İstanbul Med J 2020; 21(1): 13-7
DOI: 10.4274/imj.galenos.2019.19794

The Evaluation of Thrombospondin 1 Levels in Patients with Acromegaly

Akromegali Hastalarında Thrombospondin 1 Düzeylerinin Değerlendirilmesi

Mustafa Demirpençe[1], Hamiyet Yılmaz[1], Ayfer Çolak[2], Merve Zeytinli[2], Demet İnce[2], Barış Önder Pamuk[3]

[1]University of Health Sciences, İzmir Tepecik Training and Research Hospital, Clinic of Internal Medicine Division of Endocrinology and Metabolism, İzmir, Turkey
[2]University of Health Sciences, İzmir Tepecik Training and Research Hospital, Clinic of Clinical Biochemistry, İzmir, Turkey
[3]İzmir Katip Çelebi University, Atatürk Training and Research Hospital, Clinic of Internal Medicine, Division of Endocrinology and Metabolism, İzmir, Turkey

ABSTRACT

Introduction: Acromegaly is a rare disease caused by overproduction of growth hormone (GH) secreted from a benign pituitary adenoma. It has been shown in many studies that the incidence of cancer is increased in patients with acromegaly with increased GH and insulin-like growth factor-1 (IGF-1). Especially, colon cancer is more common. Thrombospondin-1 (TSP-1) is a glycoprotein that is thought to play an important role in cancer formation. This study aimed to evaluate circulating TSP-1 levels in patients with acromegaly.

Methods: This study was a case-control study. Fifty-two patients with active acromegaly with GH <1 and IGF-1 values higher than age were included in the study. Twenty-six age and gender-matched volunteers without acromegaly were included as the control group. Height, weight, and biochemical evaluations of all volunteers and acromegaly patients were performed. Serum TSP-1 levels were evaluated by ELISA.

Results: The median age and gender distribution of the two groups were similar (p=0.313, p=0.148, respectively). Fasting plasma glucose and lipid parameters were not different between the groups. GH and IGF-1 were higher in patients with acromegaly (p=0.001 for both). Although TSP-1 levels were lower in the acromegaly group, the differences were not statistically significant (p=0.183). There was no correlation between TSP-1 and GH (p=0.265) and IGF-1 (p=0.131).

Conclusion: It is known that the prevalence of cancer, especially colon cancer, is increased in patients with acromegaly. It has been shown in many studies that decreased TSP-1 level plays a role in cancer development. In particular, its association with somatostatin receptors suggests that it may play an important role in the future follow-up of acromegaly and treatment options. We think that studies evaluating TSP-1 levels in patients with acromegaly should be performed, especially in large patient groups diagnosed with colon cancer. Our study is the first to evaluate the level of TSP-1 in patients with acromegaly.

Keywords: Acromegaly, thrombospondin, colon cancer

ÖZ

Amaç: Akromegali genellikle iyi huylu hipofiz adenomundan salgılanan büyüme hormonunun (BH) aşırı üretimi sonucu ortaya çıkan nadir bir hastalıktır. Akromegali hastalarında artmış BH ve insülin benzeri büyüme faktörü-1 (IGF-1) ile kanser görülme sıklığının da arttığı birçok çalışmada gösterilmiştir. Özellikle kolon kanserleri daha sık görülmektedir. Trombospondin-1 (TSP-1) kanser oluşumunda önemli bir rol oynadığı düşünülen bir glikoproteindir. Bu çalışmada akromegali hastalarında dolaşımdaki TSP-1 düzeylerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu bir olgu kontrol çalışmasıdır. Çalışmamıza takip altında olan BH <1 olan ve yaşa göre beklenen IGF-1 değeri yüksek olan aktif akromegali olan 52 hasta dahil edildi. Kontrol grubu olarak yaş ve cinsiyet yönünden benzer, akromegali tanısı olmayan 26 gönüllü alındı. Tüm gönüllüler ve akromegali hastalarının boy, kilo ve biyokimyasal değerlendirmeleri yapıldı. Serum TSP-1 düzeyleri ELISA ile değerlendirildi.

Bulgular: İki grupta medyan yaş ve cinsiyet dağılımı benzerdi (sırasıyla; p=0,313, p=0,148). Açlık plazma glukozu ve lipid parametrelerinde gruplar arasında anlamlı fark yoktu. GH ve IGF-1 akromegali hastalarında daha yüksekti (Her ikisi de, p=0,001). TSP-1 düzeyleri akromegali grubunda düşük olsa da, farklar istatistiksel olarak anlamlı değildi (p=0,183). TSP-1 ile BH (p=0,265) ve IGF-1 (p=0,131) arasında korelasyon saptanmadı.

Sonuç: Akromegali hastalarında kanser ve özellikle de kolon kanseri prevalansının arttığı bilinmektedir. Azalmış TSP-1 düzeyinin kanser gelişiminde rol oynadığı birçok çalışmada gösterilmiştir. Özellikle somatostatin reseptörleri ile ilişkili olması gelecekte akromegali takibinde ve tedavi seçenekleri konusunda önemli bir rol oynayabileceğini düşündürmektedir. Akromegali hastalarında TSP-1 düzeyinin değerlendirildiği ve özellikle kolon kanseri tanısı almış olan geniş hasta gruplarında değerlendirildiği çalışmalar yapılması gerektiğini düşünüyoruz. Çalışmamız akromegali hastalarında TSP-1 düzeyinin değerlendirildiği ilk çalışma olması yönünden değerlidir.

Anahtar Kelimeler: Akromegali, thrombospondin, kolon kanseri

Address for Correspondence/Yazışma Adresi: Mustafa Demirpençe MD, University of Health Sciences, İzmir Tepecik Training and Research Hospital, Clinic of Internal Medicine Division of Endocrinology and Metabolism, İzmir, Turkey
Phone: +90 505 525 23 37 **E-mail:** dr.mustafa.demirpence@gmail.com **ORCID ID:** orcid.org/0000-0002-6813-0253

Cite this article as/Atıf: Demirpençe M, Yılmaz H, Çolak A, Zeytinli M, İnce D, Pamuk BÖ. The Evaluation of Thrombospondin 1 Levels in Patients with Acromegaly. İstanbul Med J 2020; 21(1): 13-7.

Received/Geliş Tarihi: 09.03.2019
Accepted/Kabul Tarihi: 29.10.2019

Introduction

Acromegaly is a clinical disease caused by excessive growth hormone (GH) secretion. The most common cause of acromegaly is GH secreting benign adenoma in the anterior pituitary. The onset of acromegaly is insidious and generally slow. The most classic clinical feature of acromegaly is acral growth with the growth of hands and feet and coarse facial features. The clinical features of acromegaly are caused by increased GH and resulting in liver-derived insulin-like growth factor-1 (IGF-1) secretion (1). The prevalence of acromegaly ranges from 2.8-13.7, with an annual incidence of 0.2-11.1 cases/100.000 individuals. However, the actual incidence is estimated to be higher (2,3). The most common cause of morbidity and mortality in acromegalic patients is cardiovascular complications and cancer. There are three treatment methods in the management of acromegaly, including surgery, medical, and radiotherapy. Treatment targets in acromegaly are keeping serum IGF-1 levels within age- and gender-appropriate range values and GH levels below <1.0 ng/mL (4). In patients with uncontrolled and delayed diagnosis of acromegaly, colon, thyroid, breast, and prostate cancers are more common, but many organs are reported to have increased cancer risk (5). In a meta-analysis in which 23 studies were evaluated, an increased risk was observed in colorectal, breast, thyroid, gastric, and urinary system cancers in acromegaly patients without treatment response (6). It has been reported that acromegaly patients in whom target values are not reached or who are not treated may have an increased risk for hyperplastic polyps, adenomas, and cancer in the digestive system and especially in the colon (7,8). In patients with acromegaly, high serum IGF-1 levels were associated with the presence of colorectal neoplasms, increased prevalence of colorectal adenoma, and adenocarcinoma (9,10).

The extracellular matrix (ECM) is a complex supporting structure between the cells in mammalian tissue. ECM consists of proteins that are reshaped continuously due to the balance between synthesis, storage, and disintegration. Changes in the interaction between cells and ECM may facilitate the formation and progression of cancer cells (11). Thrombospondins (TSP-1 to -5) are glycoproteins secreted into the ECM (12). The first identified glycoprotein is TSP-1. TSP-1 is a 450-kDa protein that is considered an inhibitor of angiogenesis. TSP-1 plays an essential role in pathological angiogenesis, inflammation, and cancer formation. Studies have shown that TSP-1 inhibits cell proliferation and induces apoptosis. It is thought that TSP-1 performs some anti-angiogenic functions via receptor CD36 (13).

Somatostatin (SST) is a 14-amino acid peptide hormone released from the D-cells of the islets of the pancreas and the hypothalamus. It is also known as a factor that inhibits the release of GH from the pituitary gland. SST is also an inhibitory hormone in the pancreas and gastrointestinal tract. In addition to exocrine and endocrine functions, it has a vasoconstrictor effect and an inhibitory effect on intestinal absorption (14). SST receptors (SSTRs) are numbered between 1 and 5. Each receptor is more densely present in different tissues. Especially, SSTR2 and SSTR5 are more common in pituitary adenomas, and many endocrine tumors (15). SST analogs and SSTR antagonists used in the medical treatment of acromegaly are particularly useful on these SSTR2 and SSRT5 (4). In a study by Laklai et al. (16) including patients with pancreatic cancer, decreased SSTR2 activity was shown in patients with low TSP-1. Low SSTR2 activity may also be effective in the treatment response of acromegaly patients. Decreased levels of TSP-1 may make it challenging to control IGF-1 and GH values in acromegaly. Uncontrolled acromegaly increases the risk of malignant diseases.

In this study, we aimed to evaluate the TSP-1 level, which is thought to be an effective molecule in cancer formation and progression in acromegaly patients. This is the first study in the literature to evaluate the level of TSP-1 in acromegaly patients.

Methods

This study included 52 uncontrolled acromegaly patients with high IGF-1 values according to age or with random GH level >1 who were followed in the outpatient clinic of Endocrinology and Metabolic Diseases Clinic of our hospital between September 1, 2017, and September 1, 2018. Also, 26 age- and gender-matched controls without acromegaly were included. Participants with a history of malignant disease, pregnancy, and those under 18 years of age were not included in the study.

Ethical Evaluation

The Ethics Committee of University of Health Sciences, İzmir Tepecik Training and Research Hospital approved this study on 17.08.2017 (decision no: 7). Our study was consistent with the Declaration of Helsinki. Written consent was obtained from all participants.

Biochemical Evaluation

Blood samples were taken from all volunteers following 10 hours of fasting by venous puncture technique with ethylene diamine tetraacetic acid without the need for anticoagulants for biochemical tests. Serum samples were obtained after centrifugation of blood samples at 4.000 rpm for 10 minutes. Obtained serum samples were put into polypropylene tubes and stored at -80 °C until biochemical analysis. Serum GH and IGF-1 levels were measured by chemiluminescent immunometric assay (Immulite XPi, Siemens, Germany). The normal range of IGF-1 was age-dependent (21-25 years: 116-358; 26-30 years: 117-329; 31-35 years: 115-307; 36-40 years: 109-284; 41-45 years: 101-267; 46-50 years: 94-252; 51-55 years: 87-238; 56-60 years: 81-225; 61-65 years: 75-212 years, 66-70 years: 69-200; 71-75 years: 64-188; 76–80 years: 59-177 ng/mL). Serum concentrations of TSP-1 were determined by solid-phase ELISA (Quantikine ELISA human TSP-1 immunoassay kit, R&D systems, Minneapolis, MN, USA). The sensitivity limit of the test was 0.355 ng/mL. The intra-variability and inter-assay coefficients of the test were below 6.7% and 6.2%, respectively.

Statistical Analysis

All data were analyzed using SPSS version 15 (SSPS, Inc., Chicago, Illinois, USA). An alpha level of 0.05 was used to determine statistically significant differences. Shapiro-Wilk tests were performed to evaluate the normality of distribution. Results were reported as mean ± standard deviation (SD) for normally distributed continuous variables, and as minimum, maximum, and median for non-normally distributed variables. Variables between acromegaly and control groups were compared by independent t-test. The non-normally distributed variables

were compared by the Mann-Whitney U test between acromegaly and control group. Non-parametric Spearman test was used for correlation analysis. In this study, $p<0.05$ was considered statistically significant.

Results

A total of 78 volunteers, including 52 active acromegaly patients and 26 controls, were included in the study. There was no difference between sex and gender distributions in both groups. There was no difference between the groups in terms of rates of type 2 diabetes and hypertension. Demographic and anthropometric data are shown in Table 1. While GH and IGF-1 levels were higher ($p<0.001$, both) in patients with acromegaly, there was no significant difference in other biochemical parameters. Although the median value of the TSP-1 level was lower in the acromegaly group compared to the control group, no statistically significant difference was observed ($p=0.183$). The results are presented in Table 2. There was no significant correlation between TSP-1 and GH ($p=0.265$) and IGF-1 ($p=0.131$). There was no significant correlation between TSP-1 and other parameters. The correlation analysis results between the TSP-1 level and demographic, anthropometric, and biochemical parameters are shown in Table 3.

Discussion

Colorectal neoplasms are known to be a common complication of acromegaly. In a meta-analysis, 701 acromegaly patients and 1573 non-acromegaly controls were evaluated, and it was found that the risk of colon cancer was 4.3 times higher in acromegaly patients compared to the control group (8). However, data on the prevalence of colorectal neoplasms in patients with acromegaly are limited. Also, different factors

Table 1. Comparison of demographic and anthropometric characteristics between acromegaly and control groups

	Acromegaly, n=52	Control, n=26	p
Gender			
Male/Female	27/25	9/17	0.148
Age			
Mean ± SD*, years	45.77±12.37	45.07±14.4	0.313
Type 2 diabetes			
Yes/No	25/27	11/15	0.81
Hypertension			
Yes/No	20/32	10/16	0.60
Systolic blood pressure, mm/Hg**, median (min-max)	119 (92-147)	125 (105-160)	0.093
Diastolic blood pressure, mm/Hg**, median (min-max)	80 (65-105)	147.5 (65-100)	0.284
Weight, kg**, median (min-max)	88.7 (54-158)	79 (55.4-127.1)	0.042
Body mass index, kg/m2**, median (min-max)	30.6 (20.83-50.2)	26.21 (20.35-44.71)	0.179
Waist circumference, cm**, median (min-max)	95 (70-126)	94 (75-118)	0.380

*SD: standard deviation, **min: minimum, max: maximum

Table 2. Comparison of biochemical parameters between acromegaly and control groups

	Acromegaly (n=52) Median (min-max)	Control (n=26) Median (min-max)	p
Glucose, mg/dL	104 (77-338)	96 (77-220)	0.284
LDL, mg/dL	115 (60-208)	123.5 (84-246)	0.309
HDL, mg/dL	49 (20-104)	48 (32-97)	0.867
Triglyceride, mg/dL	134 (31-314)	149 (54-532)	0.539
Total cholesterol, mg/dL	189 (139-307)	218 (155-364)	0.088
Urea, mg/dL	29 (12-86)	27 (16-52)	0.925
Uric acid, mg/dL	4.8 (2.60-7.43)	5.15 (3.20-8.80)	0.245
Creatinine, mg/dL	0.9 (0.6-1.7)	0.9 (0.7-1.3)	0.168
AST, U/L	18 (11-34)	22 (12-45)	0.765
ALT, U/L	14 (7-32)	19 (10-56)	0.243
TSH, mIU/L	1.0 (0.35-3.34)	1.34 (0.37-5.84)	0.137
IGF1, µg/L	408 (95-1357)	210 (60-290)	0.001*
Growth hormone, µg/L	1.9 (0.08-40)	0.115 (0.05-0.90)	0.001*
Thrombospondin-1, ng/mL	840.8 (122.2-9445)	1275.05 (179.8-7418)	0.183

*SD: standard deviation, min: minimum, max: maximum, HDL: high-density lipoprotein, LDL: low-density lipoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TSH: thyrotropin-stimulating hormone, IGF-1: insulin-like growth factor 1

Table 3. Correlation analysis between thrombospondin-1 levels and independent variables

	r	p
Age, years	0.199	0.75
Growth hormone	-0.127	0.265
IGF-1	0.199	0.131
Weight, kg	0.098	0.401
Body mass index, kg/m^2	0.056	0.357
Waist circumference, cm	0.171	0.142
Glucose, mg/dL	0.028	0.802
LDL, mg/dL	0.111	0.335
HDL, mg/dL	-0.090	0.427
Triglyceride, mg/dL	0.088	0.438
Total cholesterol, mg/dL	0.160	0.157
Urea, mg/dL	0.019	0.868
Uric acid, mg/dL	0.121	0.299
Creatinine, mg/dL	0.046	0.688
AST, U/L	0.003	0.977
ALT, U/L	0.032	0.776
TSH, mIU/L	-0.110	0.335

HDL: high-density lipoprotein, LDL: low-density lipoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TSH: thyrotropin-stimulating hormone, IGF-1: insulin-like growth factor 1

have been suggested in the etiopathogenesis of colorectal neoplasms in patients with acromegaly. High serum IGF-1 levels were associated with increased colorectal adenoma. Increased IGF-1 and IGF-binding protein 3 ratio were associated with the prevalence of colon adenocarcinoma (9,10). Among tumor angiogenesis inhibiting agents, TSP-1 is the most well-known molecule. Low TSP-1 levels have been reported in ovarian cancer (17), gastric cancer (18), breast cancer (19), lung cancer (20), renal cell carcinoma (21), and pancreatic cancer (16). Also, a low TSP-1 level was associated with increased tumor invasion and metastasis rate, and it was thought to be effective in the prognosis of malignancies. These studies suggest that low or incomplete expression of TSP-1 is associated with advanced-stage cancer. Also, decreased expression of TSP-1 is associated with poor prognosis in colorectal carcinoma (22-24). In a study by Jo et al. (23), it was observed that TSP-1 was strongly expressed in healthy colon epithelial cells, whereas TSP-1 loss was observed in early colonic adenomas and TSP-1 was not detected in epithelial cells of invasive colon cancer. In a study performed in patients with colon cancer treated with bevacizumab, Marisi et al. (25) found that high TSP-1 level was associated with better clinical outcome. This study suggests that increased circulating levels of TSP-1 can also be used as a marker for evaluating treatment response. In our study, although the median value of the TSP-1 level was lower in acromegaly patients compared to the control group, no statistically significant difference was observed. Low TSP-1 level and SST relationship may make it challenging to control IGF-1 and GH values in acromegaly. In our study, no significant correlation was found between TSP-1 and IGF-1 and GH levels.

Although our study was the first to evaluate TSP-1 levels in acromegaly patients, there were some limitations. First, the sample size was relatively small. Secondly, all patients with a history of cancer were not included in our study in the selection process. Thirdly, this study was carried out in a single tertiary center.

Conclusion

Our study is the first study in the literature to evaluate the level of TSP-1 in acromegaly. It has been shown in many studies that low TSP-1 levels play a role, especially in the development of colorectal cancer. TSP-1 can be used as a marker for assessing treatment response in the future in acromegaly patients and for monitoring increased cancer risk. It may be more appropriate to perform studies evaluating the TSP-1 level with uncontrolled acromegaly patients who were diagnosed with colon cancer.

Ethics Committee Approval: The Ethics Committee of University of Health Sciences, İzmir Tepecik Training and Research Hospital approved this study on 17.08.2017 (decision no: 7).

Informed Consent: Written consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - M.D., B.Ö.P.; Concept - M.D., H.Y., B.Ö.P.; Design - M.D., H.Y., A.Ç.; Data Collection and/or Processing - M.D., H.Y., A.Ç., M.Z., D.İ.; Analysis and/or Interpretation - M.D., A.Ç., M.Z., D.İ.; Literature Search - M.D., H.Y., D.İ., B.Ö.P.; Writing Manuscript - M.D., H.Y., M.Z., B.Ö.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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