Endocrinología, Diabetes y Nutrición 68 (2021) 1–2

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

EDITORIAL

Acromegaly: Diabetes and HOMA-IR☆

Diabetes y HOMA-IR en la acromegalia

Betina Biagetti[a,*], **Rafael Simó**[a,b]

[a] *Servicio de Endocrinología y Nutrición, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, Grupo de investigación en Diabetes, Endocrinología y Metabolismo, Instituto de Investigación Vall d'Hebron (VHIR)*
[b] *Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III (ISCIII), Madrid, Spain*

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is classically considered to be a good insulin resistance (IR) index in acromegaly (ACRO).[1] However, recent studies have provided data against the long assumed classical concept that insulin resistance is the main reason for the high prevalence of type 2 diabetes mellitus (DM2) in patients with ACRO.[2,3] In addition, the underlying pathophysiological mechanisms contributing to altered glucose metabolism in ACROs are not fully understood, and may be different from those traditionally implicated in DM2.[4,5] On the other hand, insulin-like growth factor type I (IGF-1) is more closely correlated to glucose abnormalities than growth hormone (GH) measured randomly or after a glucose overload.[4] Thus, although DM2 is a well-recognized comorbidity in ACRO, it remains subject to debate whether or not IR is the main underlying mechanism.

HOMA-IR is a surrogate marker of IR based on the relationship between fasting glucose and insulin levels proposed by Matthews in 1985,[6] the formula being expressed as follows depending on the units in which glucose is expressed:

$$\text{HOMA-IR} = \text{Fastinginsulin(mIU/mL)} \times \textit{Fastingglucose(mmol/l)}/22.5$$

$$\text{HOMAIR} = \text{Fastinginsulin(mIU/mL)} \times \textit{Fastingglucose(mg/dl2)}/405$$

Its use in ACRO is widespread, though there are certain aspects inherent to this disease condition that should be considered when interpreting HOMA-IR:

(1) In patients with ACRO, the HOMA-IR values could lead to falsely elevated results due to the cross-reactivity between IGF-1 and endogenous insulin observed in some of the currently available kits for measuring circulating insulin.
(2) It is not easy to determine whether a patient with ACRO has diabetes as a result of acromegaly or presented previous diabetes.
(3) Somatostatin analogs (SSAs) widely used in the treatment of ACRO can bind to somatostatin receptor subtypes 2 and 5 of the pancreatic beta cell, inhibiting insulin secretion,[7] and thus invalidating the use of the Matthews formula in this context.

☆ Please cite this article as: Biagetti B, Simó R. Diabetes y HOMA-IR en la acromegalia. Endocrinol Diabetes Nutr. 2021;68:1–2.

* Corresponding author.
E-mail addresses: bbiagetti@hotmail.es, bbiagetti@vhebron.net (B. Biagetti).

https://doi.org/10.1016/j.endien.2020.11.005

The prevalence of DM2 in ACRO differs significantly among studies, ranging from 19 to 56%.[4,8,9] This prevalence is not only higher than that of the general population, but is also higher than that of population groups at high risk of developing diabetes.[4] Although this classically has been attributed to the diabetogenic action of growth hormone (GH), other possible implicated factors should be considered.

Potential diagnostic bias is one such factor, since most patients undergo an oral glucose tolerance test during the ACRO diagnostic procedure. In addition, factors other than those traditionally involved in the development of DM2, such as the ectopic presence and dysfunction of visceral adipose tissue and alterations to certain adipokines,[10] as well as increased gluconeogenesis, could contribute to glycemic worsening in these patients.[1,5,11] In this regard, our group found a reduction in branched-chain amino acid levels in 30 patients with active ACRO as compared to age-matched controls, consistent with activation of this gluconeogenic pathway.[12] In addition, an increased prevalence of diabetes was reported during the follow-up of these patients,[13] probably reflecting the influence of other confounding factors such as age, specific treatment of acromegaly, and/or beta-cell deterioration.[3,14] Overall, other factors in addition to GH appear to play a significant role in explaining the high prevalence of diabetes in patients with ACRO.

In order to clarify the significance of HOMA-IR in patients with ACRO, we conducted a meta-analysis assessing HOMA-IR in patients with ACRO with and without diabetes as compared to their reference population.[15] The results of this meta-analysis showed that HOMA-IR in previously untreated patients with active ACRO was higher than in the reference population, even in patients without diabetes. This finding confirms that insulin resistance is an early event in ACRO. In addition, the metabolic impact was different after surgery than it was when SSAs were used. Thus, although a decrease in HOMA-IR was seen with both treatments, it proved more effective with surgery at the expense of post-treatment improvement in basal glucose, which was not seen after SSA administration. This finding deserves specific comment, because the reduction in insulin levels induced by SSAs led to lower HOMA-IR values, which did not imply parallel reductions in insulin resistance. In fact, these patients had higher basal blood glucose levels associated with lower insulin levels. These findings suggest that HOMA-IR is not useful as a measure of insulin resistance in patients treated with SSAs.

In sum, in patients with active ACRO without medical treatment, there is an increase in IR as assessed by HOMA versus the reference population, even in patients without diabetes. However, HOMA-IR is not a good method for assessing IR in ACRO patients treated with SSAs.

Lastly, stricter monitoring of glucose levels in patients treated with SSAs seems advisable.

References

1. Møller N, Schmitz O, Jøorgensen JO, Astrup J, Bak JF, Christensen SE, et al. Basal- and insulin-stimulated substrate metabolism in patients with active acromegaly before and after adenomectomy. J Clin Endocrinol Metab. 1992;74:1012–9.
2. Niculescu DA, Dusceac R, Caragheorgheopol A, Popescu N, Poiana C. Disposition index in active acromegaly. Front Endocrinol. 2019;10.
3. Kinoshita Y, Fujii H, Takeshita A, Taguchi M, Miyakawa M, Oyama K, et al. Impaired glucose metabolism in Japanese patients with acromegaly is restored after successful pituitary surgery if pancreatic β-cell function is preserved. Eur J Endocrinol. 2011;164:467–73.
4. Frara S, Maffezzoni F, Mazziotti G, Giustina A. Current and emerging aspects of diabetes mellitus in acromegaly. Trends Endocrinol Metab. 2016;27:470–83.
5. Ferraù F, Albani A, Ciresi A, Giordano C, Cannavò S. Diabetes secondary to acromegaly: physiopathology, clinical features and effects of treatment. Front Endocrinol (Lausanne). 2018;9:358.
6. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
7. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol. 1999;20:157–98.
8. Mestron A, Webb SM, Astorga R, Benito P, Catala M, Gaztambide S, et al. Epidemiology, clinical characteristics, outcome, morbidity and mortality in acromegaly based on the Spanish Acromegaly Registry (Registro Espanol de Acromegalia, REA). Eur J Endocrinol. 2004;151:439–46.
9. Maione L, Brue T, Beckers A, Delemer B, Petrossians P, Borson-Chazot F, et al. Changes in the management and comorbidities of acromegaly over three decades: the French Acromegaly Registry. Eur J Endocrinol. 2017;176:645–55.
10. Olarescu NC, Bollerslev J. The impact of adipose tissue on insulin resistance in acromegaly. Trends Endocrinol Metab. 2016;27:226–37.
11. Hannon AM, Thompson CJ, Sherlock M. Diabetes in patients with acromegaly. Curr Diab Rep. 2017;17:8.
12. Biagetti B, Herance JR, Ferrer R, Aulinas A, Palomino-Schätzlein M, Mesa J, et al. Metabolic fingerprint of acromegaly and its potential usefulness in clinical practice. J Clin Med. 2019;8:1549.
13. Jonas C, Maiter D, Alexopoulou O. Evolution of glucose tolerance after treatment of acromegaly: a study in 57 patients. Horm Metab Res. 2016;48:299–305.
14. Kasayama S, Otsuki M, Takagi M, Saito H, Sumitani S, Kouhara H, et al. Impaired beta-cell function in the presence of reduced insulin sensitivity determines glucose tolerance status in acromegalic patients. Clin Endocrinol (Oxf). 2000;52:549–55.
15. Biagetti B, Aulinas A, Casteras A, Pérez-Hoyos S, Simó R. HOMA-IR in acromegaly: a systematic review and meta-analysis. Pituitary. 2020.