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Overexpression of hepatic 5α-reductase and 11β-hydroxysteroid dehydrogenase type 1 in visceral adipose tissue is associated with hyperinsulinemia in morbidly obese patients

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ARTICLE INFO

Article history:
Received 7 January 2011
Accepted 3 May 2011

ABSTRACT

11-β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts cortisone to cortisol, mainly in the liver and visceral adipose tissue (VAT), and has been implicated in several metabolic disorders. The absence of systemic hypercortisolism in central obesity could be due to increased inactivation of cortisol to its tetrahydrometabolites by the hepatic enzymes 5α- and 5β-reductases. Our aim was to assess the expression of the reductases in the liver and of 11β-HSD1 in the liver and VAT in morbidly obese patients and to analyze their association with clinical, anthropometric, and biochemical parameters. Hepatic and VAT samples were obtained during bariatric surgery. 5α- and 5β-reductases, 11β-HSD1, and 18S expression was measured using real-time polymerase chain reaction. Anthropometric and biochemical variables were analyzed. Forty-one patients were recruited (age, 41.8 ± 10.6 years; body mass index, 42.1 ± 6.6 kg/m^2; 71% women). The expression of hepatic 5α- and 5β-reductases was positively correlated (r = +0.53, P = .004), and their expression levels were correlated with hepatic 11β-HSD1 expression (r = +0.61, P < .001 for 5α-reductase and r = +0.50, P < .001 for 5β-reductase). Hepatic 5α-reductase was associated with insulin (r = +0.34, P = .015). Visceral adipose tissue 11β-HSD1 expression was associated with glucose (r = +0.37, P = .025) and

Author contributions: René Baudrand: design of the study; laboratory work; data collection, analysis, and interpretation; manuscript writing. José Miguel Domínguez: design of the study; laboratory work; data collection, analysis, and interpretation; manuscript writing. Cristian A Carvajal: laboratory work; data collection, analysis, and interpretation; manuscript writing. Arnoldo Riquelme: data collection, analysis, and interpretation; manuscript writing. Carmen Campino: data analysis and interpretation; manuscript writing. Stefano Macchiavello: data analysis and interpretation; manuscript writing. Milan Bozinovic: data analysis and interpretation; manuscript writing. Mauricio Morales: laboratory work; data collection, analysis, and interpretation. Margarita Pizarro: laboratory work; data collection. Nancy Solis: laboratory work; data collection. Alex Escalona: data collection. Camilo Boza: data collection. Marco Arrese: design of the study; data analysis and interpretation; manuscript writing. Carlos E Fardella: design of the study; data analysis and interpretation; manuscript writing.

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doi:10.1016/j.metabol.2011.05.001

insulin (r = +0.54, P = .002). Our results showed that 5α-reductase and VAT 11β-HSD1 expressions were associated with insulinemia. These findings suggest that overexpression of 5α-reductase, through a higher inactivation of cortisol in the liver, could have a protective role in preserving hepatic sensitivity to insulin. The overexpression of liver reductases in obesity could be an adaptive response to an increase in cortisol production by the liver and visceral 11β-HSD1 to avoid systemic hypercortisolism.

1. Introduction

During the past decades, there has been a significant increase in the prevalence of obesity and its associated metabolic disorders, such as alterations in glucose metabolism, dyslipidemia, and arterial hypertension. These metabolic abnormalities have been associated with an increased risk of diabetes mellitus type 2 (DM2), cardiovascular morbidity and mortality, and nonalcoholic fatty liver disease [1].

Patients with central obesity have a similar phenotype and metabolic alterations to patients with systemic hypercortisolism or Cushing syndrome, including hypertension, insulin resistance, DM2, and dyslipidemia, among others [2]. However, patients with central obesity have normal plasmatic and urinary cortisol concentrations [3]. A plausible explanation for this phenomenon is that obesity is associated with alterations of cortisol metabolism in local tissues and in the splanchnic bed, combined with functional hypercortisolism due to subtle alterations of the hypothalamic-pituitary-adrenal axis [4].

In patients with central obesity, splanchnic hypercortisolism could arise from cortisol production by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts inactive cortisone to active cortisol mainly in the liver, but also in the visceral and subcutaneous adipose tissue [5,6]. Recent studies with murine models and human data have shown a potential pathogenic role of 11β-HSD1 and splanchnic hypercortisolism in central fat distribution [7]; DM2; metabolic syndrome [8,9]; hypertriglyceridemia; low high-density lipoprotein (HDL) [10]; and, as published recently by our group, arterial hypertension [11].

The absence of systemic hypercortisolism in patients with central obesity could be due to the action of the hepatic enzymes 5α- and 5β-reductases, which metabolize cortisol to its inactive tetrahydrometabolites, thus preventing the activation of the glucocorticoid receptors at a systemic level [12,13]. However, no information is available regarding the potential changes in the expression of these reductases in human obesity. Thus, the aim of this study was to evaluate the expression of the hepatic enzymes 5α- and 5β-reductases and 11β-HSD1 in hepatic and visceral adipose tissue (VAT) in morbidly obese patients and to determine their association with clinical, anthropometric, and biochemical parameters.

2. Materials and methods

All patients were recruited from the Obesity Program, which belongs to the Department of Surgery, Pontificia Universidad Católica de Chile, during a 27-month period. Patients who met the criteria for surgical treatment of their obesity (body mass index [BMI] >40 kg/m^2 or BMI >35 kg/m^2 with metabolic disorders) were evaluated by a multidisciplinary team and underwent a clinical and biochemical evaluation. We excluded obese patients with chronic or endocrine diseases such as advanced renal failure, symptomatic heart failure, Cushing syndrome, and primary aldosteronism. This study was approved by the Ethical Committee of the Pontificia Universidad Católica, and all patients gave their informed consent before undergoing the bariatric surgery.

Age and BMI before surgery, calculated as weight (kilograms)/height (square meters), were considered as clinical parameters for this study. Blood samples for each individual were obtained between 9:00 and 10:00 AM after a 12-hour overnight fast. The patients rested for 10 minutes before blood samples were withdrawn to measure glucose, insulin, lipid profile, high-sensitivity C-reactive protein (hs-CRP), hepatic aminotransferases, and adiponectin. Plasma and tissue samples were stored at -80°C until analysis.

2.1. Hormonal and biochemical assays

Blood samples from each individual were obtained. Fasting serum concentration of glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipid profile were measured using an automated Roche Hitachi Modular chemical analyzer (Hitachi, Tokyo, Japan). Serum fasting insulin concentration was measured with the Advia Centaur XP equipment (Siemens, Deerfield, IL), and the intra- and interassay coefficients of variation (CVs) were 3.2% and 2.6%, respectively. Insulin resistance was estimated with the homeostasis model assessment of insulin resistance index (HOMA-IR). Acosta et al defined insulin resistance in Chile as HOMA-IR greater than 2.6 in nondiabetic subjects [14]. The hs-CRP was measured with a latex particle-enhanced nephelometric immune assay in BN ProSpec equipment (Dade Behring, Deerfield, IL); and the intra- and interassay CVs were 2.6% and 1.3%, respectively. Adiponectin concentration was measured using the Quantikine enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN); and the intra- and interassay CVs were 2.5% and 6.8%, respectively. Liver samples were obtained by intraoperative biopsy, and VAT was obtained from the greater omentum. Samples were retrieved and stored, and RNA was extracted as described previously by our group [6].

2.2. Assessment of enzyme expression in tissue samples

Real-time polymerase chain reaction (PCR) was performed with a Taq DNA Polymerase kit (Fermentas, Hanover, MD) using primers and probes for the 11β-HSD1 gene described

previously [6]. 5α-Reductase (sense primer 5′- ATGAACCT-GGGTGGCTTATG-3′, antisense primer 5′-GCAAGCAGCATG-TAACCTCA-3′, and probe CATGACCCTGGATGGCTACT) and 5β-reductase (sense primer 5′- TCTCAGTGCTGCAAGTCACC-3′, antisense primer 5′-GCCCCATCAATATGTCGGTA-3′, and probe 5′- CCATCATCGGACTTGGTACC-3′) transcripts were amplified in a Rotor-Gene 6000 real-time thermocycler (Corbett, Concorde, Australia). Reaction conditions were as follows: 3 minutes at 95°C, followed by 40 cycles of 15 seconds at 95°C, 15 seconds at 58°C, and 20 seconds at 72°C. The real-time data were obtained during the extension phase, and threshold cycle values were obtained at the log phase of each gene amplification. The results are expressed in arbitrary units (AU) and normalized against 18S RNA expression. The specificity of PCR products was confirmed by melting temperature determination of the PCR product and high-resolution 4% agarose gels (Invitrogen, Carlsbad, CA). Gene-specific primers were obtained from IDT (Coralville, IA), and their specificity was confirmed using BLAST analysis software.

2.3. Data analysis

Normal distribution of continuous variables was assessed with Shapiro-Wilk test. Comparison of enzyme expression values and biochemical parameters was performed using Mann-Whitney nonparametric test. Data are presented as median and interquartile range (percentile [p]25-p75). Spearman test was used to determine correlations between genetic expressions of the enzymes. To compare tissue gene expression in the liver and VAT, we used a generalized linear model. A P value < .05 was considered statistically significant. Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS, Chicago, IL) and GraphPad Prism 5 (La Jolla, CA).

3. Results

A total of 41 patients met the inclusion criteria: 29 (70%) out of 41 were female, median age was 41.0 (p25-p75, 34.0-47.5) years, and median BMI was 36.5 (p25-p75, 36.5-47.0) kg/m^2. In this cohort, 14% had DM2 and 39% had hypertension. Despite an unbalanced sex ratio, when analyzing our data by sex, we did not find any significant difference in the results presented below. Biochemical characteristics are shown in Table 1.

3.1. Hepatic 5α- and 5β-reductase messenger RNA expression in morbidly obese patients

When analyzing all patients, we observed that 5α-reductase messenger RNA (mRNA) expression correlated positively with 5β-reductase mRNA expression (r = +0.53, P = .001). The mRNA expression of 5α-reductase was approximately 3-fold lower than the mRNA expression of 5β-reductase in our patients.

The mRNA expression of both reductases did not correlate with anthropometric variables such as body weight or BMI. Hepatic 5α-reductase mRNA expression was associated with biochemical parameters; it showed a positive correlation with fasting serum insulin (r = +0.39, P = .015, Fig. 1B) and an inverse correlation with ALT (r = –0.32, P = .045) (Table 2). There was also a trend for a positive correlation between hepatic 5α-reductase mRNA expression and fasting serum glucose (r = +0.28, P = .081). 5α- or 5β-reductase mRNA expression did not correlate with hs-CRP, triglycerides, HDL, low-density lipoprotein (LDL), AST, or adiponectin. Sex analysis showed no differences in 5α- and 5β-reductase mRNA expression or in their relationship with anthropometric or biochemical parameters.

Table 1 – Biochemical features of recruited patients

n = 41	Median (p25-p75)
Glucose (mg/dL)	108 (85.0-182.0)
Insulin (μIU/mL)	15.2 (9.3-20.2)
HOMA-IR	4.1 (2.6-6.0)
LDL (mg/dL)	124.5 (101.2-5.7)
HDL (mg/dL)	48.0 (39.5-57.0)
Triglycerides (mg/dL)	137 (85.0-169.5)
hs-CRP (mg/L)	3.6 (2.4-6.5)
Adiponectin (μg/mL)	3.9 (20.6-5.7)
Hepatic 11β-HSD1 (AU)	27.2 (20.6-38.3)
VAT 11β-HSD1 (AU)	1.4 (1.0- 5.6)
Hepatic 5α-reductase (AU)	4.7 (2.7-6.6)
Hepatic 5β-reductase (AU)	17.0 (11.8-23.9)

3.2. 11ß-Hydroxysteroid dehydrogenase type 1 mRNA expression in morbidly obese patients

Hepatic 11β-HSD1 mRNA expression correlated positively with the mRNA expression of both reductase enzymes (r = +0.61, P < .001 for 5α-reductase enzyme [Fig. 1A] and r = +0.50, P < .001 for 5β-reductase enzyme). However, VAT 11β-HSD1 mRNA expression did not correlate with 5α- and 5β-reductase enzymes mRNA expression.

When analyzing anthropometric variables, hepatic 11 β-HSD1 mRNA expression was negatively correlated with BMI (r = –0.33, P = .04). Visceral adipose tissue 11β-HSD1 enzyme mRNA expression was not associated with anthropometric variables.

When analyzing biochemical variables, hepatic 11β-HSD1 was positively associated with both aminotransferase enzymes (r = +0.45, P = .004 for ALT and r = +0.49, P = .005 for AST), but was not associated with serum insulin, glucose, or HOMA-IR. Visceral adipose tissue 11β-HSD1 enzyme mRNA expression was associated with fasting glucose (r = +0.37, P = .025) and fasting insulin (r = +0.54, P = .002, Fig. 1C) (Table 2). We did not observe an association between hepatic or VAT 11β-HSD1 expression with hs-CRP, triglycerides, HDL, LDL, or adiponectin. Sex analysis showed no differences in hepatic and VAT 11β-HSD1 mRNA expression or in their relationship with biochemical parameters.

4. Discussion

In the present study, we found that, in morbidly obese patients, hepatic 5α- and 5β-reductase mRNA expressions were positively correlated with hepatic 11β-HSD1 mRNA expression. This observation could reflect that, in central obesity, there is an increased local cortisol production by the

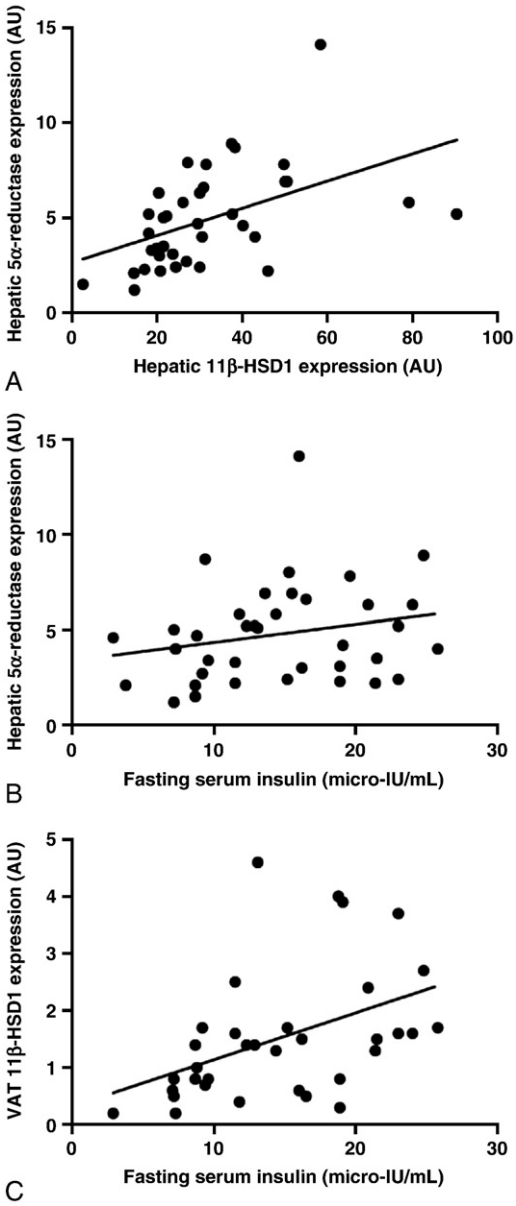

Fig. 1 – Correlations between the expression of enzymes and insulinemia. A, Correlation between of hepatic 11ß-HSD1 mRNA expression and 5α-reductase mRNA expression (r = +0.61, P < .001, Spearman correlation test). B, Correlation between hepatic 5α-reductase mRNA expression and fasting serum insulin (r = +0.39, P = .015, Spearman correlation test). C, Association between VAT mRNA 11ß-HSD1 expression and fasting serum insulin (r = +0.54, P = .002, Spearman correlation test).

contribution of liver 11β-HSD1 expression. Recently, it was reported that the liver accounts for most splanchnic cortisol production in obese nondiabetic humans [15] and that local hypercortisolism could induce an upregulation of the expression of hepatic reductases, which metabolize cortisol to its inactive tetrahydrometabolites, thus avoiding glucocorticoid receptor activation [15-17].

The positive correlation between hepatic 5α-reductase expression and fasting insulin could be also interpreted as an adaptive response to alterations in cortisol metabolism [18]. The increase in cortisol production could be counterbalanced through enhanced 5α- and 5β-reductase activities, decreasing local glucocorticoid availability in the liver, with the aim of preserving hepatic sensitivity to insulin [17].

The positive correlation between VAT 11β-HSD1 expression and fasting insulin could reflect that secondary splanchnic hypercortisolism may induce hepatic insulin resistance, thus enhancing pancreatic production of this hormone. Studies in healthy subjects have shown that cortisol generates impaired suppression of hepatic glucose production by insulin in the postprandial state [19,20]. New studies support the hypothesis that 11β-HSD1 could induce a local diabetogenic effect by increased glucose production, pancreatic β-cell damage, and decreased glucose-stimulated insulin secretion, with an increased risk for hyperinsulinemia, glucose intolerance, and DM2 [21,22].

The positive correlation found between hepatic 11β-HSD1 and aminotransferases (ALT and AST) could be related to nonalcoholic steatohepatitis, which is frequently observed in morbidly obese patients. Furthermore, hepatic steatosis is prevalent in patients with Cushing syndrome; and cortisol metabolism alterations in the liver have been proposed as a pathogenic factor in subjects with nonalcoholic steatohepatitis [23-25].

Murine model with overexpression of the 11β-HSD1 in the liver and adipose tissue is associated with an increased risk of diabetes, hyperlipidemia, and visceral obesity [26]. Moreover, a knockout mouse model for this enzyme shows an opposite phenotype [27]. Further studies in humans have demonstrated an increase of 11β-HSD1 activity in adipose tissue in overweight patients compared with lean subjects and in patients with DM2 compared with subjects without it [8,28]. Recently, some authors have tested the effect of different selective oral inhibitors of 11β-HSD1 in hepatic glucose production [29]. Feig et al [28] reported that a new oral 11β-HSD1 inhibitor had modest improvements in glycosylated hemoglobin, body weight, and blood pressure in patients with DM2 and metabolic syndrome.

Although the phenotypic similarities between central obesity and patients with glucocorticoid excess have

Table 2 – Summary of significant associations found between the expression of hepatic 5α-reductase, and hepatic and VAT 11ß-HSD1 with anthropometric and biochemical variables

Enzyme	Biochemical parameter
Hepatic 5α-reductase	Serum glucose r = +0.28, p=0.081
	Serum insulin r = +0.39, p= 0.015
	ALT r = −0.32, p=0.045
Hepatic 11β-HSD1	BMI r = −0.33, p=0.04
	ALT r = +0.45, p=0.004
	AST r = +0.49, p=0.005
VAT 11β-HSD1	Serum glucose r = +0.37, p=0.025
	Serum insulin r = +0.54, p=0.002

suggested that cortisol contributes to their pathogenesis, there is still debate relating to the contribution of the liver and VAT to portal cortisol production in humans and the role of hypothalamic-pituitary-adrenal axis hyperactivation [30-32]. Regardless of this controversy, upregulation of hepatic reductase expression, enhancing cortisol metabolism to its inactive tetrahydrometabolites, is a final path to avoid systemic hypercortisolism.

The strength of our work is to analyze, in human tissues including liver and VAT, 2 enzymatic mechanisms that counterbalance, suggesting that local hypercortisolism could upregulate the expression of hepatic reductases, decreasing glucocorticoid receptor activation. One limitation regarding the interpretation of our results is the fact that we could only evaluate 11β-HSD1 mRNA expression. Previous reports have found a good correlation between 11β-HSD1 mRNA and protein levels in adipose tissue [27]. Although we have not measured the expression of 5α- and 5β-reductases in adipose tissue, previous work has demonstrated that 5α-reductase activity correlates with fasting insulin [17]. A complementary assessment of 11β-HSD1 activity in vivo, not performed in this study, is the determination of urinary corticosteroid metabolites. A study from our group showed that decreased 11β-HSD type 2 and 5β-reductase activities evaluated by urinary tetrahydrometabolites could be fundamental to the pathogenesis of essential hypertension [11]. As our results cannot prove causality, it would be interesting to evaluate in the future the mRNA expression of hepatic reductases after weight loss in these patients to support our hypothesis.

In conclusion, our results suggest that overexpression of hepatic 5α-reductase, through a higher inactivation of cortisol in the liver, could have a protective role in the maintenance of insulin sensitivity in the liver. The overexpression of liver reductases could be a response to an increase in cortisol production by the liver and visceral 11β-HSD1 in obesity to avoid systemic hypercortisolism.

Funding

This study was supported by Chilean grants FONDEF D08I1087 and FONDECYT 1110455 and by Millenium Nucleus in Immunology and Immunotherapy (NMII P07/088-F).

Conflict of Interest

The authors have nothing to declare.

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