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Is urotensin 2 levels related to disease progression in acromegaly

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Abstract

The study aimed to compare serum Urotensin-2 stages in the patients having active acromegaly with healthy individuals and to reveal and discuss the possible effects of UII on vascular changes in acromegaly patients. In this prospective, serum urotensin stages of 30 active acromegalic patients who are followed up in the experienced adult endocrinology center were compared with the serum urotensin stages of 30 healthy volunteers. Patients' IGF-1 along with GH were carefully measured by ECLIA method, and serum urotensin stages, by ELISA method. There was no variation between two groups comparing there age ($p = 0.43$). Patient group, mean GH was 6.60 ng / mL with mean IGF-1 stage of 355.2 ng / mL. The mean urotensin stage was 3.62±2.27 pmol / L in the acromegaly group, 4.82±2.87 pmol / L in the healthy control group. There was no significant positive correlation of urotensin with IGF-1 stages ($r = 0.11$, $p>0.05$). Similarly, the results did not display significant positive correlation urotensin stage with GH ($r = 0.13$, $p>0.05$). Serum urotensin-2 stage was lower in acromegaly patients compared to the healthy group (control) and this variation was not statistically significant.

Keywords: Urotensin-2, acromegaly, vasoconstriction, vasodilation

Introduction

Acromegaly is mostly induced by pituitary adenomas after secreting a high stage of growth hormone. GH (Growth hormone) induce and stimulate the production of insulin-homologous growth factor-1 (IGF-1) on liver. Increased stages of GH + IGF-1 lead to somatic growths with many morbidities [1]. Cardiovascular complications of acromegaly have recently received great attention among scientists.

Cardiac complications include cardiomyopathy characterized by decreased diastolic function with cardiac output at early and advanced stages, along with advanced congestive heart break with dilated cardiomyopathy of later stages [2,3]. Additionally, acromegaly is also related to increased hyperlipidemia, hypertension, and high prevalence of type 2 diabetes mellitus,that can accelerate atherosclerotic diseases. Impairment in cardiac functions that are important determinants of death in acromegaly [4-6].

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Urotensin-2 (UII), another peptide having eleven amino acids. UII was 1st separated and isolated from the neurosecretory system in teleost fish. The days it is established that UII is likewise secreted from human liver, white blood cells, vascular endothelium, heart, thymus, adrenal glands, small intestine, kidneys, spleen and central nervous system . UII receptors were identified in smooth vascular muscle cells [7]. So thherefore, it is proposed that UII plays a role in cardiovascular illness and has been extensively studied [7]. In addition, a correlation between UII stages and essential hypertension has been identified [8]. UII is the strongest vasoconstrictors in human body [9]. However, there is only one clinical study describing the relationship between acromegaly and cardiovascular risk in which high UII stages were related with the severity of cardiovascular disease factors, that also include epicardial fat thickness (EFT) and carotid intima media thickness (cIMT) in acromegalic subjects [10]. In that study, no correlation was found between GH & UII and IGF-1. However, literature data reveals that both acromegaly and urotensin-2 increase cardiovascular mortality. Therefore, we aimed to identify the possible relationship of UII with GH and IGF-1, as well as to investigate the role of UII that is the most common cause of mortality of acromegaly cardiovascular disease.

Materials and Methods

Participants

This study contained all patients having a diagnosis for acromegaly, followed by the Internal diseases and endocrinology clinics and who are still under treatment. The researcher explained all the patients why they were included in the study and received their written consent. A written acceptance was taken from the Medical Ethics Committee of the Fırat University (Project Number: 15, Approval Date, 24.01.2019).

Samples

The prospective study population consisted of 30 patients selected randomly and had active acromegaly (posttreatment or untreated cases or that showed no remission) along with 30 healthy volunteers; who matched for their body mass, sex, index andage, At the time of admission, 3 mL blood samples were taken both from the patients with a diagnosis of acromegaly and from the healthy control group patients, in addition to the blood required for routine examinations. All samples were taken between 0800 and 0900 in the morning, following an 8-hour fasting period. The samples were subjecgted to centrifuge at 3500 rpm for 600 seconds, then taken into eppendorf tubes followed by storing at -80C° till the inception of analysis.

Biochemical Measurements

The IGF-1 and GH stages of the patients were carefully measured in the Immulite 2000 device by the electrochemiluminescence (ECLIA) method. Since these parameters were routinely studied in patients with acromegaly, no additional blood sample was taken.

Urotensin II (UII / UCN2) stages in serum samples, (Human UII / UCN2); Catalog number: 201-12- 5285 Sunred Biological Technology Co., Ltd, Shanghai, CHINA) was studied in agreement with the working po-rotocols mentioned in the respective kit catalogs by Elisa method. The Human UII / UCN2 measurement range after subjecting to elisa kit was: 0.1-15 pmol / L, Intra-Assay: CV value <10%, Inter-Assay: CV value <12%, Sensitivity was 0.055 pmol / L. Automatic washer Bio-Tek ELX50 (BioTek Instruments, USA) was utilized for plate washings, ChroMate, Microplate Reader P4300 device (Awareness Technology Instruments, USA) was utilized for absorbance readings. The Test end results are shown in pmol / L.

Exclusion Criteria

The Patients younger than 18 years or older than 65 years, with an inflammatory disease, pregnant women, chronic diseases, malignancy, with advanced chronic liver risks, history of kidney and heart failure, patients with active psychiatric disease and acromegalic patients who had a curative surgery were not included in the study.

Statistical analysis

All data analyzes were subjected to Statistical Package for the Social Sciences software SPSS version 22.0 (IBMSPSS Inc., Chicago, USA) program using variance analysis anddescriptive statistical methods, Student's t-test equivalents . This study had $p < 0.05$ and was taken statistically significant. The Correlation coefficients with their significance were also calculated using the Pearsons test

Results

The average age in the acromegaly group consisting of 30 patients was 47 (18-64) years. Sixteen of these cases were women (53%), while 14 of them were male (47%). Thirteen of the patients in the control group included in the research were female (43%), and 17 were male (57%). The mean age of the control group was 44. There was non significant difference in the age of two groups comparing age ($p = 0.43$). The mean GH and IGF-I stage was 6.60 ng / mL (0.22-70.00) and 355.2 ng / mL (147-911) in the same order (Table 1). There was no significant difference between the acromegaly and control groups in terms of urotensin levels. The p value was > 0.05 (Figure 1, Table 2). There was no significant positive correlation between the urotensin level and IGF-1 stage ($r = 0,11$). The p value was > 0.05. There was also no positive correlation between the urotensin level and GH ($r = 0.13$). The p value was >0.05 (Table 3)

Table 1. The demographics and laboratory data in the study groups

	Acromegaly (n=30)	Control (n= 30)
Female/Male	16/14	17/13
Mean Age (years)	47	44
Mean creatinine(mg/dL)	0.82	0.94
Mean ALT (U/L)	27	23
GH(ng/mL)	6.60	Normal range
IGF-1(ng/mL)	355.2	Normal range

ALT: Alanin aminotransferaz; GH: Growth hormon; IGF 1: Insulin Growth Factor-1

Table 2. Serum urotensin-2 levels

Group	Serum urotensin (pmol/L)	P value
Acromegaly	3.62±0.41	p>0.005
Control	4.82±0.52	p>0.005

Table 3. Pearson correlation analyses

Urotensin	IGF-1	BH
r value	0.11	0.13

GH: Growth hormon; IGF 1: Insulin Growth Factor-1

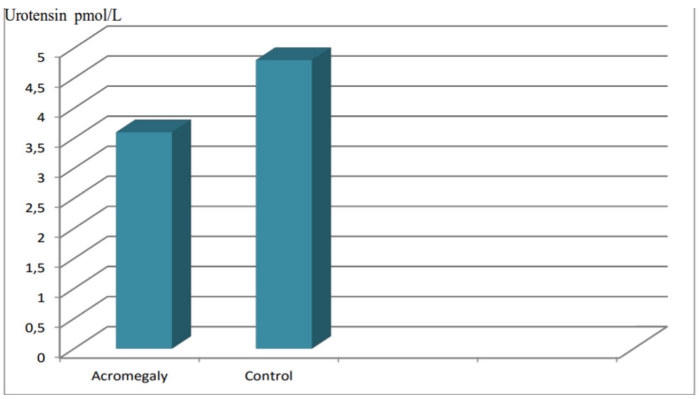

Figure 1. Serum urotensin-2 levels in acromegaly and control group

Discussion

The study aimed to compare serum Urotensin-2 stages in the patients having active acromegaly with healthy individuals and to reveal and discuss the possible effects of UII on vascular changes in acromegaly patients. Urotensin-2, which is among the widely known vasoconstrictor peptides, is a peptide molecule similar to somatostatin [11]. Their role in human physiology is yet to beunderstood. In humans, increased plasma UII concentrations have been associated with diabetes and kidney chronic heart failure patients [12]. While urotensin 2 shows vasoconstriction effect in diseases like heart failure, or hypertension vasodilation was observed in healthy people. Plasma urotensin 2 levels were found to be high in renal failure, heart failure, portal hypertension and hypertension so it is considered a hormone by some researchers [13-15]. Urotensin 2 has also been shown in studies that cause hypertrophy in the heart, reflex tachycardia, fibrosis, coronary vasoconstriction and cardiomyositis [16]. It is well established that hypertension affects the UII stages and this issue was subjected to a number of studies [8, 17]. In few analyses, increased UII stages have been identified in hypertensive patients [8]. However, some other studies have shown that there is no significant variation between patients together with or without any hypertension [17]. Mosenkis et al. [18] denied the existence of a relationship between UII stage and blood hypertension and Bottrill et al. [19] announced that UII is a strong and endothelium-dependent vasodilator. Affolter et al. [20] intervened with saline placebo and intravenous UII on10 healthy males (volunteers), and identified that intravenous UII infusion had no effect on arterial stiffness or systemic hemodynamic, and concluded that its physiological role had low short-term regulation of blood pressure or UII vascular tone in humans. Debiec et al. [21] examined the UII system in the control (genetic) of kidney function and blood pressure. They found that there was no variation in renal expression of the UII system between hypertensive and normotensive subjects. This result suggests that genes of UII system are unlikely to effect a significant participation in the genetic control of human kidney function and blood pressure. Xie et al. [22] conducted a possible cohort study related with UII and hypertension risk which included the largest patient number. They showed that UII presumably take part in the growth and development of hypertension. Zyang et al. [23] suggested that the effect of the endothelium and the effect of UII may be caused by modulating it with vasorelaxant factors derived from endothelium such as nitric oxide. Therefore, endothelial dysfunction might lead to the vasoconstrictor effect of UII. There is only one clinical study describing the relationship between acromegaly and cardiovascular risk. The study aimed to determine if circulating UII stages had changed in patients with acromegaly and also to define relationship between carotid intima media thickness (cIMT) and UII and and epicardial fat thickness (EFT), that are hormonal (GH and IGF-1) or cardiometabolic parameters. there was a significant increase in circulating UII stages compared to the healthy control group in both active and controlled acromegaly cases. No significant variation in circulating UII stages between controlled and active acromegaly groups. In patients with acromegaly, both EFT and cIMT increased significantly compared to controls. UII showed positive correlation with HOMA-IR, BMI, EFT and cIMT. No correlation war identified between UII and GH, IGF-1 (10). In our prospective study, we found that serum urotensin stage was lower in acromegaly patients when compared to the volunteers in healthy group (control) and this variation was not statistically significant. There was no significant positive correlation between and GH and Urotensin stage, IGF-1 & stages. There is only one study on the correlation between acromegaly and the urotensin. Therefore, in the discussion section, we focused on the effects of acromegaly on vascular system. Urotensin 2 shows its effects via this system, and therefore the studies on this subject were taken into account. Study Limitations, our study has several limitations. These can be listed as the low number of patients, the cross-sectional study design, the heterogeneous group of patients, the absence of additional markers related to the vascular system and the lack of measurement of urotensin 2 stages after treatment.

Conclusion

In conclusion, as a result, in our study, serum urotensin 2 stages were identified low in the patients with acromegaly. The causal connection between UII and acromegaly could not be established. This is attributed to the diverse literature data on urotensin 2, its release from most tissues in the body, its different effects on systems and tissues, its vasodilator effect on the endothelium and its vasoconstrictive effect due to the damage of this tissue.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The researcher explained all the patients why they were included in the study and received their written consent. A written acceptance was taken from the Medical Ethics Committee of the Fırat University (Project Number: 15, Approval Date, 24.01.2019).

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