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Leptin, ghrelin and adiponectin evaluation in transsexual subjects during hormonal treatments

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Abstract

Context: Gender differences in adiponectin, leptin and ghrelin levels have been described in normal population. This is important for understanding differences between males and females in the regulation of food intake, weight gain, body fat distribution and cardiovascular risk. It is unclear how endogenous and exogenous sex hormones may regulate circulating levels of these factors. Transsexuals during hormonal treatment may represent an ideal model to ascertain role of exogenous sex hormones on these parameters.

Objective: To evaluate adiponectin, ghrelin and leptin levels in transsexual subjects during hormone therapy and to compare the results with males and females.

Subjects: 26 non diabetic transsexuals, 15 male-to-female (M-to-F, group 3), and 11 female-to-male (F-to-M, group 4) and 29 age- BMI-matched controls, 15 males (group 1) and 14 females (group 2).

Results: Leptin levels were significantly lower in group 1 compared with group 2 (P=0.04), and group 3 (P=0.01), no differences were recorded between the other groups. Adiponectin levels were significantly higher in group 3 compared with group 4 (P=0.03). No differences were found between the four groups for ghrelin levels.

Conclusion: Our data confirm the sexual dimorphism in serum leptin levels in normal subjects and demonstrate an increase in M-to-F. While ghrelin does not show any sexual differences and it seems not influenced by exogenous sex hormone administration, the lower adiponectin levels in F-to-M during treatment confirm that androgens may decrease plasma adiponectin levels. This latter observation suggests that F-to-M transsexual patients could have a higher cardiovascular risk.

Introduction

Gender differences in ghrelin, leptin and adiponectin values have been described in normal subjects. It has been shown that ghrelin secretion is sexually dimorphic in humans, with women in the late follicular stage having higher levels than men (Barkan et al, 2003; Greenman et al, 2004) and short-term changes of circulating sex hormones are able to modify ghrelin levels (Gambineri et al, 2005). Moreover, in polycystic ovary syndrome (PCOS), circulating ghrelin and androgen levels are inversely related (Panidis et al, 2005), anti-androgen treatment increases circulating ghrelin levels in obese women with PCOS (Gambineri et al, 2003). Estrogen replacement therapy may increase active ghrelin levels (Kellokoski et al, 2005). Testosterone replacement therapy restores normal ghrelin in hypogonadal men (Pagotto et al, 2003).

Gender differences in adiponectin levels are documented during the progression of puberty and seem linked to serum androgen levels (Bottner et al, 2004). In fact, testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes (Page et al, 2005; Seftel et al, 2005). Moreover androgen-induced hypoadiponectinemia may be related to the high risks of insulin resistance and atherosclerosis in men (Nishizawa et al, 2002). Increased levels of androgens in post menopause and low SHBG are connected with decreased production of adiponectin (Chu et al, 2006). It has been also demonstrated that testosterone may decrease adiponectin levels in female-to-male transsexuals (Berra et al, 2006). In contrast, recent data show that sex differences in circulating adiponectin levels in older adults cannot be explained by sex hormone regulation (Laughlin et al, 2007).

Sexual dimorphism in serum leptin levels has been described as well, with higher concentrations in women than in men, even adjusted to body fat (Saad et al, 1997; Pardo et al, 2004). These observations are potentially important for the understanding of differences between men and women in regulation of food intake, weight gain, and body fat distribution. Androgen supplementation decreases serum leptin concentrations, whereas androgenic suppression increases serum leptin levels in healthy men, independently from changes in the body fat mass (Elbers et al, 1997; Hislop et al, 1999). In rats, testosterone plays a role in plasma leptin turnover by increasing leptin clearance rate and shortening plasma leptin half-life (Castrogiovanni et al, 2003). The fact that leptin levels are always higher in females, even after correcting for body fat content, suggests that the interaction between the adipose tissue and the reproductive system is modulated in a different way in males and females by sexual hormones (Casabiell et al, 2001). It

seems that adipocytokines may represent the link between postmenopausal hormonal changes, excess of visceral fat and increased risk of cardiovascular diseases.

Sexual dimorphism in leptin levels is not simply explained as differences in total adiposity between sexes, but there are genes, which are differently expressed depending on sex, that influence variation in serum leptin (Martin et al, 2002). Moreover the sexual dimorphism in leptin concentrations appears to reflect the effect of circulating concentrations of gonadal steroids (Rosenbaum et al, 2001).

The sexual dimorphism in these three hormones could be important for understanding the differences between males and females in the regulation of food intake, weight gain, body fat distribution and cardiovascular risk. However, it is still unclear how endogenous, as well as exogenous, sex hormones may regulate the circulating levels of these factors. Transsexual subjects during hormonal treatment may represent an ideal model to ascertain the role of exogenous sex hormones on these parameters. Since only few data are available on the role of sexual hormone therapies on the level of these three factors, we evaluated adiponectin, ghrelin and leptin levels in transsexuals during hormonal treatments.

Materials and methods

Subjects and treatments

We evaluated 26 non diabetic transsexual subjects, without dyslipidemia, with normal BMI: 15 male-to-female (M-to-F, group 3, mean age 33.21±2.1 yrs), and 11 female-to-male (F-to-M, group 4, mean age 30.90±1.81 yrs) and 29 age- BMI-matched subjects, 15 males (group 1) and 14 females (group 2), who served as controls. Control females were not using oral estrogen (contraceptive pills). We compared each group of transsexuals with both male and female healthy subjects: each group of transsexuals was, therefore, compared with two control groups (males and females). Cholesterol, both total and LDL, and triglycerides were normal in all groups (Table).

The duration of exposure to cross-sex hormone treatment in transsexual patients was 9 ± 2.31 years for M-to-F and 10 ± 1.48 years for F-to-M. The study protocol was approved by the local ethical committee and a written informed consent was obtained from all subjects.

Transsexuals and controls underwent overnight fasting blood sampling for measurement of serum leptin, ghrelin, adiponectin, insulin, glucose, lutenizing hormone (LH), follicle stimulating hormone (FSH), testosterone and estradiol. In controls females LH, FSH, estradiol and testosterone were measured in follicular fase.

Two M-to-F patients, previously underwent surgery for sex reassignment, were in therapy only with estradiol during the study. Thirteen M-to-F, three of them previously underwent surgery for sex reassignment, were treated with antiandrogen (12 with ciproterone acetate, 100 mg/day and 1 with spironolactone, 200 mg/day) and estrogen (estradiol hemihydrate transdermal or oral tablets, 4 mg/day). As concomitant treatments, 2 were in therapy with antidepressive drugs and one with thyroxin for nodular goiter. The time elapsed between surgery for sex reassignment and the present study was 6.80 ± 1.91 years.

One F-to-M previously underwent surgery for sex reassignment nine years before the present study. All were in therapy with depot testosterone (250 mg i.m. every 21 days): two subjects with testosterone enantate, the remaining subjects with an androgenic preparation for intramuscular administration containing four different ester of the natural hormone testosterone (testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, testosterone decanoate 100 mg). The hormonal samples were performed about midway between two injections of testosterone depot, therefore the hormonal value were comparable among the subjects. As concomitant treatments, only one was tacking taking thyroxin for nodular goiter.

Analytical methods

Serum leptin was assayed by radio-immuno assay (DRG Diagnostcs GmbH, Germany). Sensitivity of the method was 0.5 µg/l. Intra-assay and inter-assay percent coefficents of variation (CV) were lower than 3.9% and 4.7%, respectively.

Serum ghrelin levels were measured by a commercial radio-immuno assay (Phoenix Pharmaceuticals, Belmont, CA) that uses125I-labeled bioactive ghrelin as a tracer and a rabbit polyclonal antibody raised against full-length octanoylated human ghrelin that recognised both acylated and desacylated ghrelin. Sensitivity of the method was 10 pg/ml. The intra assay CV was 8,7% and inter assay CV was 11,2 %.

Serum adiponectin levels were measured in duplicate by commercial radioimunoassay (DRG Diagnostics-Germany). Sensitivity of the method was 1 ng/ml. The intra assay CV was 3,9% and inter assay CV was 8,4%. All measurements of leptin, ghrelin and adiponectin were made in duplicate in the same batch, after separation, serum samples were stored at -20 °C until analysis.

Serum glucose and insulin concentrations were measured respectively by enzymatic method (Randox-UK) and sandwich immunoradiometric assay (Immunotech SA-France).

Insulin sensitivity was estimated according to the HOMA IR (Matthews et al,1985). The HOMA cut-off point of >2.5 indicates presence of insulin resistance in adults. Estradiol and total testosterone were measured with commercial chemiluminescent assay (Immulite 2000, DPC Los Angeles, California), FSH and LH were measured with commercial immunoenzymometric assay, IEMA (Radim, Roma, Italy).

Statistical analysis

Statistical analysis of data was carried out by the SPSS software, version 12 for Windows. The analysis was performed using the Mann-Whitney Test for non parametric data both for the comparison between patients and controls and inside the single groups. The quantitative variables were expressed as mean±SEM.

Results

No significant differences were found in HOMA and insulin levels between the two groups of transsexuals and between transsexuals and controls. Transsexual subjects did not displayed insulin resistance. Similarly, no statistically significant differences were found between the four groups for ghrelin levels.

Leptin levels were significantly lower in group 1 compared with group 2 (P=0.004), and group 3 (P=0.01) whereas, no differences were found between the other groups. Conversely, adiponectin levels were significantly higher in group 3 compared with group 4 (P=0.03), whereas no differences were found between the other groups.
No correlations between the levels of estrogen and testosterone with those of ghrelin, adiponectin and leptin in the two groups of transsexuals have been found.
BMI and sex hormones evaluations are reported in the Table, whereas the distribution of insulin, leptin, ghrelin, adiponectin, as well as HOMA in the four groups are graphically illustrated in Figure 1.

Discussion

The results of our study confirm the gender differences in leptin levels. Indeed, females displayed significantly higher leptin levels than males. Whereas, there were no differences in leptin levels between females and M-to-F transsexuals, while males leptin levels are significantly lower than in M-to-F transsexuals. These two evidences suggest that leptin levels in M-to-F transsexuals are comparable to those recorded in females.
Moreover, in the F-to-M group there was a strong variability in leptin levels (Figure 1E). Indeed, a number of F-to-M subjects showed leptin levels similar to those measured in females, whereas, other F-to-M subjects had leptin levels similar to males. This could be related to the already known individual variability in the response to androgen administration. Moreover, there are a lot of factors that make gender differences in leptin levels, both genetic (Martin et al, 2002) and hormonal (Casabiell et al, 2001; Rosenbaum et al, 2001). However, tacking together, these data suggest that estrogens and antiandrogens therapies may increase leptin levels, and this may be in line with other data showing that androgens reduce leptin levels (Elbers et al,1997; Saad et al, 1997; Hislop et al, 1999; Castrogiovanni et al, 2003; Pardo et al, 2004).
In the literature there are conflicting data regarding adiponectin and sex hormone influence (Page et al, 2005; Seftel et al, 2005; Laughlin et al, 2006; Laughlin et al, 2007). However, males seem to have lower adiponectin levels than females, and this androgen-induced hypoadiponectinemia may contribute to the higher cardiovascular risk in males. Adiponectin deficiency (hypoadiponectinaemia) is an independent risk factor for endothelial dysfunction, hypertension, coronary heart disease, myocardial infarction and other cardiovascular complications (Giannessi et al, 2007).

F-to-M could have an increase of their cardiovascular risk in terms of changes in body composition (Elbers et al, 2003). Moreover hyperandrogenism, usually resulting from PCOS, is associated with an unfavorable cardiovascular risk (Gooren et al, 2008). Association of hypoadiponectinemia with metabolic syndrome in patients with PCOS is reported, adiponectin as an endogenous biologically relevant modulator of vascular remodeling may have a role in the development of metabolic syndrome in PCOS patients (Gulcelik et al, 2008).

The evidence of significantly lower adiponectin levels in F-to-M transsexuals in comparison with M-to-F confirms the literature data that androgens decrease plasma adiponectin levels. Indeed, F-to-M transsexuals have lower adiponectin levels compared with males. Subjects with low adiponectin levels are considered at high cardiovascular risk, because adiponectin plays a role in the pathogenesis of atherosclerosis, especially in obese and insulin-resistant patients (Dunajska et al, 2004). Therefore, F-to-M transsexuals may potentially develop an higher cardiovascular risk due to their low adiponectin levels, even lower than males, as a consequence of the exogenous androgens administration. However, the clinical consequences associated to the lower adiponectin levels might need more time to become evident. Indeed, these subjects maintain normal cholesterol and triglycerides levels, as well as HOMA, probably due to the short duration of exposure to cross-sex hormones.

In contrast, estrogen therapy may increase adiponectin levels in M-to-F transsexuals. Hypoandrogenemia in males and hyperandrogenemia in females are associated with increased risk of coronary artery disease, especially when there is the coexistence of visceral obesity, insulin resistance, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, low-density lipoprotein (LDL) cholesterol and plasminogen activator inhibitor (PAI-1) (Eckardstein and Wu, 2003).

Our results indicate that exogenous sex hormone do not influence ghrelin levels in transsexuals during treatments. These results are apparently in contrast with the few data in literature about gender differences and influence of estrogen and/or androgen treatment on ghrelin levels (Gambineri et al, 2003; Pagotto et al, 2003; Kellokoski et al, 2005). Indeed, in PCOS, circulating ghrelin and androgen levels are inversely related (Panidis et al, 2005). Therefore, we expected F-to-M displaying lower levels of ghrelin than normal females. However, probably the high variability in ghrelin levels in our female control group might account for the lack of a significant difference between the two populations in this study. In fact, if we consider the median in Figure 1C (the middle line of the box-plot), we

could speculate that it is higher in females compared to both F-to-M and males. Another potential explanation might be also the relative short time of exposure to androgens of F-to-M transsexuals. However, the data on sexual dimorphism of ghrelin are scant and further studies are warranted to clarify this aspect.

In conclusion our data confirm the sexual dimorphism in serum leptin levels in normal subjects and show an increase in M-to-F transsexuals. The lower adiponectin levels in females treated with androgens confirm the literature data that androgens decrease plasma adiponectin levels and suggest that F-to-M transsexual subjects could have a higher cardiovascular risk factor due to the lower adiponectin levels. Ghrelin does not display sexual differences and it seems not influenced by exogenous sex hormones administration. However, further studies are needed to shed light in how sex steroids may regulate these hormones.

Table. Clinical and hormonal parameters in transsexual and normal subjects

	M-to-F (n.15)	F-to-M (n.11)	Males (n.15)	Females (n.14)
BMI	21.4 ± 0.62	21.45 ± 0.57	20.21 ± 0.51	21.06 ± 0.65
COL (TOT)	146.60 ± 11.11	142.81 ± 18.30	160.35 ± 7.54	164.90 ± 12.5
LDL	90.30 ± 6.67	112.6 ± 8.02	99.25 ± 4.32	85.24 ± 5.32
HDL	55.30 ± 3.35	47.4 ± 1.98	61.1 ± 3.22	79.66 ± 7.18
Triglycerides	84.76 ± 11.93	78.4 ± 5.40	85.41 ± 6.35	75.26 ± 4.75
LH	5.73 ± 3.65	2.95 ± 0.62	4.50 ± 2.70	5.10 ± 2.45
FSH	5.73 ± 5.22	7.0 ± 2.17	5.23 ± 1.25	6.50 ± 1.32
Estradiol	56.7 ± 10.56	9.09 ± 6.53	20.0 ± 1.2	77.0 ± 3.25
Total testosterone	1.14 ± 0.48	4.98 ± 0.92	5.30 ± 1.20	0.60 ± 0.10

Normal ranges: LH 0.6-16 UI/l; FSH 1.5-13 UI/l (follicular fase); Total testosterone 0.2-0.8 ng/ml for females and 3.5-10 ng/ml for males; Estradiol 20-80 pg/ml for females and <50 pg/ml for males.

Total Colesterol: 130-200 mg/dl; Triglycerides: 40-170 ng/ml; LDL: 0-120 mg/dl; HDL: >40 mg/dl for males, >45 mg/dl for females

Figure legend

Figure 1. Hormonal parameters in the four groups
A) Insulin, μUI/ml, B) HOMA, C) ghrelin, pg/ml, D) adiponectin, μg/ml, E) leptin, μg/l
Groups: Males (15 subjects); Females (14 subjects); Male-to-Female transsexuals (M-to-F, 15 subjects); Female-to-Male transsexuals (F-to-M, 11 subjects).
* = P<0.05, ** =P<0.001

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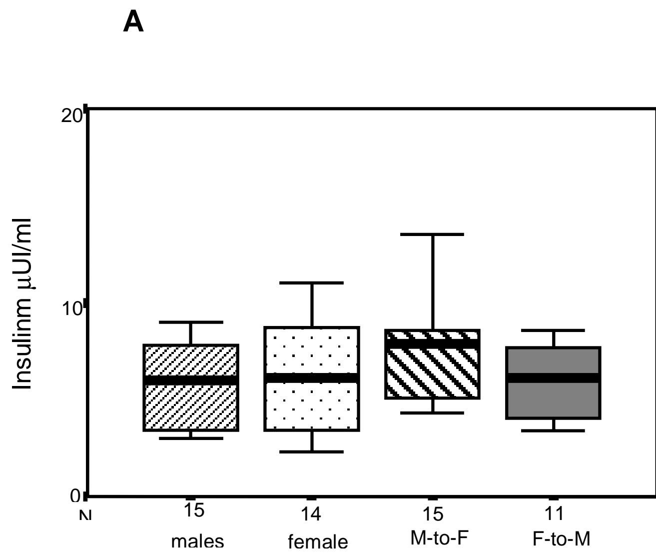
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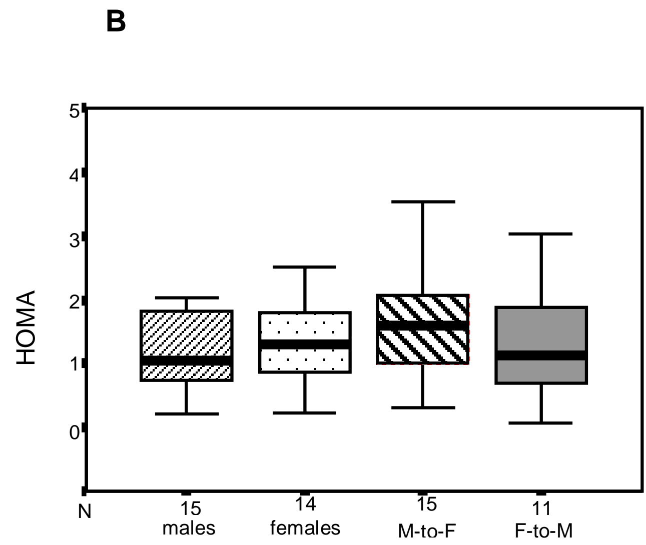
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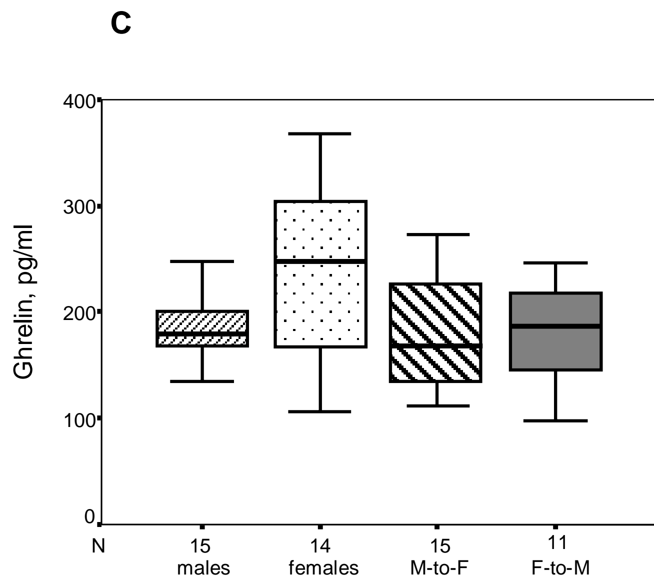
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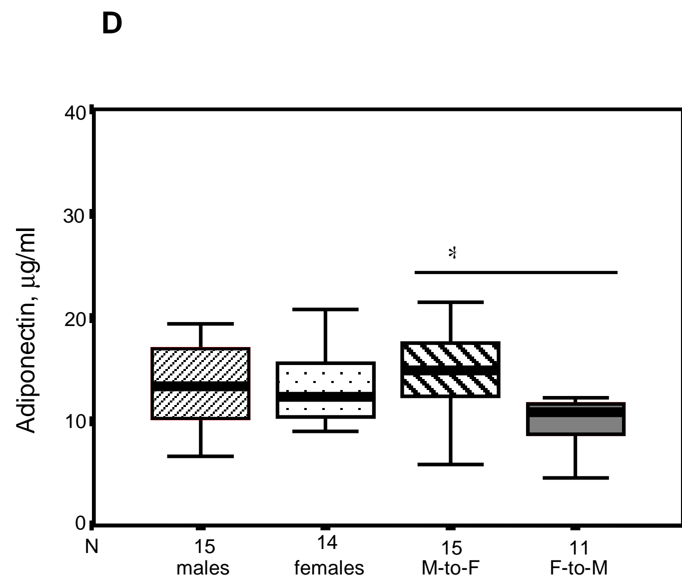
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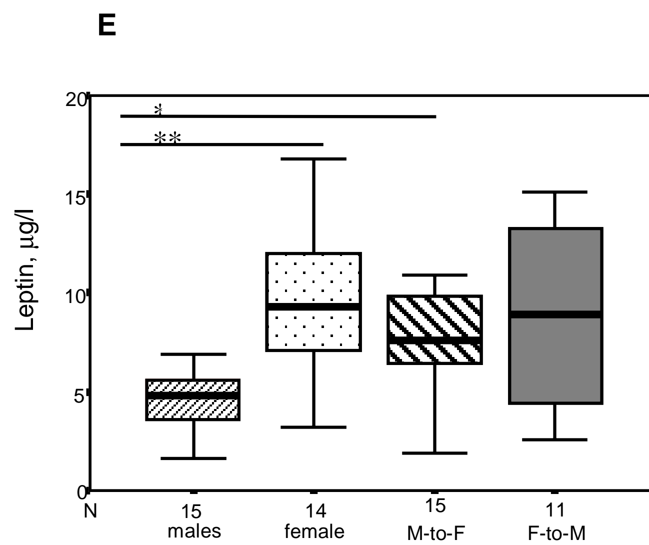
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