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The differences between aromatizable and non-aromatizable androgens in relation to body composition and metabolic syndrome risk factors in men

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ABSTRACT

The relationships between the parameters of metabolic syndrome and non-aromatizable metabolites of testosterone have been discussed in literature. Some papers describe these metabolites as one of the possible causes of male-type obesity. On the contrary, other studies show a protective influence of dihydrotestosterone on visceral obesity.

The aim of this study to analyse the relationship between anthropometric parameters, lipid spectrum, glycemia and the level of endogenous testosterone and dihydrotestosterone, and to compare the effects of these androgens. Our population-based study involved 232 healthy men ranging from 20 to 78 years with BMI 18 to 39 kg/m^2. Serum testosterone, dihydrotestosterone and sex hormone binding globulin SHBG levels, lipid spectrum, glucose metabolism parameters were measured and the oral glucose tolerance test was carried out in all subjects. Their anthropometric parameters (weight, height, waist, hips, waist-to-hip ratio, 14 skin folds) and body composition parameters were determined and calculated by the Antropo program. Multiple regression analysis showed a correlation between hormonal levels, esp. of testosterone and dihydrotestosterone, and the anthropometric data, lipid spectrum and parameters of glucose regulation. Low testosterone and/or dihydrotestosterone was correlated to a higher body-mass index, fat content, waist diameter, total-, HDL-, LDL-cholesterol and triglycerides, fasting glucose, insulin resistance and lower muscle and bone mass. In addition, statistical analysis using multivariate regression with reduction in dimensionality did not discover any striking difference between aromatizable and non-aromatizable androgens in their association to lipid and glucose metabolism parameters in healthy, normosthenic men. In conclusion, the association of endogenous testosterone and dihydrotestosterone to anthropometric data, lipid spectrum and insulin sensitivity are of the same quality; however, the effect of the circulating levels of dihydrotestosterone is quantitatively smaller.

1. Introduction

Fat distribution is one of the secondary sexual characteristics. Men have a tendency to deposit fat abdominally and have a greater amount of visceral fat than premenopausal women. This type of fat deposit is associated to a higher risk of diabetes mellitus and cardiovascular diseases. In women the preferential fat distribution is gluteofemoral and women have a greater percentage of body fat in total. Androgens can affect fat tissue formation and localization in men through the androgenic receptor or indirectly after aromatization by stimulation of the estrogenic receptor. Dihydrotestosterone (DHT) is an androgen with the greatest effect; its affinity to the androgen receptor (AR) is about five times higher compared to testosterone (T). The DHT–AR complex has a longer half-life and a higher DNA binding affinity than the T–AR complex. Therefore, the effective dose of DHT, required to activate an androgen responsive marker gene by 50%, is about 10-fold lower than that required to achieve the same level of induction with T [1]. The actual androgenic efficiency within the target tissues is about two or three times higher [2].

The concentration of DHT in men's serum is one order of magnitude lower than the concentration of T. In the literature the data on DHT-to-T ratio differ [3,4]. In our previous study on DHT levels over a lifetime we found a constant ratio of both total and free DHT/T over a lifetime starting with puberty [5,6].

DHT plays a key role in prenatal differentiation of external genitalia. It is a control hormone for the descent of the testes and differentiation and development of external genitalia and prostate development and growth. DHT effects are important for spermatozoid maturation in epididymis [7]. DHT also influences the

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skin adnexa (hair follicle and sebaceous glands) and plays a role in the development of androgenic alopecia. Androgenic alopecia, as a symptom of dihydrotestosterone abundance, is related to a higher occurrence of prostate hyperplasia and prostate carcinoma [8–10] and it is also considered a risk factor for cardiovascular and metabolic diseases [11–13].

The syndrome of Imperato-McGinley can serve as a natural model of DHT-insufficiency [14].

DHT is irreplaceable by T in the effects on external genitalia development, prostate development and on skin adnexa. In other roles both hormones are similar. DHT, contrary to testosterone, is a non-aromatizable androgen and so its effects cannot be explained by its transformation to estrogens. Several papers have discussed the effect of dihydrotestosterone on some anthropometric indicators and metabolic parameters and especially on male fat deposition [15–19].

In our study we tried to answer the question of whether endogenous DHT has the same or a different effect on body composition, glucose tolerance and lipid spectrum than testosterone, and whether both hormones are identical in this respect.

2. Materials and methods

A group of 232 healthy men (except of obesity and associated symptoms) at the age of 20–78 with a broad range of body mass index (BMI) 18–39 was enrolled in this study. Anthropometric parameters (*i.e.* weight, height, waist, hips, waist-to-hip ratio, 14 skin folds, BMI, percentage representation of muscle and fat tissue) were measured. Laboratory analyses of metabolic parameters (lipid spectrum – triglycerides, total cholesterol, HDL, LDL, glucose metabolism parameters – glycemia, immunoreactive insulin – IRI, C-peptide, oral glucose tolerance test (oGTT)) and steroid hormones dihydrotestosterone (DHT), testosterone (T), 17alpha-hydroxy-progesterone (17-OH), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulphate (DHEAS), 4-androstene-3,17-dione (A2), LH, FSH, 17alpha-hydroxy-pregnenolone (Preg17) and sex hormone binding globulin (SHBG) were also carried out. The overall characteristics of the male volunteers in subgroups of lean and obese participants are listed in Table 1.

The Ethical Committee approved the study and all patients signed informed consent form before taking part in the study.

2.1. Anthropometric data

Anthropometric data were obtained in a fasting state. Body weight, height, waist and hip circumferences were measured in all participants in order to calculate body mass index (BMI) and to evaluate visceral fat accumulation by means of waist circumference, waist-to-hip ratio (WHR). Furthermore, 14 skin folds (c1–c14) were measured. Body composition (% of subcutaneous fat mass, % of muscle mass, and % of bone mass from the total body weight) was then calculated using the ANTROPO program [20]. Weight (to the nearest 0.1 kg) and height (to the nearest cm) were measured. Circumferences were measured in a standing position, waist in halfway between the lower ribs and the crest of the pelvis and hip circumference at the level of the greater trochanters. Body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2) and waist-to-hip ratio (WHR) as waist divided by hip circumference.

2.2. Biochemical analysis

After an overnight fast, venous blood samples were obtained in order to determine biochemical parameters. The blood glucose level was measured by the glucose oxidase method (Beckman Glucose Analyzer 2). Glycosylated proteins (Glykop) (spectrophotometric redox reaction using nitro blue tetrazolium as a sensitive redox indicator for the specific quantification of fructosamine in alkaline solution) were determined. Immunoreactive insulin (IRI) was assayed using an immunoradiometric assay and serum levels of C-peptide were evaluated by the immunoradiometric assay (Immunotech IRMA, Marseilles, France). Total cholesterol (Merckotest, CHOD-PAP-Method), high-density lipoprotein cholesterol (HDL, Merck System Cholesterol, CHOD-PAP-Method), and triglyceride concentrations (Merck System, GPO-PAP-Method) were measured in serum using the analyzer Merck (Vitalab Eclipse). Low-density lipoprotein cholesterol (LDL) levels were calculated as: LDL = total cholesterol-(TG/2.2)-HDL. The 3-h oral glucose tolerance test (oGTT) with 75 g of glucose load was performed in all subjects.

2.3. Steroid analysis

Serum testosterone was determined by standard radioimmunoassay (RIA) using antiserum anti-testosterone-3-carboxymethyloxim: BSA and testosterone-3-carboxymethyl-oxim-tyrosylmethyl-ester-[^{125}I] as a tracer. Intra-assay and inter-assay coefficients variants were 7.2% and 10%, respectively, and sensitivity was 0.21 nmol/l. Androstenedione was determined by standard RIA with antiserum anti-androstenedione-6-carboxymethyloxim: BSA and [^{3}H] androstenedione as tracer. Intra-assay and inter-assay coefficients variants were 8.1% and 10.2% and sensitivity was 0.39 nmol/l. Sexual hormones binding globulin was assayed by IRMA kit (Orion, Espoo, Finland). Commercial kits (Immunotech, Marseilles, France) were used for the determination of LH, FSH (IRMA kit), 17-hydroxyprogesterone (Prog17), DHEA and DHEAS (RIA kit). DHT was determined by original methodology [21]. 17-Hydroxy-5-pregnenolone (Preg17) was determined by an in house RIA method.

2.4. Statistical data analysis

To eliminate skewed data distribution and heteroscedasticity, the original data was transformed to a Gaussian distribution by a Box-Cox transformation before further processing using the statistical software Statgraphics Centurion, version XVI from Statpoint Inc. (Herndon, VA, USA). The differences between the groups with successful and unsuccessful treatment were evaluated by age-adjusted ANCOVA.

To simultaneously evaluate the relationships between anthropometric indices and markers of insulin resistance on the one hand (matrix **X**), and steroids and related substances on the other hand (matrix **Y**), to compare the predictive value of individual variables and to explain the structure in the data, we applied multivariate regression with reduction of dimensionality, known as bidirectional orthogonal projections, to latent structures (O2PLS). The O2PLS method is bidirectional and enables the prediction of variables constituting the matrix **Y** from variables constituting the matrix **X** and *vice versa.* The predictivity of individual variables for the model may be simply expressed as a correlation of the variable with a common predictive component. The predictive component extracts variability from the **X** and **Y**, which is shared between **X** and **Y** from variability within the matrixes **X** and **Y**, which is separated into the orthogonal components.

The transformed data underwent processing by the O2PLS method, which is effective in coping with the problem of severe multicollinearity within the matrixes of both dependent and independent variables. The O2PLS enabled us to find the variables with high predictive value for the description of the relationships