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■ Original Article

## Fatty liver in patients with acromegaly

### *Akromegali hastalarında yağlı karaciğer*

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#### ABSTRACT

**Aim:** Patients with acromegaly are at risk of metabolic diseases, such as diabetes mellitus, insulin resistance and hypertriglyceridemia. We aimed to investigate what is effective in the development of non-alcoholic fatty liver disease (NAFLD) in patients with acromegaly.

**Materials and Methods:** 60 (33 female, 27 male) patients with acromegaly, and a healthy control group of 52 persons (27 female and 25 male) were retrospectively studied. Mean age of the patients and the control group were 44.11 ±13.83 and 39.12±14.99 respectively. Body mass index (BMI), liver ultrasound and laboratory findings were taken from the records in the files. Statistical analyzes were performed using SPSS statistical software package version 22 (IBM Corporation, USA).

**Results:** Fasting blood sugar, triglyceride, insulin like growth factor, growth hormone(GH) and CRP levels were significantly higher, HDL levels were significantly lower in acromegaly group. BMI and NAFLD were similar between groups. We found that, BMI and GH are the most important two factors in the presence of NAFLD in patients with acromegaly. NAFLD correlates significantly positively with the patient's BMI, weight and age; significantly negatively with the GH levels.

**Conclusion:** In people with acromegaly, BMI and GH levels are the things that affect development of NAFLD.

**Keywords:** acromegaly; non-alcoholic fatty liver disease; body mass index

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## ÖZ

**Amaç:** Akromegali hastalarında, diabetes mellitus, insülin direnci ve hipertrigliseridemi gibi metabolik durumlara sıklıkla rastlanır. Bizim amacımız, akromegali hastalarında, non alkolik yağlı karaciğer (NAFLD) gelişmesinde etkili olan faktörleri saptamaktır.

**Gereç ve Yöntemler:** 60 (33 kadın, 27 erkek) akromegali hastası ve 52 sağlıklı kişiden (27 kadın ve 25 erkek) oluşan kontrol grubu retrospektif olarak incelendi. Hastaların ve kontrol grubunun ortalama yaşı sırasıyla  $44.11 \pm 13.83$  ve  $39.12 \pm 14.99$ 'du. Beden kitle indeksi (BKİ), karaciğer ultrasonografisi ve laboratuvar sonuçları dosyalarındaki kayıtlardan alındı. İstatistik analizlerde IBM SPSS Versiyon 22.0 istatistiksel paket programı (IBM Corporation, USA) kullanıldı.

**Bulgular:** Akromegali hastalarında açlık kan şekeri, trigliserid, insülin benzeri büyüme faktörü, büyüme hormonu (GH) ve CRP seviyeleri kontrol grubuna göre anlamlı derecede yüksek, HDL düzeyleri anlamlı derecede düşük bulundu. Grupların BKİ ve NAFLD oranları benzerdi. Akromegali hastalarında BKİ ve GH'un NAFLD gelişmesinde en önemli iki faktör olduğu sonucuna ulaştık. NAFLD, hastanın BKİ, kilo ve yaşı ile anlamlı derecede pozitif, GH düzeyi ile anlamlı derecede negatif korelasyon gösterdi.

**Sonuç:** Akromegali hastalarında, NAFLD gelişmesini etkileyen faktörler BKİ ve GH'dur.

**Anahtar kelimeler:** akromegali; non alkolik yağlı karaciğer hastalığı; beden kitle indeksi

## Introduction

Growth hormone (GH) is produced by anterior pituitary gland. GH hypersecretion is usually caused by a GH-secreting pituitary adenoma and leads to acromegaly. GH hypersecretion leads to overproduction of insulin-like growth factor 1 (IGF-1). IGF-1 is a polypeptide hormone which has functional homology with proinsulin and can be synthesized by liver and many tissues and stimulates growth in specific cells through paracrine and autocrine mechanisms. IGF-1 is widely involved in inflammation, glucose and lipid metabolism, stimulates free fatty acid (FFA) use in muscle [1]. Mature hepatocytes and adipocytes have abundant insulin receptors, while virtually no IGF-1 receptors. Vascular smooth muscle cells have abundant IGF-1 receptors and minimal insulin receptors.

Acromegaly is a slowly developing disease and often diagnosed in 10 years or more after its onset. The mean age at diagnosis of acromegaly ranges from 40–47 years, with a prevalence of 28–137 per million and an incidence of 2–11 cases / year [2]. Overgrowth on the acral parts of the skeleton, soft tissue swelling and periarticular and cartilaginous thickening occurs. Deep voice, hyperhidrosis, proximal muscle weakness and fatigue, joint pain, arthropathy, sleep apnea, generalized visceromegaly, diabetes mellitus, hypertension, coronary artery disease, heart and respiratory failure can be seen clinically. Hypertension is caused by plasma volume overload, increased cardiac output and structural changes in

the vascular system. GH acts at the distal nephron and has antinatriuretic effects. Epithelial sodium channel subunit transcription in the cortical collecting duct is induced by GH. There is insulin resistance (IR) due to GH elevation, decreased peripheral glucose utilization, increased gluconeogenesis and lipolysis. GH stimulates lipid oxidation [3] and white adipose tissue (AT) lipolysis [4] which leads reduced visceral AT and FFA release into the muscles [3] and increases FFA oxidation in the liver [1]. In acromegaly, body fat depots are diminished. GH in skeletal muscle increases lipoprotein lipase activity. At supraphysiological levels, GH induces IR in liver and muscle. FFA released from AT can lead to IR in the liver. In acromegaly, increased lipolysis and IR theoretically have opposite effects on the NAFLD. Lipid accumulation occurs in the liver in cases of GH abundance or deficiency [5]. GH stimulates triglyceride (TG) uptake and storage in the muscle and liver by inducing LPL and/or hepatic lipase (HL) expression. GH promotes intra hepatic TG storage by repressing lipolysis, or lipid oxidation, or by promoting lipogenesis [6].

In the diagnosis, clinical features of acromegaly, elevated IGF-1 levels, and nadir postglucose GH levels are important. IGF-1 levels are stable, and reflect elevated GH levels. IGF-1 enhances glucose uptake in peripheral tissues.

Metabolic complications of acromegaly which closely linked to the increased cardiovascular risk are impaired FBS, impaired glucose tolerance, diabetes mellitus, IR, reduced TC, increased TG, increased nitrogen retention [7].

The liver is the central organ for fatty acid metabolism, participates in TG synthesis, export, uptake and oxidation. Fatty acids are collected in the liver by both hepatocellular uptake from plasma and biosynthesis in the liver. In healthy persons, small amounts of fatty acids are stored as triglycerides in liver. Persistent dysfunctions in liver metabolism lead to the accumulation of TG within hepatocytes, namely NAFLD [8]. It is considered to be the hepatic manifestation of the IR, metabolic syndrome and its components (diabetes mellitus, hypertension, obesity, dyslipidemia). Prevalence of NAFLD is 25% to 45% in the Western population [9]. NAFLD is considered a predominant hepatopathy worldwide and a leading cause of chronic liver disease in not only United States but much of the world. In USA, NAFLD affects nearly a third of the population and the 10-year cost of managing NAFLD complications can bring an economic burden of US\$908 billion [10].

We aimed to investigate what is effective in the development of NAFLD in patients with acromegaly.

## Material and Methods

60 (33 female, 27 male) patients with acromegaly who were followed in Erzurum Regional Education and Research Hospital endocrinology outpatient clinic were retrospectively evaluated and the findings which they were first diagnosed were compared with a healthy cross-matched control group of 52 persons (27 female and 25 male). 27 out of 60 acromegaly patients were men. Mean age of the patients and the control group were  $44.11 \pm 13.83$  and  $39.12 \pm 14.99$  respectively. All patients, had the clinical features of acromegaly, their IGF-1 levels were high for age and serum GH concentration  $>1$  ng/mL during 75 g oral glucose tolerance test at the time of acromegaly diagnosis. Who had accompanying infectious or inflammatory diseases and other malignities were excluded. Serum glucose was measured with a standard spectrophotometric method. Serum total IGF-1, high-sensitivity CRP, thyroid stimulating hormone, insulin were determined by solid-phase, enzyme-labeled chemiluminescent immunometric assays (Immulite 1000 immunoassay system, Siemens medical solutions Diagnostics, Los Angeles, CA, USA). Plasma lipid levels including low-density lipoprotein (LDL), high-density lipoprotein (HDL), TG, and TC were measured using standardized enzymatic methods.

Statistical analyzes were performed using SPSS statistical software package version 22 (IBM Corporation, USA).

Descriptive statistics were performed, continuous variables are expressed as mean  $\pm$  standard deviation. The Kolmogorov-Smirnov test was used to assess normality. Student's t-test and Mann-Whitney U-test were used to compare normally distributed and non-normal distributed continuous variables, respectively. The relationships between variables were assessed using Spearman correlation coefficient for non-normally distributed data. Multivariate logistic regression analysis was used to determine the effects of FBS, BMI, HDL, LDL, TG and TC on NAFLD. For all comparisons,  $P < 0.05$  was accepted as significant.

Local Ethics Committee for Clinical Research approved this study. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects were applied in this study. Informed consent was obtained from all involved persons prior to study inclusion.

## Results

Mean FBS ( $97.42 \pm 13.10$  and  $88.21 \pm 6.87$  mg/dL), TG ( $137.62 \pm 84.02$  and  $102.92 \pm 43.06$  mg/dL), IGF-1 ( $562.92 \pm 408.75$  and  $163.57 \pm 77.85$  ng/mL) and CRP levels ( $3.50 \pm 3.31$  and  $1.32 \pm 1.24$  mg/L) were significantly higher, HDL levels ( $41.55 \pm 10.51$  and  $50.57 \pm 10.69$  mg/dL) were significantly lower in acromegaly group than the control group respectively,  $p < 0.05$ .

Mean weight of the acromegaly group was significantly higher than the control group ( $82.60 \pm 16.83$  and  $73.52 \pm 19.56$  kg respectively),  $p < 0.05$ , but BMI ( $29.66 \pm 5.49$  and  $26.93 \pm 7.16$  kg/m<sup>2</sup>) and NAFLD (29.03 and 41.90 %) were similar between groups,  $p > 0.05$ .

Characteristics and biochemical test results of patients with acromegaly and controls are summarized in Table 1.

In table 2, multiple logistic regression analysis of parameters affecting NAFLD in acromegaly is shown.

BMI and GH are the most important factors in the presence of NAFLD in patients with acromegaly.

Correlation analysis of NAFLD with BMI, weight, age and GH in acromegaly is seen in Table 3.

In patients with acromegaly, NAFLD disease correlates positively with the patient's BMI, weight and age; negatively with the GH levels.

**Table 1.** Characteristics and biochemical test results of patients with acromegaly and controls.

	Acromegaly (Mean±Std. Deviation)	Control (Mean±Std. Deviation)	P value
Number	31	31	>0.05
Age (years)	44.11± 13.83	39.12± 14.99	,081
Gender			
female	33 (55%)	27 (51.9%)	>0.05
male	27 (45%)	25 (48.1%)	>0.05
BMI (kg/m <sup>2</sup> )	29.66± 5.49	26.93± 7.16	,051
Weight (kg)	82.60± 16.83	73.52± 19.56	,028
Height (m)	1.67±.10	1.65±.10	,490
FBS (mg/dL)	97.42± 13.10	88.21± 6.87	,000
LDL (mg/dL)	125.52±31.55	115.60±30.48	,174
T Chol (mg/dL)	194.02±44.33	177.52±42.77	,113
HDL (mg/dL)	41.55± 10.51	50.57± 10.69	,001
TG (mg/dL)	137.62±84.02	102.92±43.06	,035
IGF-1 (ng/mL)	562.92±408.75	163.57±77.85	,000
TSH (μIU/ML)	1.18±.93	1.54±1.03	,120
CRP (mg/L)	3.50±3.31	1.32±1.24	,002
Insulin (μU/mL)	20.10±19.30	8.47±6.74	,071
GH (ng/mL)	3.33±4.47	-	,000
NAFLD (number)	9	13	0,28

BMI: body mass index, FBS: fasting blood sugar, LDL: low density lipoprotein, T Chol: total cholesterol, HDL: high density lipoprotein, TG: triglyceride, IGF-1: insulin-like growth factor, TSH: thyroid stimulating hormone, CRP: C-reactive protein, GH: growth hormone, NAFLD: Non-alcoholic Fatty Liver

**Table 2.** Multiple logistic regression analysis of parameters affecting non-alcoholic fatty liver in acromegaly.

	B	p value	Odd ratio
FBS	-,093	,145	,911
BMI	,428	,024	1,534
HDL	-,028	,621	,973
LDL	,028	,295	1,028
TG	-,010	,376	,990
T Chol	-,003	,846	,997
Growth hormone	-,182	,045	,834
IGF 1	,003	,225	1,003

FBS: fasting blood sugar, BMI: body mass index, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, T Chol: total cholesterol

**Table 3.** Correlation analysis of nonalcoholic fatty liver disease with BMI, weight, age and GH in acromegaly.

		BMI	weight	age	GH
Fatty liver	r	0.514**	0.544**	0.394**	-0.428*
	p	0.000	0.000	0.002	0.042

\*\* Correlation is significant at the 0.01 level (2-tailed), \* Correlation is significant at the 0.05 level (2-tailed).  
BMI: body mass index, GH: growth hormone

## Discussion

This is the first study to determine the risk factors of NAFLD in patients with acromegaly. The multiple regression analysis of NAFLD and other risk factors was performed (Table 2). BMI and GH were independent predictive factors of NAFLD in patients with acromegaly.

We found that, mean FBS, TG, IGF-1 and CRP levels were significantly higher, HDL levels were significantly lower in acromegaly group than the control group respectively,  $p < 0.05$ . TC, LDL and insulin levels were similar. A study in 2013 in Greece showed that TC, LDL and TG levels were increased in patients with acromegaly as opposed to the control group, while HDL cholesterol was decreased [11]. In some studies, patients with acromegaly were found to have hypertriglyceridemia [11, 12]. As TG levels are high, there is a risk of developing NAFLD [13]. When 62 patients with acromegaly were compared with 36 healthy persons, patients with acromegaly were found to have significantly higher mean values of FBS, TC, LDL, TG as well as lower mean levels of HDL; CRP levels were similar [14]. In 2002, in a study it was found that patients with acromegaly had lower CRP and higher insulin levels than healthy controls [15].

In our study, at ultrasound imaging, the frequency of NAFLD was found similar in acromegaly and control groups. In a study, of twenty-four newly diagnosed acromegalic patients, 45.8% was found to have high visceral adiposity index which shows early metabolic risk [16]. In another study, whole-body magnetic resonance imaging of 24 patients with acromegaly showed that, visceral AT was less than control group [17]. Unlike this, seven patients with acromegaly and cross matched healthy volunteers were enrolled in a study and magnetic resonance spectroscopy was used to assess in vivo lipid deposition of liver and found markedly elevated liver fat content in acromegaly [18].

In our study, NAFLD correlates negatively with the GH levels in acromegalic patients. Ciresi et al found that, in acromegaly, hepatic steatosis index is related with the reduction of GH

and IGF-1 levels [5]. GH directly acts as a promoter in lipolytic signaling and in contrast, GH might promote lipid synthesis and storage by induction of IGF-1 [19]. 55 patients with NAFLD were enrolled in a study, and decreased GH was found associated with hepatic steatosis [20]. GH deficiency found to be associated with dyslipidemia and NAFLD [13, 21].

We found that, mean weight ( $82.60 \pm 16.83$  and  $73.52 \pm 19.56$  kg) of the acromegaly group was significantly higher than the control group respectively,  $p < 0.05$ , but BMI ( $29.66 \pm 5.49$  and  $26.93 \pm 7.16$  kg/m<sup>2</sup>) was similar between groups,  $p > 0.05$ . In some studies, body weight and BMI in patients with acromegaly were higher compared to healthy controls [22, 23].

A higher BMI increases the prevalence of NAFLD in population [24]. The prevalence of NAFLD increases with age, overweight/obesity and hypertriglyceridemia in general population [25]. In patients with acromegaly, we found that, NAFLD correlates positively with the patient's BMI, weight and age, just as normal population.

In conclusion, BMI and GH were found to be independent predictive factors of NAFLD in patients with acromegaly.

### Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

### References

1. Clemmons DR. Metabolic Actions of Insulin-Like Growth Factor-I in Normal Physiology and Diabetes. *Endocrinol Metab Clin North Am* 2012; 41: 425–43.
2. Türkiye Endokrinoloji ve Metabolizma Derneği Hipofiz Çalışma Grubu. Hipofiz Hastalıkları Tanı, Tedavi ve İzlem Kılavuzu. ANKARA: 2018. p. 29–35.
3. Rabinowitz D, Klassen GA, Zierler KL. Effect of Human Growth Hormone on Muscle and Adipose Tissue Metabolism. *J Clin Invest* 1965; 44: 51–61.
4. Moøller N, Joørgensen JOL. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. *Endocr Rev* 2009; 30: 152–77.
5. Ciresi A, Guarnotta V, Campo D, Giordano C. Hepatic Steatosis Index in Acromegaly: Correlation with Insulin Resistance Regardless of the Disease Control. *Int J Endocrinol*. 2018; 5421961.
6. Vijayakumar A, Novosyadlyy R, Wu YJ, Yakar S, LeRoith D. Biological effects of growth hormone on carbohydrate and lipid metabolism. *Growth Horm IGF Res* 2010; 20: 1–7.
7. Colao A, Ferone D, Marzullo P, Lombardi G. Systemic Complications of Acromegaly: Epidemiology, Pathogenesis, and Management. *Endocr Rev* 2004; 25: 102–152.
8. Alves-Bezerra M, Cohen D. Triglyceride Metabolism in the Liver. *Compr Physiol* 2017; 8: 1–8.
9. Rinella ME. Nonalcoholic fatty liver disease a systematic review. *JAMA - J Am Med Assoc* 2015; 313: 2263–73.
10. Ofosu A, Ramai D, Reddy M. Non-alcoholic fatty liver disease: Controlling an emerging epidemic, challenges, and future directions. *Ann Gastroenterol* 2018; 31: 288–95.
11. Kostoglou-Athanassiou I, Gkountouvas A, Keramidas I, Xanthakou E, Chatjimarkou F, Kaldrymidis P. Lipid levels in acromegaly. In: *Endocrine Abstracts* 32. 2013. p. 172.
12. Nikkilä EA, Pelkonen R. Serum lipids in acromegaly. *Metabolism* 1975; 24: 829–38.
13. Marino L, Jornayvaz FR. Endocrine causes of nonalcoholic fatty liver disease. *World J Gastroenterol* 2015; 21: 11053–76.
14. Vilar L, Naves L, Costa S, Abdalla L, Coelho C, Casulari L. Increase of Classic and Nonclassic Cardiovascular Risk Factors in Patients with Acromegaly *Endocr Pract*. 2013; 13: 363–72.
15. Sesmilo G, Fairfield WP, Katznelson L et al. Cardiovascular risk factors in acromegaly before and after normalization of serum IGF-I levels with the GH antagonist pegvisomant. *J Clin Endocrinol Metab* 2002; 87: 1692–99.
16. Ciresi A, Amato MC, Pizzolanti G, Giordano Galluzzo C. Visceral adiposity index is associated with insulin sensitivity and adipocytokine levels in newly diagnosed acromegalic patients. *J Clin Endocrinol Metab* 2012; 97: 2907–15.
17. Freda PU, Shen W, Heymsfield SB et al. Lower visceral and subcutaneous but higher intermuscular adipose tissue depots in patients with growth hormone and insulin-like growth factor I excess due to acromegaly. *J Clin Endocrinol Metab* 2008; 93: 2334–43.
18. Szendroedi J, Zwettler E, Schmid AI et al. Reduced basal ATP synthetic flux of skeletal muscle in patients with previous acromegaly. *PLoS One* 2008; 3: e3958.
19. Wolf P, Winhofer Y, Krššák M, Krebs M. Heart, lipids and hormones. *Endocr Connect* 2017; 6: 59–69.
20. Ichikawa T, Nakao K, Hamasaki K et al. Role of growth hormone, insulin-like growth factor 1 and insulin-like growth factor-binding protein 3 in development of non-alcoholic fatty liver disease. *Hepatol Int* 2007; 1: 287–94.

21. Nishizawa H, Iguchi G, Murawaki A et al. Nonalcoholic fatty liver disease in adult hypopituitary patients with GH deficiency and the impact of GH replacement therapy. *Eur J Endocrinol* 2012; 167: 67–74.
22. Kozakowski J, Rabijewski M, Zgliczynski W. Lowered ghrelin levels in acromegaly-normalization after treatment. *Endokrynol Pol* 2005; 56: 862–70.
23. Dimopoulou C, Sievers C, Wittchen HU et al. Adverse anthropometric risk profile in biochemically controlled acromegalic patients: Comparison with an age- and gender-matched primary care population. *Pituitary* 2010; 13: 207–14.
24. Hashimoto E, Tokushige K. Prevalence, gender, ethnic variations, and prognosis of NASH. *J Gastroenterol* 2011; 46: 63–9.
25. Ratzia V, Bellentani S, Cortez-Pintoc H, Dayd C, Marchesinie G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; 53: 372–84.