

Ferriman-Gallwey Score correlates with obesity and insulin levels in Polycystic Ovary Syndrome – an observational study

Correlação da escala de Ferriman-Gallwey com a obesidade e níveis de insulina na Síndrome dos Ovários Policísticos – um estudo observacional

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ABSTRACT

BACKGROUND: The Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy and one of the main causes of infertility in women. **OBJECTIVES:** This study aimed to evaluate the correlation between clinical hyperandrogenism assessed by modified Ferriman-Gallwey (F-G) score and metabolic parameters in Polycystic Ovary Syndrome women. **METHODS:** This observational study included fifty Polycystic Ovary Syndrome subjects. Detailed information about body mass index (BMI) and abdominal circumference (AC) were obtained from each subject. F-G score was applied to assess hirsutism through visual method. Serum levels of insulin, glucose and testosterone were measured. **RESULTS:** A positive correlation was observed between F-G score with body mass index, abdominal circumference and insulin. **CONCLUSIONS:** Obesity, mainly abdominal adipose tissue, and insulin levels correlate with hyperandrogenism in Polycystic Ovary Syndrome women, analyzed by F-G score. F-G score could be a marker to evaluate metabolic disorders in Polycystic Ovary Syndrome women.

Keywords: Polycystic ovary syndrome; Obesity; Insulin resistance; Hirsutism; Body mass index; Infertility, male; Linear models

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RESUMO

JUSTIFICATIVA: A Síndrome dos Ovários Policísticos (SOP) é a endocrinopatia mais comum e uma das principais causas de infertilidade em mulheres. **OBJETIVOS:** O presente estudo teve como objetivo avaliar a correlação entre hiperandrogenismo clínico, avaliado pela escala de Ferriman-Gallwey (FG) modificada e parâmetros metabólicos em mulheres com a Síndrome dos Ovários Policísticos. **MÉTODOS:** Este estudo observacional incluiu cinquenta mulheres com Síndrome dos Ovários Policísticos. Informações detalhadas sobre o índice de massa corporal (IMC) e circunferência abdominal (CA) foram obtidas de cada participante. A escala FG foi aplicada para avaliar o hirsutismo através do método visual. Níveis séricos de insulina, glicose e testosterona foram também avaliados. **RESULTADOS:** Observou-se uma correlação positiva entre a escala FG e o índice de massa corporal, circunferência abdominal e insulina. **CONCLUSÕES:** A obesidade, principalmente o tecido adiposo abdominal, e os níveis de insulina se correlacionam com hiperandrogenismo em mulheres com Síndrome dos Ovários Policísticos, analisados por meio da escala FG. Desta forma, esta escala poderia ser um marcador para avaliar distúrbios metabólicos em mulheres com Síndrome dos Ovários Policísticos.

Descritores: Síndrome do ovário policístico; Obesidade; Resistência à insulina Hirsutismo; Índice de massa corporal; Infertilidade feminina; Modelos lineares

INTRODUCTION

The Polycystic Ovary Syndrome (PCOS) is a heterogenic condition that affects four to eight percent of women in their reproductive age. It is the most common endocrinopathy and one of the main causes of infertility in this group⁽¹⁾. PCOS is characterized by the presence of chronic oligo or anovulation and polycystic ovary morphology. Besides infertility, the disease is also associated with other obstetric manifestations and hyperandrogenism⁽²⁾.

Hyperandrogenism in women leads to clinical features of varied intensity, including early puberty, acne, alopecia, seborrhea, menstrual dysfunction, metabolic syndrome, psychological disorders, virilization and hirsutism⁽³⁾. Simple laboratory measurements of total and free testosterone, dehydroepiandrosterone (DHEA) sulfate, and androstenedione identifies about half of the patients with hyperandrogenism⁽⁴⁾.

Hirsutism represents a primary clinical indicator of hyperandrogenism⁽⁵⁾ and is defined as the presence of excess body or facial terminal hair growth in females in a male-like pattern, as a result of androgen excess or increased sensitivity of hair follicle to normal levels of androgen⁽⁶⁾. The modified Ferriman-Gallwey (F-G) score is used to determine the severity of hirsutism by assessing the extent of hair growth in nine key anatomical sites⁽⁷⁾.

The intensity and extension of these clinical manifestations depend on several factors and there is no strict correlation between the intensity of clinical conditions and biochemical alterations⁽⁹⁾. Thus, clinical evaluation of hyperandrogenism is recommended to identify the hyperandrogenic women with no alterations in androgen levels detected by current laboratory assays.

Metabolic disorders are found in patients with PCOS, mainly insulin resistance and compensatory hyperinsulinemia, increased risk for glucose intolerance, type 2 diabetes mellitus (DM2), metabolic syndrome, and development of cardiovascular diseases⁽⁸⁾. Furthermore, obesity is a common feature of PCOS women of whom 38 to 88% present overweight or obesity^(9,10). There is a close correlation between adiposity and clinical severity in PCOS women, and even the smallest reductions in weight generally leads to significant improvements in menstrual regularity, fertility and hyperandrogenic features⁽⁹⁾. Therefore, adipose tissue plays an important role in the development and maintenance of PCOS and influences the severity of both its clinical and endocrine features⁽¹¹⁾.

In this study, we aimed to correlate clinical defined hyperandrogenism assessed by modified F-G score and metabolic variables in PCOS women.

METHODS

Ethics

The study was approved by our local Ethical Committee – *Comitê de Ética em Pesquisa* (COEP) from *Universidade Federal de Minas Gerais*. Informed consent was obtained from all participants after a full explanation of the study.

Subjects

This study included 50 PCOS subjects who were recruited at *Hospital Borges da Costa* at *Universidade Federal de Minas Gerais*, Brazil.

The criteria for PCOS were established according to the Rotterdam American Society for Reproductive Medicine and The European Society of Human Reproduction and Embryology (ESHRE/ASRM) - sponsored PCOS consensus⁽¹²⁾. Exclusion criteria included diabetes mellitus 1 or 2, hypo-thyroidism, auto-immune diseases, nephrotic syndrome, chronic renal failure, kidney disease, cancer, acute inflammatory disease, congenital adrenal hyperplasia, Cushing syndrome, androgen secretor tumors, thyroid pathologies, hyperprolactinemic diseases, hypo or hypergonadotrophic hypogonadism and pregnant subjects. Subjects under treatment with the following medicines were also excluded: steroids, isotretinoin, cyclosporine, antiretroviral,

insulin, metformin, as well as anti-inflammatory, oral contraceptive and anti-androgen drugs. If these medicines were finished 3 months before the sample collection, no consumption was considered.

Detailed information about body mass index (BMI) and abdominal circumference (AC), measured at the top of the hip bone) were obtained from each subject at the moment of the sample collection. Classification of hypertension was considered in participants who had systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg at the time of the interview or in women who were in regular use of antihypertensive medication. In order to assess hirsutism, modified F-G score⁽⁷⁾ was applied through visual method. The density of terminal hairs at upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, upper arms and thighs was visually scored on a scale of zero to four where zero indicates no terminal hair growth and four indicating full male-pattern hair growth. Total score was calculated. A single examiner scored all subjects to avoid bias in the classification.

Sample collection and laboratory determinations

A serum sample was collected from all subjects which was then centrifuged at 2.500 rpm for 20 min for separation. Insulin was measured in *Abbott ARCHITECT*[®] in a chemiluminescent assay. Glucose and testosterone were measured using Vitros, by Johnson and Johnson[®] (New Brunswick/USA), and insulin using *Abbott ARCHITECT*[®] (Chigaco/USA), according to the manufacturer's instructions.

Statistical analysis

The statistical analysis was performed in SPSS 13.0 software. In order to evaluate normal distribution, Shapiro-Wilk test was conducted. Spearman correlation was tested in non parametric variables and Pearson's correlation in parametric variables. A 0.05 p value was considered significant.

RESULTS

We evaluated a total of 50 PCOS patients with mean age of 31 (± 5) years old. The majority of the patients were overweight (19/50 – 38%) or obese (19/50 – 38%), considering BMI 25 to 29kg/m² and >30kg/m², respectively. Only 12 women (12/50 – 24%) presented BMI <25kg/m². Regarding the AC, 12 patients had AC <88cm (24%) and 38 showed AC >88cm (76%). The range of F-G score was 0 to 30. Hypertension was observed in only 2 patients. The mean/median of lipid profile did not show association to dyslipidemia, as recommended in the III Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention (total cholesterol >240mg/dL, LDL-cholesterol >160mg/dL, HDL-cholesterol >40mg/dL and triglycerides >201mg/dL)⁽¹³⁾. The biochemical variables evaluated are presented in table 1.

F-G score was correlated with each anthropometric and biochemical variables in PCOS women. A positive correlation was observed with BMI (p=0.035; r=0.302), AC (p=0.009, r=0.367) and insulin (p=0.010, r=0.477) (Figure 1). No correlation

between fasting glucose ($p=0.654$, $r=0.084$), testosterone ($p=0.218$, $r=0.194$) and F-G score was found (Table 2).

DISCUSSION

Many studies have been performed in order to characterize variables linked to hirsutism in women. Although testosterone is the most commonly evaluated hormone in this condition, some PCOS hirsute women do not present elevated testosterone levels as measured by routine laboratory methods⁽⁶⁾. Indeed, we did not observe a correlation between testosterone levels and F-G score, indicating that testosterone levels may not be as sensitive as clinical evaluations to estimate hyperandrogenism.

In contrast, a positive correlation between F-G score versus BMI and F-G score versus AC was observed, suggesting that obesity and abdominal adiposity correlate with a higher hirsutism grade in PCOS women. In fact, obesity *per se* represents a condition of sex hormone imbalance in women. Levels of the sex

hormone-binding globulin (SHBG) tend to linearly decrease as body fat increases, and this may lead to an increased fraction of free androgens delivered to target sensitive tissues⁽¹³⁾. This may particularly occur in the presence of the abdominal phenotype of obesity in which fat abdominal tissue is characterized by specific hormonal and metabolic activities. On the other hand, this type of adipose tissue might increase metabolic syndrome development risk⁽¹⁴⁾.

Women with central fat tissue distribution generally have lower SHBG levels when compared with age- and weight-matched controls with peripheral obesity. Furthermore, women with abdominal obesity have higher testosterone and dihydrotestosterone levels than those with peripheral obesity, which may exceed their metabolic clearance rates⁽¹⁵⁾. Increased production rate is also observed even for androgens not bound to SHBG, such as androstenedione and DHEA⁽¹⁶⁾. Therefore, the abdominal phenotype of obesity can be defined as a condition of relative functional hyperandrogenic state.

Fasting glucose did not show a correlation with F-G score, as expected, since diabetic women were excluded from this study. However, insulin levels showed a significant and positive correlation with F-G score. This finding suggests that increases in insulin levels due to insulin resistance are associated to PCOS women with hirsutism. It is known that insulin increases synergistically with androgen production and that clinical and/or biochemical signs of hyperandrogenic state in PCOS results from increased synthesis and release of ovarian androgens. Moreover, insulin resistance reduces SHBG and raises free circulating testosterone⁽¹⁷⁾. In addition, hyperinsulemia increases the production of insulin growth factors I (IGF-I) and II in the liver⁽¹⁸⁾. The direct effect of insulin and IGF-I is the increase of 17-hydroxylase activity in ovaries leading to androgen hyperproduction, mainly androstenedione, testosterone and 17-hydroxyprogesterone (testosterone precursor)⁽¹⁹⁾. Besides, IGF-I inhibits aromatase which prevents the conversion of testosterone into estrogen. Moreover, insulin seems to increase LH action in ovaries⁽²⁰⁾. Hyperinsulinemia also decreases the liver production of SHBG and insulin growth factor binding protein – I (IGFBP-I) (the latter, the protein which transports IGF-1), contributing to an increased activity of free testosterone and IGF-1, respectively, in target cells⁽²¹⁾.

Table 1. Clinical and biochemical characteristics of PCOS women

Variable	N/mean or median
Age (range)	31±5 (14-42)
BMI (range)	28.9±5.3 (18.3-40.0)
AC (range)	96.0±13.5 (65.0-142.0)
F-G score (range)	11±7 (0-30)
Fasting glucose	87.1±9.7
Insulin	11.7; 8.6*
Testosterone	58.0±37.1
Hypertension (yes)	2
TC	189.7±31.8
LDL	116,6±30.9
HDL	46.7±13.1
VLDL	19.0; 20.0*
Triglycerides	95.0; 102.0*

Values represented as mean + standard deviation (parametric variables). *Median and interquartile range (non parametric variables). BMI: body mass index; AC: abdominal circumference, F-G (Ferriman-Gallwey); TC: total cholesterol.

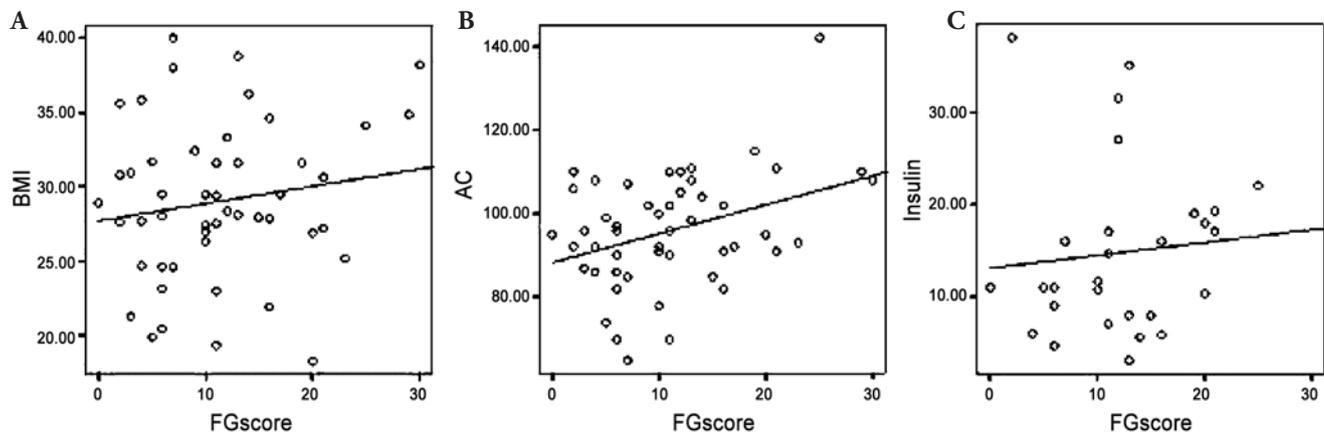


Figure 1. Scatterplot showing correlation between Ferriman-Gallwey modified score (x axis) and BMI (A), AC (B) and Insulin (C) (y axis). BMI (body mass index), AC (abdominal circumference).

Table 2. Correlation between F-G score and anthropometric and biochemical variables in PCOS women

Variable	r	p-value
BMI	0.302	0.035*
AC	0.367	0.009*
Insulin	0.477	0.010*
Fasting glucose	0.084	0.654
Testosterone	0.194	0.218

*Significant $p < 0.05$. F-G (Ferriman-Gallwey); BMI: body mass index; AC: abdominal circumference.

This study analyzed, for the first time, the correlation of F-G score and metabolic features of PCOS associated with insulin resistance and cardiovascular risk. A limitation of this study is the small sample group. However, our results open new perspectives to continuous this investigation in other populations with larger sample group.

Taken together, our results suggest that F-G score may be a good parameter to evaluate the association between hyperandrogenism and cardiovascular risk in PCOS women. Furthermore, weight loss and insulin levels control may impact hyperandrogenism status in PCOS women, contributing to better quality of life and preventing further possible complications of this disease. Nevertheless, further studies with a larger subject sample providing a comparison of hyperandrogenism assessed by current laboratory tests versus hyperandrogenism assessed by F-G score would be enlightening to better understand the sensibility of this tool in evaluating this condition.

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