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The Effects of Serum Neurotensin-C Levels on Insulin Resistance in Polycystic Ovary Patients

Polikistik Over Tanısı Alan Hastalarda İnsülin Rezistansı Üzerine Serum Neurotensin-C Düzeylerinin Etkisi

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Abstract

Aim: Neurotensin has a role in the onset of diabetes mellitus. In this study, we aim to compare serum neurotensin levels between obese and non-obese patients with PCOS.

Materials and Methods: Patients were divided into four groups. We measured and calculated the following parametres: age, BMI, biochemical and hormonal profiles, and serum neurotensin levels. The results were compared within the groups. As statistical methods, we used the chi-square test and the Mann-Whitney-U test.

Results: We found certain differences between the PCOS patients and control groups. Mean values of age, FGS, and LH levels were higher than those of the control groups. LH levels were higher in the non-obese PCOS patients than the non-obese control group patients. Weight, BMI, LDL, and triglycride levels were also higher in the obese PCOS patients than the non-obese PCOS patients. HOMA-IR values were found to be highest in the obese PCOS patients. There was no significant difference between the groups in terms of NT. Evaluating the results, we observed that NT levels were similar in the non-obese PCOS patients (NT:0,67±0,709) and obese control group patients (NT:0,66±1,47). Similarly, NT levels were quite similar in the obese PCOS patients (NT: 0,43±0,362) and non-obese control patients (NT:0,47 ±0,406).

Conclusion: It was determined that lipid profile and HOMA-IR values are higher in patients with PCOS. Also, in non-obese PCOS patients and obese control group, the lipid profile, HOMA-IR values, fasting glucose and fasting insulin levels are determined to be significantly higher than the values of the non-obese control group. However, no significant difference was found in NT values between the patient groups.

Keyword: Polycystic Over Syndrome; Diabetes Mellitus; Neurotensin-C.

Öz

Amaç: Bu çalışmada polikistik over sendromu tanısı olan obez ve non-obez hastalarda diyabetes mellitus insidansını belirleyen serum nörotensin düzeyinin kontrol gruplarıyla karşılaştırılması amaçlanmıştır.

Gereç ve yöntemler: Hastalar 4 gruba ayrıldı. Bu hastaların yaş, VKİ, biyokimyasal ve hormonal profilleri ile NT düzeyleri karşılaştırıldı. İstatistiksel yöntem olarak Ki-Kare testi, Mann-Whitney U testi kullanıldı.

Bulgular: PKOS olan hastalar ile PKOS olmayan hastalarda yaş, FGS, FSH, LH değerleri arasında istatiksel olarak anlamlı farklılık tespit edildi. PKOS hastaların yaş ortalaması, FGS ve LH değerleri PKOS olmayan hastalardan daha yüksek tespit edildi. Non-obez PKOS hastalar ile non-obez kontrol grubundaki hastalar arasındaki karşılaştırmada LH, PKOS hastalarında daha yüksek olarak tespit edilmiştir. Obez PKOS hastalarında kilo, VKİ, LDL ve trigliserid non-obez PKOS hastalarına oranla daha yüksek olarak bulunmuştur. HOMA-IR değerinin ise obez PKOS hasta grubunda en yüksek olduğu tespit edilmiştir. Nörotensinin (NT) gruplar arasındaki dağılımına bakıldığında non-obez PKOS hasta grubunun (NT:0,67±0,709) obez kontrol grubuyla (NT:0,66±1,47) hemen hemen yakın değerlere sahip olduğu gösterilmiştir. Obez PKOS hastalar (NT: 0,43±0,362) ile non-obez kontrol grubunda (NT:0,47 ±0,406) NT düzeyi birbirine oldukça yakın olarak tespit edilmiştir.

Sonuçlar: PKOS tanısı alan hastalarda lipid profilinin ve HOMA-IR değerinin daha yüksek olduğu tespit edildi. Obezitesi olmayan PKOS ve obez kontrol hastalarında benzer şekilde lipid profilinin, HOMA-IR değerinin, açlık glukoz ve açlık insülin değerlerini obez olmayan kontrol grubundan anlamlı olarak yüksek olduğu tespit edilmiştir. Ancak nörotensin düzeyi açısından hasta grupları arasında anlamlı bir fark tespit edilemedi.

Anahtar Kelimeler: Polikistik Over Sendromu; Diyabetes Mellitus; Neurotensin-C.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common reproductive endocrine disorder seen in women of reproductive age. Although the overall frequency varies according to different diagnostic criteria, its incidence is around 6-8% in childbearing age (1). It was first defined by Stein and Leventhal in 1935 within an amenorrhea, hirsutism, and obesity triad. Although significant improvements have been recorded in the intervening 70 years in terms of PCOS, there are still ongoing debates as to the pathogenesis and diagnosis of the syndrome (2). Insulin resistance plays an important role in its etiopathogenesis; yet, hyperinsulinemia together with insulin resistance leads to abnormalities and changing gonadotropin responses in the metabolism of androgens in the ovaries. These hormonal changes, bring about clinical symptoms such as menstrual disorders, anovulation, and hyperandrogenism (3).

Combination of deterioration in glucose tolerance and type 2 diabetes mellitus is frequently seen in PCOS patients. PCOS is recognized as an independent risk factor for the development of type 2 diabetes mellitus; therefore, all PCOS patients are recommended to undergo screening for diabetes mellitus. In this patient group, too, insulin resistance is known to play a major role in the development of this condition (4).

Primarily released from the central nervous system and gastrointestinal tract, neurotensin is a peptide consisting of 13 amino-acid types. Neurotensin secretion is stimulated by food intake at the periphery while this also regulates gastric motility and the pancreas and bile secretion. At low levels of glucose, neurotensin is observed to increase insulin and glucagon secretion. Studies have shown that patients with high levels of neurotensin have a lower risk of diabetes in the long term (5).

MATERIALS and METHODS

We included 42 women volunteers in the study who met the Rotterdam PCOS diagnosis criteria. The volunteers were selected from women of reproductive age (16-38 years) presenting at the Gynecology and Obstetrics Clinic at Inonu University, School of Medicine, Turgut Ozal Medical Centre. The control group consisted of healthy women. A total of 84 patients - the 42 volunteers who met the Rotterdam PCOS criteria and 42 PCOS-free volunteers - were divided into 4 different groups. Sample size was determined by power analysis. Patients with a body mass index (BMI) of over 30 were evaluated in the obese group. The first group contained PCOS patients with BMI less than thirty (non-obese PCOS); the second group comprised of PCOS patients with BMI of over thirty (obese PCOS); the third group were non-PCOS patients BMI over thirty (obese control group); and the fourth group consisted non-PCOS patients with BMI under thirty (non-obese control group).

From each individual involved in the study, we obtained antecubital venous blood samples in the early follicular phase (on the 2nd-5th days of the regular or progesterone-induced menstruation) after 12-hour fasting. These samples were put in anticoagulant-free tubes. The serums of the samples were separated after 5-minute centrifugation at 4000 rpm. Until they were examined, the samples were stored in eppendorf tubes at 20° C.The samples were evaluated after they were cooled down to room temperature. While evaluating the results obtained in this study, we used average, standard deviation, rating, and frequency values for the descriptive statistics of the data. In the analysis of quantitative data, we used the Mann-Whitney U test.

For the qualitative data analysis, we made use of the chi-square test; in cases when the conditions were not met for the chi-square, we preferred Fisher's exact test. We used SPSS 17.0 software for the analysis and p value <0.05 was considered to be statistically significant.

RESULTS

We calculated the demographic and anthropometric averages of the groups. Statistically, we primarily conducted general comparisons between the groups. We determined the statistically significant differences and compared the groups once again within one another (Table 1). We found out that there was no significant differences between the groups in terms of age and height. However, BMI values varied between groups. The average BMI results for the groups were as follows: Group 1: 20.4; Group 2: 31.8; Group 3: 32.9; and Group 4: 22.3.

Table 1. Anthropometric data of the patients. **BMI:** Body mass index; **FGS:** Ferriman Galleway Score

Parameters	Group1 (n:21)	Group2 (n:21)	Group3 (n:21)	Group4 (n:21)	*P value*
Age	22,9±4,5	25±6,6	31,9±5,5	27,8±7,4	*0,0001*
Height	164,04±5,7	160,8±5,6	160,4±6,1	162,2±6,9	*0,119*
Weight	56±5,7	81,4±4,5	84,2±10,5	59,5±9,4	*0,0001*
BMI	20,4±2,08	31,8±1,8	32,9±4,04	22,3±2,5	*0,0002*
FGS	19,7±10,3	21,04±11,08	0,90±4,14	1,19±5,4	*0,0001*

First, the groups were compared in terms of hirsutism and oligomenorrhea, two factors that could not be measured in quantity. There were significant differences between non-PCOS groups (group 3-4) and PCOS groups (groups 1-2) in terms hirsutism and oligomenorrhea. The differences concerning hormonal

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and biochemical parameters between the groups are summarised in Table 2. There were also significant differences between the groups as far as LH, SHBG, triglycerides, LDL cholesterol, fasting glucose, fasting insulin, and HOMA-IR values were concerned. Evaluating the neurotensin distribution between the groups, we observed that non-obese PCOS patient group (NT: 0.67 ± 0.709) had similar values with the obese control group (NT: 0.66 ± 1.47).

Table 2. Serum biochemstry and hormonal data of the patients. **FSH:** Follicle stimulating hormone; **LH:** Luteal hormone; **E2:** Estradiol; **tTestesteron:** Total Testosterone; **fTestosterone:** Free Testesteron; **DHEAS:** Dehydroepiandrosterone Sulphate; **SHBG:** Sex hormone-binding globulin; **LDL:** Low density lipoprotein; **HDL:** High density lipoprotein; **HOMA-IR:** Homeostasis model assessment–IR (fasting glucose (mg/dL) x fasting insulin (pmol/L) / 405).

Parametres	Group1 (n:21) M± SD	Group2 (n:21) M± SD	Group3 (n:21) M± SD	Group4 (n:21) M± SD	*P value*
FSH	4,7±1,3	4,9±0,94	6,6±2,3	6,1±2,7	*0,019*
LH	5,7±2,3	7,2±8,05	3,1±1,3	3,5±1,6	*0,0001*
E2	63,5±32,2	69,4±61,1	58,01±14,2	46,9±16,3	*0,143*
tTestesteron	33,3±16,8	43,8±23,7	29,8±16	28,6±13,8	*0,020*
fTestesteron	1,4±0,42	1,9±0,79	1,5±0,61	1,4±1,03	0,013
DHEAS	212,8±130,3	200,3±90,1	166,4±63,9	171,7±88,6	*0,78*
SHBG	58,8±38,8	49,9±51,2	27,6±15,01	56,1±43,1	*0,008*
Triglyceride	85,4±43,8	140±55,6	132,2±57,9	117,7±93,5	*0,003*
Cholesterol	152,2±30,5	182,1±41,5	178,1±40,5	176,6±35,9	*0,28*
LDL	88,04±23,3	115,09±31,9	142,04±132,4	115,6±34,9	*0,003*
HDL	49,1±6,3	45,5±9,1	41,6±7,7	46,1±8,6	*0,024*
Fasting glucose	86,6±7,6	89,9±7,04	100,8±26,5	77,4±6,2	*0,0001*
Fasting insuline	12,2±8,1	22,6±14,6	25,6±23,05	9,71±4,07	*0,0001*
HOMA-IR	2,5±1,5	4,9±3,4	7,4±7,8	1,74±0,76	*0,0001*
Neurotensin	0,67±0,7	0,43±0,36	0,66±1,4	0,47±0,4	*0,555*

The NT levels were found to be quite close to each other in the obese PCOS patients (NT: 0.43 ± 0.362) and non-obese PCOS-free patients (NT: 0.47 ± 0.406). Considering these differences between PCOS and non-PCOS groups, we observed that healthy patients had higher neurotensin levels (0.56 ± 1.07) while this was not statistically significant.

DISCUSSIONS

Polycystic ovary syndrome is the most common ovulatory dysfunction. While its overall clinical perspective is very wide, it often accompanies hyperandrogenism, ovulatory dysfunction, and polycystic ovaries with an incidence rate of 6-8%. PCOS is a systemic pathology ranging from reproductive function weakness to cardiovascular diseases and cancer in the long-term (1, 6). Indeed, researchers have been curious for many years to understand how an ovary-induced pathology can have systemic impacts to this extent and focused on insulin resistance for an answer (3). Developing insulin resistance affects blood lipid levels, increases central obesity as well as the incidence of cardiovascular diseases. In return, increasing obesity worsens insulin resistance and has negative affects on glucose tolerance by increasing fasting glucose values (7). As far as the insulin-receptor interaction is concerned, the relationship between this pathology, which is thought to be caused by post-receptor intracellular signal transmission, and hyperandrogenism was first defined by Burghen et al. Since then, there have been other studies focusing on the relationship between these two (8). It is inevitable as well as, time and again, reported that PCOS patients would naturally have high fasting glucose, fasting insulin, and HOMA-IR values due to their insulin resistance. Gerard et al.'s study on 131 patients has shown that patients in the obese PCOS group had higher fasting glucose levels than the patients in the non-obese PCOS (9). Likewise, Li X et al.'s study conducted on 192 PCOS patients has reported that fasting insulin and fasting glucose levels were higher in the obese PCOS patients compared to non-obese PCOS group patients (10). Amisi et al.'s study on 104 patients has similarly shown that PCOS patients had higher HOMA-IR values than the patients in the control group (11). In our study, too, PCOS patients who had BMI>30 and were diagnosed with obesity had significantly higher fasting glucose, fasting insulin, and HOMA-IR values than non-obese PCOS patients.

Although how insulin resistance develops is known, its cause still remains a mystery to this day. There is a great number of studies trying to unveil this mystery. In these studies, focusing on serum neurotensin levels has become more popular in recent years. Pancreatic beta cells contain neurotensin receptors. It is through these receptors that insulin secretion takes place due to increased intracellular calcium. Besides, it is an insulin-sensitive regulator that plays key role in transporting glucose to muscle and fat tissues (12). Because of its effect on pancreatic, muscular, and fat tissues, neurotensin is considered as a mediator preventing the development of diabetes. There are several animal studies describing the relationship between neurotensin and blood glucose as well as lipid concentration. Boules et al.'s study on rodents has shown that small rodents, which were given analogous neurotensin, gain less weight than the control group. It was also determined that rodents receiving analogous neurotensin experience weight reduction due to decrease in food intake. It was

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shown that neurotensin increases blood glucose levels and corticosterone in some rodents (13). Sahu et al.'s on rats has shown that intracerebral and intraperitoneal administration of neurotensin antiserum blocks the effect of leptin while Kim et al.'s study has reported that rats that lack neurotensin do not show the effects of leptin (14, 15). Considering the results of these studies, we can conclude that leptin, which affects the feeling of satiety and nutrition habits in humans, creates this impact in some relation to neurotensin, that neurotensin mediates in the leptin effect, and that low serum neurotensin levels are in an indirect relationship with weight gain and obesity. In our study, the serum neurotensin levels of obese patient group were lower than the non-obese patients; yet, this relationship was not statistically significant.

Trying to explain the effect of neurotensin through leptin is inadequate; yet, extensive studies in recent years have shown that it has relationship with different mediators as well. Leinninger et al.'s study has shown that leptin, which affects neurotensin-mediated neurons, controls the release of orexin (16). Tsuneki et al.'s study on rats has revealed that orexin receptor agonists inhibit insulin resistance and that patients with low orexin levels also have greater insulin resistance (17). Yılmaz et al.'s research on PCOS patients has shown that PCOS patients have lower orexin levels (3).

CONCLUSION

The pathology of the patients diagnosed with PCOS is based on insulin resistance. Despite numerous pathophysiological mechanisms behind the development of insulin resistance, causes of this resistance have not been set out clearly yet. Even though neurotensin is a mediator that has received much interest in recent years, it is often studied on animals in relation to the development of diabetes mellitus and weight balance.

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