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Research Article

Growth Hormone Responses to Oral and Intravenous Glucose in Acromegaly

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ABSTRACT

While evaluating acromegalic patients, a discordance can be seen between insulin like growth factor-1(IGF-1) and GH response to oral glucose tolerance test (OGTT). In this study, the supressions and discordances of GH between OGTT and intravenous glucose tolerance test (IVGTT) were invastigated in acromegalic patients.
Oral GTT and IVGTT performed to 18 acromegalic subjects. Serum levels of GH and glucose were analysed at 0, 30, 60, 90 and 120 minutes during OGTT and IVGTT, and compared.
The supression of the serum GH levels during IVGTT were insignificantly higher than the serum GH levels during OGTT ($p > 0.05$). At 30^{th} minutes, serum levels of glucose in IVGTT was significantly higher than OGTT ($p < 0.001$). Moreover, compared to IVGTT, serum glucose levels were higher at 60^{th}, 90^{th} and 120th minutes during OGTT ($p=0.036$, $p<0.001$ and $p<0.001$, respectively). But the GH responses to the glucose, there were no significant differences between OGTT and IVGTT in all times of the analyses ($p>0.05$).
There were obvious differences between OGTT and IVGTT in patients with acromegaly in terms of glucose elevation in time. Whereas, growth hormone levels did not reach statistical differences, even if growth hormones were found higher at all times in OGTT than in IVGTT.

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Araştırma Makalesi

Akromegalide Oral ve İntravenöz Glukoz Tolerans Testine Büyüme Hormonu Yanıtı

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Ö Z E T

Akromegali hastaları değerlendirilirken, oral glukoz tolerans testine (OGTT) insülin benzeri büyüme faktörü-1 (IGF-1) ve büyüme hormonu (BH) yanıtlarında uyumsuzluk görülebilir. Bu çalışmada akromegali hastalarında, intravenöz glukoz tolerans testi (IVGTT) ve OGTT arasında BH baskılanması ve uyumsuzluğun değerlendirilmesi amaçlanmıştır.

Onsekiz akromegali hastasına OGTT ve IVGTT uygulandı. OGTT ve IVGTT uygulanması takiben 0, 30, 60, 90 ve 120'inci dakikalarda serum BH ve glukoz düzeyleri çalışılarak istatistiksel karşılaştırılmalar yapıldı.

IVGTT sonrası serum BH düzeyleri baskılanması, OGTT sonrası serum BH düzeyleri ile karşılaştırıldığında istatistiksel anlamlı olmayan bir yükseklik vardı ($p > 0.05$). IVGTT sonrası 30'uncu dakikadaki serum glukoz değerleri, OGTT sonrasına göre anlamlı olarak yüksek bulundu ($p < 0.001$). Bununla birlikte, OGTT sonrası 60, 90 ve 120'inci dakikalardaki serum glukoz değerleri IVGTT sonrası aynı sürelerle karşılaştırıldığında daha yüksekti (sırasıyla; $p=0.036$, $p<0.001$ ve $p<0.001$). Fakat glukoza BH yanıtında, OGTT ve IVGTT sonrası değerler arasında anlamlı bir fark bulunmadı ($p>0.05$).

Akromegalili olgularda IVGTT ile anlamlı yükseklikte glukoz artışları saptanmaktadır. Ancak OGTT'ye göre BH değerlerinde baskılanma fazla, ancak anlamlı düzeyde değildir. Yeterli glukoz artışı sağlanamayan OGTT yapılmış olgularda gastro-enteropankreatik yolağı devreden çıkaran IVGTT tercih edilebilir.

1. Introduction

Acromegaly caused by excessive secretion of growth hormone (GH) is a chronic systemic disease. GH stimulates IGF-1 (insulin like growth factor-1) production and secretion in liver and other tissues. IGF-1 is responsible for major part of somatic and metabolic effects. Excess secretion of GH is

associated with somatic overgrowth; phenotypic changes, numerous systemic complications, impaired quality of life and reduction in life expectancy. As a result; a multidisciplinary approach is essential for true diagnosis and management of disease (1, 2).

Growth hormone secreting pituitary adenoma is responsible for 95% of patients (3). Measurement of IGF-1 level should be initial test in patients who have typical symptoms and signs, also several associated conditions because of long half-life and stable Random GH is not recommended to diagnose of acromegaly (4). On the other hand glucose loading suppresses GH secretion in healthy subjects (5). In patients with acromegaly, this inhibitory action is severely impaired or completely lost (6-8). Because of that; measurement of GH during oral glucose tolerance test (OGTT) has been widely used in the diagnosis and follow-up of acromegaly for many years (6). Sometimes a discordance can be seen between IGF-1 and GH response to OGTT, while evaluating the activity of the disease in clinical practice (4).

In this study, we aimed to compare GH responses obtained during oral and intravenous glucose tolerance test (OGTT and IVGTT) in patients with acromegaly.

2. Material and Methods

This study was conducted with a retrospective analysis of the author's data on GC's specialist thesis (Zonguldak Karaelmas University Medical Faculty, Department of Internal Medicine, 2010). This prospective study was conducted in the Department of Endocrinology and Metabolism, Furthermore the pregnants, those receiving estrogen replacement and the patients with heart, renal or hepatic failure and obesity were excluded from the study. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by locally ethic commitee. Informed consent was obtained from all individuals.

2.1. Study Protocol

A total of 18 patients with acromegaly, admitted to our outpatient clinicof endocrinology were enrolled in this study. All patients underwent a baseline evaluation including weight, height, body mass index (BMI) , a detailed medical history, typical physical examination and blood tests including glucose, GH and insulin like growth factor-1 (IGF-1) . Acromegaly was diagnosed by finding of a random enhanced GH secretion, and unsupressed GH levels in response to OGTT and increased IGF-1 level compared with the age- and sex-adjusted normal range, besides the typical disfigurement that related to the progression of acromegaly (1, 7). The tests were performed by the same subjects to one or more days intervals.

2.1.1. Oral glucose tolerance test with 75-g glucose

Oral GTT with 75-g glucose was performed in all subjects. Basal plasma glucose, insulin, GH and insulin like growth factor-1 (IGF-1) levels were determined in venous blood after 8-10 hours fasting between 08.00-09.00 a.m. Then, patients drank 75-g glucose dissolved in 300 ml water in 5 minutes, and serum glucose and GH levels were measured after 30, 60, 90, and 120 minutes.

2.1.2. Intravenous glucose tolerance test

Venous cannulas were placed in each forearm after a 10-12 hours fasting between 08.00-09.00 a.m. Blood samples were taken for measurement of plasma glucose, insulin, GH and IGF-1 levels. These samples were considered as -5 minute samples. 0.5 g/kg 10 % dextrose solution was infused in 5 minutes from one cannula. The end of infusion was considered as 0 minute. Samples for plasma glucose and GH were obtained at 0, 10, 30, 60, 90 and 120 minutes from the other canule.

2.1.3. Laboratory examination

Plasma glucose levels were measured by enzymatic method using an ADVIA 2400 automated autoanalyser (Bayer Diagnostics, Tarrytown, NY, USA). The intra- and interday variations of coefficients for plasma glucose was 0.00–0.93 and 1.68–1.83%. The coefficient of variability of the assay ranged from 5.9-8%. IGF-1 concentrations were determined by an automated two-site, solid-phase chemiluminescent assay system (Immulite 1000, Diagnostic Products Corp., Los Angeles, CA, USA). Reagent preparation and sample analyses were performed according to the manufacturer's instruction. The Immulite standards were calibrated to the World Health Organization international reference reagent (IGF-1: 87/517, IGFBP-3: 93/560). The calibration range of the IGF-1 assay was up to 1600 ng/ml and analytical sensitivity was 20 ng/ml. The within- and total- run variations of coefficient values for the different levels were <5% and <9%, respectively. Growth hormone was measured by a solid-phase, enzyme-labeled chemiluminescent immunometric assay with Immulite 1000 analyzer (Diagnostic Products Corp, Los Angeles, CA, USA). The intraassay coefficients of variations were both less than <6.5% (the within run variations of coefficients are 5.3, 6.0 and 6.5% for the GH levels of 1.7, 7.8 and 31 ng/ml, respectively). The interassay coefficients of variations were both less than <6.2% (the within run

variations of coefficients are 5.7, 6.2 and 6.1% for the GH levels of 3.0, 9.3 and 18 ng/ml, respectively. The analytical sensitivity was 0.01 ng/ml and measuring range was 0.01–40 ng/ml.

2.2. Statistical analysis

SPSS 19,0 for Windows used for statistical analysis. Categorical variables are given with frequency and percent, numerical variables are given with median, minimum and maximum values. Kolmogorov-Smirnov test was used for normality tests. Paired-Samples test was used for numerical variables among measurements of OGTT and IVGTT at 0, 30, 60, 90 and 120 minutes. Mann Whitney U test was used for GH and serum glucose regarding the presence of diabetes mellitus and Wilcoxon test was used for GH and serum glucose at 0, 30, 60, 90 and 120 minutes of OGTT and IVGTT. For all statistical analysis with p value under 0,05 is assumed as there is a statistical significance.

3. Results

The characteristics of eighteen patients (Female/Male: 11/7, mean age: 46,4 ± 10,4) that were diagnosed by a combination of the clinical symptoms and biochemical assessments have been seen in table. Mean height was 164±7,5 cm; mean weight was 90.39±14,3 kg; mean Body mass index (BMI) was 33.57±6,2 kg/m^2; mean duration of disease was 63,5 ±73,7 months, mean levels of IGF-1 was 465,3±218,6 ng/ml.

There was no significant differences between the initial serum glucose responses to OGTT and IVGTT (p=0.399). But, at 30, 60, 90 and 120 minutes showed significant differences when compared to each other (p<0.001, p=0.036, p<0.001, p<0.001, respectively) (Fig 1) Consequently, the supression at GH levels were higher at IVGTT compared to OGTT

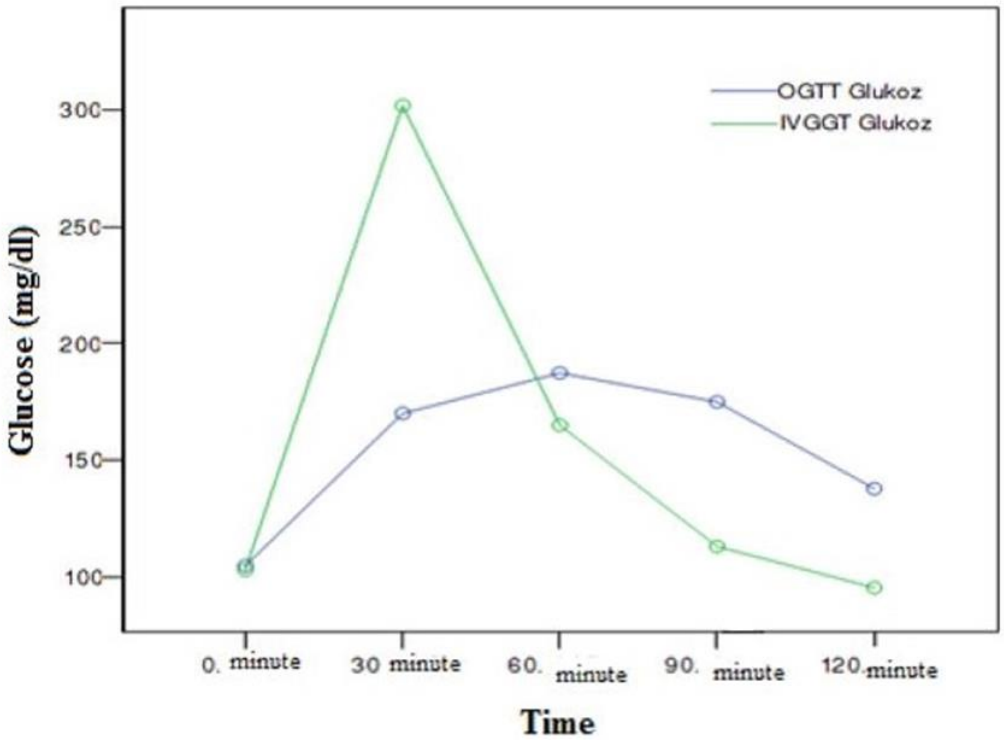

Figure 1. Synchronous glucose response to OGTT and IVGTT

There was no significant differences between the initial serum glucose responses to OGTT and IVGTT (p=0.399). But, at 30, 60, 90 and 120 minutes showed significant differences when compared to each other (p<0.001, p=0.036, p<0.001, p<0.001, respectively) (Fig 2) Consequently, the supression at GH levels were higher at IVGTT compared to OGTT but not at significant values. Although there were no significant differences between OGTT and IVGTT (p> 0.05) at initial glucose levels of the tests, glucose level in IVGTT was significantly higher than OGTT at 30 minute (p=0.001). Moreover, compared to IVGTT, glucose levels were revealed higher in OGTT at 60, 90 and 120 minutes markedly (p=0.036, p<0,001 and p<0.001, respectively) (Table 1). Seven patients have just been diagnosed with diabetes incidentally while assessing the GH responses to the glucose load tests.

Table 1:Plasma glucose and GH levels during OGTT and IVGTT

	Minute	OGTT	IVGTT	P value
Glucose (mg/dL)	**0**	105.15±18.37	103.36±17.70	0.393
	30	170.26±31.65	301.68±114.70	**<0.001**
	60	187.57±47.90	165.21±45.36	0.036
	90	175.15±57.11	113.42±43.12	**<0.001**
	120	138.10±51.35	95.84±31.43	**<0.001**
GH (µg/L)	**0**	16.89±27.47	14.99±21.19	0.727
	30	17.15±28.84	15.95±22.79	0.619
	60	21.23±35.89	17.21±27.20	0.459
	90	18.59±36.73	17.12±30.23	0.601
	120	18.56±39.64	17.49±30.99	0.372

GH: Growth hormone, OGTT: oral glucose tolerance test, IVGTT: intravenous glucose tolerance test.

Baseline IGF-1 levels were ranging from 125 to 750 ng/ml (median 465.33±218.56 ng/ml). There was no difference between GH levels at 0^{th}, 30^{th}, 90^{th} and 120^{th} minutes during OGTT and IVGTT (p=0.727, p=0.619, p=0.459, p=0.601 and p=0.372 respectively). It were observed that GH supression at OGTT was less than GH supression at IVGTT, statistically insignificant (Figure 2).

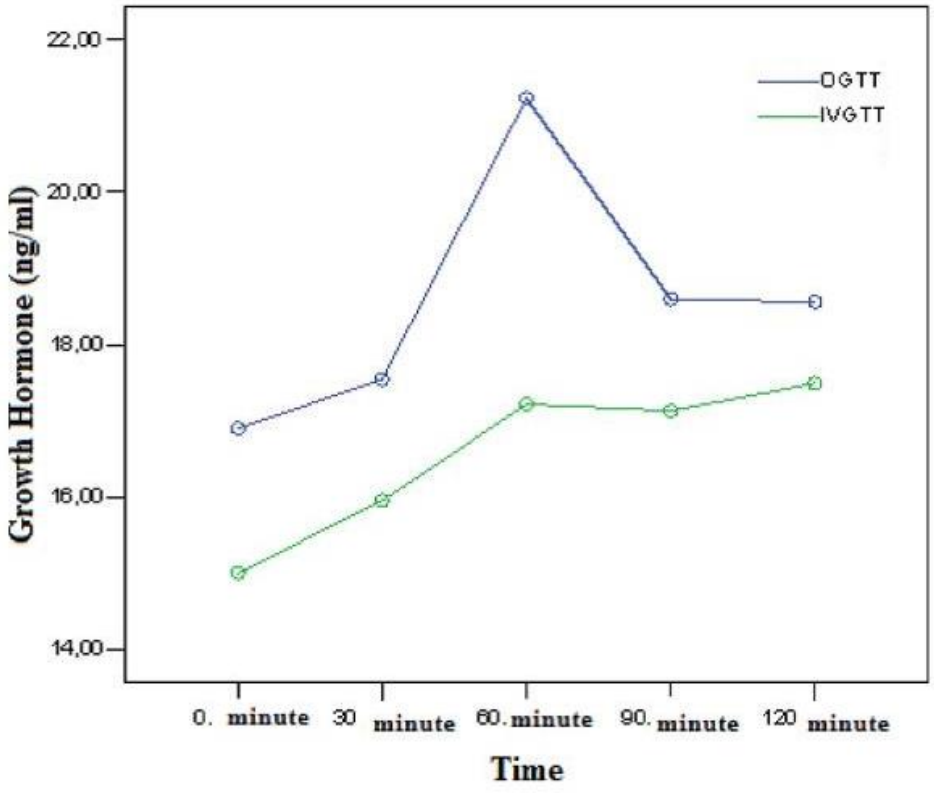

Figure 2. The synchronous GH response to OGTT and IVGTT

4. Discussion

The mechanisms of GH supression with oral and intravenous glucose loading has not been identified exactly both and same healthies and acromegalic subjects (9). However, nadir level of GH responses at 0, 30, 60, 90 and 120 minutes during oral glucose loading is a dynamic biochemical test to evaluate for the diagnosis and follow-up of acromegaly (10). Glucose loading modulates secretion of hypothalamic neuropeptids, especially somotostatin. Somotostatin is major inhibitor for GH secretion (11-13). Causes of unsupressed GH response during glucose loading in patients with acromegaly may be the deficiency of somatostatin release as a response to acute hyperglycemia as well as the supressions of thyrotropin secretion in these patients are found to be less than healthy individuals in some studies(14). Individual variations in gastrointestinal pathway might effect responses to GH suppression during OGTT both in healthy subjects and in patients with acromegaly. Also, oral glucose loading does not bypass of ghreline hormone. Ghreline is produced in stomach and a potent endogenous stimulator of GH (15, 16). In this study, it was aimed to exclude personal differences in gastrointestinal pathway by using IVGTT instead of OGTT and tried to determine nadir GH level in patients with acromegaly. The role of oral or intravenous glucose load has not been illustrated sufficiently to explain the discordance between the IGF-1 and GH separately. In this study, we aimed to determine the GH responses to OGTT-IVGTT and to compare the GH responses to these tests that applied to acromegalic patients, among themselves despite the studies about GH responses to OGTT in healthies and acromegalic subjects. There are few descriptive small studies in the literature that assessed the GH response to OGTT and IVGTT together (7, 8).

Mancini et al. performed OGTT and IVGTT on the 12 acromegalic patients and in their study, they observed a partial supression of GH response to OGTT although supression of GH response to IVGTT was not seen despite the glucose levels were higher during administration of IVGTT than OGTT (17). Mancini et al, claimed that glucose load which was taken orally might induced somatostatin secretion originated from the human gastrointestinal tract. Therefore increased somatostatin might supressed the GH response to OGTT. And the reason why GH response to IVGTT was not affected by somatostatin was the different way of administration of glucose load so that gastrointestinal tract was by passed using intravenous way.

Intravenous glucose might have caused initial rise and then a rapid decrease in plasma glucose resulting with relative hypoglycemia and unsuppressed GH secretion (18). In this study with more subjects, the results of GH responses to OGTT and IVGTT at 0, 30, 60, 90 and 120 minutes were not significant when compared to each other, however it was observed that GH supression at OGTT was less than GH supression at IVGTT. Both oral and intravenous glucose loading tests were terminated at 120th minute and we did not observe reactive hypoglycemia in patients with acromegalia. The major finding was that suppression GH during IVGTT was higher than during OGTT, but there was no statically significant differences in two groups ($p=0.619$). The serum levels of GH during IVGTT due to lack of ghrelin effect secreted from stomach and our results toughtthis hypothesis (19). However, it should be noted that there is also evidence showing decreased serum ghrelin hormone levels after intravenous glucose. We didin't analysed the ghrelin levels in our subjects, and this is one limitation of this study.

The levels of IGF-1 and GH regarding healthy population and acromegalic patients are correlated each other (19-21). However, discordance between IGF-1 and GH levels can be seen among 30 percent of the patients after the treatment of acromegaly (16,22). In a major part of these patients, there were GH levels in normal range with increased IGF-1 values as well as GH levels were high when IGF-1 values were in the age- and sex-matched normal range in minority of these patients. The discordance may be caused by insufficient sampling of GH and standardization of the random or dynamic tests that were performed. Furthermore, the factors including age, comorbidity, genetic differences, half-time and pulsatile release of GH may also contribute to the discordance between IGF-1 and GH values (23-27). Even if, IGF-1 levels remain high after 3-6 months from an operation of pituitary, GH responses to OGTT and multiple sampling of GH (3-5 times of GH testing during two hours periods) should be performed as recommended by the studies previously (20, 28-30).

In the present study, in accordance with IVGTT, level of GH responses at all times during OGTT seemed high but there were similar values in both tests. However, glucose levels did not differ at the beginning of both tests. Glucose level was higher in IVGTT than OGTT at 30 minute significantly. On the other hand glucose levels were higher in OGTT than IVGTT at 60, 90 and 120 minutes prominently. Differences in glucose levels in patients with acromegaly during tests should be considered for clinical significance. Our results might indicate that IVGTT will not affect the diagnosis and follow up criteria for acromegaly.

Conflict of Interest

All authors declare that no conflict of interest.

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