

Low Levels of Cystatin C in Patients with Acromegaly

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Research Article

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Abstract

Background: Cyst C is a cysteine protease inhibitor produced by all nucleated human cells. Studies show that Cyst C levels are associated with increased risk of cardiovascular events.

Aim: We aimed to figure out Cyst C levels in acromegaly patients and to compare with control subjects who don't have acromegaly.

Methods: Forty-five subjects (24 female, 21 male, mean ages of 48.4 ± 10.3) with acromegaly and 37 gender and age matched subjects (25F, 12 M, mean ages of 50.0 ± 8.0) as control group were recruited. Acromegaly patients were classified into two groups as active acromegaly (AA, n=28) and controlled acromegaly (CA, n=17). Demographic, anthropometric and laboratory values were recorded. Framingham Coronary Heart Disease Risk Score was used to estimate risk of heart attack in 10 years. Framingham Risk Score was calculated from the web site of www.mdcalc.com/framingham-coronary-heart-disease-risk-score. Serum Cyst C levels were measured with N latex Cystatin C kit by using latex-enhanced immunonephelometry method. Results Cystatin C levels were significantly lower in the acromegaly group when compared to the control group (0.632 ± 0.174 mg/L, 0.729 ± 0.117 mg/L as mean values, respectively, p=0.005). When multiple regression analysis was performed; it was found that only age, homocysteine and GFR.cyst (ß coefficient=-0.005 p<0.001, ß coefficient=-0.009 p<0.001, ß coefficient=0.009 p=0.001, respectively) were independent determinants of the Cystatin C levels in the acromegaly group (R2=0.882).

Conclusions: Cystatin C levels were significantly lower in the acromegaly group when compared to control group. Cystatin C levels were independently associated with homocysteine levels.

Keywords: Acromegaly; Cystatin C; Cardiovascular risk

Introduction

Acromegaly is a rare disease characterized by excessive growth hormone (GH) and insulin like growth factor-1 (IGF-1) secretion mostly caused by pituitary adenoma [1]. Acromegaly is associated with insulin resistance, type 2 diabetes, hypertension, dyslipidemia and abdominal adiposity which are increased risk factors for cardiovascular mortality in acromegaly [2]. It is stated that there is cardiac hypertrophy in acromegaly due to high GH/IGF-1 levels [2]. Whereas whether prevalence of coronary artery disease is increased in acromegaly is controversial [3-5]. Akutsu et al. [4] demonstrated that acromegaly per se did not increase the risk of the coronary artery disease.

Cystatin C (Cyst C) is an alternative molecule used for estimation of glomerular filtration rate [6]. It is freely filtered by the glomeruli and is less affected by the age, gender and muscle mass compared to creatinine [7]. Cyst C is a cysteine protease inhibitor produced by all nucleated human cells [8].

Cyst C was found to be a strong predictive marker for the cardiovascular events in older population and in type 2 diabetic patients [9-11]. Qing et al. [12] showed that Cyst C was associated with asymptomatic coronary artery disease in patients with metabolic

syndrome. Imai et al. [13] depicted that higher Cyst C concentrations were correlated with early stage coronary atherosclerotic plaques.

Studies show that Cyst C levels are associated with increased risk of cardiovascular events. So, we aimed to figure out Cyst C levels in acromegaly patients by comparing to subjects who had no acromegaly and same Framingham Risk Score as with acromegaly patients. Secondly, our aim was to investigate the association of Cyst C levels with other cardiovascular risk factors and parameters.

Materials and Methods

Forty-five subjects (24 F, 21 M, mean ages of 48.4 ± 10.3) of acromegaly patients who were followed-up in Ege University Hospital Endocrinology Clinic were recruited for this study. Acromegaly was diagnosed according to the criteria if there was failure of suppression of serum GH concentration below 1 mg/mL after 75-g oral glucose tolerance test (OGTT) together with fasting serum IGF-1 concentrations above the normal ranges for age and gender [14].

Acromegaly patients were classified into two groups as active acromegaly (AA) and controlled acromegaly (CA) based on the criteria in which 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/m L and IGF-1 values were in the reference ranges for age and gender [14,15].

Twenty-eight of the acromegaly patients were AA and 17 of them were CA patients. The control group without acromegaly consisted of 37 gender and age matched subjects (25F, 12 M, mean ages of 50.0 ± 8.0). The control group was similar with acromegaly group as far as Framingham Risk Score (FRS) was concerned. The subjects with renal and liver dysfunction were excluded. Written informed consent was obtained from all participants.

Detailed medical history was recorded including demographic data, duration of acromegaly, smoking history, comorbidities, use of medication, surgery and radiotherapy history. Physical examination was performed for each subject. Duration of acromegaly was 48 months (1-336) as median (min-max). Thirty-eight of 45 (84.4%) patients were treated with surgery, 7 (15.5%) were treated with radiotherapy. As far as medical therapy was concerned, 31 (68.8%) of acromegaly patients were on medical therapy. Thirteen of 43 (28.8%) acromegaly patients had hypopituitarism which was treated with hormone therapies. Out of 45, 6 acromegaly patients had one hormone deficiency and 7 acromegaly patients had more than one hormone deficiencies

Hypertension was defined as follows: systolic blood pressure (SBP) was \geq 140 mmHg, diastolic blood pressure (DBP) was \geq 90 mmHg or current use of antihypertensive medication. Dyslipidemia was defined as follows: serum total cholesterol levels were \geq 200 mg/dL; serum triglyceride levels were \geq 150 mg/dL; serum low density lipoprotein cholesterol (LDL-c) levels were \geq 130 mg/dL; serum high density lipoprotein cholesterol (HDL-c) levels were <40 mg/dL for male, <50 mg/dL for female subjects or use of statin treatment for dyslipidemia [16].

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 midaxillary line.

Blood samples were collected after overnight fasting for serum lipid profile, fasting blood glucose, creatinine, liver function tests, HbA1c, fasting insulin, high sensitive C reactive protein (hs-CRP). Blood samples stored at -80°C immediately.

The estimate of insulin resistance was calculated using the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) index, with the following formula: insulin resistance=fasting plasma insulin (in micro units per milliliter) × fasting plasma glucose (in millimoles per litre)/22.5.

Framingham Coronary Heart Disease Risk Score was used to estimate risk of heart attack in 10 years. Framingham Risk Score was calculated from the web site of www.mdcalc.com/framingham-coronaryheart-disease-risk-score.

Glomerular filtration rate based on creatinine (GFR.cre), Cystatin C (GFR.cyst), creatinine and Cystain C together (GFR.cre.cyst) were calcuated by using the www.mdrd.com website.

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 measured with an Immulite 2000 (Siemens) autoanalyzer via chemiluminescence method. Serum Cyst C levels was measured with N latex Cystatin C kit by using latex-enhanced immunonephelometry method. Range of measurement was 0.62-1.11 mg/L.

Statistical Analysis

The Statistical Packages for Social Sciences SPSS verison 21.0 was used for the data analysis. Continous variables were presented as mean \pm standard deviation (SD) or median (min-max) according to distribution pattern. Categorical variables were presented as numbers and percentages. Variable distribution was assessed by the Kolmogorov-Smirnov normality test. Student's t test or Mann-Whitney U test were used for comparison of two groups according to variable distribution. When AA, CA and control group were compared, oneway ANOVA followed by Bonferroni's post-hoc comparison test or Kruskal Wallis U test were used. Categorical variables were performed using Spearman's coefficient. Multiple linear regression analysis (stepwise method) was used to explain the variability of Cyst C levels. A p value of less than 0.05 was accepted as statistically significant.

Results

Demographical, clinical and laboratory parameters of acromegaly and control subjects are shown in Table 1. The two groups were age and gender matched. Hypertension, dyslipidemia and smoking status rates were similar between the acromegaly and the control groups. FRS was not significantly different between groups (p=0.146). Cyst C levels were significantly lower in the acromegaly group when compared to the control group ($0.632 \pm 0.174 \text{ mg/L}$, $0.729 \pm 0.117 \text{ mg/L}$ as mean values, respectively, p=0.005). There were significant difference between AA ($0.615 \pm 0.138 \text{ mg/L}$), CA ($0.660 \pm 0.223 \text{ mg/L}$) and the control ($0.729 \pm 0.117 \text{ mg/L}$) groups as regards Cyst C levels (p=0.012). Cyst C levels were significantly lower in the AA group compared to the control group (p=0.01 AA vs. control).

Variables	Acromegaly	Control	P value	
	n=45	n=37	, and c	
Ages (years) ¶	48.4 ± 10.3	50.0 ± 8.0	0.46	
Gender (F/M)	24/21	24-Dec	0.259	
BMI (kg/m ²)	30.6 ± 5.09	27.0 ± 3.9	0.004 *	
WC (cm)	101.0 ± 11.3	94.8 ± 10.7	0.011*	
FPG (mg/dL)	105.4 ± 20.2	94.6 ± 8.4	0.002 *	
HbA1c (%)	6.0 ± 0.6	5.5 ± 0.4	0.001 *	
HOMA-IR	3.1 ± 2.7	3.0 ± 1.6	0.24	
Total cholesterol (mg/dL)	107.8 ± 39.1	210.1 ± 38.3	0.157	
Triglyceride (mg/dL)	116.6 ± 66.3	118.5 ± 52.7	0.412	
HDL-C (mg/dL)	55.3 ± 13.8	57.7 ± 15.1	0.455	
LDL-C (mg/dL)	119.1 ± 66.3	128.5 ± 32.7	0.412	

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Smoking (+/-)	18/27	8/29	0.097
	40%	21.60%	
Hypertension (+/-)	15/30	10/27	0.632
	33.30%	27%	
Dyslipidemia (+/-)	27/18	22/15	0.569
	60%	59.40%	
FRS	2.2(0-19)	1.5(0.1-16.8)	0.146
Fibrinogen (mg/dL)	374.9 ± 73.6	340.3 ± 53.7	0.001 *
hsCRP (mg/dL)	0.107(0.015-1.542)	0.219(0.024-1.298)	0.006 *
Uric acid (mg/dL)	4.5 ± 1.2	4.4 ± 1.03	0.478
Homocysteine (µmol/L)	10.7 ± 2.8	12.0 ± 4.5	0.063
Creatinine (mg/dL)	0.72 ± 0.18	0.72 ± 0.14	0.968
GFR.cre (ml/dak/1.73 m ²)	106.0(45.0-131.0)	101.3(72.0-121.0)	0.191
GFR.cyst (ml/dak/1.73 m ²)	117.3 ± 17.1	109.0 ± 14.9	0.027
GFR.cre.cyst (ml/dak/1.73 m ²)	113.7 ± 17.5	107.4 ± 13.3	0.087
Cystatin C (mg/L)	0.632 ± 0.174	0.632 ± 0.174 0.729 ± 0.117	

Values were expressed as mean ± SD.

Values were expressed percentage (%).

Values were expressed as median, (min-max).

*p<0.05 was significant.

BMI, body mass index; WC, waist circumference, FPG, fasting plasma glucose; HOMA-IR, Homeostasis model assessment-insulin resistance; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; FRS, Framingham Risk Score; hsCRP, high sensitive C reactive protein; GFR.cre, Glomerular filtration rate based on creatinine; GFR.cyst, Glomerular filtration rate based on cystatin C; GFR.cre.cyst, Glomerular filtration rate based on creatinine and cystatin C.

 Table 1: Demographical, clinical and laboratory parameters of acromegaly and control subjects.

While there were 15 type 2 diabetic patients in the acromegaly group, no type 2 diabetic patient was present in the control group. When the type 2 diabetic patients were subtracted from the acromegaly group, analysis showed that Cystatin C levels remained significanly different between the acromegaly and the control groups (0.627 mg/L and 0.743 mg/L as median, respectively, p=0.002).

Demographic, clinical and laboratory parameters of the AA and the CA groups were presented in Table 2. Duration of acromegaly, the rate of hypopituitarism were not different between two groups of acromegaly based on the activity of the disease. While the rate of acromegaly patients who had undergone surgery didn't change but more acromegaly patients were taking medical therapy in AA group (Table 2). There was no significant difference between the AA and CA groups in respect to FRS.

Variables	AA	CA	P value
	n=28	n=17	
Ages (years)	45.0 ± 10.9	53.7 ± 10.5	0.012*
Gender (F/M)	24/21	24/12	0.259
BMI (kg/m2)	31.7 ± 5.6	28.8 ± 3.5	0.040*
WC (cm)	102.6 ± 12.6	98.4 ± 8.6	0.236
FPG (mg/dL)	109.3 ± 19.7	104.2 ± 25.9	0.455
HbA1c (%)	6.0 ± 0.5	6.1 ± 0.8	0.646
HOMA-IR	3.73 ± 3.11	2.08 ± 1.10	0.015*
Smoking (+/-)	13/15	05/12	0.351
	46.40%	29.4%	
Hypertension (+/-)	10/18	05/12	0.752
	64.20%	29.4%	
Dyslipidemia (+/-)	14/14	13/04	0.118
	50%	76.4%	
FRS	2.1(0-19)	2.4(0.6-18.6)	0.406
Duration of acromegaly (months)	42(1-264)	72(6-336)	0.236
Hypopituitarism	08/20	05/12	0.324
	28.5%	29.4%	
Surgical treatment (+/-)	24/04	14/03	0.538
	85.7%	82.3%	
Medical treatment (+/-)	24/04	07/10	0.003*
	85.7%	41.1%	
Radiotherapy (+/-)	06/22	01/16	0.301
	21.40%	5.8%	
Creatinine (mg/dL)	0.67 ± 0.15	0.79 ± 0.20	0.038*
GFR.cre (ml/dak/1.73m ²)	109.6 ± 13.8	94.7 ± 18.4	0.004*
GFR.cyst (ml/dak/1.73m ²)	120.0 ± 13.1	113.1 ± 21.4	0.217
GFR.cre.cyst (ml/dak/1.73m ²)	118.0 ± 12.8	107.0 ± 21.8	0.049*
GH (ng/mL)	3.59(0.44-29.20)	0.50(0.05-1.49)	<0.001*
IGF-1 (ng/mL)	740.1 ± 485.4	175.7 ± 67.3	<0.001*
Cystatin C (mg/L)	0.615 ± 0.138	0.660 ± 0.223	0.005*

Values were expressed as mean ± SD.

Values were expressed percentage (%)

Values were expressed as median, (min-max).

*p<0.05 was significant.

AA, active acromegaly; CA, controlled acromegaly; BMI, body mass index; WC, waist circumference, FPG, fasting plasma glucose; HOMA-IR, Homeostasis model assessment-insulin resistance; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; FRS, Framingham Risk Score; GFR.cre, Glomerular filtration rate based on creatinine; GFR.cyst,

Glomerular filtration rate based on Cystatin C; GFR.cre.cyst, Glomerular filtration rate based on creatinine and Cystatin C.

Table 2: Demographic, clinical and laboratory parameters of the active and controlled acromegaly groups.

According to the correlation analysis, Cyst C levels were associated with age (p=0.010, r=0.380), waist circumference (p=0.002, r=0.344), FRS (p=0.009 r=0.384), creatinine (p<0.001, r=0.516), GFR.cre (p=0.013, r=-0.369), GFR.cyst (p<0.001, r=-0.876), GFR.cyst.cre (p<0.001, r=-0.760), homocysteine (p=0.001, r=0.495) and uric acid (p=0.016, r=0.364) in the acromegaly group. Table 3 shows that Cyst C levels were associated with age, total cholesterol, LDL-c, GFR.cyst and GFR.cyst.cre in the control grup. Cyst C levels were not associated with FRS (p=0.055) and homocysteine levels (p=0.614) in the control group.

Independent	Acromegaly	group	Control group		
variables	r	р	r	р	
Age	0.38	*0.010	0.182	*0.019	
WC	0.344	*0.002	0.125	0.46	
BMI	0.238	0.116	0.206	0.227	
FPG	0.043	0.777	0.176	0.298	
HOMA-IR	0.121	0.43	0.072	0.674	
SBP	0.142	0.351	0.224	0.182	
DBP	0.21	0.185	0.046	0.789	
Total Cholesterol	-0.202	0.182	0.407	*0.013	
LDL-C	-0.202	0.182	0.329	*0.047	
HDL-C	-0.145	0.342	0.272	0.104	
Triglyceride	0.103	0.501	0.017	0.921	
FRS	0.384	*0.009	0.318	0.055	
Creatinine	0.516	*<0.001	-0.009	0.958	
IGF-1	-0.076	0.623	-	-	
GFR.cre	-0.369	*0.013	-0.317	0.059	
GFR.cyst	-0.876	*<0.001	-0.905	*<0.001	
GFR.cyst.cre	-0.76	*<0.001	-0.778	*<0.001	
Fibrinogen	0.152	0.32	0.031	0.36	
hs-CRP	0.16	0.295	0.214	0.255	
Homocysteine	0.495	*0.001	0.086	0.614	
Uric acid	0.364	*0.016	0.148	0.397	

Spearman correlation analysis was used. r stands for correlation coefficient.

*p<0.05 was considered significant.

WC, waist circumference; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FRS, Framingham Risk Score; IGF-1, insulin like growth factor-1; GFR.cre, Glomerular filtration rate

based on creatinine; GFR.cyst, Glomerular filtration rate based on Cystatin C; GFR.cre.cyst, Glomerular filtration rate based on creatinine and Cystatin C; hs-CRP, high sensitive C reactive protein.

Table 3: Spearman correlation analysis for Cystatin C in the acromegaly and the control groups.

When multiple regression analysis was performed; it was found that only age, homocysteine and GFR.cyst (β coefficient=-0.005 p<0.001, β coefficient=-0.009 p<0.001, β coefficient=0.009 p=0.001, respectively) were independent determinants of the Cyst C levels in the acromegaly group (R²=0.882) (Table 4).

Independent variables	Cystatin C Spearman's correlation analysis		Cystatin C Multiple regression analysis			
		r p	β	95% CI		p
	r			Lower bound	Upper bound	
Age	0.38	0.01	-0.005	-0.006	-0.003	<0.001
FRS	0.384	0.009	-			
WC	0.344	0.002	-			
Creatinine	0.516	<0.001	-			
GFR.cre	-0.369	0.013	-			
GFR.cyst	-0.876	<0.001	-0.009	-0.010	-0.008	<0.001
GFR.cyst.cre	-0.76	<0.001				
Homocyst	0.495	0.001	0.009	0.004	0.014	0.001
Uric acid	0.364	0.016				

Spearman correlation analysis was used. r stands for correlation coefficient. Multiple regression analysis was used to define the independent association of Cystatin C with age, FRS, WC, creatinine, GFR.cre, GFR.cyst, GFR.cre.cyst, homocysteine, uric acid.

β stands for the unstandardized regression coefficient.

*p <0.05 was considered significant.

Cl, confidence interval; FRS, Framingham Risk Score; WC, waist circumference; GFR.cre, Glomerular filtration rate based on creatinine; GFR.cyst, Glomerular filtration rate based on Cystatin C; GFR.cre.cyst, Glomerular filtration rate based on creatinine and Cystatin C

Table 4: Spearman correlation analysis and multiple regression analysis for Cystatin C levels in acromegaly patients.

Discussion

We have shown for the first time that Cyst C levels were significantly lower in subjects with acromegaly compared with the control group. Age, GFR.cyst and homocysteine levels were independent predictors of Cyst C levels in the acromegaly patients.

The studies in general and specific populations like diabetic ones show that high Cyst C levels are associated with increased cardiovascular risk [13]. Cyst C levels which were associated with homocysteine levels pointing to the cardiovascular risk were significantly lower in the acromegaly group. Acromegaly is already known to be associated with hypertension, dyslipidemia, type 2 diabetes which increases the cardiovascular risk. In our study, acromegaly group had similar FRS with the control group but while the acromegaly group had type 2 diabetic subjects, the control group did not have. When diabetic patients were subtracted, analysis showed that Cyst C levels were still significantly lower in the acromegaly group compared with the control group.

In a prospective cohort study performed by Luc et al. [17] showed that plasma Cyst C levels were associated with the incidence of myocardial infarction, coronary death and angina. Cyst C was found to be positively associated with BMI, LDL-c, triglycerides and fibrinogen, C reactive protien (CRP), interleukin-6 (IL-6), tumor necrosis factoralpha (TNF-alpha) and negatively associated with HDL-c. The association of high Cyst C levels with cardiovascular disease may be related to the inflammatory process in the arteries. As CRP, IL-6 and TNF-alpha were associated with Cyst C, inflammatory cells in the atherosclerotic lesions may be inducing the secretion of Cyst C [17]. Cyst C that is endogenous inhibitors of cathepsins may be increasing as a compensatory mechanism to balance the effect of cathepsins which have pro-atherogenic activity [18]. In our study, while Cyst C levels were associated with FRS in the acromegaly group, Cyst C was not associated with FRS in the control group.

It was shown that increased Cyst C levels were associated with high BMI and obesity [19-21]. Cyst C levels were also associated with waist circumference as a marker of visceral adiposity [20]. In agreement with the literature, we figured out that high Cyst C levels were associated with high waist circumference in the acromegaly group. However, it was figured out waist circumference was not an independent predictor for the Cyst C levels in the acromegaly group when other variables were pooled in the multiple regression analysis. Age is another factor influencing the Cyst C levels in which Cyst C levels are increased by 0.047 mg/L for every 10 years of age [22]. Age was found to be one of the independent predictors of the Cyst C levels in the acromegaly group.

In the literature, there are two studies regarding to Cyst C levels in the acromegaly. One of them by Aulinas et al. [23] showed that Cyst C levels were not significanty different between the acromegaly and the control groups. In this study, epicardial adipose thickness (EAT) and Cyst C levels as predictors of increased cardiovascular risk were evaluated in the acromegaly patients. While increased EAT index and Cyst C levels were associated with the coronary artery disease in the acromegaly group, this association was not observed in the control group. But, they showed that acromegaly patients had low coronary risk based on the data obtained by multi-detector computed tomography scanner. As a limitation to our study, we didn't perform any interventional or imaging radiological methods to evaluate coronary status of the subjects. We hypothesize that acromegaly per se may not be increasing the cardiovascular risk. Akutsu et al. [4] followed-up acromegaly patients about 4.5 years to evaluate the development of coronary artery disease from new onset of acromegaly through treatment. They observed that coronary artery disease risk was low in the acromegaly group at the beginning and remained stable after acromegaly treatment when compared to the control group by depicting lower coronary artery calcification in the acromegaly group. So, they suggested that GH excess independent from other risk factors did not create an additional risk for coronary artery disease. In agreement with this study, Otsuki et al. [24] also showed that carotid intima media thickness was lower in the acromegaly group than the control group. In the acromegaly group, patients with atherosclerosis had higher IGF-1 levels than acromegaly patients without atherosclerosis. Besides, CIMT was associated negatively with the IGF-1 levels in the acromegaly group. They suggested that IGF-1 may be protective in subjects with acromegaly in respect to atherosclerosis.

In the study of Aulinas et al. [23], they found that Cyst C levels were associated with low HDL-c, high triglyceride, FRS and EAT index. In our study, Cyst C levels were found to be positively associated with age, FRS, waist circumference, creatinine, homocysteine and uric acid and associated negatively with GFR.cre, GFR.cyst, GFR.cyst.cre in the acromegaly group. But Cyst C levels were associated only with age, high total cholesterol, high LDL-c and were associated with GFR.cyst, GFR.cyst.cre negatively in the control group.

The other study in the literature regarding to Cyst C levels in acromegaly by Sze et al. [25] searched for the effect of GH on Cyst C levels in newly diagnosed acromegaly patients and after transsphenoidal surgery leading to normal GH levels. Acromegaly is known to be associated with lower creatinine and higher GFR levels [26]. As an interesting finding Cyst C decreased after acromegaly treatment although GFR decreased with the treatment of acromegaly. They suggested that GH was another parameter influencing the Cyst C levels independent of renal function. Sze et al. [25] indicated that correction of insulin resistance and decrease in BMI may have been factors affecting the decrease of Cyst C levels in subjects with acromegaly after surgical treatment.

The fact that the subjects with the diagnosis of acromegaly were not new onset ones could be a limitation for our study. Medical treatment for the acromegaly may be altering the Cyst C levels in the acromegaly group. Based on the multiple regression analysis; age, homocysteine and GFR.cyst are independent predictors for the Cyst C levels in the acromegaly group. Holy et al. [27] depicted that high homocysteine and Cyst C levels were predictors of cardiovascualr risk in type 2 diabetic patients. Although Cyst C levels were low in the acromegaly group, it was associated with homocysteine which was a cardiovascular risk factor. It may be speculated that low Cyst C levels could reflect low cardiovascular risk in acromegaly patients.

Limitations

Being cross sectional design of the study is another limitation. Prospective studies with large sample size will be helpful to enlighten the association of cardiovascular risk and Cyst C levels in the acromegaly patients.

Conclusion

In conclusion, Cyst C levels were independently associated with homocysteine levels. Cyst C levels could be a useful marker to screen patients with the diagnosis of acromegaly in respect to cardiovascular risk. It has been shown that Cyst C levels were low in the acromegaly patients. The further studies are needed to investigate whether acromegaly per se increase the cardiovascular risk.

Conflict of Interest

The authors have nothing to disclose.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional

and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all participants.

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