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Research Article

Gender-dependent association of *HSD11B1* single nucleotide polymorphisms with glucose and HDL-C levels

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Abstract

In this study, we investigated the influence of two SNPs (rs846910 and rs12086634) of the *HSD11B1* gene that encodes 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1), the enzyme that catalyzes the conversion of cortisol to cortisone, on variables associated with obesity and metabolic syndrome in 215 individuals of both sexes from southern Brazil. The *HSD11B1* gene variants were genotyped using the TaqMan SNP genotyping assay. Glucose, triglycerides, total cholesterol, HDL-cholesterol and LDL-cholesterol were measured by standard automated methods. Significant results were found in women, with carriers of the G allele of SNP rs12086634 having higher glucose levels than non-carriers. Carriers of the A allele of SNP rs846910 had higher levels of HDL-cholesterol. The involvement of both polymorphisms as independent factors in determining the levels of glucose and HDL-cholesterol was confirmed by multiple regression analysis ($\beta = 0.19 \pm 0.09$, $p = 0.03$ and $\beta = 0.22 \pm 0.10$, $p = 0.03$, respectively). Our findings suggest that the *HSD11B1*SNPs studied may indirectly influence glucose and HDL-cholesterol metabolism in women, possibly through down-regulation of the *HSD11B1* gene by estrogen.

Keywords: HSD11B1 gene, men, metabolism, metabolic syndrome, women.

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Introduction

The *HSD11B1* gene located at 1q32.2 (Tannin *et al.*, 1991) encodes the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) that is responsible for the conversion of the hormone cortisol (also known as stress hormone) to its metabolically inactive form cortisone (Ricketts *et al.*, 1998). An imbalance in the levels of cortisol is associated with visceral fat, insulin resistance and hyperlipidemia, all of which are related to obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (Paterson *et al.*, 2004).

Various studies have suggested an important functional role of 11β-HSD1 in the metabolic processes underlying these pathologies. In knockout animals, the absence of 11β-HSD1 had a protective effect against insulin resistance and hyperglycemia because of the lack of glucocorticoid regeneration in the liver and adipose tissue (Kotelevtsev *et al.*, 1997; Morgan and Tomlinson, 2010). The reverse situation was seen in transgenic animals with overexpression of 11β-HSD1, with an increase in the concentration of intra-adipocyte glucocorticoid, hyperglycemia and a marked central obesity phenotype (Masuzaki *et al.*, 2001). In particular, the G allele of SNP rs12086634 was associated with lower 11β-HSD1 transcription *in vitro* (Draper *et al.*, 2003).

The association between the rs846910 polymorphism in the P2 promoter region and rs12086634 in an enhancer of the *HSD11B1* gene has been investigated in several clinical contexts (Gambineri *et al.*, 2011; Moon *et al.*, 2011; Utriainen *et al.*, 2012). In Pima Indians, these two SNPs were associated with T2DM, but not with obesity (Nair *et al.*, 2004). Gambineri *et al.* (2011) found that the combination of these SNPs in Caucasian women of northern Italy was associated with a higher risk of metabolic syndrome, regardless of the diagnosis of polycystic ovary syndrome. In other studies, both SNPs were associated with T2DM and/or hypertension (Freedman *et al.*, 2001; Goff *et al.*, 2005).

Considering the wide range of biochemical and physiological effects of cortisol, it is possible that temporal or tissue-specific changes in the levels of this hormone could influence a wide range of complex diseases, including obesity and metabolic syndrome. Since the occurrence of genetic polymorphisms in the *HS11B1* gene could influence

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cortisol levels, in this study we investigated the influence of two SNPs of the *HSD11B1* gene (rs846910 and rs12086634) on anthropometric and biochemical variables associated with obesity and metabolic syndrome in an adult population from southern Brazil.

Materials and Methods

Subjects

The sample consisted of 215 workers of Euro-Brazilian descent employed by the Federal University of Paraná in southern Brazil. Since the aim in selecting the volunteers was to obtain a sample representative of the population heterogeneity, no pathology was used as an inclusion or exclusion criterion.

One hundred and forty-seven women (22-72 years old, 56% overweight and obese) and 68 men (23-60 years old, 23% overweight and obese) participated in the study. Assessment of the physical activity of the volunteers for seven days using a pedometer (Yamax Digi-Walker SW-700) showed that 23% were sedentary, 37% had low physical activity, 26% were active and 14% had high physical activity [according to criteria proposed by Wyatt *et al.* (2005) and Tudor-Locke *et al.* (2011)].

Individuals were considered obese when the body mass index (BMI) was ≥ 30 kg/m^2 and non-obese when the BMI was < 30 kg/m^2. Weight and height were measured with an accuracy of 0.1 kg and 0.1 cm, respectively. Glucose, triglycerides (TG), total cholesterol (TC) and HDL-cholesterol (HDL-C) were measured by standard automated methods. LDL-cholesterol (LDL-C) levels were calculated using the Friedewald equation (Friedewald *et al.*, 1972). The study was approved by the ethics committee of the Federal University of Paraná.

DNA analysis

DNA was extracted from peripheral blood by a salting-out method (Lahiri and Nurnberger Jr, 1991) and then diluted to a final concentration of 20 ng/μL. The variant located in the P2 promoter 5'URR (rs846910; SNP1; G/A) and the variant in the enhancer region of intron 3 (rs12086634; SNP2; T/G) were genotyped with a TaqMan SNP genotyping assay (Applied Biosystems). The reactions were done in a Mastercycler Realplex 2 (Eppendorf) using the following conditions: 50 °C for 2 min, 95 °C for 10 min and 50 cycles of 95 °C for 15 s and 62 °C for 1 min. Three previously sequenced control samples, representative of each of the possible genotypes, were included in each reaction for both SNPs.

Statistical analysis

The results were expressed as the mean ± SEM. Frequency distributions, variances, the Shapiro-Wilk normality test, Students *t*-test and the Mann-Whitney test were calculated using Statistica for Windows v. 5.0 (StatSoft Inc. 1996, Tulsa, Oklahoma). Chi-square tests were done using Clump (Sham and Curtis, 1995). Multiple regression analyses were done using SPSS for Windows v. 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the allele frequencies of the two SNPs in the sample stratified by sex and BMI. The genotype frequencies in the overall sample and in the groups were in Hardy-Weinberg equilibrium. There was no difference in allele frequency between obese and non-obese men ($\chi^2 = 0.62$, $p = 0.43$), nor between obese and non-obese women ($\chi^2 = 0.17$, $p = 0.67$) for SNP1. A similar result was found in comparisons between obese and non-obese men and women for SNP2 allele frequencies ($\chi^2 = 0.33$, $p = 0.56$ and $\chi^2 = 0.67$, $p = 0.41$, respectively).

Analyses performed with the stratification of the sample only by gender, showed that there was no significant difference in the BMI of men and women (26.87 ± 4.00 and 27.20 ± 5.44, respectively; $p = 0.97$). However, there were significant differences in the HDL-C, TG and glucose levels of men and women, regardless of the *HSD11B1* genotype ($p = 0.00001$, $p = 0.001$ and $p = 0.006$, respectively) (Figure 1).

Combination analysis with the two SNPs (rs846910 and rs12086634) revealed no significant associations, in contrast to the findings of Gambineri *et al.* (2011). However, when the effects of each of the two *HSD11B1* SNPs on the biochemical variables and BMI were analyzed separately in men and women, significant differences were found only in women (Table 2). Carriers of the A allele (rare) of SNP1 had significantly higher HDL levels when compared to individuals homozygous for the G allele (common). Similarly, carriers of the G allele (rare) of SNP2 had higher glucose levels (tending to significance, $p = 0.06$) compared to women homozygous for the T allele (common). Multiple regression analysis was used to confirm the effect of these genetic variants on HDL and glucose levels (Table 3). When HDL-C was used as the dependent variable and SNP1, age and BMI as the independent variables, the analyses showed that BMI and SNP1 were independent factors in determining the HDL-C levels in women ($\beta = -0.37 \pm 0.11$, $p = 0.002$ and $\beta = 0.22 \pm 0.10$, $p = 0.03$, respectively). Similar results were obtained when glucose was used as the dependent variable and age, BMI and SNP2 were the dependent variables, *i.e.*, BMI and SNP2 were independent factors for increasing glucose levels ($\beta = 0.46 \pm 0.10$, $p = 0.00002$ and$\beta = 0.19 \pm 0.09$, $p = 0.03$, respectively).

Discussion

The importance of gender differences in molecular biology is being increasingly recognized. Cellular re-

Table 1 - Allele frequencies (%) of SNPs 1 and 2 of the *HSD11B1* gene in samples stratified by sex (men and women) and BMI (obese and non-obese).

	Men		Women	
SNP	Obese (n = 16)	Non-obese (n = 52)	Obese (n = 38)	Non-obese (n = 109)
SNP1: rs846910				
Allele A	6.1 ± 4	11.0 ± 3	6.9 ± 2	8.5 ± 1
Allele G	93.8 ± 4	89.0 ± 3	93.0 ± 2	91.5 ± 1
SNP2:rs 12086634				
Allele G	15.6 ± 6	20.1 ± 3	18.4 ± 4	22.9 ± 2
AlleleT	84.4 ± 6	79.8 ± 3	81.6 ± 4	77.1 ± 2

The results are expressed as the mean % ± SEM. Obese individuals: BMI ≥ 30 kg/m^2; non-obese individuals: BMI < 30 kg/m^2.

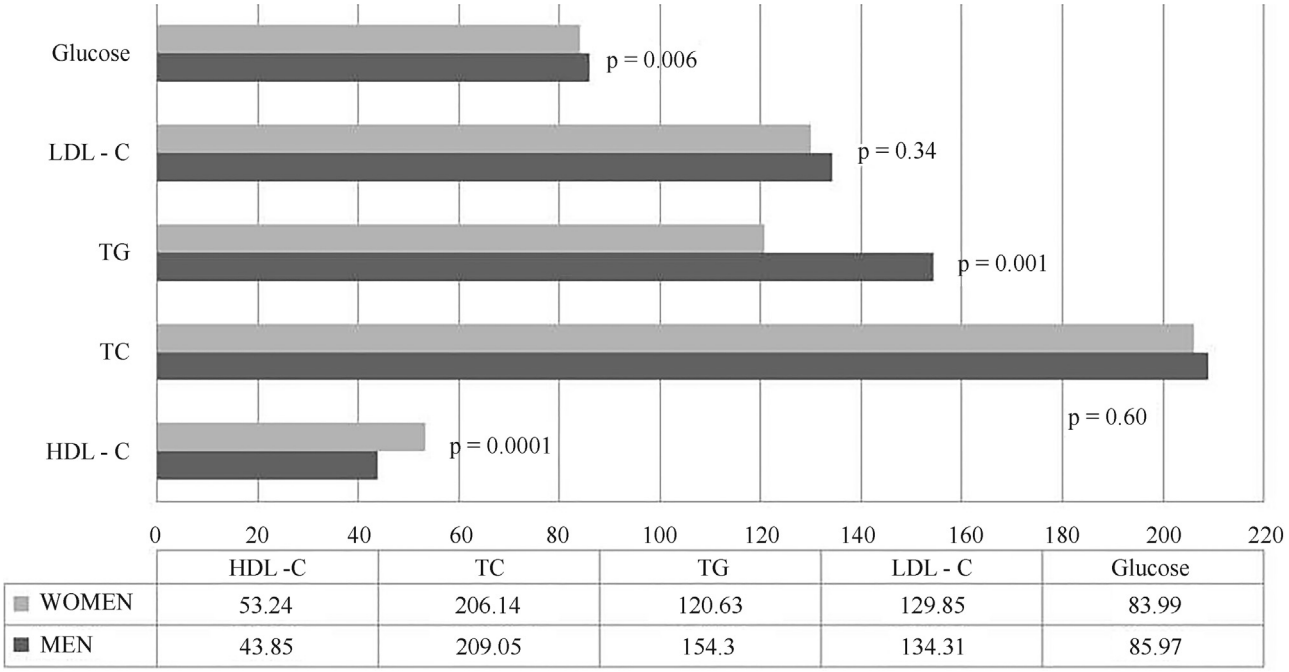

Figure 1 - HDL-C, TC, TG, LDL-C and glucose levels in men and women. The columns represent the mean of 68 men and 147 women. All values are expressed in mg/dl. Statistical comparisons were done using Students *t*-test.

sponses to stress, even before exposure to sex hormones, are different in men and women (Du *et al.*, 2004) and probably reflect gender-related differences in metabolic pathways (Pollitzer, 2013). Indeed, the higher prevalence of obesity and diabetes in women compared to men, especially after the onset of menopause (Ryan, 2009), indicates that gender-related metabolic differences can influence the mechanisms of these diseases. The greater amount of visceral fat and higher fat content in the liver correlate with the lack of a protective effect of estrogen in premenopausal women (Geer and Shen, 2009). However, the effect of estrogen on the metabolism of adipose tissue is not fully understood. Premenopausal women have a higher density of antilipolytic α_2-adrenergic receptors than men (Richelsen, 1986). Pedersen *et al.* (2004) demonstrated that estradiol increases the expression of this receptor in human adipocytes through activation of ER-α receptors only in subcutaneous adipose tissue, with no effect on visceral adipose tissue. Estradiol thus favors the deposition of subcutaneous fat at the expense of visceral deposition. The activity of LPL (lipoprotein lipase), which controls fat uptake in adipocytes, is also influenced by estradiol since this hormone has transcriptional inhibitory effects (Homma *et al.*, 2000) and decreases the transcription and enzymatic activity of 11β-HSD1 in rodents (New *et al.*, 2000). Postmenopausal women with normal weight show enhanced 11β-HSD1 activity in adipose tissue and liver (Andersson *et al.*, 2009), suggesting that low estrogen levels may up-regulate 11β-HSD1 activity and contribute to the imbalance of energy metabolism influenced by cortisol. In a study of inflammatory bowel disease, 11β-HSD1 expression was higher in

Table 2 - -Comparison of the BMI, HDL-C, TC, TG, LDL-C and glucose levels in men and women stratified as carriers of common (G or T) or rare (A or G) alleles of SNPs 1 and 2.

SNP	Men			Women		
SNP1: rs846910	A allele carriers (n = 13)	Non-carriers (n = 55)	p	A allele carriers (n = 21)	Non-carriers (n = 126)	p
BMI (kg/m^2)	26.21 ± 3.76	27.05 ± 4.22	0.51	26.57 ± 4.85	27.20 ± 5.42	0.61
HDL (mg/dL)	45.83 ± 9.06	43.22 ± 9.13	0.37	59.65 ± 16.29	50.94 ± 14.74	**0.03**
TC (mg/dL)	215.83 ± 23.72	209.42 ± 36.91	0.56	202.40 ± 53.49	205.77 ± 35.34	0.71
TG (mg/dL)	156.91 ± 45.14	156.83 ± 86.99	0.51	124.40 ± 70.08	117.85 ± 60.68	0.83
LDL (mg/dL)	139.41 ± 21.69	132.14 ± 37.48	0.52	123.58 ± 39.59	130.18 ± 29.99	0.39
Glucose (mg/dL)	86.91 ± 7.25	86.07 ± 9.72	0.60	88.95 ± 40.88	80.97 ± 18.73	0.33
	Men			Women		
SNP2: rs12086634	G allele carriers (n = 24)	Non-carriers (n = 44)	p	G allele carriers (n = 58)	Non-carriers (n = 89)	p
BMI (kg/m^2)	26.04 ± 3.90	27.33 ± 4.11	0.20	27.44 ± 5.30	27.05 ± 5.53	0.67
HDL (mg/dL)	44.27 ± 7.85	43.71 ± 9.62	0.81	51.43 ± 14.23	54.34 ± 13.34	0.23
TC (mg/dL)	206.50 ± 25.73	209.20 ± 38.72	0.76	202.07 ± 39.60	208.61 ± 38.27	0.34
TG (mg/dL)	138.81 ± 61.08	157.60 ± 78.82	0.33	116.92 ± 51.93	122.89 ± 64.22	0.92
LDL (mg/dL)	134.90 ± 22.75	133.90 ± 34.90	0.90	129.68 ± 29.77	129.95 ± 33.27	0.77
Glucose (mg/dL)	84.72 ± 7.56	86.64 ± 9.84	0.42	85.39 ± 16.20	83.14 ± 21.47	**0.06**

The data are expressed as the mean ± SEM of the number of individuals indicated in parentheses. Statistical comparisons between men and women (stratified by genotype) were done using Students *t*-test (*t*) for parametric data and the Mann-Whitney test (Z) for non-parametric data. Significant differences (p) are indicated in bold.

Table 3 - Results of the multiple regression analysis.

Dependent variable	Independent variable considered	Independent variable confirmed	β ± SEM	p
HDL-C levels	SNP1, age and BMI	BMI and SNP1	(-0.37 ± 0.11) and (0.22 ± 0.10), respectively	0.002 and 0.03, respectively
Glucose levels	SNP2, age and BMI	BMI and SNP2	(0.46 ± 0.10) and (0.19 ± 0.09), respectively	0.00002 and 0.03, respectively

male than in female patients, whereas 11β-HSD2 showed not gender-specific regulation in its expression (Stegk *et al.*, 2009).

As shown here, only in women was the presence of the rare SNP2 allele associated with higher glucose levels, whereas women homozygous for the common SNP1 allele showed lower HDL-C levels compared to rare allele carriers. The combination of higher glucose levels and lower HDL-C levels may have an important role in the development of pathologies associated with obesity. Lower than normal levels of HDL-C have been related to the early development of T2DM (Von Eckardstein *et al.*, 2000), and conditions such as insulin resistance and obesity may also be related to lower HDL-C levels and to the generation of small particles of HDL-C that can result in several functional changes (Goff *et al.*, 2005).

Men and woman show different responses to the same food intake. Compared to women, men have higher levels of postprandial insulin and TG (Cohn *et al.*, 1988), suggesting that estrogen also has a beneficial effect on TG levels in response to food ingestion (Westerveld, 1998). The sexual dimorphism in TG levels was striking in our study: women had a normal mean TG level, whereas men had a borderline mean TG level, based on age- and gender-related reference values for TG.

Since the women in this study were more sensitive to the effects of the *HSD11B1* gene polymorphisms investigated here, it is possible that such variations influence the modulation established between estrogen and 11β-HSD1. The presence of the two SNPs may alter the down-regulation caused by estrogen and possibly lead to an imbalance in the metabolic pathways involved in glucose and fat metabolism.

Divergent results have been reported for the effect of these variants on *HSD11B1* expression. The G allele of SNP rs12086634 was associated with lower transcriptional activity *in vitro* (Draper *et al.*, 2003), whereas the less frequent allele combination (A and G) for these two SNPs

(rs846910 and rs12086634, respectively) was associated with higher mRNA levels and 11β-HSD1 activity in adipose tissue in southern European Caucasian women with and without polycystic ovary syndrome (PCOS) (Gambineri *et al.*, 2011). Other studies found no relationship between one or both variants and 11β-HSD1 levels (Nair *et al.*, 2004; Millan *et al.*, 2005; White, 2005; Malavasi *et al.*, 2010). The genetic variants investigated here may have increased the *HSD11B1* transcriptional levels, leading to an imbalance of homeostasis via estradiol down-regulation in women. A similar effect was not detected in males, suggesting that mechanisms other than estradiol suppress the influence of these genetic polymorphisms on the metabolic variables investigated in this study.

Such polymorphisms may represent only a minor contribution to the mechanisms underlying this imbalance. Our results showed that the SNPs and BMI had an independent effect on glucose and HDL-C levels in women, although other factors need to be considered. Other variables such as smoking (Brischetto *et al.*, 1983), abdominal fat distribution (Ostlund *et al.*, 1990) and aerobic exercise training (Kokkinos and Fernhall, 1999) have also been related to HDL-C levels. Moreover, a decline in HDL-C levels simultaneous to the decline in estrogen levels in post-menopausal woman has been described (Li *et al.*, 1996; Senoz *et al.*, 1996; Pasquali *et al.*, 1997); insulin and glucose levels have also been related to HDL-C, which suggests an influence of carbohydrate metabolism and sex hormone status on the levels of this lipoprotein (Sowers and Sigler, 1999).

Among the limitations of this study was the sample size, which may not have been large enough to detect any other significant results. In addition, a functional relationship between the variants studied would be better established in a case-control study, especially with post-menopausal women.

In conclusion, we found that the SNPs investigated here acted as independent factors in determining glucose and HDL-C levels only in women. This finding suggested a potentially important sexually dimorphic effect that may be related to gene regulation exerted by estrogen.

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