-1<WAZ<+1)	12	42.9	7	70.0	19	50.0
Total	28	100.0	10	100.0	38	100.0

No significant differences between boys and girls (P=0.201)

Table 4. Children's nutritional status according to Weight-for-Height Z-Score (WHZ).

Nutritional Status	Male		Female		Total	
	Number	Percent	Number	Percent	Number	Percent
Severe malnutition (WHZ<-3)	0	0.0	0	0.0	0	0.0
Moderate malnutition (-3<WHZ<-2)	1	9.1	1	3.33	2	14.3
Mild malnutition (-2<WHZ<-1)	3	27.3	1	3.33	4	28.6
Normal (-1<WHZ<+1)	5	45.5	1	3.33	6	42.9
Overweight	2	18.2	0	0.0	2	14.3

No significant differences between boys and girls (P=0.653)

Table 5. Micronutrients' status in patients with primary antibody deficiency.

Micronutrients Status	Low		Normal		High	
	Number	Percent	Number	Percent	Number	Percent
Zinc	2	5.3	33	86.8	3	7.9
Iron	0	0.0	30	85.7	5	14.3
Selenium	15	37.5	25	62.5	0	0.0
Copper	1	2.7	10	27.0	26	70.3

**Normal ranges of micronutrients were considered 70-150mg/dl (<70 low, >150 high) for zinc; 50-175 µg/dl (<50 low, >175 high) for iron; 80-150 µg/dl (1-9 years) (<80 low, >150 high); 80-121 µg/dl (10-14 years) (<80 low, >121 high); and 64-160 µg/dl (15-19 years) (<64 low, >160 high) for copper.[18,19]

Weight-for-Age Z-Score (WAZ)

The frequencies of severe, moderate and mild malnutrition and normal according to WAZ are demonstrated in table 3. There were no significant differences between both sexes (P=0.265).

Weight-for-Height Z-Score (WHZ)

The frequencies of severe, moderate and mild malnutrition and normal dietary status according to WHZ are shown in table 4. There were no significant differences between both sexes (P=0.653).

Micronutrients' Status

Table 5 shows the serum status of zinc, iron, selenium and copper in these patients.The results showed that 70.3% of the patients had high serum levels of copper and that 37.5% of the patients had low selenium levels. Most of the patients had serum zinc and iron levls within the normal range.

DISCUSSION

Primary hypogammaglobulinemia disorders are characterized by low levels of serum immunoglobulin, and such patients are susceptible to recurrent infections and prone to secondary malnutrition. These patients often present with frequent and severe episodes of infections before diagnosis.[14,21] The standard treatment, intravenous immunoglobulin (IVIG) has been available for the past 20 years.[22] The presence of recurrent infections is known to be associated with a series of metabolic events leading to a state of negative nitrogen balance and significant loss of lean body mass with nutritional imbalance.

Increased energy expenditure and increased loss of nutrients secondary to diarrhoea and/or malabsorption further contribute to the nutritional wasting observed in children with chronic infections.[23]

To the best of our knowledge, this is the first study investigating the prevalence of malnutrtion in patients with primary antibody deficiency. There is little data on the nutritional status in this heterogeneous group of immunodeficient patients. Recently, Aukrust et al. reported decreased vitamin A levels in CVID patients.[24] Also, Muscaritoli et al. reported high prevalence of protein-energy malnutrition (PEM) in CVID patients and assessed the prevalence of PEM by means of anthropometric parameters.[14] Other reports have shown that duodenal villous atrophy was very frequent in symptomatic CVID patients with relevant clinical and immunological implications. Specifically, this histological alteration is significantly associated with anemia, malnutrition and low blood CD4+ lymphocyte levels.[25]

In this research, the most prevalent disorders were CVID and XLA, which were also reported in previous studies.[21]

Anthropometric measurments are a simple and reliable method to assess the nutritonal status in children. In this study, 38 primary humoral immunodeficient patients were investigated for anthropometric indices and serum micronutients.

BMI Assessment

Seventy-five percent of the patients were male. According to BMI, under weight, overweight and obesity were observed in 21.1%, 7.9%, and 2.6% of the patients, and BMI showed no significant differences between males and females (P=0.779). About 21.1% of the patients had malnutrition, although only 5% of the population was expected to have malnutrition according to the CDC standard. As a result, the frequency of malnutrition was four times higher than that in normal subjects based on the CDC standard. Also, there was a significant differences between the malnourished patients and the CDC standard (P=0.01). In the Muscaritoli Study, BMI values < 18.5 were reported in 23% of adult CVID patients.[14] The prevalence of highly underweight (BMI<15) and underweight (BMI=15-19.9) in high-school girls in Kerman, Iran was reported 1.6% and 54.6%, respectively.[26] BMI was considered as a predictor in AIDS, and serial measurements of BMI was considered as a predictor in the development of AIDS. Higher BMI and increases in BMI are associated with a decreased risk of HIV progression. It has been reported that increases in BMI are associated with slight increases in CD4 cell counts in HIV infected patients.[27,28]

Z-Score

Z-scores for weight-for-age, height-for-age and weight-for-height were calculated with The US National Center for Health Statistics' reference data as standards. According to the height-for-age criteria, 63.2 % of the patients were malnourished, and 26.4% had severe + moderate malnutrition or stunting or past malnutrition.

According to the weight-for-age criteria, 57.5 % of the patients had malnutrtion, and 28.9% had severe + moderate malnutrition or underweight or past-present malnutrition.

According to the weight-for-height criteria, 42.9% of the patients had malnutrtion or wasting or present malnutrition; and 14.3% and 28.6% had moderate and mild malnutrition, respectively. The above-mentioned criteria also showed wasting or past-present malnutrition. The frequency of stunting and under-weight were higher than that of wasting. Overweight was not observed in these patients on the basis of these criteria. Severe and moderate cases of stunting were more frequent in females, while mild stunting was more frequent in males. Severe and moderate cases of under weight were more common in males, and moderate under weight was also more frequent in males. Mild and moderate cases of wasting were more frequent in females. No significant differences were observed in the indicators between both sexs.

Phimmasone et al, reported that girls were less malnourished than boys, albeit not significantly.[29]

Sexual discrimination, socioeconomic conditions, parents' education, parents' nutritional knowledge and cultural differences may affect on nutritinal status in both sexes. In this research, however, low number, specially in females, may have affected the results.

According to a 1995 survey in Iran (ANIS Study), the prevalences of moderate + severe underweight, stunting and wasting in under five-year-old children were 15.7%, 18.9%, and 6.6%, respectively, which decreased to 10.9%, 15.9%, and 4.9% by 1997, whereas the prevalence of overweight was 4.3%.[30] Malnutrition was more frequent in the subjects of the

present study than that in the Iranian children discussed in the ANIS Study.

Anthropometric data showed that malnutrition was more frequent in these patients compared to CDC standard, which may be due to recurrent infections or inappropriate diets.

Micronutrients

Almost all nutrients in the diet play a crucial role in maintaining an "optimal" immune response, and both insufficient and excessive intakes can have negative consequences on the immune status and thus increase susceptibility to a variety of pathogens.[31]

In this study, low serum selenium levels were observed in 37.5% of the primary antibody deficient patients. There is no study on the serum selenium levels in primary antibody deficiency to compare with the present study, but selenium deficiency has been reported in many diseases such as Kashin-Beck disease, infertility, AIDS, thyroid diseases, mood disorders, cancers,[32-35] An important role for selenium in human immunodeficiency virus (HIV) disease has been suggested. Decreased selenium levels, as found in persons with HIV infection or AIDS, are sensitive markers of disease progression. Selenium deficiency, an independent predictor of mortality in both HIV-1-infected adults and children, is an essential micro-nutrient that is associated with an improvement of T-cell function and reduced apoptosis in animal models. In addition, adequate selenium may enhance resistance to infections through modulation of interleukin (IL) production and subsequently the Th1/Th2 response.[36]

Increased serum copper levels were observed in 71.3% of the patients. Increased serum copper levels were reported in CVID.[15] Bacterial infection has consistently been demonstrated to alter plasma levels of various trace elements. The alternation of trace elements is postulated to be an integral mechanism in the host response to infection. Copper deficiency produces impairment in various immunologic parameters, as well as an increased susceptibility to infection. In addition, increased copper has an inhibitory effect on bacterial growth. Copper is an acute phase response protein, a primary host defense mechanism composed of immunologic, endocrine, neurologic, metabolic, and behavioral modifications.[37] During the inflammatory process, a reduced serum zinc level is accompanied by an increase in serum copper, and a decrease in serum iron levels.[21] These changes are influenced by interleukin-1,[38] tumor necrosis factor-α,[39] ACTH and glucpcorticoids.[40]

Most of the patients had normal serum levels of iron and zinc in this research, but low serum zinc and iron were observed in the Litzman et al. study in CVID. Malabsorption of zinc and iron in inflamm-atory processes have been described as an explanation for decreased serum zinc and iron levels in CVID patients.[15] In the present study, the patients with malabosption according to history and clinical evidence were excluded. Alteration in iron meta-bolism is one of the proposed mechanisms underlying the anaemia, inflammation and chronic diseases, the most common disorder in hospitalized patients. Iron metabolism parameters in inflammatory diseases are characterized by a blockage of tissue iron release, decreased serum iron and total iron binding capacity and an elevated serum ferritin level, reflecting augmented ferritin synthesis as part of the acute-phase response.[41]

Anthropometric data show that malnutrition is common in primary antibody deficiency patients. In order to provide a standard diet and decrease the risk of infection, concerted collaboration of clinical immunologists and nutritionists is strongly recommended. Furthermore, raising the educational levels and nutritional awareness of patients and their families, improving their socioeconomic conditions, organizing protection committees and providing better micronutrient supplementation and immediate treatment of infections seem advisable.

REFERENCES

1. Corman LC. The relationship between nutrition, infection, and immunity. Med Clin North Am 1985; 69(3):519-31.
2. Kawakami K, Kadota J, Iida K, Shirai R, Abe K, Kohno S. Reduced immune function and malnutrition in the elderly. Tohoku J Exp Med 1999; 187(2):157-71.
3. Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. Am J Clin Nutr 1997; 66(2):464S-477S.
4. Scrimshaw NS, Taylor CE, Gordon AJE. Interactions of Nutrition and Infection. WHO monograph series no. 57 1968 World Health Organization Geneva, Switzerland.
5. Keusch GT. The History of Nutrition: Malnutrition, Infection and Immunity. Symposium: Nutrition and

Infection, Prologue and Progress Since 1968. J Nutr 2003; 133(1):336S-40S.
6. Chandra RK. Nutrition and the immune system: an introduction. Am J Clin Nutr 1997; 66(2):460S-3S.
7. Chandra RK. Nutrition and immunology: from the clinic to cellular biology and back again. Proc Nutr Soc 1999; 58(3):681-3.
8. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, et al. Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol 2002; 22(6):375-80.
9. Cooper MA, Pommering TL, Koranyi K. Primary immunodeficiencies. Am Fam Physician 2003; 68 (10):2001-8.
10. Sorensen RU, Moore C. Antibody deficiency syndromes. Pediatr Clin North Am 2000; 47(6):1225-52.
11. Goldman AS, Goldblum RM. Primary deficiencies in humoral immunity. Pediatr Clin North Am 1977; 24 (2):277-91.
12. Ballow M. Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 2002; 109(4):581-91.
13. Buckley RH. Humoral immunodeficiency. Clin Immunol Immunopathol 1986; 40(1):13-24.
14. Muscaritoli M, Fanfarillo F, Luzi G, Sirianni MC, Iebba F, Laviano A. et al. Impaired nutritional status in common variable immunodeficiency patients correlates with reduced levels of serum IgA and of circulating CD4+ T lymphocytes. Eur J Clin Invest 2001; 31(6):544-9.
15. Litzman J, Dastych M, Hegar P. Analysis of zinc, iron and copper serum levels in patients with common variable immunodeficiency. Allergol Immunopathol (Madr) 1995; 23(3):117-20.
16. primary immunodeficiency disease. repot of a WHO scientific group. Clin Exp Immunol 1997; 109(Suppl 1):1-28.
17. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM. Advance data from vital and health statistics. Hyattsville, MD: National Center for Health Statistics, 2000; 314:1-28. http:// www.cdc.goc/growth charts.
18. Understanding Z-Scores, Data Analysis Workshop, November 7, 2000. http://fantaproject.org/downloads/pdfs/dataanalysis/zscoresp.PDF
19. Maha KL, Escott-stump S, editors. Food nutrition, and diet therapy. Philadelphia: W.B. Saunders, 2000: 1050-1.
20. Sly M. Allergic disorders. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson textbook of pediatrics. Philadelphia: W.B. Saunders, 2000: 144-5.
21. Kainulainen L, Varpula M, Luppo K, Svedstrom E, Nikoskelainen J, Ruuskanen O. Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 1999; 104(5):1031-6.
22. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002; 109(6):1001-4.
23. Screimshaw NS. Effect of infection on nutrients requirement. J Parenter Enter Nutr 1991; 15: 589-600.
24. Aukrust P, Müller F, Ueland T, Svardal AM, Berge RK, 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(3):252.
25. Luzi G, Zullo A, Iebba F, Rinaldi V, Sanchez Mete L, Muscaritoli M, et al. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. Am J Gastroenterol 2003; 98(1):118-21.
26. Janghorbani M, Parvin F. P revalence of overweight and thinness in high-school girls in Kerman, Iran. Int J Obes Relat Metab Disord 1998; 22(7):629-33.
27. Jones CY, Hogan JW, Snyder B, Klein RS, Rompalo A, Schuman P, et al. HIV Epidemiology Research Study Group. Overweight and human immunodeficiency virus (HIV) progression in women: associations HIV disease progression and changes in body mass index in women in the HIV epidemiology research study cohort. Clin Infect Dis 2003; 37(Suppl 2):69-80.
28. Maas JJ, Dukers N, Krol A, van Ameijden EJ, van Leeuwen R, Roos MT, et al. Body mass index course in asymptomatic HIV-infected homosexual men and the predictive value of a decrease of body mass index for progression to AIDS. J Acquir Immune Defic Syndr 1998; 19(3):254-9.
29. Phimmasone K, Douangpoutha I, Fauveau V, Pholsena P. Nutritional status of children in the Lao PDR. J Trop Pediatr 1996; 42(1):5-11.
30. The Ministry of Health and Medical Education. The nutritional status of Children. Tehran: United Nations Children's Fund, Unicef, 1999.

31. Ferencik M, Ebringer L. Modulatory effects of selenium and zinc on the immune system. Folia Microbiol (Praha) 2003; 48(3):417-26.
32. Scott R, MacPherson A, Yates RW, Hussain B, Dixon J. The effect of oral selenium supplementation on human sperm motility. Br J Urol 1998; 82(1):76-80.
33. Baum MK, Miguez-Burbano MJ, Campa A, Shor-Posner G. Selenium and Interleukins in person with Human Immunodeficiency viruse type I. J Infect Dis 2000; 182(suppl 1):569–73.
34. Contempre B, Duale NL, Dumont JE, Ngo B, Diplock AT, Vanderpas J. Effect of selenium supplementation on thyroid hormone metabolism in an iodine and selenium deficient population. Clin Endocrinol 1992; 36(6):579-83.
35. Rayman M. The importance of selenium to human health. Lancet 2000; 356(9225):233-41.
36. Baum MK, Miguez-Burbano MJ, Campa A, Shor-Posner G. Selenium and interleukins in persons infected with human immunodeficiency virus type 1. J Infect Dis 2000; 182(Suppl 1):69-73.
37. Exton MS, Bull DF, King MG, Husband AJ. Paradoxical conditioning of the plasma copper and corticosterone responses to bacterial endotoxin. Pharmacol Biochem Behav 1995; 52(2):347-54.
38. DiSilvestro RA, Cousins RJ. Mediation of endotoxin-induced changes in zinc Metabolism in rats. Am J Physiol 1984; 247(4 Pt 1):E436-41.
]39. Warren RS, Starnes HF, Gabrilove JL, Oettgen HF, Brebba MF. The acute metabolic effects of tumor necrosis factor administration in humans. Arch Surg 1987; 122(12):1396-400.
40. Falchuck KH. Effect of acute disease and ACTH on serum zinc proteins. N Engl J Med 1977; 296(20):1129-34.
41. Konijn AM. Iron metabolism in inflammation. Baillieres Clin Haematol 1994; 7(4):829-49.