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CASE STUDY

Plasma Levels of Antioxidant Vitamins in Patients with Acromegaly: A Case-Control Study

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Abstract

OBJECTIVE: The aim of this study was to compare antioxidant vitamin C and vitamin E levels in the non-acromegaly control group and in patients with acromegaly with and without remission.
MATERIAL AND METHODS: In this study, 100 cases, acromegaly patients of 57% (n=57, 29F, 28M, mean ages of 49.5±12.1) and control subjects of 43% (n=43, 29F, 14M, mean ages of 49.6±9.2). Acromegaly patients were classified into two groups; active acromegaly (AA; n=33) and controlled acromegaly (CA; n=24).
RESULTS: Vitamin C levels were significantly lower in the acromegaly group [7.6 (4.7) mg/L, as median (IQR)] when compared to the control group [12.2 (5.5) mg/L, as median (IQR)] (p <0.001). Vitamin E levels didn't show a significant difference between the acromegaly and the control groups (14.2±3.6 vs. 14.8±3.7, as mean±SD, respectively, p = 0.439). Correlation analysis showed that vitamin C levels were not significantly associated with clinical, anthropometric and laboratory parameters in the acromegaly group. Vitamin E levels were significantly associated with the total cholesterol, triglyceride, LDL-C, HDL-C, APO A1, APO B both in the acromegaly and the control groups.
CONCLUSION: This study is the first one to investigate the relationship between the levels of vitamin C & E and anthropometric & metabolic parameters in acromegaly patients and control group. In our study, vitamin C level was significantly lower in the acromegaly group compared to the level in the control group. There was no significant difference in vitamin E levels between the acromegaly and control group.

INTRODUCTION

Acromegaly is characterized by excess growth hormone (GH) and caused usually by pituitary adenoma. Acromegaly is associated with insulin resistance, type 2 diabetes, dyslipidemia (Colao *et al.* 1997; Colao *et al.* 2004). It is known that cardiovascular morbidity and mortality is increased

in acromegaly due to endothelial dysfunction (Paisley *et al.* 2009; Lombardi *et al.* 2012). Oxidative stress is caused by the production of reactive oxygen species pointing to the excess free radical activity taking role in cardiovascular diseases like hypertension, dyslipidemia and diabetes (Kondo *et al.* 2009). Although there are limited studies investigating oxidative stress in acromegaly, Anognostis et al. reported increased levels of oxidative stress and decreased antioxidant capacity in acromegaly (Anagnostis *et al.* 2013).

Vitamin C (ascorbic acid) is a hydrophilic antioxidant that can have both pro and antioxidative functions depending on the dose (Mandl *et al.* 2009). The antioxidant effect of vitamin C is due to its ability to donate electrons from both the second and third carbon. Highly reactive free radicals are reduced by ascorbate, and the newly generated ascorbyl radical is poorly reactive. Ascorbic acid has direct antioxidant effects as a result of this poorly reactive ascorbyl radical. Vitamin C has antioxidant effect and physiological roles in high concentrations. In low concentrations, however, it shows prooxidant effect by increasing lipid peroxidation and changing membrane phospholipid structure and reducing Na+-K+-ATPase activity. In this way, vitamin C shows a paradoxical effect dependent on dose (Seven & Candan, 1996; Pohanka *et al.* 2012).

Lipid-soluble Vitamin E encompasses a group of compounds, including α, β, γ, and δ tocopherols. It is the most active antioxidant with a strong antioxidant effect in biological membranes. Vitamin E protects the cell membrane from hemolysis by preventing the spread of free radicals formed by lipid peroxidation to membrane and plasma lipoproteins. The hydroxyl group of tocopherol reacts with the peroxyl radical to form the tocopheryl radical. The tocopheryl radical reacts with vitamin C and is reduced to form tocopherol again. In this way the cell membrane is protected from the harmful effects of the peroxyl radical (Maret *et al.* 2011; Maret *et al.* 2007; Montonen *et al.* 2004).

Studies on the investigation of strong antioxidants such as vitamin C and vitamin E in acromegaly have not been found in the literature. The aim of this study was to compare antioxidant vitamin C and vitamin E levels in non-acromegaly control group and in patients with acromegaly with and without remission. Another aim of the study was to investigate the relationship between vitamin C and E regarding metabolic parameters and anthropometric measurements.

MATERIAL AND METHODS

Subjects

In this study, 100 cases, acromegaly patients of 57% (n=57, 29F, 28M, mean ages of 49.5±12.1) and control subjects of 43% (n=43, 29F, 14M, mean ages of 49.6±9.2) who were followed up by Endocrinology Department of Ege University were included. Acromegaly was diagnosed according to the criteria as follows: failure of suppression of serum GH concentration below 1 ng/mL after 75-g oral glucose tolerance test (OGTT) together with fasting serum IGF-1 concentrations above the normal ranges for age and gender (Katznelson *et al.* 2014). Acromegaly patients were classified into two groups; active acromegaly (AA; n=33) and controlled acromegaly (CA; n=24). Controlled acromegaly was defined as GH below 1.0 ng/mL on a 75-g OGTT or random GH level was below 1.0 ng/mL and IGF-1 values were in the reference ranges for age and gender (Katznelson *et al.* 2014; Katznelson *et al.* 2011). Only IGF-1 value was taken to state disease activity for patients on Pegvisomant therapy at the time of measurement (Trainer *et al.* 2000). Written informed consent was obtained from all participants.

A detailed medical history was recorded including demographic data, duration of the acromegaly, smoking history, comorbidities, use of medication, surgery and radiotherapy history. Each patient was physically examined. The duration of the acromegaly disease was 48 months (84), as median, IOR.

The control group consisted of subjects who were matched according to age and gender and had no acromegaly. The rate of smoking and hypertension was similar between the acromegaly and the control groups. Presence of diabetes mellitus and prediabetes was classified as glucose intolerance.

Anthropometric and laboratory measurements

Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference was measured at the midpoint between the inferior costal margin and the superior border of the iliac crest on the mid-axillary line. Hip circumference(cm) was measured at the widest point around the greater trochanter. Fat mass and lean body mass were measured by using Tanita TBF-215 Body Composition Analyzer device based on Bioelectric Impedance Analysis (BIA) method. For the visceral fat measurement, Tanita Viscan AB-101 device was used.

Blood samples were collected after overnight fasting for serum lipid profile, fasting blood glucose, creatinine, ApoA1, liver function tests, HbA1c, fasting insulin, high sensitive C reactive protein (hs-CRP), fibrinogen, homocysteine. Blood samples were stored at -80 °C immediately. The estimate of insulin resistance was calculated using the HOMA-IR index, with the following formula: insulin resistance = fasting plasma insulin (in micro units per milliliter) × fasting plasma glucose (in millimoles per liter)/22.5.

Serum samples for GH and IGF-1 analyses were obtained early in the morning after an overnight fasting. Serum IGF-1 levels were measured with an immunoradiometric assay using a Beckman-Coulter Immunotech kit. Age and gender matched normal reference ranges were used. Serum GH levels were

Tab. 1. Demographic, anthropometric, clinical and laboratory parameters of the acromegaly and the control groups

Variables	Acromegaly n=57		Control n=43		*p* value
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	
BMI (kg(/m^2)	31.0±5.1	30.0 (7.9)	28.1±4.0	27.6 (4.9)	0.005[a]
WC (cm)	102.1±12.5	101.0 (16.0)	94.9±10.1	95.0 (13.7)	0.009[a]
HC (cm)	111.7±10.8	110.0 (10.8)	105.2±7.0	107.0 (10.1)	0.004[a]
Visceral fat (%)	14.1±6.0	12.5 (7.5)	11.7±4.7	11.0 (6.2)	0.048[a]
Lean body mass (kg)	60.6±13.9	54.9 (22.8)	51.7±11.2	48.3 (14.6)	0.001[a]
Fat mass (kg)	44.4±10.1	40.20 (16.7)	37.8±8.2	35.4 (10.7)	0.001[a]
TC (mg/dL)	197.5±44.3	203.0 (57.5)	212.4±41.0	214.0 (40.0)	0.089[b]
TG (mg/dL)	116.8±61.2	98.0 (65.5)	114.0±49.2	110.0(50.0)	0.757[a]
HDL-C (mg/dL)	56.5±16.2	52.0(22.0)	57.5 (14.0)	53.0 (23.0)	0.068[a]
LDL-C (mg/dL)	118.5±34.2	122.0 (46.5)	131.7(35.9)	127.0 (39.2)	0.556[b]
APOA1 (mg/dL)	154.2±28.3	150.0 (40.00)	164.93±29.40	159.0 (50.0)	0.036[a]
APOB (mg/dL)	100.1±23.3	104.0 (31.0)	114.0±37.4	109.0 (25.2)	0.099[a]
Lipoprotein a (nmol/L)	73.5±82.3	38.50 (120.50)	45.13±65.91	18.0 (56.5)	0.041[a]
GH (ng/mL)	3.5±5.80	1.2 (3.83)	-	-	-
IGF-1 (ng/mL)	481.2±461.1	296.0 (469.00)	-	-	-
FPG (mg/dL)	108.3±23.7	106.0 (29.50)	96.26±9.11	98.0 (14.0)	0.004[a]
HOMA-IR	3.3±3.5	2.1 (3.6)	3.1±1.4	2.7 (1.8)	0.167[a]
A1c (%)	6.1±0.6	6.0 (0.9)	5.6±0.4	5.6 (0.7)	<0.001[b]
hs-CRP (mg/dL)	0.2±0.3	0.09 (0.2)	0.3±0.3	0.2 (0.3)	0.003[a]
Homocysteine (µmol/L)	11.4±3.6	10.4 (4.4)	13.1±5.2	12.1 (4.30)	0.032[a]
Fibrinogen (mg/dL)	384.3±77.1	376.5 (109.5)	327.3±51.7	327.5 (81.7)	<0.001[b]
Vitamin C (mg/L)	7.55±3.9	7.6 (4.7)	13.8±8.3	12.2 (10.5)	<0.001[a]
Vitamin E (mg/L)	14.2±3.6	14.5(4.9)	14.8±3.7	14.3 (5.5)	0.439[b]
	n	%	n	%	
Gender (F/M)	29/28	50.8/49.2	29/14	67.4/32.6	0.097[c]
Glucose tolerance status (DM+/DM-/prediabetes)	23/12/22	40.3/21.1/38.6	1/23/16	2.3/60.5/37.2	<0.001[c]
Hypertension (+/-)	22/35	38.5/61.5	12/31	27.9/72.1	0.264[c]
Smoking (+/-)	22/35	38.6/61.5	10/33	37.2/62.8	0.103[c]

SD: Standard Deviation; IQR: Interquartile Range; [a]Mann-Whitney U Test; [b]Independent Samples t-test; [c]Chi-Square Test
$p<0.05$ was considered as statistically significant
BMI, body mass index; WC, waist circumference; HC, hip circumference; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; APOA1, apolipoprotein A1, APOB, apolipoprotein B; GH, growth hormone, IGF-1, insulin like growth factor-1; FPG, fasting plasma glucose; HOMA-IR, homeostatic model assessment-insulin resistance; hs-CRP, high sensitive C reactive protein; DM, diabetes mellitus.

measured with an Immulite2000 (Siemens) autoanalyzer via chemiluminescence method. Vitamin C and E concentrations were quantified by High Performance Liquid Chromatography (HPLC).

Statistical analysis

All statistical analyses were conducted using the IBM SPSS software version 21.0 (Statistical Package of Social Science Inc, USA). Shapiro-Wilk test was used to check the normality assumption of the continuous variables. Mean±standard deviation (mean±SD) and median (interquartile range, IQR) were used according to the distribution pattern. Mann–Whitney U test and Student's t test were used to compare the two independent groups whether the continuous variables were distributed normally or not. In addition to this, one-way ANOVA or Kruskal Wallis test for more than 2 independent groups were used according to the variable

Tab. 2. Correlation analysis for vitamin C in the acromegaly and the control groups

Independent variables	Acromegaly group		Control group	
	r	*p*	*r*	*p*
Age	0.040	0.783	0.488	***0.001**
WC	-0.248	0.118	-0.187	0.254
HC	0.019	0.908	-0.014	0.931
BMI	-0.035	0.809	-0.005	0.973
Visceral fat	-0.308	0.050	-0.126	0.458
Lean body mass	-0.046	0.774	-0.417	***0.010**
Fat mass	-0.080	0.621	0.120	0.480
FPG	0.053	0.718	0.182	0.254
HbA1c	-0.118	0.419	-0.162	0.324
HOMA-IR	-0.012	0.934	-0.088	0.596
Total cholesterol	0.192	0.187	-0.117	0.465
Triglyceride	-0.049	0.741	-0.050	0.758
LDL-C	0.088	0.549	-0.099	0.537
HDL-C	0.159	0.276	0.127	0.427
APOA1	0.249	0.084	0.049	0.760
APOB	0.157	0.282	-0.080	0.626
Lipoprotein a	0.069	0.651	0.447	***0.005**
GH	0.029	0.842	-	-
IGF-1	0.022	0.883	-	-
Duration of acromegaly	0.044	0.765	-	-
hs-CRP	0.044	0.765	-0.432	***0.012**
Homocysteine	-0.252	0.081	0.181	0.257
Fibrinogen	-0.094	0.524	0.045	0.790
Uric acid	0.088	0.563	-0.176	0.292

Spearman correlation analysis was used. *r* stands for correlation coefficient.
* $p < 0.05$ was considered as statistically significant.
WC, waist circumference; HC, hip circumference; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; GH, growth hormone; IGF-1, insulin like growth factor-1; hs-CRP, high sensitive C reactive protein.

distribution. Chi-square test was used to examine the relationship between the categorical variables. Correlation analyses were performed using Spearman's correlation coefficient. Multiple linear regression analysis (stepwise method) was used to explain the variability of vitamin E levels. A *p*-value of less than 0.05 was accepted as statistically significant.

RESULTS

Demographical, anthropometric, clinical and laboratory parameters of the acromegaly and the control groups are shown in Table 1. There were no significant differences between the two groups regarding age, gender, hypertension, lipid profile and smoking status (Table 1). Glucose intolerance (diabetes mellitus + prediabetes) was observed at a higher rate in the acromegaly group (78.9%) compared to the control group (39.5%). While visceral fat was higher in the acromegaly group ($p = 0.048$), lean body mass was significantly different ($p = 0.001$) from the control group [54.9 (22.8) vs. 48.3 (14.6) as median (IQR), respectively].

As shown in Table 1, Vitamin C levels were significantly lower in the acromegaly group [7.6 (4.7) mg/L, as median (IQR)] when compared to the control group [12.2 (5.5) mg/L, as median (IQR)] ($p < 0.001$). Vitamin E levels didn't show a significant difference between the acromegaly and the control groups (14.2±3.6 vs. 14.8±3.7, as mean±SD, respectively, $p = 0.439$).

Vitamin C levels were 7.6 (4.6) mg/L as median (IQR) in the AA group; and were 7.6 (5.3) mg/L, as median (IQR) and were 12.2 (10.5) mg/L as median (IQR) in the control group ($p = 0.001$) (AA vs. control $p = 0.001$, CA vs. control $p = 0$ 0.003).

Tab. 3. Correlation analysis for vitamin E in the acromegaly and the control groups

Independent variables	Acromegaly group		Control group	
	r	*p*	*r*	*p*
Age	0.488	***0.001**	0.257	0.101
WC	-0.187	0.254	-0.196	0.231
HC	0.019	0.619	-0.082	0.619
BMI	0.090	0.515	-0.180	0.260
Visceral fat	-0.149	0.323	-0.272	0.104
Lean body mass	-0.115	0.445	-0.291	0.081
Fat mass	0.274	0.065	0.123	0.467
FPG	-0.225	0.099	-0.014	0.931
HbA1c	0.086	0.532	0.112	0.492
HOMA-IR	-0.105	0.444	-0.278	0.082
Total cholesterol	**0.739**	***<0.001**	**0.729**	***<0.001**
Triglyceride	**0.370**	***0.005**	**0.543**	***<0.001**
LDL-C	**0.583**	***<0.001**	**0.488**	***0.001**
HDL-C	**0.295**	***0.029**	**0.410**	***0.007**
APO A1	**0.459**	***<0.001**	**0.511**	***0.001**
APO B	**0.650**	***<0.001**	**0.539**	***<0.001**
Lipoprotein a	0.240	0.087	0.239	0.143
GH	0.019	0.889	-	-
IGF-1	-0.066	0.663	-	-
Duration of acromegaly	-0.099	0.472	-	-
hs-CRP	-0.052	0.708	0.065	0.723
Homocysteine	0.078	0.572	-0.183	0.247
Fibrinogen	0.228	0.097	0.204	0.214
Uric acid	-0.030	0.833	-0.187	0.254

Spearman correlation analysis was used. *r* stands for correlation coefficient.
* $p < 0.05$ was considered as statistically significant
WC, waist circumference; HC, hip circumference; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; GH, growth hormone; IGF-1, insulin like growth factor-1; hs-CRP, high sensitive C reactive protein

Vitamin C deficiency, which was defined as lower than 4 mg/L, was significantly higher with a ratio of 18.7% in the acromegaly group compared to the control group with a rate of 2.4% ($p = 0.015$).

Correlation analysis showed that vitamin C levels were not significantly associated with clinical, anthropometric and laboratory parameters in the acromegaly group (Table 2). Vitamin C levels were positively associated with age ($p = 0.001$ $r = 0.488$), lipoprotein a ($p = 0.005$ $r = 0.447$) and were negatively associated with lean body mass ($p = 0.01$ $r = -0.417$), hs-CRP ($p = 0.012$ $r = -0.432$) in the control group. However; vitamin E levels were significantly associated with the total cholesterol, triglyceride, LDL-C, HDL-C, APO A1, APO B both in the acromegaly and the control groups (Table 3). Besides, vitamin E levels were positively associated with the age ($p = 0.001$ $r = 0.488$).

When multiple regression analysis was performed in the acromegaly group; total cholesterol, triglyceride and APOA1 were the independent parameters predicting vitamin E levels among the age, total cholesterol, triglyceride, LDL-C, HDL-C, APOA1, APOB (Table 4).

DISCUSSION AND CONCLUSIONS

This study is the first one to investigate the relationship between the levels of vitamin C and E, and anthropometric and metabolic parameters in acromegaly patients and control group. In our study, vitamin C level was found to be statistically low in acromegaly group compared to the control group. Vitamin C deficiency (vitamin C level less than 4 mg / L) was significantly higher in the acromegaly group compared to the control group. There was no significant difference in vita-

Tab. 4. Multiple regression analysis for vitamin E levels in acromegaly patients

Independent variables	Vitamin E $R^2 = 0.68$			
	ß	95% CI		*p
		lower bound	upper bound	
TC	0.043	0.025	0.060	<0.001
TG	0.024	0.014	0.034	<0.001
APOA1	0.031	0.004	0.058	0.024

Multiple regression analysis was used to define the independent association of vitamin E.
ß stands for the unstandardized regression coefficient.
* p <0.05 was considered significant.
CI, confidence interval; TC, total cholesterol, TG, triglyceride; APOA1, apolipoprotein A1.

min E levels between the acromegaly and control group. While vitamin C levels were not significantly associated with anthropometric and laboratory parameters in the acromegaly group, vitamin E levels were found to be associated with total cholesterol, triglyceride, LDL-C, HDL-C, APO A1, APO B in both the acromegaly and control groups.

It is known that endothelial dysfunction develops in patients with acromegaly and this is associated with increased cardiovascular risk. Anagnostis et al. showed increased oxidative stress and decreased total antioxidant capacity in patients with acromegaly. Total antioxidant capacity (TAC), catalase activity and glutathione concentration for antioxidative capacity; and total oxidized glutathione and thiobarbituric acid reactive substance (TBARS) were measured to show oxidative stress (Anagnostis *et al.* 2013). Nitric oxide (NO) and endothelial NO synthase activity have been shown to decrease in GH overexpressing mice and acromegalic patients (Andersson *et al.* 2006; Ronconi *et al.* 2005; Paisley *et al.* 2009). Increased TBARS levels as a marker of lipid peroxidation have been demonstrated in patients with acromegaly, suggesting that they may be associated with atherosclerosis (Boero *et al.* 2010; Yarman *et al.* 2003). In their study Nishizawa et al. found TBARS levels increased in GH-transgenic rats and showed that tissue oxidative stress damage was increased in vascular smooth muscle cells and cardiomyocytes in the aorta of these rats. Serum TBARS and 8-hydroxy-2-deoxyguanosine (8-OHdG) levels have been shown to increase in patients with acromegaly (Nishizawa *et al.* 2012).

Unlike these studies showing increased oxidative stress in acromegaly; Boero et al. did not observe any differences in ceruloplasmin levels, myeloperoxidase activity and TBARS levels between the acromegaly and control group (Boero *et al.* 2010). Ozkan et al. did not find a significant difference when TAC, high mobility group box 1 (HMGB1) and oxidized LDL values in the acromegaly group were compared to the values in the control group. The interpretation of those authors was that oxidative stress does not contribute to early atherosclerosis observed in acromegaly (Ozkan *et al.* 2015).

Ilhan et al. found that the levels of superoxide dismutase (SOD) and TAC showing antioxidative capacity in patients with acromegaly decreased compared to the control group (Ilhan *et al.* 2018). In our study, antioxidant vitamin C was found to be significantly lower in acromegaly patients, but an association between vitamin C levels and metabolic parameters compatible with the literature was not found (Ilhan *et al.* 2018; Abdilla *et al.* 2007).

There is epidemiological data suggesting that increasing the intake of antioxidants by diet reduces the risk of coronary heart disease (CHD) (Kushi *et al.* 1996; Rimm *et al.* 1993). Antioxidant vitamins can provide vascular defense against oxidative stress by protecting NO from inactivation and sweeping free radicals. Antioxidant administration improves the endothelial function of coronary and peripheral vessels in hypercholesterolemia and CHD (Levine *et al.* 1996; Ting *et al.* 1997). No study has been found to evaluate the use of antioxidant vitamins in acromegaly patients. In our study, vitamin C deficiency was found to be significantly higher in the acromegaly group. As a limitation of our study, vitamin C and E intake were not evaluated. There is a need for prospective studies evaluating the effects of vitamin C on endothelial dysfunction in patients with acromegaly.

In our study, vitamin E levels did not show a significant difference between the acromegaly and control group, whereas vitamin E levels were found to be associated with total cholesterol, triglyceride, LDL-C, HDL-C, APO A1, APO B in both the acromegaly and control groups. Lopes et al found a positive correlation between vitamin E and triglyceride levels (Lopes *et al.* 2004). Gupta et al also found a positive correlation between vitamin E levels and triglyceride and LDL levels (Gupta *et al.* 2009). However, Amani et al. found a negative correlation between vitamin E levels and total cholesterol, triglyceride, VLDL, and LDL levels in type 2 diabetic patients (Amani *et al.* 2015).

In conclusion, in our study, vitamin C level was significantly lower in the acromegaly group compared to the level in the control group. There was no significant difference in vitamin E levels between the acromegaly

and control group. In our study, vitamin C levels were not found to be significantly associated with anthropometric and laboratory parameters in the acromegaly group; however, vitamin E levels were associated with total cholesterol, triglyceride, LDL-C, HDL-C, APO A1, APO B in both the acromegaly and control groups. Further studies are needed to investigate the effects of intake of separate and combined vitamin C and E vitamins on insulin resistance and lipid parameters in acromegaly.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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