Endocrinol Diabetes Nutr. 2017;64(1):26–33

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Zinc alpha-2 glycoprotein is overproduced in Cushing's syndrome

Xavier Escoté[a,1], Gloria B. Aranda[a,1], Mireia Mora[a,b,c], Gregori Casals[d], Joaquim Enseñat[c,e], Oscar Vidal[c,f], Yaiza Esteban[a], Irene Halperin[a,b,c,1], Felicia A. Hanzu[a,b,c,*,1]

[a] *Group of Endocrine Disorders, IDIBAPS, Barcelona, Spain*
[b] *Department of Endocrinology and Nutrition, Hospital Clínic, Barcelona, Spain*
[c] *University of Barcelona, Spain*
[d] *Biochemistry and Molecular Genetics, Hospital Clínic, Barcelona, Spain*
[e] *Department of Neurosurgery, Hospital Clínic, Barcelona, Spain*
[f] *Department of Endocrine Surgery, Hospital Clínic Barcelona, Spain*

Received 30 May 2016; accepted 18 October 2016
Available online 18 January 2017

KEYWORDS
Cushing syndrome;
Zinc alpha-2 glycoprotein;
Lipolysis;
Fat redistribution;
Glucocorticoids

Abstract
Introduction: Cushing syndrome (CS), an endogenous hypercortisolemic condition with increased cardiometabolic morbidity, leads to development of abdominal obesity, insulin resistance, diabetes and proatherogenic dyslipidemia. Zinc alpha-2 glycoprotein (ZAG) is a recently characterized lipolytic adipokine implicated in regulation of adipose tissue metabolism and fat distribution. *In vitro* and animal studies suggest that glucocorticoids interact with ZAG secretion and action. To assess the relationship between ZAG and glucocorticoids in a human model of hypercortisolism, circulating ZAG levels were tested in patients with CS and its counterpart controls.
Methods: An observational, cross-sectional study on 39 women, 13 with active CS and 26 controls matched by age and body mass index. Plasma ZAG levels (μg/ml) were measured by ELISA and correlated with hypercortisolism, metabolic, and phenotypic parameters.
Results: Plasma ZAG levels were significantly higher in patients with CS compared to controls (64.3 ± 16.6 *vs.* 44.0 ± 16.1, $p = 0.002$). In a univariate analysis, ZAG levels positively correlated to 24-h urinary free cortisol ($p = 0.001$), body mass index ($p = 0.02$), non-esterified fatty acids ($p = 0.05$), glucose ($p = 0.003$), LDL-C ($p = 0.028$), and type 2 diabetes mellitus ($p = 0.016$), and were inversely related to total adiponectin levels ($p = 0.035$). In a multivariate analysis,

* Corresponding author.
E-mail address: fhanzu@clinic.ub.es (F.A. Hanzu).
[1] These authors have contributed equally to this work.

http://dx.doi.org/10.1016/j.endinu.2016.10.002

after adjusting for CS, ZAG levels only correlated with body mass index ($p = 0.012$), type 2 diabetes mellitus ($p = 0.004$), and glucose ($p < 0.001$).
Conclusion: This study provides initial evidence that plasma ZAG levels are higher in patients with CS as compared to controls. The close relationship of ZAG with metabolic and phenotypic changes in CS suggests that ZAG may play a significant role in adipose tissue changes in hypercortisolism.

PALABRAS CLAVE
Síndrome Cushing;
Zinc alfa-2 glucoproteína;
Lipólisis;
Redistribución tejido adiposo;
Glucocorticoides

Aumento de la glucoproteína zinc alfa-2 en el síndrome de Cushing

Resumen
Introducción: El síndrome de Cushing (SC) es un estado de hipercortisolismo endógeno en el que se observa un incremento del riesgo cardiovascular asociado al desarrollo de obesidad abdominal, insulinorresistencia, diabetes y dislipidemia aterogénica. La zinc alfa-2 glucoproteína (ZAG) es una adipocina lipolítica recientemente caracterizada que está implicada en la regulación del metabolismo del tejido adiposo y la distribución de la grasa. Estudios *in vitro* y en animales indican que los glucocorticoides interaccionan con la secreción y acción de ZAG. Para evaluar la relación entre ZAG y los glucocorticoides en un modelo humano de hipercortisolismo, se analizaron los niveles circulantes de ZAG en pacientes con SC y sus correspondientes controles.
Métodos: Estudio observacional en 39 mujeres, 13 con SC activo y 26 controles pareadas por edad e índice de masa corporal. Los niveles plasmáticos de ZAG (μg/ml) se determinaron mediante ELISA y se correlacionaron con los parámetros de hipercortisolismo, metabólicos y fenotípicos.
Resultados: Las concentraciones plasmáticas de ZAG fueron significativamente más elevadas en los pacientes con SC ($64{,}3 \pm 16{,}6$ vs. $44 \pm 16{,}1$; $p = 0{,}002$). En el análisis univariante los niveles de ZAG se correlacionaron positivamente con cortisol libre urinario ($p = 0{,}001$), índice de masa corporal ($p = 0{,}02$), ácidos grasos no esterificados ($p = 0{,}05$), glucosa ($p = 0{,}003$), c-LDL ($p = 0{,}028$) y diabetes mellitus ($p = 0{,}016$) e inversamente con adiponectina total ($p = 0{,}035$). En el análisis multivariante, después de ajustar por el SC, los niveles de ZAG solo se correlacionaron con el índice de masa corporal ($p = 0{,}012$), la diabetes mellitus tipo 2 ($p = 0{,}004$) y la glucosa ($p < 0{,}001$).
Conclusión: Nuestro estudio proporciona la primera evidencia de las concentraciones plasmáticas de ZAG en el SC. Los pacientes con SC presentan concentraciones más elevadas de ZAG que los controles. La estrecha relación de ZAG con las alteraciones metabólicas y fenotípicas del SC indica que ZAG podría desempeñar un papel importante en las alteraciones del tejido adiposo en el hipercortisolismo.

Introduction

Cushing's syndrome (CS) is a complex, rare endocrine condition, with an incidence ranging from 1.2 to 2 patients/million in population. It is characterized by a chronic exposition to endogenous glucocorticoid (GC) excess, which exerts important changes in body composition by the induction of central fat accumulation and reduction in lean body mass. If untreated, CS evolution is marked by severe complications, with a high cardio-metabolic morbidity and cardiovascular mortality.[1,2] One of the hallmarks of this syndrome is the trunk accumulation of adipose tissue; the strongest predictor of cardio-metabolic disease relative to fat accumulated elsewhere.[3,4] GC exert different effects on human fat depots according to their localization, mainly due to the higher expression of the GC receptor in visceral fat, with a paradoxical effect, consisting of adipogenesis, and lipolysis induction, free fatty acid release and direct decrease of insulin sensitivity.[5,6]

On the other hand, the adipokines secreted by the visceral adipose tissue are currently considered main effectors of outstanding metabolic events, such as inflammation, atherosclerosis, and insulin resistance. They represent an important link between visceral adiposity and idiopathic obese cardio-metabolic disease.[3,4,7] I*n vitro e*xperiments have demonstrated that GC treatment on the adipocyte cell line 3T3-L1 induces changes in the expression and secretion of pro-inflammatory serum amyloid A-3 (SAA-3) and pro-thrombotic plasminogen activator inhibitor-1 (PAI-1), but suppresses interleukin 6 and adiponectin.[6] *In vivo*, CS patients present alterations in the pattern of various adipokines associated with an increased risk of atherothrombotic disease, such as a higher level of soluble tumour necrosis factor receptor 1 (sTNF-R1), resistin, PAI-1 and heterogeneous levels of adiponectin.[8]

Zinc alpha-2 glycoprotein is a recently characterized adipokine.[9,10] Data from *in vivo* and *ex vivo* studies revealed that as a consequence of its similarities with the