

Determination the concentration of insulin-like growth factor-I (IGF-I) in saliva of acromegalic patients, and comparison it with the levels of serum IGF-I.

Shiamaa Zwain, B.D.S.⁽¹⁾

Sahar H. Alani, B.D.S., M.Sc., Ph.D. ⁽²⁾

Abdilkarim Yahia Alsammaraie, M.bCh.B., M.Sc. Ph. ⁽³⁾

ABSTRACT

Acromegaly is a metabolic disorder characterized by an acquired progressive somatic disfigurement, mainly involving the face, extremities and many other organs, that are associated with systemic manifestations, caused by excessive secretion of growth hormone and a resultant persistent elevation of insulin-like growth factor-I concentrations. In more than 90% of cases originates from a monoclonal benign pituitary adenoma. Aim of this study to assess the level of insulin-like growth factor-I (IGF-I) in saliva of acromegalic patients, and to compare it with the basal levels of serum IGF-I. Sixty specimens of serum and saliva collected from two groups of subjects (forty acromegalic patients and twenty healthy persons). The specimens were centrifuged and stored at -20°C then IRMA kits were used for estimating insulin like-growth factor-I. The results show that acromegalic patients had significantly higher salivary insulin like growth factor-I concentrations than healthy subjects (mean 21.26 vs. 20.48ng/mL; $p=0.041$), serum insulin like growth factor-I concentrations (mean 782.21 vs. 199.87ng/mL; $p<0.001$), there is significant correlation between salivary and serum insulin like growth factor-I in acromegalic group, while no significant correlation in control group, Salivary IGF-I concentration may not represent the corresponding serum concentration adequately, so cannot be considered it as alternative diagnostic tool to the acromegalic patients. (J Bagh Coll Dentistry 2018; 30(2): 47-50)

INTRODUCTION

Acromegaly is a metabolic disorder characterized by an acquired progressive somatic disfigurement, mainly involving the face, extremities and many other organs, that are associated with systemic manifestations, caused by excessive secretion of growth hormone (Somatotropin) and a resultant persistent elevation of insulin-like growth factor-I (Somatomedin-C) concentrations⁽¹⁾. The condition occurs after puberty (oversecretion of GH in children, before epiphyseal closure, causes gigantism)⁽³⁾. More than 90% of cases are caused by a pituitary gland tumor, which is usually a benign tumor. In acromegaly the most typical clinical signs are the coarse facial features, large, spade shaped hands, and enlarged feet resulting from soft tissue swelling and bony enlargement.⁽¹⁾

Importantly, acromegaly is associated with an increased rate of mortality due to changes in various vital organs. Among them is cardiovascular, cerebrovascular, and respiratory system.⁽²⁾

The facial aspect is characteristic, and patients with established acromegaly are generally alike in this respect: The nose is widened and thickened, the cheekbones are obvious, the forehead bulges, the lips are thick and the facial lines are marked. The forehead and overlying skin is thickened, sometimes leading to frontal bossing. There is a tendency towards mandibular overgrowth with prognathism and jaw malocclusion⁽⁴⁾.

Others complications associated with excess growth hormone include cardio-vascular complications like concentric biventricular hypertrophy or heart failures or respiratory complications like sleep apnea. Metabolic complications include impaired glucose intolerance due to growth hormone-induced insulin resistance and lipid abnormalities like hypertriglyceridemia. Musculoskeletal complications and arthropathy along with other endocrinal disturbances including benign thyroid overgrowth, hypogonadism, and gonadal dysfunction may also be observed as associated complications.⁽⁵⁾

Several biochemical tests may be used to diagnose acromegaly, these include random measurement of GH serum concentrations, mean 24-h GH serum concentrations, GH response to oral glucose tolerance test (OGTT), and random measurement of IGF-I concentrations. Diagnosis of acromegaly based on measurement of basal or

(1) Master Student, Alnajaf health institution, Ministry of Health.

(2) Assistant professor, Department of Oral Diagnosis, College of Dentistry, University of Baghdad

(3) National Diabetes Center

random serum GH concentrations is uncertain because of the pulsatile secretion of GH, which occurs in normal individuals, in patients with active acromegaly, and in successfully treated patients. Thus single random measurements of serum GH concentrations are of limited value in the diagnosis of acromegaly. Serial GH concentrations over a 24-h period provide an overview of GH secretion and can be used in diagnosing acromegaly, but this method is impractical in an office setting. Oral glucose tolerance testing is useful in the clinical setting and considered the gold standard test by some investigators. It has recently been proposed that diagnosis of acromegaly should not be based solely on the GH nadir after OGTT but should be made by a combination of clinical features, random GH and IGF-I measurements using a highly sensitive assay (IRMA or ELISA), and the GH nadir concentration after OGTT (6).

Saliva is a mirror to the general health condition that reflects various systemic changes in the body (7). It is a colorless viscous liquid mixture of oral fluid which includes secretion from both the major and minor salivary glands. Additionally, it contains several constituents of non salivary origin: gingival crevicular fluid, expectorated bronchial and nasal secretions, serum and blood derivatives from oral wounds, bacteria and bacterial products, viruses and fungi, desquamated epithelial cells, leukocytes, electrolytes, immunoglobulins, proteins and enzymes and food debris, etc. (8). It has recently been reported that IGF-I in human mixed saliva is present in the free form only and that it could be a good measure for predicting the overall somatotropin Status. Unlike lipophilic 'drugs or steroid hormones, which are plasma ultrafiltrates, it is assumed that the IGFs in saliva are derived from the salivary glands (9). There is also immunohistochemical evidence that IGF-I is present in salivary glands of rats and mice (10). The present study was undertaken to establish the value of IGF-I levels in the saliva of acromegalic patients and to compare it with serum IGF-I.

MATERIALS AND METHODS

Twenty healthy volunteers, 10 females and 10 males, aged 29-54 years, and forty patients with acromegaly, 22 females and 18 males, aged 28-63 years, all patients were selected among patients attending the National Centre for diabetes and endocrinology at the Mustansiriyah University, where diagnosed by an endocrinology specialist as acromegaly. Diagnosis was performed on the basis of typical

clinical presentation and laboratory criteria, including elevated level of GH, which were not suppressed during oral glucose load, and elevated insulin-like growth factor. Blood samples were collected from each subject after an overnight fast between 8.0-11.0 a.m. Following the collection, the blood sample was centrifuged at (3000 r/m) for 10 minutes. The resulting supernatant serum was stored at -20°C until time of analyses. Resting whole saliva was collected between 8.0-11.0 a.m. under resting condition. Patients were asked to avoid any oral hygienic procedure, food and fluid (apart from water) and rinse their mouth with water and to generate saliva in their mouth and to spit into a wide test tube. Following the collection, the saliva was centrifuged at (3000 r/m) for 10 minutes. The resulting supernatant was stored at -20°C until time of laboratory analyses. The analyses of samples were done in National Centre for diabetes and endocrinology at the Mustansiriyah University. Insulin like growth factor 1 was determined by IRMA using kit supplied by Immunotech Company France. The applied statistical analyses were the following: mean value, standard deviation, standard error, correlation coefficient (pearson), and significance for various numeric variables included in the present study.

RESULTS

Mean, SD and SE of clinical parameters for healthy and acromegalic patients are presented in table (1). There were increasing in the level of serum IGF-I and salivary IGF-I in acromegalic patients compared to healthy subjects. However, half of the acromegalic patients have salivary IGF-I within the normal range. Some patients had paradoxically low levels of salivary IGF-I, while serum IGF-I concentration was well above the normal range.

Figure 1 and 2 show the correlation of salivary IGF-I to serum IGF-I in both acromegaly and control groups. Acromegalic group shows significant correlation between salivary IGF-I and serum IGF-I concentration, while the control group shows no significant correlation between salivary IGF-I and serum IGF-I concentration.

DISCUSSION

The newer and more sensitive currently available immunoradiometric assay (IRMA) was used for IGF-I measurement to overcome the limitations were inherent to the previous methodology which used to diagnose acromegaly like radioimmunoassay (RIA) (Cordero and Barkan, 2008).

The present study showed that patients with acromegaly have significantly higher mean serum IGF-I levels than healthy individuals. From 40 patients with acromegaly, 36 patients (90%) had increased values of serum IGF-I. Previous study found that insulin-like growth factor-I correlate well with GH activity as measured by mean GH concentration over a 24-h period in healthy individuals. In patients with acromegaly, there is a positive logarithmic-linear relationship with GH and IGF-I, respectively In patients with active acromegaly, IGF-I levels are persistently seen to be elevated to a range that is distinct from that in healthy individuals and this is a key to use serum IGF-I concentration in diagnosis of acromegaly^(11,12,13)

The patients with acromegaly have higher mean salivary IGF-I than the healthy individuals. The acromegalic group shows significant correlation between salivary IGF-I and serum IGF-I concentration, while the control group shows no significant correlation between salivary IGF-I and serum IGF-I concentration. Costigan et al. found a statistically significant difference between normal subjects and active acromegalics for both serum and salivary IGF-I levels. Comparison of the levels of IGF-I in serum and saliva of normal subjects and acromegalic patients pointed to a significant positive linear correlation⁽¹⁴⁾.

Halimi et al. also found that acromegalics have significantly higher mean serum IGF-I and somatotropin concentrations and higher salivary IGF-I levels than the normal subjects. In the group of healthy individuals and those with acromegaly, no significant correlation between salivary IGF-I and serum IGF-I serum IGF-I. Nevertheless, in the combined group of healthy subjects and active acromegalics (n = 30), a significant correlation between serum and salivary IGF-I was observed⁽¹⁵⁾.

A disadvantage of saliva as a sample may arise from the fact that it is an open System where the concentration of IGF-I may depend on the IGF-I content of the gland during salivation ⁽¹⁴⁾. A biological Variation and patient's hydration level could further decrease the salivary IGF-I value in acromegalic pateints. In contrast, serum is a defined System with a long half-life (several hours) of IGF-I ⁽¹⁶⁾ due to association with its binding proteins ⁽¹⁷⁾, and is less influenced by the patient's hydration condition. In conclusion, the measurement of salivary IGF-I concentration may not represented the corresponding serum concentration adequately, so cannot be considered it as alternative diagnostic tool to the acromegalic patients.

Table (1): Mean, SD and SE of clinical parameters for healthy and acromegalic patients

Parameter	Acromegaly group			Control group			P
	Mean	SD	SE	Mean	SD	SE	
Serum IGF-I	782.21ng/mL	333.67	52.76	199.87ng/mL	60.03	13.42	<0.001
Salivary IGF-I	21.26ng/mL	1.15	0.18	20.48ng/mL	0.49	0.11	0.041

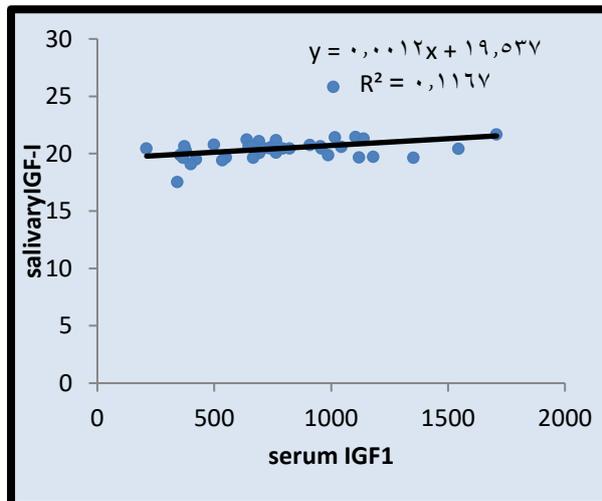


Figure 1: Correlation between serum IGF1 and salivary IGF-I in acromegaly (r = 0.342, p = 0.031)

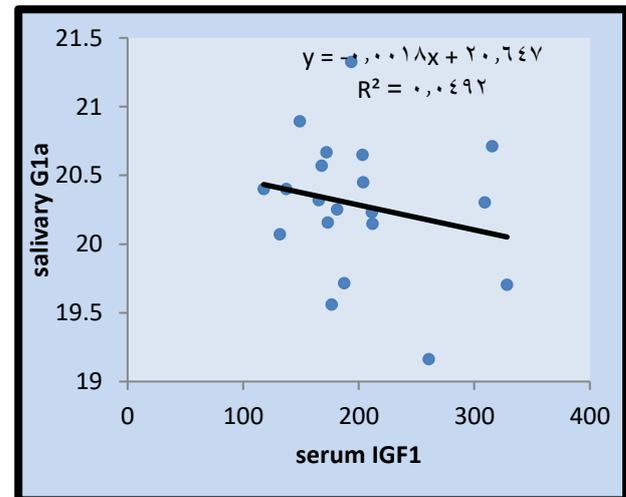


Figure (2): Correlation between serum IGF1 and salivary IGF-I in control (r=-0.222, p=0.347)

REFERENCES

1. Chanson PH, Salenave S. Acromegaly. Orphanet Journal of Rare Diseases 2008; 13(17): 1-17.
2. Jenkins PJ, Carroll PV. Acromegaly. Endocrine Centre 2012; pp.20-28.
3. Melmed S. Medical progress: acromegaly. N Engl J Med 2006; 355:2558–2573.
4. Giustina A, Casanueva FF, Cavagnini F, Chanson P, Clemmons D, Frohman LA, Gaillard R, Ho K, Jaquet P, Kleinberg DL, Lamberts SW, Lombardi G, Sheppard M, Strasburger CJ, Vance ML, Wass JA, Melmed S. Diagnosis and treatment of acromegaly complications. J Endocrinol Invest 2003; 26:1242-1247.
5. Aart J, Albert B, Adrian F, Steven W J, David R. Acromegaly pathology diagnosis and treatment 1st edition. Medical e-Library, 2005;P 20-26.
6. Cordero RA, Barkan AL. Current diagnosis of acromegaly. Reviews in Endocrine and Metabolic Disorders 2008; 9:13–19.
7. Nagler RM. Saliva analysis for monitoring dialysis and renal function. Clin Chem 2008; 54(9): 1415-1417.
8. Edgar WM. Saliva and dental health. Clinical implications of saliva of consensus meeting. B dent J 1990; 169(3-4): 96-98.
9. Ryan, J., Mantle T, Costigan DC. A normal population study of human salivary insulin-like growth factor I (IGF 1) concentrations from birth through puberty. J. Clin. Endocrinol. Metab 1992; 74(4):774-778.
10. Hansson, H. and Tunhall, S. Epidermal growth factor and insulin-like growth factor I are localized in different compartments of salivary gland duct cells. Immunohisto-chemical evidence. Acta Physiol. Scand, 1988; 134: pp. 383-389.
11. Ho K, Weissberger A. Characterization of 24 hour growth hormone (GH) secretion in acromegaly: implications for diagnosis and therapy. Clin Endocrinol 1994; pp. 75-83.
12. Barkan A, Beitins I, Kelch R (1988) Plasma insulin-like growth Factor-I/somatomedin-C in acromegaly: correlation with the degree of growth hormone hypersecretion. J Clin Endocrinol Metab 67:69–73.
13. Clemmons D, Van Wyk J, Ridgway E, Kliman B, Kjellberg R, Underwood L Evaluation of acromegaly by radioimmunoassay of somatomedin-C. N Engl J Med, 1979; 301:1138–1142.
14. Costigan, C. D., Guyda, H. J. & Posner, B. I. Free insulin-like growth factor I (IGF-I) and IGF-II in human saliva. J. Clin. Endocrinol. Metab 1988; 66:1014-1018.
15. Halimi S, Tepavcevic D, Suchanec D, Giljevic Z, Plavsic V and Korsic V. Measurement of Salivary Insulin-Like Growth Factor-I in Acromegaly. Eur. J. Clin. Chem. Clin. Biochem, 1994; 32: 705-707.
16. Guler HR, Zapf J, Schmid C, Froesch RE. Insulin-like growth factors I and II in healthy man. Estimations of half-lives and production rates. Acta Endocrinol. (Copenh.), 1989; 727: 753-758.
17. Hintz RL, Liu F. Demonstration of specific plasma protein binding sites for somatomedin. J. Clin. Endocrinol. Metab. 1977; 45:988-995.