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Case Report

# An acromegalic patient with low Insulin-Like Growth Factor-1 levels: it may not be found to be elevated during diagnosis of acromegaly each time

## *Düşük Insulin-Like Growth Factor-1 düzeyleri olan bir akromegalik hasta: IGF-1 akromegali tanısı sırasında her zaman yüksek bulunmayabilir*

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### ABSTRACT

The diagnosis of acromegaly is based on demonstration of excess growth hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) secretion. IGF-1 is the most reliable biochemical indicator of activity of acromegaly. However, there are some pitfalls in the interpretation of change of plasma IGF-1 levels. We aim to report a case with acromegaly that has low IGF-1 levels and elevated GH levels associated with poorly controlled type 2 diabetes mellitus and malnutrition.

A 38-years-old woman was admitted to emergency departmant due to hyperglycemia, weakness, cough, dyspnea, high fever. She has been complaining for enlargement of her hands and feet for ten years and she was cachectic for a long time. During oral glucose tolerance test (OGTT), serum growth hormone levels were found to be higher than normal range according to the matching age and sex subjects but IGF-1 and IGFBP-3 levels were measured lower than the reference range. A macroadenoma of 3x2.5 cm diameter was determined in magnetic resonance imaging of the pituitary gland. As a conclusion, determining elevated IGF-1 levels are very important for the diagnosis and activity of acromegaly, but careful interpretation of IGF-1 levels is necessary in type 2 diabetic patients with acromegaly.

**Key Words:** Acromegaly, IGF-1, malnutrition, type 2 diabetes mellitus.

### ÖZET

Akromegali tanısı aşırı GH ve Insulin-Like Growth Factor-1 (IGF-1) sekresyonunun gösterilmesine dayanır. IGF-1 akromegalinin aktivasyonunun en güvenilir göstergesidir. Bununla birlikte plazma IGF-1 düzeylerinin değişikliklerinin yorumlanmasında bazı tuzaklar vardır. Biz kötü kontrollü tip 2 diabetes mellitus ve malnütrisyon ile ilişkili olarak düşük IGF-1 ve artmış GH düzeyleri olan bir akromegalili olguyu sunmayı amaçladık.

Otuzsekiz yaşındaki kadın hasta hiperglisemi, halsizlik, öksürük, dispne, yüksek ateş yakınmaları yüzünden acil servise baş vurdu. On yıldır ellerinde ve ayaklarında büyüme olmasından yakınmaktaydı ve uzun zamandır kaşektikti. OGTT sırasında serum growth hormon düzeyleri yaş ve cinsiyete göre olan normal sınırlardan yüksek bulundu. Fakat IGF 1 and IGFBP-3 normal referans aralığından düşük ölçüldü. Hipofizin manyetik rezonans görüntülemesinde 3x2.5 cm çaplı bir pituiter makroadenom saptandı. Sonuç olarak, artmış IGF-1 düzeyleri akromegali tanı ve aktivitesinde çok önemlidir, ancak tip 2 diyabetli akromegalilerde IGF-1' in dikkatli yorumlanması gereklidir.

**Anahtar Kelimeler:** Akromegali, IGF-1, malnutrisyon, tip 2 diabetes mellitus

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## Introduction

The clinical features of acromegaly is due to excessive secretion of growth hormone (GH) and Insulin-Like Growth Factor-1 (IGF-1) [1]. Diagnosis of acromegaly is not difficult when acral enlargements are manifested. But, specific changes of acromegaly may not become clinically apparent for many years. For that reason, acromegaly is an uncommonly diagnosed disorder with annual estimated incidence of 3 to 4 cases per million people [2]. It is well known that acromegaly is associated with increased premature mortality due to cardiovascular diseases so, early diagnosis of acromegaly is very important for preventing premature mortality [3].

The biochemical diagnosis of acromegaly is based on demonstration of excess GH and IGF-1 secretion [4]. Because GH has a short half-life, a single random GH testing is considered to be of little value in diagnosing acromegaly [5]. On the other hand, IGF-1 is the most reliable indicator for acromegaly [6], and elevated serum IGF-1 level according to age and gender is a useful screening test [7]. High levels of IGF-1 are correlated better with the clinical manifestations of acromegaly [8,9]. Nevertheless, previous studies reported that elevated growth hormone concentration and inappropriately normal IGF-1 levels may be found in type 2 diabetic acromegalic patient [10]. Both of poorly controlled diabetes mellitus and malnutrition may impact on GH/IGF-1 axis [11,12].

We aimed to report a case of acromegaly which had normal IGF-1 levels and elevated GH levels associated with poorly controlled type 2 diabetes mellitus and malnutrition. This report may pay attention for difficulty of interpretation of GH and IGF-I levels in acromegalic patients with poorly controlled type 2 diabetes mellitus and malnutrition.

## Case Report

A 38- years-old woman was admitted to emergency room due to hyperglycemia, weakness, cough, dyspnea, and high fever. She has been complaining for enlargement of her hands and feet for ten years and she was cachectic for a long time.

On the physical examination, body temperature was 38.5 ºC, pulse rate was 56 beats/min, blood pressure was 70/50 mmHg and respiratory rate was 22 breathes/min. The patient was 1.55 cm tall, body weight was 42 kg. Body mass index (BMI) was 17.4 kg/m². Typical physical signs of acromegaly such as frontal bossing, prognatism, acral enlargements, macroglossia, coarse facial features, deepen voice were observed (Figure1). In general appearance, she was very cachectic and very dehydrated. Pectus excavatus was present. Diminished respiratory sounds and bilaterally respiratory rales were heard at basal region.

She had normocytic anemia and thrombocytopenia (WBC: 10600/mm³, Hct: 32.3%, MCV: 87.2, PLT:42.700/mm³). Biochemical parameters were as follows; glucose: 124 mg/dL, urea:133 mg/dL; creatinine: 0.9 mg/dL; total protein: 4.0 g/L; albumine:1.33 g/L; ALT: 21 IU/L; AST: 22 U/L; total bilirubine: 0.9 mg/dL; sodium:130 mmol/L; potassium: 3.2 mmol/L. In urinalysis, keton bodies, glucose and pyuria was present, *E.coli* was determined in urine culture specimen. Transudative pleural effusion was determined at left lung with normal echocardiographic findings.

With these results, we suspected from acromegaly and performed OGTT with 75 g glucose. All growth hormone levels in OGTT were above 40 ng/dL and newly diagnosis of diabetes mellitus was determined. With these findings, we determined acromegaly, but, serum IGF-1 levels were too low for acromegaly according to age- and sex-matched reference range. In the MRI evaluation of pituitary, a large macroadenoma (3x2.5 cm diameter) was noticed (Figure 2). The other pituitary hormone levels were also found as below: TSH:0.482 uIU/mL, ACTH:12.02 pg/mL, prolactin: 7.8 ng/mL, cortisol: 33.84 ug/dL, free T3: 0.102 ng/dL, free T4:0.278 ng/dL, FSH; 0.127 mIU/mL, LH:0.100 mIU/mL.

Due to cachexic appearance, malnutrition was considered. Serum iron (Fe) level was 9 ug/dL (normal range 25-156). Iron binding capacity was 97 ug/dL (normal range 110-370). Serum ferritin level was 11 ng/mL (normal range 13-150). Vitamin B12 level was 136 pg/mL (normal range 240-900). Serum folate level was 18.84 ng/mL (normal range 2-9.1). Alkaline reflux gastritis was determined in the endoscopic evaluation. Anti parietal antibody and anti intrinsic factor antibody were positive, anti endomycium IgA, anti endomycium IgG, anti gliadin IgA and anti gliadin IgG antibody were negative. After overnight fasting period, although serum growth hormone (GH) levels were higher than normal references range, on the contrary to expectancy, IGF 1 and insulin like growth factor binding protein-3 (IGFBP-3) levels were lower than reference range according to similar age and sex matched subjects (Table 1) by measured with chemiluminescent immunometric assay. A large pituitary macroadenoma (3x2.5 cm) was demonstrated by magnetic resonance imaging (MRI) (Figure 2).

**Table 1:** Results of oral glucose tolerance test in a woman with newly diagnosed type 2 diabetes mellitus and acromegaly

| | 0th minute | 30 th minute | 60 th minute | 90 th minute | 120 th minute |
|---|---|---|---|---|---|
| Glucose (mg/dL) | 276 | 301 | 336 | 359 | 210 |
| GH (ng/dL) | >40 | >40 | >40 | >40 | >40 |
| IGF 1 (ng/mL) | 33.6 | 59.2 | 71 | 56.3 | 50.6 |
| IGFBP-3 (µg/mL) | 2.19 | 2.20 | 2.14 | 2.08 | 1.81 |
| Insulin (µU/mL) | 0.981 | 6.1 | 5.4 | 1.39 | 3.96 |
| C peptid (ng/mL) | 2.23 | 2.9 | 2.98 | 2.7 | 2.81 |

GH: Growth hormone (normal range 0.06-5 ng/mL)

IGF-1: Insulin like growth faktor-1 (normal range 55-166 ng/mL )

IGFBP-3: IGF-binding protein-3 (normal range 2.2-4.5 µg/mL)

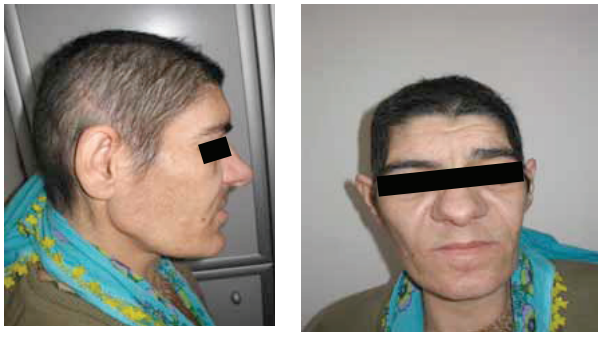

**Figure 1:** Clinical features of acromegaly in our patient show below.

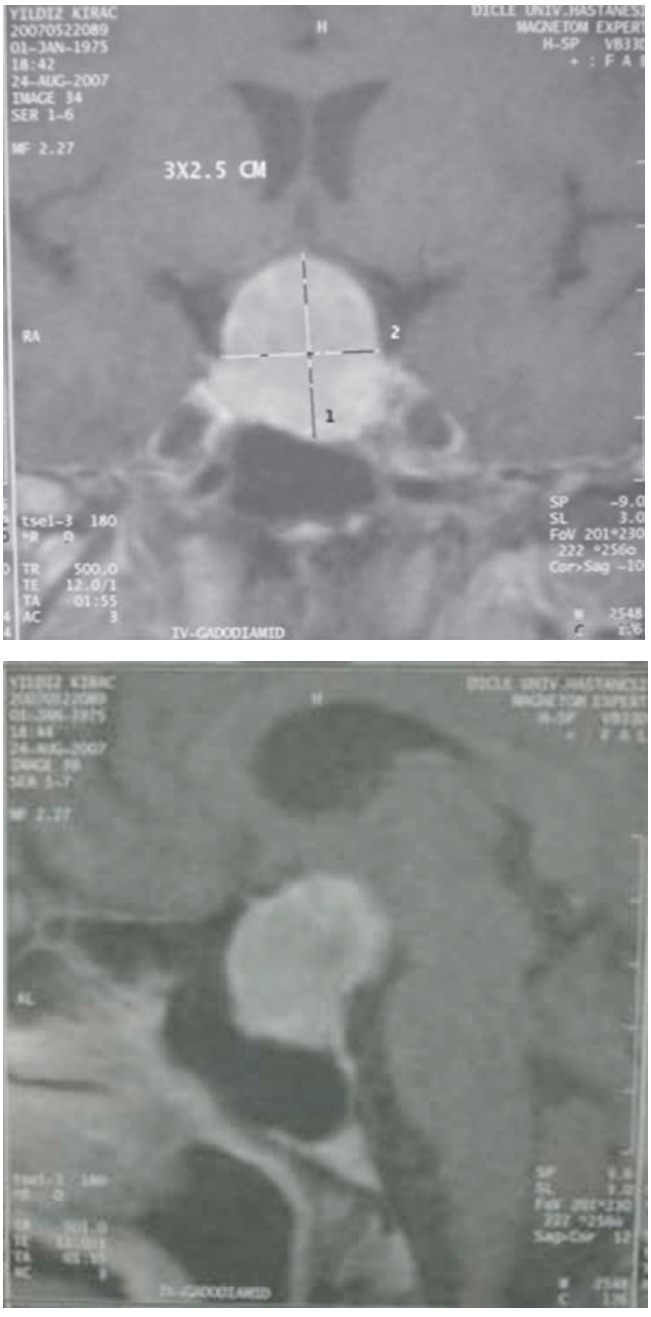


**Figure 2.** A macroadenoma (3x2.5 cm) was determined in magnetic resonance imaging (MRI) of the pituitary gland

She was treated with antibiotic, high protein contained diet (2 gr/kg; 2000 kcal/day) and enteral feeding solution (Glucerna). Thyroid hormone, cortisole, iron and vitamin B12 deficiencies were replaced. Plasma glucose levels were controlled by insulin. In the clinical observation, the patient gained weight within 25 day; her body weight and body mass index was found 48.4 kg and 20.14 kg/m² respectively. In the beginning of hospitalization, IGF-1 levels were low but after restoration of cachexia and treatment of diabetes mellitus IGF-1 levels of patient elevated. After one month, serum IGF-1 and IGFBP-3 levels were higher than normal reference range for sex and age. (GH: >40 ng/mL, IGF 1: 451 ng/mL, IGFBP3: 8.05 ug/mL, respectively). Therefore, pituitary surgery was performed, tumor was partially removed, and Octreotid LAR was applied 30 mg per 28 days.

## Discussion

We observed low IGF-1 levels in a acromegalic patient with growth hormone secreted macroadenoma. This is interesting finding, because measurement of IGF-1 levels help confirming the diagnosis and therapeutic monitoring of acromegaly [13]. There is a strong correlation between IGF-I levels and residual disease activity [14] and plasma IGF-1 levels are also a good predictor of severity of disease. But there are some pitfalls in the interpretation of plasma IGF-1 levels. For example malnutrition, malabsorption, anorexia nervosa, liver cirrhosis, renal failure, and type 1 diabetes mellitus may lead to discrepancies between growth hormone and IGF-1 levels [15], and these disorders may cause to high GH and low IGF-1, even in patients with no active acromegaly [16,17]. Some physiologic situations such as puberty or pregnancy may cause abnormally high IGF-1 levels [17]. Chronic diseases as hypothyroidism and chronic renal failure, and critical illness also influenced serum IGF-1 levels [18,19].

IGF-1 is produced in liver under GH control. Liver IGF-I gene-expression is regulated mainly by GH and it is the major constituent of circulating IGF-I. Again insulin may also play a regulatory role on IGF-1 levels. As sufficient amount of insulin is needed in order to induce expression of GH receptors on hepatocytes, an insulin deficiency in portal vein might cause a decrease in the number of GH receptors [10]. IGF-1 levels adjusted age and sex in diabetic patients were 40-50% lower than normal subject [20]. In our patient, type 2 diabetes mellitus was present; perhaps, it might have led to conflicting results of IGF-1 levels.

On the other hand, nutritional status is a very important determinant of serum IGF-1 levels. When healthy subjects are starved for 10 days, a 70% decrease occurs in serum IGF-1 levels [21]. After re-feeding, these levels return to normal level in 8 days. Malnutrition in clinically active acromegaly may cause low serum IGF-1 levels and/or GH resistance due to down regulation of GH receptors or defects at the post-receptor level [22]. Both of uncontrolled diabetes mellitus and malnutrition, therefore cachexia may be responsible for low IGF-1 levels in our patient despite GH secreted macroadenoma. As a result, serum IGF-1 levels may not be a reliable biochemical parameter of the activity of acromegaly especially in diabetic patient with malnutrition.

Our patient was cachectic and type 2 diabetic; therefore, both of cachexia and poorly controlled type 2 diabetes mellitus have led to this conflicting result between GH and IGF-1 levels. In fact at the beginning of hospitalization, IGF-1 levels of patient were low. After restoration of cachexia and glycemic control, her IGF-1 levels reached to acromegalic levels within one month. These results indicate that some disorders such as malabsorption, diabetes mellitus and cachexia may lead to discrepancies between growth hormone and IGF-1 levels in acromegalic patients.

In conclusion, although elevated IGF-1 levels were very important for diagnosis of acromegaly; some conditions such as unregulated diabetes mellitus and/or cachexia may lead to low IGF-1 levels despite high serum GH concentrations even in patient with active acromegaly. Measuring only IGF-1 levels may mask the diagnosis of active acromegaly especially in acromegalic patients with poorly controlled diabetes mellitus and/or malnutrition.

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