Correlation between myostatin and obesity or insulin resistance of patients with polycystic ovary syndrome

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Objective: To study the correlated relationship between the myostatin level and the obesity, insulin resistance of patients with polycystic ovary syndrome.
Methods: Based on cross-sectional case-control study, 165 polycystic ovary syndrome patients were divided into obese group and non-obese group. At the same time, 142 healthy women were chosen as the control group. The level of fasting glucose, fasting insulin, HOMA-IR (the index of insulin resistance), BMI, waist circumference, waist-hip ratio and the level of sex hormone were determined and compared between the control group and non-obese PCOS group, between the obese and non-obese PCOS group. The correlation between MSTN and the indicator above was analyzed by regression analysis.
Results: Compared with the control group, the MSTN level was significantly higher in the patients with PCOS (18.71±15.54 vs. 14.0±15.22, \( P=0.014 \)), but there was no significant difference between non-obese PCOS group and the control group, excluding the obesity factor. The result of regression analysis showed that the MSTN level was significantly related to the waist circumference, waist-hip ratio, BMI and the testosterone level. After adjusting the BMI and testosterone, the multivariate regression analysis showed that the MSTN level was significantly related to the PCOS present. And our study did not show the correlation between the MSTN level and the insulin resistance in PCOS patients, while the latter was closely related to the occurrence and progression of PCOS.
Conclusion: The MSTN level is significantly related to waist circumference, waist-hip ratio, BMI and the testosterone level. And the MSTN level is also significantly related to the PCOS present.

1 Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder disease among women [1]. It has serious impact on reproductive function, and also increases the risk of metabolic disorder diseases including insulin resistance (IR), abnormal glucose and lipid metabolism, diabetes, cardiovascular diseases, etc. Its pathogenesis is still unclear, and it may be related to abnormal endocrine of ovary, adrenal gland, hypophysis and hypothalamus; malfunction of androgen formation-related enzyme in ovary and adrenal gland; hyperinsulinemia, IR and genetic factors.

Myostatin (MSTN) is a new member of TGF-\( \beta \) superfamily [2]. The main biological function is to negatively regulate skeletal muscle cells, and to participate in regulation of glucose, lipid and protein metabolism [3]. It is mainly expressed in skeletal muscle and adipose tissue [4]. It is reported that MSTN can reduce even totally neutralize glucose uptake produced by insulin, in another word, it has anti-insulin effect [5]. Application of MSTN receptor antagonist can remarkably improve blood glucose level, IR and fatty degeneration in mice with high fat diet [6].

This study aims to investigate the correlation between MSTN and obesity or IR, so as to provide possible target drugs for PCOS.
2. Materials and Methods

2.1. Research subjects

This study has been approved by the Ethics Committee of Affiliated Hospital to Hainan Medical University, and has received consents from all patients. A total of 207 patients were selected, and were divided into the control group and the observation group according to diagnosis. There were 165 PCOS patients in the observation group, who complained of irregular menstruation or infertility, aged 21-42 years old. The standard of Rotterdam Convention in 2003 was used as diagnosis standard: (1) rare ovulation or no ovulation; (2) excessive androgen in clinical examination or hyperandrogenemia in biochemical test; (3) polycystic ovary manifestation: ultrasonography shows the number of 2-9 mm follicles≥12 in unilateral or bilateral ovary, or volume of unilateral or bilateral ovary 10 mL (transvaginal ultrasonography or abdominal ultrasound). Another 142 with regular menstruation and without IR healthy females were selected as the control group (menstrual cycle 25-32 d, and no IR in both clinical and biochemical test).

Subjects with endocrine abnormalities or abnormalities in systems or organs (including hyperprolactinemia, thyroid malfunction, Cushing syndrome, ovary tumor or autoimmune diseases, etc) were excluded via medical history, physical examination and laboratory tests. And no subjects had administration record and habits of smoking or drinking.

2.2. Anthropometric measurement

The height (m), weight (kg) and waistline (cm) were measured, and body mass index (BMI) and waist-hip ratio (WHR) were calculated as follows: $\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)}^2}$; $\text{WHR} = \frac{\text{waistline}}{\text{hipline}}$. It was considered as obesity as BMI ≥25 kg/m$^2$ (According to WHO standard for Asian adults in 2004); and it was considered as upper obesity as WHR 0.8.

2.3. Serum collection and determination

2.3.1. Sex hormone determination

On the 2-4 day of menstrual cycle, or when the diameter of follicle 9 mm in amenorrhea patients, the elbow vein blood was collected under fasting, and the hormones including follicle-stimulating hormone (FSH) (mIU/mL), leuteinizing hormone (LH) (mIU/mL), estrogen (E2) (pmol/L), progesterone (P) (nmol/L), prolactin (PRL) (mIU/mL) and testosterone (T) (ng/mL) were assayed by electrochemiluminescence method.

2.3.2. Fasting blood glucose (FBG), insulin and MSTN determination

All subjects were fasted after 8 PM the day before trial. After fasting for 12 h, the elbow vein blood was collected. FBG was determined by ELISA, insulin by electrochemiluminescence method and MSTN by glucose oxidase method.

2.4. Judgement standard

Homeostasis model IR (HOMA-IR) was used to assess IR degree. HOMA-IR=FBG (mmol/L) fasting insulin(mIU/L)/22.5. It was considered as IR as HOMA-IR 1.66.

2.5. Statistical analysis

All data were analyzed by SPSS13.0. Measurement data were expressed as mean±SD. t test was used to compare data between groups. Correlation between MSTN and other factors was analyzed by Logistic regression analysis. MSTN was used as dependent variable; while anthropometric indexes and BMI were used as independent variable. Entrance α was set at 0.05, and exclusion α was set at 0.1. All significant levels were set at $P<0.05$.

3. Results

The average age was (28.5±4.1) years old. There were 59 obesity cases (35.8%) out of 165 PCOS patients (BMI≥25kg/m$^2$). The MSTN level of PCOS patients were significantly higher than that of the control group (18.71±15.54 vs. 14.0±15.22, $P=0.014$). There was no significant difference in MSTN between obesity PCOS patients and PCOS patients without obesity. Compared with the control group, fasting insulin, HOMA-IR and T in PCOS patients without obesity were significantly increased. And there was no significant difference in age, weight, waistline or WHR between the control group and PCOS patients without obesity. But BMI, waistline, WHR, FBG, fasting insulin and HOMA-IR of obesity PCOS patients were significantly higher than those of PCOS patients without obesity (Table 1).

Logistic regression analysis showed that there was significant correlation between MSTN and waistline, WHR, BMI and T level (Table 2). This study showed no correlation between MSTN and HOMA-IR, which is closely related to PCOS. After correction of BMI and T by multivariable regression analysis, it showed significant correlation between MSTN and PCOS ($\beta=0.356, P=0.0005$).
4. Discussion

MSTN is a negative regulator factor in regulating weight and length of muscle in human and animal [3-4]. It can affect tissue metabolism via regulating skeletal muscle, lean body mass (body mass with fat excluded), liver and adipose tissue [8]. In humans, obesity can increase the expression of MSTN. It is reported that compared with normal females, MSTN is significantly increased in circular and muscular tissues of obesity females [9]. Our study also proves that MSTN level has such relationship with BMI, waistline and WHR, which are indicators of obesity.

Since 1980, Burghen firstly put forward that IR takes part in pathological process. IR and secondary hyperinsulinemia (HI) have been regarded as general characters of PCOS. HI induces excessive androgen, follicle development disorder, then results in reproductive dysfunction. IR and secondary hyperinsulinemia (HI) have been regarded as general characters of PCOS. Since 1980, Burghen firstly put forward that IR takes part in pathogenesis of IR, but it can aggravate IR [10]. Both obesity and non-obesity PCOS patients show IR [10]. Obesity is an important risk factor. It can’t explain the pathogenesis of IR, but it can aggravate IR [10].

The correlation between MSTN and IR is another focus of our study. It shows that MSTN can regulate sensitivity of insulin [2]. In animal models, direct injection of MSTN antibody can significantly reduce the weight, improve IR and diabetes situation [13]. We explore the relationship between MSTN and IR, BMI, waistline, etc., in this study. It indicates that compared with the control group, MSTN level of PCOS patients is increased as increasing weight. There is no significant difference in MSTN between non-obesity PCOS group and the control group, or between non-obesity PCOS group and obesity PCOS group. Regression analysis shows that MSTN level is significantly related to waistline, WHR, BMI and T level. However, it shows no correlation between MSTN and HOMA-IR, which is closely related to PCOS.

References