Nadir growth hormone after oral glucose overload in obese subjects

Nadir do hormônio de crescimento em indivíduos obesos após sobrecarga de glicose oral

Pedro Weslley Rosario[1], Daniela Santos Salles[1], Breno Bessa[1], Mariana Silva Furtado[2]

The nadir growth hormone (n-GH) in the oral glucose tolerance test (OGTT) is the gold standard for the demonstration of secretory autonomy of this hormone and a laboratory parameter necessary for the diagnosis of acromegaly (1,2). Although measurement of GH after oral glucose overload is not recommended during treatment with somatostatin analogs or GH receptor antagonists (3), normalization of n-GH continues to be necessary for the definition of "control" after surgical treatment of acromegaly (3). Nadir GH levels vary according to the assay used (4-7) and are influenced by gender, age and body mass index [BMI (4-6,8)]. The inverse correlation with BMI observed in normal subjects (4,6,8) and acromegalic patients (9) indicates the need for adjusting the n-GH cut-off as a function of BMI (4,6,8). We have previously defined n-GH reference values in subjects with a BMI ≤ 27 kg/m^2 (5). The possibility that the current reference values are inadequate (overestimated) for obese subjects led to the elaboration of the present study, for which the objective was to evaluate the n-GH in the OGTT in subjects with a BMI ≥ 30 kg/m^2.

A total of 200 volunteers (120 women and 80 men) ranging in age from 18 to 70 years (median of 44 years), matched with 200 subjects from the previous study (5), who had a BMI ≥ 30 kg/m^2 (median of 34.8 kg/m^2) were studied. The selection criteria, protocol and statistical analysis are described in detail in the previous study (5). Briefly, apparently healthy subjects (excluding pregnant women) without associated diseases who were not using medications that might interfere with GH levels and who presented no abnormalities upon minimum laboratory assessment (glycemia, blood count, albumin, creatinine, TSH, GOT, GPT and bilirubin) were selected. The study was approved by the Ethics Committee of Santa Casa de Belo Horizonte.

The GH Immulite kit (Diagnostic Products Corporation, Los Angeles, CA) was used for the measurement of GH since it is the kit most widely used in Brazil. In addition, the kit meets the requirements of calibrated standards against > 95% pure preparations of GH 22 kDa (10), its specificity for the 22 and 20 kDa isoforms is known (4), and its intra- and interassay sensitivity and variability have been previously established (5,11). The cut-off was defined as the 97.5th percentile of the values found. The Spearman correlation test was used to analyze the correlation between n-GH and age, BMI. The nonparametric Kruskal-Wallis test and the parametric Shapiro-Wilk test were used to compare GH values obtained between groups. P values < 0.05 were considered to be statistically significant.

The n-GH cut-off values for obese women and men were 0.35 µg/L and 0.15 µg/L ($p < 0.05$), respectively. No correlation was observed between n-GH levels and age. However, a difference was found when comparing women ≤ 35 years (n = 40) *versus* > 35 years (n = 80), with higher values in the former (n-GH cut-off: 0.42 µg/L *versus* 0.3 µg/L, $p < 0.05$). There was an inverse correlation between n-GH levels and

[1] Programa de Pós-graduação, Santa Casa de Belo Horizonte, MG, Brazil
[2] Faculdade de Medicina do Vale do Aço, Ipatinga, MG, Brazil

Correspondence to:
Pedro Weslley Rosario
Programa de Pós-graduação, Santa Casa de Belo Horizonte
Av. Francisco Sales, 1111, 9ºD
30150-221 – Belo Horizonte, MG, Brazil
pedrorosario@globo.com

Received on Jan/31/2010
Accepted on May/29/2010

BMI ($r = -0.48$, $p < 0.01$). Testing time necessary to reach n-GH was 30, 60, 90 and 120 min in 52, 108, 36 and 4 subjects, respectively.

In the present investigation, the use of similar selection criteria and matching for gender and age permitted the selection of a group of subjects similar to that evaluated in a previous study from our group (5), except for BMI [> 30 kg/m² (median 34.8 kg/m²) *versus* < 27 kg/m² (median 24 kg/m²), respectively]. This fact, together with the use of an identical protocol and GH assay permits us to conclude that the difference in n-GH observed (Table 1) is indeed due to differences in BMI, with the observation of lower values in obese subjects (4,6,8).

Table 1. Nadir GH values (97.5th percentile) using the Immulite GH kit according to gender, BMI and age

Group	BMI ≤ 27 kg/m² (ref. 5)	BMI ≥ 30 kg/m² (present study)
Women	0.6 µg/L (n = 120)	0.35 µg/L (n = 120)
18-35 years	0.74 µg/L (n = 40)	0.42 µg/L (n = 40)
35-70 years	0.5 µg/L (n = 80)	0.3 µg/L (n = 80)
Men	0.25 µg/L (n = 80)	0.15 µg/L (n = 80)

In the previous investigation (5) involving subjects with a BMI ≤ 27 kg/m², we found no correlation between BMI and n-GH, whereas this correlation was observed in the present study evaluating subjects with a BMI ≥ 30 kg/m² as also demonstrated by other investigators (4,8). In fact, in the study of Arafat and cols. (4), this correlation becomes clearly visible beyond this value. The hypothes is that the influence on n-GH becomes evident when BMI > 30 kg/m² explains the fact that many series (9,12-15) did not find such association since the mean BMI was < 25 kg/m² in all of them and almost all subjects had a BMI < 30 kg/m². Another finding supporting the influence of BMI on GH secretion is the correlation observed between this variable and peak GH after stimulation with GHRH + arginine, with adjustment of the cut-off (11, 8 and 4 ng/mL for BMI < 25, 25-30 and > 30 kg/m², respectively) being recommended for the diagnosis of GH deficiency in adults (16).

In obesity, chronically elevated free fatty acid levels and hyperinsulinemia seem to have a marked effect on the GH/IGF-1 axis (17). GH secretion is inhibited by free fatty acids and an increase of free IGF-1 resulting from reduced IGFBP-1 due to hyperinsulinemia has the same effect (17). On the other hand, increased peripheral sensitivity to GH due to the higher expression of its receptors preserves normal total IGF-1 levels, usually compensating for the lower secretion of GH (17).

We conclude that an inverse correlation exists between BMI and n-GH in the OGTT in obese subjects (BMI > 30 kg/m²), and that adjustment of the n-GH cut-off in the presence of obesity, as suggested by some investigators (4,6,8), indeed seems to be necessary. Nadir GH cut-off values of 0.35 and 0.15 µg/L are suggested for obese women and men, respectively, which are lower than those recommended for non-obese subjects [0.6 and 0.25 µg/L (5)] (Table 1).

Disclosure: no potential conflict of interest relevant to this article was reported.

REFERENCES

1. Melmed S. Acromegaly pathogenesis and treatment. J Clin Invest. 2009;119:3189-202.
2. Barkan A, Bronstein MD, Bruno OD, Cob A, Espinosa-de-los-Monteros AL, Gadelha MR, et al. Management of acromegaly in Latin America: expert panel recommendations. Pituitary. 2010;13:168-75.
3. Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, et al; Acromegaly Consensus Group. Guidelines for acromegaly management: an update. J Clin Endocrinol Metab. 2009;94:1509-17.
4. Arafat AM, Möhlig M, Weickert MO, Perschel FH, Purschwitz J, Spranger J, et al. Growth hormone response during OGTT: the impact of assay method on the estimation of reference values in patients with acromegaly and in healthy controls and the role of gender, age, and BMI. J Clin Endocrinol Metab. 2008;93:1254-62.
5. Rosario PW, Furtado MS. Growth hormone after oral glucose overload: revision of reference values in normal subjects. Arq Bras Endocrinol Metab. 2008;52:1139-44.
6. Colao A, Lombardi G. Should we still use glucose-suppressed growth hormone levels for the evaluation of acromegaly? J Clin Endocrinol Metab. 2008;93:1181-2.
7. Markkanen H, Pekkarinen T, Välimäki MJ, Alfthan H, Kauppinen-Mäkelin R, Sane T, et al. Effect of sex and assay method on serum concentrations of growth hormone in patients with acromegaly and in healthy controls. Clin Chem. 2006;52:468-73.
8. Vierhapper H, Heinze G, Gessl A, Exner M, Bieglmayr C. Use of the oral glucose tolerance test to define remission in acromegaly. Metabolism. 2003;52:181-5.
9. Ronchi CL, Arosio M, Rizzo E, Lania AG, Beck-Peccoz P, Spada A. Adequacy of current postglucose GH nadir limit (< 1 microg/l) to define long-lasting remission of acromegalic disease. Clin Endocrinol (Oxf). 2007;66:538-42.
10. Bidlingmaier M. Problems with growth hormone assays and strategies towards standardization. Eur J Endocrinol. 2008;159(Suppl1):S41-4.
11. Micmacher E, Assumpção RP, Redorat RG, Spina LD, Cruz IC, Silva CA, et al. Growth hormone secretion in response to glucagon stimulation test in healthy middle-aged men. Arq Bras Endocrinol Metab. 2009;53:853-8.
12. Freda PU, Landman RE, Sundeen RE, Post KD. Gender and age in the biochemical assessment of cure of acromegaly. Pituitary. 2001;4:163-71.

13. Chapman IM, Hartman ML, Straume M, Johnson ML, Veldhuis JD, Thorner MO. Enhanced sensitivity growth hormone (GH) chemiluminescence assay reveals lower postglucose nadir GH concentrations in men than women. J Clin Endocrinol Metab. 1994;78:1312-9.
14. Gullu S, Keles H, Delibasi T, Tonyukuk V, Kamel N, Erdogan G. Remission criteria for the follow-up of patients with acromegaly. Eur J Endocrinol. 2004;150:465-71.
15. Endert E, van Rooden M, Fliers E, Prummel MF, Wiersinga WM. Establishment of reference values for endocrine tests – part V: acromegaly. Neth J Med. 2006;64:230-5.
16. Ho KK, 2007 GH. Deficiency Consensus Workshop Participants. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. Eur J Endocrinol. 2007;157:695-700.
17. Maccario M, Tassone F, Grottoli S, Rossetto R, Gauna C, Ghigo E. Neuroendocrine and metabolic determinants of the adaptation of GH/IGF-I axis to obesity. Ann Endocrinol (Paris). 2002;63:140-4.