Vitamins A, D and E in Primary Immunodeficiencies

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ABSTRACT

Background: A,D and E vitamins have a very important role in humoral and cellular immunity.

Objective: The aim of this study was to compare serum levels of these vitamins in patients with various Primary immunodeficiency diseases (PIDs) and healthy controls.

Materials and methods: Thirty patients with PID and 21 sex- and age-matched healthy controls were enrolled into the study. IgG, IgA and IgM levels, lymphocyte subsets, serum vitamin A, D, and E levels were measured.

Results: Significantly decreased levels of vitamin-A and -E were found in the sera of all patients with PID compared to healthy controls. Serum levels of vitamin-A and -E were also lower in both PID subgroups than those of healthy controls. With respect to the levels of vitamin-D, no significant differences were observed in the comparisons of study groups. Serum vitamin A levels in patients with PID were positively correlated with serum vitamin E levels, respectively. There was no significant correlation among the measured vitamins in patient subgroups and healthy controls.

Discussion: The present study indicated that patients with PID have low serum levels of vitamins A and E. There was not any difference with respect to the serum vitamin D levels between patients with PID and healthy controls. Our patients with PID, decreased serum vitamin A levels were positively correlated with decreased IgG levels. However, there was no significant relationship among their immunological parameters and vitamin E levels. In conclusion, vitamin-A and -E deficiencies associate to a considerable subgroups of PID.

Keywords: IgA, IgG, IgM, vitamin A, vitamin D, vitamin E, primary Immunodeficiencies

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INTRODUCTİON

Primary immunodeficiency diseases (PIDs) are a genetically heterogenous group of disorders characterized by impaired distinct components of the innate and adaptive immune systems, such as neutrophils, macrophages, dendritic cells, complement proteins and natural killer cells, as well as T and B lymphocytes (1). Gastrointestinal tract disease is common in patients with PID who present with chronic diarrhea and malabsorption. Accordingly, the deficiency of fat soluble vitamins in PID can result from fat malabsorption. Likewise, the deficiencies of fat soluble vitamins A, D, and E were previously reported in certain PIDs, especially in patients with common variable ımmunodeficiency (CVID)(2-4). On the other hand, it is well known that these vitamins have a very important role in humoral and cellular immunity. Thus, the aim of this study was to compare serum levels of these vitamins in patients with various PIDs and healthy controls.

MATERİALS AND METHODS

Subjects

Thirty patients with PID and 21 sex- and age-matched healthy controls were enrolled into the study. Clinical and immunological characteristics of patients with PID were shown in Table 1. None of patients with PID had rheumatic disease, cancer or liver dysfunction. The clinical diagnosis of PID was based on the ESID-PAGID criteria (5). Accordingly, patients were subdivided into two groups: those who had PID with predominantly antibody defects (16 CVID, 2 X-Linked (Bruton) Agammaglobulinemia [XLA], 4 selective IgA deficiency [SIGAD], and 2 hyper-IgM syndrome [HIM]) and those who had PID associated with other major defects (4 chronic granulomatosis disease[CGD], 1 properdin deficiency [PD], 1 chronic mucocutaneous candidiasis [CMCC]). 18 patients with predominantly antibody

defects had been under treatment with intravenous immunoglobulin (IVIG) at the time of hospital admission. All patients with PID and healthy controls were on standard diet. This study was conducted in conformity to the Helsinki Declaration and approved by our local research ethics committee. Ten millilitres of venous blood was drawn and centrifuged at 3000 r.p.m. for 30 minutes for the measurements of levels of immunoglobulins (IgG, IgA and IgM) and fat soluble vitamins (A, D, and E). The specimens were stored at -20 °C until analysis. For the determination of lymphocyte subsets, 4 ml of peripheral blood samples were drawn into tubes with acid citrate dextrose, and anlysed on the same day.

Laboratory Analyses

IgG, IgA and IgM levels in the sera of patients with PID were measured by commercially available kits (antisera against IgG, IgA or IgM, respectively) and the BN II nephelometer (both Dade Behring GmbH, Marburg, Germany). Additionally, the six-color flow cytometry (FACS Canto, BD Biosciences, San Jose, CA) was used for determination of lymphocyte subsets in peripheral blood samples from patients with PID. For this purpose, monoclonal antibodies conjugated with a flourochrome were purchased from the same manufacturer.

Measurements of fat soluble vitamins

Serum vitamin A, D, and E levels were measured using an API 3200™ LC/MS/MS System (Applied Biosystems/MDS SCIEX, USA).

Statistics

All statistical analyses were performed using SPSS (SPSS 11.5, SPSS Inc., Chicago, IL, USA) statistical package. The chi-square analysis was conducted to assess gender differences. The differences between two groups were evaluated by Independent Samples Test or Mann-Whitney U Test according to the normality of data distribution. Statistical

comparisons were firstly performed between total patients and healthy controls with respect to vitamin A, D, E levels. Then, the levels of same parameters in patient subgroups were compared those of healthy controls. To investigate the relations among the variables, Spearman rank correlation test was used. P values less than or equal to 0.05 were considered to be statistically significant.

RESULTS

Anthropometric parameters and serum levels of the fat soluble vitamins A, D and E in patients with PID and healthy controls were shown in Table 2. Serum total proteins and albumin levels in all patients with PID and healthy controls were not different from each other (data not shown). Significantly decreased levels of vitamin-A and -E were found in the sera of all patients with PID compared to healthy controls (Table 2; Figure 1a, 1b). Serum levels of vitamin-A and -E were also lower in both PID subgroups than those of healthy controls (Table 2 , Figure 2a, 2b). However, the levels of these vitamins in PID subgroups were not different from each other. With respect to the levels of vitamin-D, no significant differences were observed in the comparisons of study groups. Serum vitamin A levels in patients with PID were positively correlated with serum vitamin E (Figure 3a) and IgG (Figure 3b) levels, respectively. There was no significant correlation among the measured vitamins in patient subgroups and healthy controls.

DİSCUSSİON AND CONCLUSİON

The present study indicated that patients with PID have low serum levels of vitamins A and E. We also found that these vitamins were positively correlated with each other within PID

patients. This findings are comparable to those of both Kilic et al.'s and Aukrust et al.'s studies (2,6). In their studies, serum vitamin A levels were found to be lower in CVID patients when compared with healthy controls. Additionally, Aslam et al. described two CVID patients who developed neurological disease because of vitamin E deficiency (4). In contrary, in Reichenbach et al.'s study, only slightly reduced (not significant) levels of retinol and α tocoferol were measured in plasma samples from CVID patients as compared to healthy controls (7). In our study, there was not any difference with respect to the serum vitamin D levels between patients with PID and healthy controls. However, Ardeniz et al. reported 3 patients with CVID in whom vitamin D deficiency (3).

Low dietary intake, malabsorption and reduced levels of carrier proteins are several contributing factors for the development of vitamins A and E deficiencies (6) . Althouh our patients with PID did not presented any clinical or laboratory findings related to these factors, subclinic mucosal dysfunction might lead to vitamins A and E deficiencies. Likewise, in our patients with PID, lower levels of vitamins A and E and a positive correlation between these two vitamins support this hypothesis.

On the other hand, several reports shown that while vitamin A deficiency is associated with impaired antibody production, vitamin E deficiency is associated with impaired cell mediated immunity (8,9). Accordingly, in our patients with PID, decreased serum vitamin A levels were positively correlated with decreased IgG levels. However, there was no significant relationship among their immunological parameters and vitamin E levels.

In conclusion, vitamin-A and -E deficiencies associate to a considerable subgroups of PID. The deficiency of these fat-soluble vitamins may may play an important role in the development of immunodeficiency. In addition, the deficiencies of these vitamins may lead to further infections and worsening of immunodeficiency.

Decleration of interest: The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent: This study has been approved by the ethics committee of the hospital and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. In the text all persons gave their informed consent prior to their inclusion to the study.

Author contribution statement: This work was carried out in collaboration between all authors. Ugur Musabak was responsible for writting the manuscript, researching the discussion and reviewing and editing the manuscript and he did the statistical analysis; Fevzi Demirel wrote, reviewed and edited the manuscript; Muhittin Abdulkadir Serdar and Rahsan Ilikçi Sagkan helped in biochemical analyses; and Osman Sener is the senior author and was responsible for supervision, reviewing and editing the final manuscript. All authors read and approved the final manuscript.

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Table 1. Clinical and immunological characteristics of patients with PID.

				(g/l) (g/l)	(g/l)		(%) (%)	(%)	(%)		(%)	(%)
MÇ	CGD	22	M	9,97	1,58	0,45	58,3	33,6	15,4	8,3	94,7	3,4
GK	CVID	21	M	7,16	<0,25	0,17	84,9	49,1	32,4	1,2	93,9	2,9
MA	CVID	25	M	5,49	<0,25	<0,16	89,5	51,8	34,6	2,1	99,8	12,6
YB	CVID	39	M	5,98	<0,25	<0,16	44,3	24,7	19,8	13,5	83	8,3
GÖ	SIGAD	22	M	12,4	<0,25	0,49	62,1	32,3	29,2	5,2	88	3,3
AK	CVID	20	F	2,98	<0,25	<0,16	55,2	17,8	33,5	5,9	94,6	17,3
ME	CVID	29	M	7,5	<0,25	0,46	61,6	28,8	28,4	6,7	99,8	8,9
ET	HIM	24	M	0,56	<0,25	5,14	78,5	29,5	40,8	8,4	100	7,7
ÖS	CVID	23	M	1,46	<0,25	<0,16	95,6	23,6	70,4	1,1	98,9	7,9
ÖÖ	SIGAD	23	M	7,46	<0,25	0,68	58,7	19,1	34,8	7,1	98,1	11,2
YK	HIM	26	M	1,11	<0,25	8,11	67,7	34,3	31,2	11,7	92,02	2,8
AÇ	CVID	21	M	4,83	<0,25	<0,16	75,9	27,7	40,6	3,9	96	4,4
EB	CGD	20	M	17,4	0,72	1,33	60,4	25,3	27,7	7,1	85,9	7,3
RT	CVID	19	M	12,6	4,33	2,04	74,6	40,3	23,2	6,1	95	4,9
ET	CVID	19	F	5,67	<0,25	<0.16	94,5	41,6	45,5	1,5	99,2	15,6
SY	CVID	22	M	4,62	0,38	<0,16	72,3	33,4	36,4	3,2	91	9,3
TK	SIGAD	24	M	9,45	<0,25	0,42	66,8	35,3	27,6	10,4	99,5	6,6
DÇ	XLA	27	M	11,2	<0,25	1,77	80,4	22,6	56,7	0,3	86,1	6,8
SY	SIGAD	21	M	10,9	<0,25	0,41	64,3	27,2	33,2	7,1	89	14,4
OA	PD	22	M	8,42	1,67	0,72	73	37	34,5	5,2	84	3,5
İA	CMCC	23	M	15,5	1,56	0,42	51,5	26,4	19,9	9,2	73,5	5,2

MMÖ	CGD	31	M	6,82	<0,25	<0.16	79,4	23,1	51,6	10,8	94,8	2,9
ED	XLA	28	M	0,4	<0,25	<0,16	50	18,4	30,3	0,2	75,5	5,9
TE	CVID	27	F	1,46	<0.25	<0,16	94,5	20	60,8	2,3	100	22,6
KÇ	CVID	21	M	5,05	<0.25	<0.16	72,1	25,5	43,8	12,5	96,3	5,5
YED	CVID	21	M	1,53	<0,25	0,18	72,7	17,3	49,9	7,5	93,4	18,2
NK	CGD	20	M	9,41	0,82	2,09	76,5	48,3	28,2	10,2	94,9	4,9
RB	CVID	33	M	7,7	0,47	0,25	60,9	28,5	36,8	10,8	94,5	19,1
ET	CVID	28	M	2,97	0,57	0,49	78,6	34	29,8	0,4	88,4	6,1
NY	CVID	28	M	5,54	<0,25	0,22	56,6	28,8	26,8	19,1	84,3	5,3

Abbreviations: PID: primary immunodeficiency disease, Chronic Granulomatous Disease: CGD, Common Variable İmmunodeficiency: CVID, Selective IgA Deficiency: SIGAD, Hyper-IgM Syndromes: HIM, X-Linked (Bruton) Agammaglobulinemia: XLA, Properdin Deficiency: PD, Chronic Mucocutaneous Candidiasis: CMCC

Table 2. Anthropometric parameters and serum levels of the fat soluble vitamins A, D and E in patients with PID and healthy controls.

	Healthy Controls	**Total patients with PID**	**Patient Subgroups *** Predominantly Antibody Defects*	Other Major Defects**
	n = 21	n = 30	n = 24	n = 6
Age	23.4 ± 3.1 (19 - 31, 23)	24.3 ± 4.5 (19 - 39, 23)	24.2 ± 4.7 (19 - 39, 23)	24.5 ± 4.3 (20 - 31, 23.5)
Sex (female/male)	2/19	3/27	3/21	0/6
Vitamin A (mg/l)	0.54 ± 0.18 (0.21 - 1.09, 0.56)	0.38 ± 0.14 (0.18 - 0.76, 0.34)	0.37 ± 0.15 (0.18 - 0.76, 0.32)	0.40 ± 0.09 (0.31 - 0.55, 0.40)
Vitamin D (μg/l)	35.9 ± 17.6 (5.2 - 58.0, 33.8)	45.0 ± 20.9 (7.9 - 79.5, 42.8)	43.3 ± 21.3 (7.9 - 75.0, 42.8)	51.4 ± 19.7 (29.0 - 79.5, 48.5)
Vitamin E (mg/l)	13.6 ± 2.1 (8.7 - 17.8, 13.2)	11.8 ± 2.7 (6.4 - 17.7, 11.4)	11.9 ± 2.8 (6.4 - 17.7, 11.8)	11.0 ± 2.2 (8.2 - 13.7, 10.7)

Values are given as "mean ± standard deviation" and "minimum-maximum and median" notations. * 16 of CVID, 2 of XLA, 4 of SIGAD, and 2 of HIM syndrome) and ** 3 of CGD, 1 of PD, 1 of CMCC.

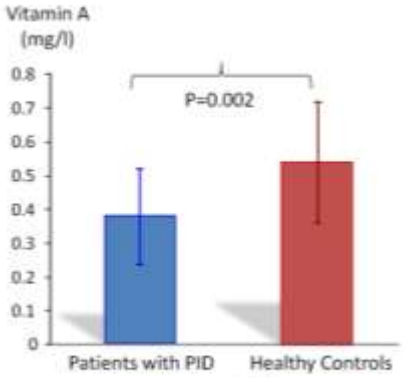

Figure 1(a)

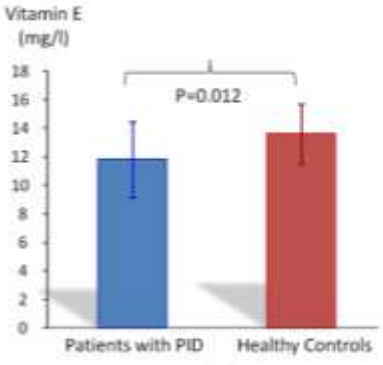

Figure 1(b)

Fig 1: The comparisons of vitamin A (a) and vitamin E (b) levels of patients with PID and healthy controls. The bars represent Arithmetic Mean ± Standard Deviation. P values were indicated above the bars or the boxes when a level of significance less than or equal to 0.05 was reached in comparisons of study groups.

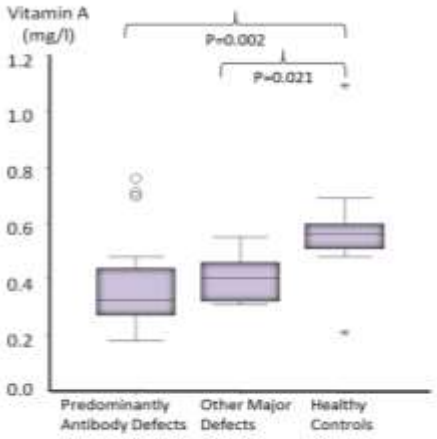

Figure 2(a)

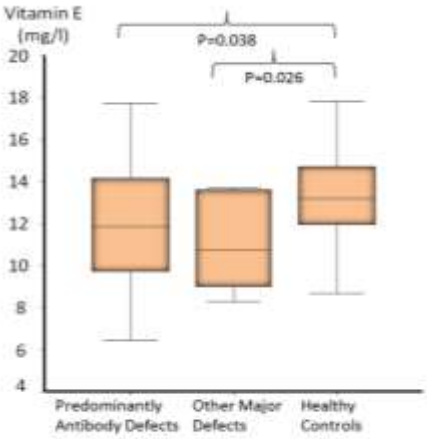

Figure 2(b)

Fig 2: The comparisons of vitamin A (a) and vitamin E (b) levels of patients with PID and healthy controls. The boxes show the ranges of 1 st and 3 rd quartiles, and the medians. Circles and asterisks respectively represent extreme values and outliers in box plots. p values were indicated above the bars or the boxes when a level of significance less than or equal to 0.05 was reached in comparisons of study groups.

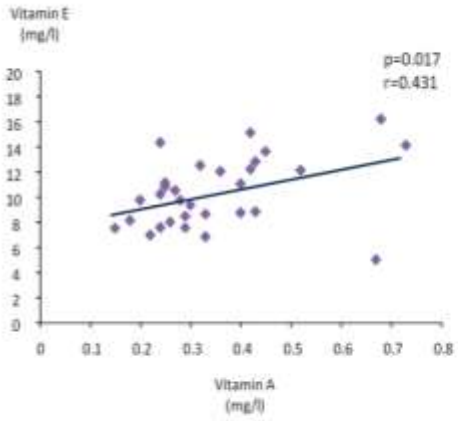

Figure 3(a)

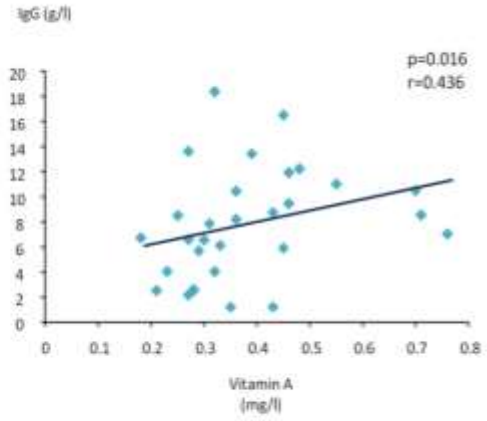

Figure 3(b)

Fig 3 (a and b).: The correlations in patients with PID