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ASSOCIATION OF THYROID STIMULATING HORMONE IN WOMEN WITH POLY CYSTIC OVARY SYNDROME AND NON POLY CYSTIC OVARY SYNDROME WITH INSULIN RESISTANCE

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Abstract

Background and Objective:

There is a relationship between thyroid function and insulin resistance and alterations in lipid profile and metabolic parameters. However, little knowledge exists on this relationship especially in women with polycystic ovary syndrome (PCOS) little and controversy.

The aim of this study was to evaluate the association between TSH level and insulin resistance (IR) in the women with PCOS and 50 matched women without PCOS as a control group.

Methods:

This was a prospective study had been conducted over a 2 year period. The participants were selected among 642 women, aged 18-45 years old, who participated in the prevalence of PCOS study in Khuzestan, Iran. A total of 115 women with PCOS diagnosed based on the Rotterdam 2004 criteria, as PCOS group, and 50 women without PCOS, as a control group, were studied.

Clinical, metabolic, and endocrine parameters as well as the HOMA-IR index in the two groups were assessed. The association between serum Thyroid Stimulating Hormone (TSH) and insulin resistance with Receiver Operating Characteristic (ROC) curve was evaluated.

Results:

Women with PCOS had a significantly higher mean serum TSH level (pcos: 1.5 ± 1.75 , Control: 1.05 ± 0.67 ; $P < 0.0001$), lipid profile, {TG: (pcos: 125, Control: 114; $P < 0.0003$), HDL (pcos:49, control: 52; $P < 0.011$)} and androgens laboratory parameters and insulin resistance (pcos: 41%, control: 2%, $P < 0.0001$), but no differences in BMI (pcos: 27, control :26; $P = 0.751$) w/h Ratio (pcos: 0.83, control: 0.81, $P = 0.358$) and BP (systolic or diastolic). Forty one percent women with PCOS and $\text{HOMA-IR} \geq 2.1$, and a mean TSH level= 1.64 and 59% women with PCOS and $\text{HOMA-IR} < 2.1$, had a mean TSH level= 1.5 ($P = 0.538$).

Conclusion:

In the PCOS group, no significant association between thyroid function, as reflected by TSH, and IR was not found. Furthermore, we could not identify a TSH cut-off value, but in our study TSH= 1.15 had the best sensitivity (60%) and specificity (55%) for identifying PCOS women with HOMA-IR.

Keywords: Polycystic Ovary Syndrome, Insulin Resistance, Thyroid Stimulating Hormone.

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous and the most common endocrine and metabolic disorder in women at reproductive ages and is a hyper androgenic syndrome which includes metabolic symptoms and gynecologic disorders (1).

In 70-50% of patients, insulin resistance and metabolic syndrome increase the risk of ischemic heart failure, diabetes mellitus type 2, obstructive sleep apnea, and endometrial cancer (2, 3).

Several studies have shown that based on the age and body mass index insulin resistance in polycystic ovary syndrome is higher than what is expected (4). Although the cause of this problem is not clear, but it seems that there are many other risk factors including androgens increasing in insulin resistance and thyroid dysfunction (5).

Previous studies have investigated the relationship between thyroid function, insulin resistance, and changes in metabolic and lipid parameters in patients with polycystic ovary syndrome (6-8). Similar relationship has been reported in patients with PCOS (9-11).

However, controversial findings have been reported on the relationship between subclinical thyroid function and PCOS as well as on the determination of the cut-off point (12-15).

In addition, PCOS women had higher levels of thyroid stimulating hormone (16, 17), while women with higher TSH had more complications associated with metabolic syndrome (13, 14). Given that most studies in this issue often hadn't the control group and didn't present the precision cut of point, the aim of this study was to determine the level of TSH in women with and without PCOS (control group) and investigate the existence of subclinical hypothyroidism and, if possible, to determine the cut-off point TSH for these clients.

Methods of Implementation and Sample Selection:

This was a prospective study had been conducted over a 2 year period. The participants were selected among 642 women, aged 18-45 years old, who participated in the prevalence of PCOS study in Khuzestan, Iran as well as among the patients referred to the outpatient clinics.

A total of 115 women with PCOS diagnosed based on the Rotterdam 2004 criteria(18), as PCOS group, and 50 women without PCOS, as a control group, were studied. Clinical, metabolic, and endocrine parameters as well as the HOMA-IR index in the two groups were assessed.

The association between serum Thyroid Stimulating Hormone (TSH) and insulin resistance with Receiver Operating Characteristic (ROC) curve was evaluated.

The inclusion criteria of this study were as follows:

1. Age range of 45-18 years old, 2. PCOS diagnosis based on the criteria: Rotterdam of on-ovulation or oligo-ovulation in PCOS (presence of 12 or more follicles in the ovary with the size of 12-9 mm and with a greater volume than 10 cc) - clinical or laboratory symptoms of hyper androgens, 3. Hyperandrogenemia- Oligo- ovulation- is known as disorders that cause anovulation or high levels of androgens, 4. No history of other disorders such as thyroid diseases, hysterectomy, and oophorectomy androgen-secreting.

The exclusion criteria were as follows:

1. History of consumption of birth control pills or corticosteroids during past 6 months
2. A history of insulin sensitizing agents during past 6 months,
3. A history of thyroid medication treatment during the last 6 months,
4. Younger than 18 years or older than 45 years old, and 5. Pregnancy or lactation.

After selecting the PCOS patients, 50 patients were selected for the control group with the following criteria:

1. Age of 45-18 years old, 2. Non PCOS, 3. Absence the signs of androgen increasing, and 4. Absence the periods without ovulation.

And the subjects of control group that had the following properties were excluded from the study:

1. Younger than 18 or older than 45 years, 2. Acne, 3. Hirsutism, 4. Hyper prolactinoma, 5. Androgen secreting tumor, and 6. Oligomenorrhea Amnoure.

The procedures of this study have been approved by the local ethic committee in Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

The aim and procedures of the study were clearly explained to the participants and the written consent forms were collected from all patients after completing oral explanations.

Patients were visited through a standard questionnaire in the following cases.

History and physical examination were carried out with emphasis on the menstrual, hirsutism, acne, infertility, gynecologic disorders, drug consumption, and also measuring height, weight, BMI, than hip/waist, ultrasound of the ovaries, fasting insulin level, level of fasting glucose, TSH, TG, cholesterol, LDL, HDL and insulin resistance based on the formulation of fasting $\text{Insulin} \times \text{Glucose}$ or $\text{IR}_{20} \times \text{IF}$.

Statistical methods of analysis

Descriptive statistics were adjusted as descriptive tables and charts. Quantitative variables were analyzed by t-test and qualitative variables.

The relationship between TSH and IR was determined using logistic regression analysis and 10-fold cross- validation calculation and probability threshold for IR and TSH.

Results:

A total of 642 women aged 45-18 years old had participated in the study of the prevalence of polycystic ovary syndrome in Khuzestan province in terms of PCOS features based on the Rotterdam criteria 2004. of them, 115 patients had PCOS according to criteria, and they entered into the study and 50 were selected as a control group who were without hirsutism and PCOS criteria.

According to the definition, in all patients with PCOS, there was oligomenorrhea or amenorrhea. Hirsutism (Ferriman-Gallway Score ≥ 6) was observed in 39 patients with polycystic ovary syndrome (33.9%).

Laboratory parameters for characteristic of PCOS had a significant difference between patients and controls groups.

Total testosterone, TSH, A4, DHEAS, FBS, TG, HDL, insulin levels were higher in patients than controls. The HOMA-IR and sonographic findings of ovarian PCOS in patients were significantly different from the control group, but this difference was not clear in BMI, W/h Ratio, systolic blood pressure and diastolic blood pressure.

Insulin resistance was observed in 47 patients (60.9%), while it was in only one of the subjects of control group (P-value= 0.0001).

Among 115 patients with PCOS, in 68 patients (59.1%) with HOMA-IR < 2.1, TSH level was equal to 1.5 ± 1.83 mu/l, and in 47 patients (40.9%) with 1 HOMA-IR ≥ 2 , TSH level was equal to 1.6 ± 1.64 mu/l, respectively (P-value= 0.538).

Five patients with PCOS had not laboratory hyperandrogenism and 110 patients had at least one androgen high levels that 46 patients (40%) of them had HOMA-IR ≥ 2.1 (P-value= 0.398).

Average TSH level in 5 patients without hyperandrogenism was 1.02 ± 0.69 and it was 1.79 ± 1.5 in 110 patients with hyperandrogenism, respectively (P-value= 0.279).

The correlation coefficients between the TSH and insulin and with FBS were $r = 0.113$ (P-value= 0.229), and $r = 0.066$ (P-value= 0.484), respectively.

At the cut-off point of TSH ≥ 2 with HOMA-IR, 94 patients had PCOS, TSH > 2 that among them only 40 subjects (42.6%) were insulin resistant. From the 21 patients who had TSH ≥ 2 , only 7 patients (33.3%) had insulin resistance (P-value= 0.473).

TSH ≥ 2.5 cut-off point included 18 patients, of which 6 cases (33.3%) were resistant to insulin. (P-value= 0.605)

According to HOMA-IR in patients with PCOS the cut off point for TSH was not significant. And according to the results of Table 13, TSH= 1.15 with 60% sensitivity and specificity was 55.3%. AUC ROC, (Area= 0.562) was less than 1.

In the present study FSH levels in PCOS group was higher than the control group, but the TSH cut-off point was not significant due to HOMA- IR. Although the studies conducted by Muller et al. (2009) (13) and Dittrich et al. (2009) (14) separately TSH ≥ 2 , TSH ≥ 2.5 had been proposed as the cut-off point for TSH in patients with PCOS.

In this study, the TSH ≥ 2 and TSH ≥ 2.5 levels were separately examined as cut-off points, but no significant relationship was observed, while TSH= 1.15 had the most sensitivity (60%) and specificity (55%) for diagnosis of PCOS in patients with insulin resistance.

However, in this study HOMA-IR > 2.1 levels (19) were higher than PCOS group which were similar to the results reported by the study of Hossein Panah et al. (2011) (15). The correlation between TSH and HOMA-IR in the PCOS group was not significant.

This finding supports the results of Anaforoglu et al. (2011) (20) and Enzevaei et al. (2014) (21) and Mitkov M (22), in which it was stated that PCOS alone cannot deal with TSH problems and even briefly high levels of TSH in the presence of T3 and T4 normal, can lead to insulin resistance in the PCOS group.

In this research, the frequency of metabolic abnormalities was evaluated in PCOS group and control group. The difference between the two groups in the FBS, TG and HDL were statistically significant, but no relationship was observed between BMI, W/h Ratio, systolic blood pressure and diastolic blood pressure. Probably it is because of high BMI in each group. The results of our study were consistent with the results of Mitkov M et al. (22) that confirmed the increase of lipid profiles with the level of TSH in patients with PCOS.

The present research was also consisted with the study of Muller et al. (2009) (13) in which BMI factor was not known as an effective in the relationship of TSH and insulin resistance TSH.

Although the levels of androgens in patients with PCOS was higher than the control group, when the relationship between TSH and increased androgens was investigated in patients with PCOS, the results were not significant and similarly no association was obtained between the insulin resistance and increased insulin level in these patients. It was not significant in studying the relationship between TSH in insulin and FBS.

Limitations and Suggestions:

The main method was to evaluate insulin resistance, Insulin Clump test, and OGTT. In reviewing patients with PCOS to insulin resistance the equation of HOMA-IR was as follows:

$$\text{HOMA-IR} = (\text{FBS} \times \text{fasting insulin}) / 405$$

was used that this is a limitation of the study.

Although more studies are needed to generalize the findings of this study to the whole populations of PCOS patients, the findings of this study on the levels of TSH levels in patients with PCOS can be used for better management of the patients (23-25).

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