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Association between Lipid Profile & Antithyroid peroxidase antibodies in Poly Cystic Ovarian Syndrome

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Abstract:

Background: major features of Poly Cystic Ovarian Syndrome (PCOS) are different hormonal and menstrual abnormalities manifested as anovulation, infertility, and hyper-androgenic state. Hypothyroidism shares a similar clinical picture, because of accompanied hyperglycemia, dyslipidemia, and sex hormone binding globulin (SHBG) low levels. In addition to that, enlarged ovarian mass with cystic changes have also been noted in hypothyroidism. Despite of the fact that both diseases have different etiopathology , yet thyroid problems are more common in PCOS patients

Objectives: to assess a status of anti- thyroid peroxidase (anti-TPO) antibodies in patients having PCOS. And to estimate the effect of low thyroid function on different biochemical (e.g. lipid profile) and clinical parameters in PCOS.

Subjects and Methods: Case control study on PCOS and its relationship to thyroid and lipids ,ninety five (95)patients included in this study where 50 patients with PCOS age range (25.3±4.6 years) and 45 healthy subject age range (24.2 ± 5.2 years) ,since August 2019 up to February 2020 enrolled in this research.

Results: concerning thyroid function study, significantly higher TSH (4.99 ± 3.6) in PCOS group compared to controls (2.6 ± 2.9) ($p< 0.0001$) and higher anti-TPO antibodies (66.88 ± 26.1) in PCOS group compared to controls (22.24 ± 13.3) ($P< 0.01$) levels and significantly lower T3 (2.77 ± 1.1) in PCOS group compared to controls (4.01 ± 0.3) ($P=0.046$) levels. Concerning T4 levels, they were slightly lower in patients with PCOS (1.13 ± 3.1 ng/dl) in comparison to controls (1.01 ± 2.2 ng/dl) that the results are considered to be statistically non-significant difference.

About Lipid profile, total cholesterol level in PCOS (239 ± 28.9) was higher if compared to control group (168 ± 21.3), TG level in PCOS (120 ± 20.3) was higher compared to control (76.7 ± 10.2), and LDL in PCOS (133 ± 18.8) obviously was (significantly) higher than control group (108 ± 21.3), while HDL (38.1 ± 15.9) of patients with PCOS obviously (significantly) lower than control subjects (54.3 ± 7.7).

Conclusions : PCOS incidence in patients with thyroid disorders is much higher than healthy individuals. Specifically , hypertension and dyslipidemia, are much greater in patients with PCOS in comparison to healthy individuals. Furthermore, dyslipidemia and hypertension are even greater in patients having both PCOS and hypothyroidism than non- PCOS individuals. A greater level of anti-TPO antibodies in PCOS group than in controls .

Key words: PCOS, Lipid profile, anti-TPO antibodies thyroid hormones

1.Introduction

Clinically, the commonest manifestations of Poly Cystic Ovary Syndrome (PCOS) are; hirsutism, infertility, oligo-menorrhea, (amenorrhea), central obesity, weight gain, and acanthosis nigricans. Concerning hormones, Luteinizing Hormone (LH) shows raised levels with normal or slightly low levels of Follicle-Stimulating Hormone(FSH), higher androgens, higher

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insulin levels, with normal Prolactin (PRL), Cortisol , Free Thyroxin (FT4), Thyroxine (T4), and Thyroid-Stimulating Hormone (TSH) levels (de Medeiros SF *et al*.,2015). Hyper-insulinemic status can be associated with Low levels of Sex Hormone Binding-Globulin (SHBG). Dysglycemia, dyslipidemia, and insulin resistance are frequent in patients with PCOS, and can raise the probability of type II diabetes mellitus and cardiovascular disease incidence (Pasquali R *et al*.,*2005*).

There were many trials to evaluate the correlation between PCOS and other endocrine diseases of auto-immune etiology e.g type 2 diabetes mellitus, thyroid dysfunction and impaired glucose tolerance (IGT), yet showed controversial results (Esca´rcega RO *et al*.,2006). Some studies reported higher Anti-Ovarian Antibodies in 50% of ladies having PCOS (Fenichel P *et al*.,1999). Although, the precise mechanism of processes of autoimmunity in pathogenesis of PCOS is needed to be more illustrated; yet Autoimmune thyroid diseases e.g. hashimoto's thyroiditis showed an association with PCOS (Kachuei M *et al*.,2012). A study done by Janssen's *et al* revealed that Auto-Immune Thyroiditis (AIT) prevalence was 3X times greater in PCOS patients in comparison to healthy individuals (Janssen OE *et al*.,2004). PCOS and AIT were presumed to have genetic predisposition. Although a common genetic background has not been established, yet both disorders seemingly have an oligo-genetic background (Kachuei M *et al*.,2012, Prapas N *et al*.,2009). Gleicher *et al* stated that occurance of PCOS can be due to functional Auto-Antibodies e.g. (anti-TPO), and Thyro-Globulin Antibodies (TG-Ab)] (Gleicher N *et al*.,2007). Ott *et al* revealed a poor response to therapy in infertile PCOS ladies observed if there was high anti-TPO levels (Ott J *et al*.,2010).

Duration and severity of underlying primary hypothyroidism affects ovarian morphologic defect severity. Ovarian morphologic changes could be striking and even be mistaken as ovarian malignancies in long standing and untreated conditions of cretinism. Van Wyk and Grumbach syndrome, is the eponymous that was given for such conditions after the scientist who first described them.(Van Wyk JJ and Grumbach MM,1960). significantly greater ovarian size observed in all ladies with primary hypothyroidism compared to healthy ladies. Patients with Euthyroid chronic lymphocytic thyroiditis (CLT) have higher PCOS incidence when compared to their control counterparts, with greater systolic blood pressure ($P< 0.001$), waist circumference, body mass index (BMI), and larger hirsutism score, larger insulin resistance score, with lesser annual menstrual cycles. That is why, hypothyroidism can lead to ovarian polycystic morphologic changes which vary with the severity and duration of thyroid dysfunction. Greater prevalence of subclinical hypothyroidism (22.5% vs. 8.75%), and goiter (27.5% vs. 7.5%) was noticed in PCOS patients in comparison to healthy persons (Sinha U *et al*.,2013). In a cohort study, Low-density lipoprotein- Cholesterol (LDL-C) was very high in subclinical hypothyroidism (Benetti-Pinto CL *et al*.,2013). The insulin resistance and increased BMI were common to both (hypothyroidism and PCOS), they were observed in (54- 68%) of them(Lim SS *et al*.,2012). There is great evidence to announce that higher TSH can be seen in individuals with large BMI (Asvold BO *et al*.,2009),(Muscogiuri G *et al*.,2013) . Over-weight is related to changeable environment with elevation in insulin resistance and pro-inflammatory cytokines. Many pathways, one ends with lowering activity of deiodinase-2 enzyme at the hypophysis level leading to minor T3 deficiency and thereby elevation in TSH level(Muscogiuri G *et al*.,2013). A second way, depends on leptin, has been revealed, showing that elevated leptin in over-weight act directly on the hypothalamus leading to higher TRH secretion (Duntas LH and Biondi B,2013). Elevated level of TSH (by any of the above mechanisms), raises fatty cells generation and stimulate pro-inflammatory cytokines secretion from them through specific TSH ligands found on them. Both insulin resistance and over-weight were highly related to increased TSH level. Autoimmunity of thyroid is higher in individuals with PCOS, as the latter have larger thyroid size and more hypo-echogenicity, and greater levels of anti-thyroid antibody (Janssen OE et al.,2004). The aim of this study was to

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assess a status of anti- thyroid peroxidase (anti-TPO) antibodies in patients having PCOS. and to estimate the effect of low thyroid function on different biochemical (e.g. lipid profile) and clinical parameters in PCOS.

2.Subjects , Material and Methods

2.1. Subjects

The present research involved ninety five (95) subjects with PCOS were collected from the Endocrinology clinic for the out-patients in Al-Imamain Al-Kadhimain city hospital since August 2019 up to February 2020.

Socio-demographic data were taken from all of the patients: medical (present and previous) history, and family history, disease duration, onset age of the PCOS, if there is any medication intake.

2.2. Exclusion Criteria

- Cushing's syndrome.
- virilizing tumors.
- Congenital adrenal hyperplasia (CAH).
- hyper-prolactinemia.
- Patients undergoing dexamethasone suppression test and ACTH-stimulated 17-OH-progesterone test.
- if hyper-cortisolemia is clinically suspected.
- cases with hyper-androgenemia.

2.3. Inclusion criteria: physically , mentally, and emotionally healthy individuals without any therapeutics usage.

2.4. Blood Sampling

Five milliter (5 ml) Blood samples were drown from PCOS patients (whose their diagnostic criteria consistent with the WHO protocol), and from healthy individuals (controls) into specialized vacutainers (BD Vacutainer Systems, Plymouth, UK). And after separation by centrifugation, sera were immediately stored at − 20° C until analyzed

2. 5.Methodology

2.5.1. Serum thyroid hormones and lipid profile

Anti-TPO antibodies and thyroid hormones levels quantitatively assessed by using a commercially obtainable kit thyroid hormones by ELISA technique in a single laboratory. All parameters were assessed according to manufacturer's instruction by commercial kits (AccuBindELISA Microwells, Monobind, Inc. Lake Forest, CA, USA).

2.5.2.Lipid profile measurements

Lipid profile was assessed by Cobas c-311 clinical chemistry analyzer (Roche Diagnostics Ltd., Mannheim, Germany) using protocol of manufacturer.

2.6. Statistical analysis

Using statistics program for social sciences (SPSS) (version -25) in windows XP, all data were analyzed . summarization of verifying data done using, standard deviation (SD), mean, and $P< 0.05$ which considered statistically significant.

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3. Results:

35 individuals diagnosed with PCOS and 30 healthy subjects were involved in the present research. PCOS and control groups were age and BMI- matched. Age mean for patients with PCOS was 25.3±4.6 years , while for the healthy individuals was 24.2 ± 5.2 years. The group of PCOS displayed significantly greater mean levels of Body Mass Index (30.9 ± 9.1 kg/m2), in comparison to group of healthy subjects (28.8 ± 6.2 kg/m2).

On estimation of thyroid picture, significantly higher TSH (4.99 ± 3.6) compared to controls (2.6 ± 2.9) ($p< 0.001$) and higher anti-TPO antibodies (66.88 ± 26.1) in ladies with PCOS compared to controls (22.24 ± 13.3) ($P< 0.01$) levels and significantly lower T3 (2.77 ± 1.1) also in ladies with PCOS compared to controls (4.01 ± 0.3) ($p< 0.05$) . While T4 levels were non-significantly lesser in ladies with PCOS (1.13 ± 3.1 ng/dl) compared to controls (2.01 ± 2.9 ng/dl), as shown in Table (1).

About Lipid profile, total cholesterol in PCOS (239 ± 28.9) higher levels compared to control group (168 ± 21.3), TG in PCOS (120 ± 20.3) higher compared to control (76.7 ± 10.2), and LDL in PCOS (133 ± 18.8) was significantly greater than control group (108 ± 21.3), while HDL (38.1 ± 15.9) in ladies with PCOS was significantly lesser than control (54.3 ± 7.7) as observed in Table (1).

Statistical analysis also showed the correlation between TSH level with lipid profile in PCOS women. These analysis revealed that the TSH level was positively related to TG, ($r =0.079, P=0.001$), TC($r=0.096, P=0.055$), LDL ($r =0.033, P=0.166$), and negatively related to HDL ($r = -0.016, P=0.861$).

The present study showed a significantly higher TSH (4.99 ± 3.6)in PCOS group compared to controls (2.6 ± 2.9) ($p< 0.0001$) and higher anti-TPO antibodies (66.88 ± 26.1) in PCOS group compared to controls (22.24 ± 13.3) ($P< 0.01$) levels and significantly lower T3 (2.77 ± 1.1) in PCOS group compared to controls (4.01 ± 0.3) ($P=0.046$) levels. Concerning T4 levels, they were slightly lower in patients with PCOS (1.13 ± 3.1 ng/dl) in comparison to controls (1.01 ± 2.2 ng/dl) that the results are considered to be statistically non-significant difference.

Table: (1): Comparison between PCOS Subjects and Control groups with respect to the, BMI, profile of Lipids, anti-TPO antibodies and thyroid hormones.

Variables	PCOS Mean± SD	Non-PCOS Mean ± SD	P-value
NO.	50	45	……..
Age (years)	25.3±4.6	24.2 ± 5.2	0.319
BMI	30.9 ± 9.1	28.8 ± 6.2	0.377
T4, µg/dl	1.13 ± 3.1	1.01 ± 2.2	0.266
T3, ng/ml	2.77 ± 1.1	4.01 ± 0.3	0.046
TSH (mIU\ml)	4.99 ± 3.6	2.6 ± 2.9	0.0001
anti-TPO antibodies	66.88 ± 26.1	22.24 ± 13.3	0.01

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Total Cholesterol (TC) (mgs/ dL)	239 ± 28.9	168 ± 21.3	0.0001
Triglyceride (TG) (mgs / dl)	120 ± 20.3	76.7 ± 10.2	0.007
HDL-C (mgs / dL)	38.1 ± 15.9	54.3 ± 7.7	0.0001
LDL-C (mgs / dL)	117.33 ± 36.19	96.97 ± 23.17	0.001

4. Discussion

thyroid disorder and PCOS are the commonest hormonal abnormalities in women, despite of the great difference between them. This study included 65 subjects, 35 with PCOS and 30 as control group were analyzed clinically and biochemically.

In this study in PCOS patients, triglycerides and Total Cholesterol were significantly greater in ladies with PCOS than controls. Such results are consistent with that of study done by Pagotto et al.,(2002) where serum triglycerides and serum Total Cholesterol were elevated in PCOS compared to control group. In addition, Cinar et al., (2011) illustrated significantly greater level of Total Cholesterol and LDL in PCOS compared to control,

Results of studies by Talbott et al.,(1995) and Orio et al.(2004) in Italy; Legro et al.,(2001) and Erel et al.(2003) in Turkey; Dunaif et al., (1989) and Roa et al. (2009) in Venezuela, were in general go with this study's results concerning the amount of (Total Cholesterol, TG, LDL) in ladies with POCS were greater and HDL level was lesser than normal subjects.

Different types of dyslipidemia in women with PCOS was attributed to the influence of hyper-androgenism and insulin resistance that is commonly seen in women with PCOS along with diet, exercise and genetic predisposition. The atherogenic dyslipidemia (low HDL cholesterol along with raised LDL cholesterol and triglycerides) that was observed in this study was also seen in various other studies conducted across the world. This PCOS-associated dyslipidemia may predispose these women to increased risk of premature atherosclerosis, and early preventive interventions may be required to halt the progress of atherosclerosis in these women.

American PCOS ladies had greater BMI and TG amounts in comparison to Italian women.(Essah PA and Nestler JE,2008) In young Korean women with PCOS, substantial increase in the prevalence of dyslipidemia was seen in the absence of obesity.(Kim JJ and Choi YM,2013) WC and WHTR were associated with composite CV risk factors in women with PCOS in studies conducted by Gateva *et al*.(2012) In studies conducted by Zabulienė *et al*.,(2013) increased skin and subcutaneous adipose tissue mass along with decreased muscle mass was observed in lean women with PCOS compared to controls. Studies conducted by Kar (2013) and Sujatha *et al*.(2014) revealed great over-weight prevalence and lipid abnormalities in PCOS ladies, as in this study. Differences in weight of the body and composition might not fully clarify variations in dyslipidemia in ladies with PCOS of various geographical and ethnic backgrounds. Inheritance and milieu e.g. sedentary life and diet can predispose to these differences. Low caloric diet and physical exercise induced weight loss in women with PCOS were associated with significant improvement in anthropometric parameters in studies conducted by Crosignani *et al*.(2013)

Many published papers illustrated raised occurrence of thyroid dysfunction in PCOS ladies. A

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study done by Sinha *et al*. in which he showed that significantly greater occurrence of subclinical hypothyroidism (22.5% vs. 8.75%) and goiter (27.5% vs. 7.5%) in ladies with PCOS versus healthy individuals (Sinha U et al, 2003)

Few studies have documented greater occurrence of thyroid autoimmunity in PCOS ladies. Result of the present study consistent with that obtained by Janssen *et al*. who showed that PCOS ladies have larger thyroid sizes, greater thyroid auto-antibody amount, and more thyroid hypo-echogenicity (consistent with thyroiditis) in comparison to healthy ones. Furthermore, in their study, ladies with PCOS showed greater TSH mean amount exceeded the upper limits in comparison to healthy ones(Janssen OE *et al.*,2004). Kachuei *et al*. illustrated much greater level of anti-thyroglobulin auto-antibody in ladies with PCOS ($p = 0.04$) in comparison to healthy ones of Iranian society; despite of that, they discovered that serum TSH level was not different from control population(Kachuei, M *et al*.,2012). Garelli *et al*. also found higher prevalence of TPO Ab positivity in PCOS ladies (27%) versus healthy ones (8%). (Garelli S *et al*.,2013)

The pathophysiologic mechanisms associating the 2 disorders have not been fully clarified up to this moment, yet a multidirectional link with sophisticated enrolling of over-weight, PCOS, autoimmunity and thyroid dysfunction, acting to induce different manifestations, can be the best explanation for the moment.

a study by Petrikova et al illustrated that anti-TPO antibodies prevalence but not AIT was significantly greater in ladies with PCOS versus healthy ones, and suggested that obesity and high BMI were the probable reason behind presence of subclinical hypothyroidism in ladies with POCS (J. Petrikova *et al*.,2015).

Associated Insulin resistance and pro-inflammatory situation, can cause reduction in deiodinase-2 activity, and eventually to relative low T3 and greater TSH amounts, yet the mechanism is still unknown

Conclusion*:* It's concluded that PCOS is related to greater incidence of thyroid dysfunction in comparison to healthy individuals. In addition to that, dyslipidemias and hypertension are obviously greater in ladies with PCOS in comparison to healthy ones. Furthermore, the above-mentioned risky factors showed to be even greater in ladies with PCOS having low thyroid function versus those with-out PCOS and greater anti-TPO auto-antibodies in ladies with POCS versus healthy ones.

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