How to Cite:
Rosivari, P. S., Kalki, H., & Deekala, R. S. (2022). A study regarding the interrelation between subclinical hypothyroidism & insulin resistance among PCOS women. *International Journal of Health Sciences*, *6*(S5), 8401–8411. https://doi.org/10.53730/ijhs.v6nS5.10565

A study regarding the interrelation between subclinical hypothyroidism & insulin resistance among PCOS women

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***Abstract*---**Background: Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder (5-10%) in women of reproductive age. It is characterized by clinical and biochemical hyperandrogenism, menstrual irregularities, infertility and metabolic syndrome. Hypothyroidism is more common in PCOS. Subclinical hypothyroidism may aggravate insulin resistance. Objective: To find any relationship between subclinical hypothyroidism and Insulin resistance in PCOS patients. Materials and Methods: Study Design: A hospital based cross sectional study, Study Subjects: PCOS cases fulfilling the inclusion and exclusion criteria, SAMPLE SIZE: 100 PCOS cases attending to Gynaecology OPD, Study Setting: Gynaecology OPD of a Medical College hospital, Study Duration: January 2015 to August 2016. This included all PCOS patients, who had the criteria of Rotterdam for PCOS. Clinical examination, height, weight, BMI and lab data were measured including thyroid hormone and biochemical profile. Data were analysed by SPSS software version 21. Results: Out of 100 study subjects 52 were Euthyroid (TSH < 5) and 48 were SCH (TSH ≥ 5). Fasting serum Insulin, and HOMA IR were significantly elevated in SCH group compared to Euthyroid group (p = < 0.05.). There was a significant positive correlation present between mean TSH Vs mean HOMA IR (r= 0.357, p = 0.013) in SCH group compared to Euthyroid group of PCOS women, indicates that significant relationship present between SCH and IR.

Conclusion: Significant relationship present between Insulin resistance and subclinical hypothyroidism in PCOS patients.

***Keywords*---** Polycystic Ovary Syndrome, sub clinical hypothyroidism, Insulin resistance.

Introduction

Polycystic ovarian syndrome (PCOS) is one of the common endocrine disorders in women of reproductive age [1]. More than half of subjects with PCOS are associated with Insulin resistance (IR), hyperglycaemia, weight gain, and metabolic syndrome (MBS) [2,3]. The relationship between Insulin resistance and hypothyroidism has been studied for decades, but similar effects of subclinical hypothyroidism (SCH) on various clinical and metabolic parameters have not received much attention in these patients. [4, 5, 6] The present study was undertaken to assess the impact of SCH on various clinical and biochemical parameters including those indicating Insulin resistance in PCOS.

Aim

To study the interrelation between Subclinical Hypothyroidism and Insulin resistance among PCOS women.

Objectives

- To estimate FT3, FT4 and TSH levels in study group.
- To calculate HOMA IR in study group.
- To study the levels of serum lipid profile in study group.
- To study the relationship between Insulin resistance and Sub clinical hypothyroidism among study group

Material and Methods

Study design

A hospital based cross sectional study.

STUDY SUBJECTS

PCOS cases fulfilling the inclusion and exclusion criteria.

Sample size

100 PCOS cases attending to Gynaecology OPD.

Study setting

Gynaecology OPD of a Medical College hospital.
Study Duration: January 2015 to August 2016.

Inclusion criteria

According to Rotterdam criteria patients with two out of the following three features considered as PCOS.

1. Oligo ovulation and/or anovulation.

2. Clinical and /or biochemical signs of hyper androgenism.
3. Polycystic ovaries on ultrasound examination (the presence of 12 or more follicles measuring 2-9 mm in diameter).

Exclusion criteria

Patients who had known history of

1. Diabetes Mellitus
2. Hyper prolactinemia
3. Congenital adrenal hyperplasia
4. Hypothyroidism/Hyperthyroidism
5. Cushing's disease
6. Renal/Hepatic/Cardiac dysfunction
7. History of ovarian/ adrenal neoplasm
8. Those using any medication [Ex: OCPs, insulin sensitivity drugs, statins, radioactive iodine, levo thyroxin, corticosteroids, GnRH agonist and antagonists].

Anthropometric and biochemical Measurements

Complete systemic clinical examination and anthropometric assessment including height, weight, body mass index (BMI), waist and hip circumferences was done for every patient by a single person and with the same instruments in the clinic. Waist circumference was measured on bare skin during mid-respiration at the narrowest indentation between the 10th rib and iliac crest to the nearest 0.1cm while the patient was standing.

Laboratory Measurements

After 12hours of fasting venous blood samples obtained and were immediately centrifuged (3000 rpm) for 10 minute; the sera were separated and frozen at -8°C until analysis. Fasting blood glucose, triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low- density lipoprotein- cholesterol (LDL-C) and Very low- density lipoprotein cholesterol (VLDL- C) were measured using the enzymatic colorimetric method by a Selectra 2 auto-analyzer.

Serum free thyroxin (FT4), free tri idothyronine (FT3), TSH, fasting serum Insulin and serum total testosterone were assayed by the electro chemiluminescence immunoassay (ECLIA) method. Insulin resistance, defined by the homeostasis model assessment of Insulin Resistance (HOMA-IR), was calculated using the following equation: HOMA-IR= Fasting Insulin (μIU/L) × Fasting blood glucose (mmol /L)/22.5.
Healthy Range: 0.5–1.4.
Less than 1.0 means Insulin-sensitive.
Above 1.9 indicates early Insulin resistance.
Above 2.9 indicates significant Insulin resistance.
TSH level >5 m IU/L (according to laboratory normal range) with normal free T4 and free T3 were assumed as subclinical hypothyroidism. The normal biochemical range for TSH according to our laboratory measures is 0.3-5 m IU/L. The

reference range for serum FT3 in an apparently healthy individual was 2.3-4.2pg/ml and FT4 was 0.89-1.76ng/dl.
SCH is defined as a serum Thyroid stimulating hormone (TSH) above the defined upper limit of the reference range (TSH: 0.3-5 mIU/L), with a serum free tri idothyronin (FT3) and free Thyroxin (FT4) within the reference range. (FT3: 2.3-4.2 Pg/ml; FT4: 0.89-1.76 ng/dl).

Statistical analysis

The data was analyzed by using means, proportions and required appropriate tests with help of SPSS statistical software version 21.Student t-test was used for the comparison of means of Euthyroid and SCH groups. Associations of variables were calculated by using Chi-square test. Analysis between variables was done by using Spearman's correlation coefficients. A p value < 0.05 was considered statistically significant.

Results

Most of the study participants (50%) belong to 26 - 30 years age group followed by 21 - 25 years age group (33%). (Table 1). Out of 100 PCOS cases 52 % of the study subjects were Euthyroid (TSH < 5mIU/ml) and 48 % were SCH TSH ≥ (5mIU/ml). (Table2)

In the present study, FBS and Fasting serum Insulin were measured from which HOMA IR was calculated to find out Insulin resistance. Based on HOMA IR, 51% belongs to Early Insulin Resistant (EIR) group, followed by 37% were IR group and remaining 12% were Insulin sensitive (IS) group.(Table 3). Mean anthropometric and biochemical characteristics were compared between Euthyroid (N= 52) and SCH (N = 48) subjects. TSH, fasting serum Insulin, and HOMA IR values were significantly elevated in SCH group compared to Euthyroid group (p = < 0.05). (Table 4)

In the present study among 52 Euthyroid cases, 12(23%) were Insulin sensitive, 25(48%) were Early Insulin resistant and 15(28%) were Insulin resistant. Among SCH group, 26(54%) were Early insulin resistant, 22(48%) were Insulin resistant and there was no Insulin sensitive group in SCH group. (Table 5)

Discussion

PCOS is the most prevalent endocrine disorder among women and is generally defined in the form of hyper androgenic syndrome, with a complex aetiology and pathogenesis[7]. Recent studies have considered PCOS as not only a reproductive endocrine disease but also metabolic disorder. About 50-70% of these patients are hyperinsulinemic Insulin resistant and suffer from metabolic syndrome which by itself increases the risk of type II diabetes and cardiovascular disorders. IR and concurrent hyperinsulinemia was reported to play a key role in its occurrence and pathophysiology. Obesity and Insulin resistance occur frequently in association with this syndrome. Cardiovascular risk factors seem to cluster in women with PCOS compared with general population.

Dyslipidaemia is one of the important risk factor associated with PCOS.[20]The increase in triglycerides may be due the accumulation of triglycerides, which may occur due to the increased lipogenesis, decreased clearance of reduced fatty acid oxidation. Increased secretion of VLDL particles by the liver results in elevated plasma triglycerides concentration.[8] This may occur due to Insulin resistance, which is seen in PCOS patients. Insulin resistance also contributes to more catabolism of HDL particles and formation of LDL particles[8]. Cholesterol ester transfer protein may contribute for this. Both Insulin resistance and hyper androgenemia contribute to this atherogenic lipid profile. Testosterone decreases lipoprotein lipase activity in abdominal fat cells, and insulin resistance impairs the ability of insulin to exert its anti lipolytic effects [9].

Cardiovascular risk factors are usually present even in younger age and this suggests that the chronic disturbances in hormonal and metabolic status typical for the syndrome predispose the patients to development of early atherosclerosis and premature clinical presentation of cardiovascular disease [10].

Thyroid dysfunction alters glucose and lipid metabolism which is an important risk factor for cardiovascular disorders [23]. Various studies have mentioned an increased Insulin levels in hypothyroidism .The relationship between hypothyroidism and IR has been of interest for many decades with the availability of ultra-sensitive TSH assays and more awareness about SCH and its association with early coronary artery disease, similar interest is developing in the association between SCH and IR state. The present study implicates the utility of serum Insulin and TSH in PCOS subjects for evaluating risk of metabolic and endocrine disorders which would be helpful for an early medical intervention.[11]

The present study was hospital based cross sectional study “To study the interrelation regarding IR and SCH among PCOS women”. It was conducted in 100 PCOS patients attending to Gynaecology OPD, Narayana Medical College & Hospital, a tertiary care centre, Nellore, Andhra Pradesh.

Age Distribution

PCOS is a one of the most common disorders in women of childbearing age [1]. Mean age of distribution was found to be around 26 years in different studies. In the present study also the mean age (26yrs) was found to be in par with the above studies. (Table 7). In all the above mentioned studies, the mean ages of distribution in the Euthyroid and the SCH groups of PCOS women were found to be around 26yrs. In the present study also the mean age (26yrs) was found to be same in both the groups, but the difference in mean age between the two groups was not statistically significant (P>0.05).

TSH

Thyroid disorders are the second most common glandular disorder of the endocrine system and are increasing predominantly among women. The function of Thyroid gland is regulated by TSH .[11]

The mean TSH in both Euthyroid and SCH groups of PCOS women in different studies were found to have significant p value which was seen in our study also ($p<0.001$). (Table 8)

Fasting Serum Insulin (FSI)

The relationship between glucose and Insulin in the basal state reflects the balance between hepatic glucose output and Insulin secretion, which is maintained by a feedback loop between the liver and β-cells. The mean fasting serum Insulin of Euthyroid (8-10μIU/ml) and SCH groups (10-12μIU/ml) of PCOS women in different studies were found to be similar to the present study**,** mean values (Eu-10.97; SCH-13.6). The PCOS women with SCH had higher levels of FSI compared to those with Euthyroid group, which was statistically significant between both the groups.(Table 9)

HOMA IR

About 50–75% of all women with PCOS have some degree of IR[8]. HOMA-IR is a sensitive method for evaluation of IR in PCOS. The mean HOMA IR of Euthyroid and SCH groups of PCOS women were found to be ranging around 1-2.8 and 1.9-4.2 respectively in different studies. The corresponding figures in the present study were 2.2 and 2.9 respectively with a significant p value, thus showing the positive relation between mean HOMA IR and IR. (Table 10)

Mean TSH VS Mean HOMA IR-PCOS

In women with PCOS, who frequently have Insulin resistance and metabolic syndrome, the additional development of SCH may aggravate Insulin resistance and other risk factors. In particular, women with Insulin resistance and higher serum TSH values are described as having a higher risk for dyslipidemia and severe cardiovascular risk factors.[12]

Different studies showed a positive correlation between mean TSH and mean HOMA IR of PCOS women with significant p value. The present study results were also in par with the above with significant p value ($p<0.001$). (Table 11)

Summary

The present study is a hospital based cross sectional study conducted in the department of Obstetrics and Gynaecology, Narayana Medical College & Hospital, a tertiary care centre, Nellore, Andhra Pradesh. The aim is “To study the interrelation between SCH and IR among PCOS cases .In the current study 100 PCOS patients fulfilling the inclusion and exclusion criteria were recruited into the study. 100 PCOS women of 18 - 35 years age were participated. Complete systemic clinical examination and anthropometric assessment including height, weight, BMI, waist and hip circumferences was done for every patient. Lab data were measured including Thyroid function tests, fasting insulin, HOMA-IR index of Insulin resistance, and hormonal and biochemical profiles.

Out of 100 study subjects 52 were Euthyroid (TSH < 5) and 48 were SCH (TSH ≥ 5). Mean anthropometric and biochemical characteristics were compared between Euthyroid and SCH subjects. The PCOS cases in both the groups matched well with regards to mean age, BMI and WHR.

Fasting serum Insulin, and HOMA IR were significantly elevated in SCH group compared to Euthyroid group (p = < 0.05.). There was a significant positive correlation present between mean TSH Vs mean HOMA IR (r= 0.357, p = 0.013) in SCH group compared to Euthyroid group of PCOS women. It indicates that significant relationship present between SCH and IR.

In women with PCOS, who frequently have Insulin resistance and metabolic syndrome, the additional development of SCH may aggravate Insulin resistance and other risk factors. In particular, women with Insulin resistance and higher serum TSH values are described as having a higher risk for dyslipidemia and severe cardiovascular risk factors. It is evident that there was a definitive positive correlation between SCH and IR in PCOS women, which contributes to the strength of the study. It is quite beneficial to screen PCOS patients for SCH also, so as to avoid the associating short term and long term ill effects.

Conclusion

In the present study SCH is associated with higher Insulin levels and Insulin resistance which correlates positively with TSH levels. There is a risk of development of Insulin resistance disorders such as metabolic syndrome, cardiovascular disorders in patients with SCH. SCH is diagnosed either on routine TSH screening or when non-specific symptoms are evaluated. Hence regular screening by TSH should be done in PCOS women and Thyroid treatment should be started at an early stage. Frequent monitoring of fasting blood glucose and fasting serum Insulin levels should be done in order to avoid the associating ill effects.

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Tables

Table 1: Study Group-Age Distribution

Age group	Frequency (%)
< 20	5
21 – 25	33
26 – 30	50
31 – 35	12
Total	100

Table 2: Study Group- Thyroid Status

Thyroid status	Frequency (%)
Euthyroid (TSH <5)	52
SCHT (TSH ≥ 5)	48
Total	100

Table 3 Study Group – Insulin Resistance According To HOMA IR

HOMA IR	Frequency (%)
Insulin Sensitive(IS)	12
Early Insulin Resistant (EIR)	51
Insulin Resistant(IR)	37
Total	100

Table 4: Anthropometric and Biochemical Characteristics Of Pcos Group

Parameters	Euthyroid (N = 52)	Std. Deviation	SCHT (N = 48)	Std. Deviation	P value (t test)
Age(yrs)	26.63	3.44	26.83	4.25	0.79
HT(cms)	154.27	3.71	153.92	4.06	0.65
WT(kgs)	64.04	6.05	65.58	6.3	0.21
BMI(kg/mt2)	26.98	2.33	27.7	2.62	0.11
WHR	0.88	0.04	0.87	0.03	0.30
TSH(mIu/ml)	4.13	0.85	6.41	1.53	< 0.001
fT3(pg/ml)	2.77	0.54	2.81	0.55	0.72
fT4(ng/dl)	1.04	0.13	1.05	0.13	0.67
Fasting serum Insulin (µIU/mL)	10.97	5.16	13.60	5.5	0.015
FBS(mg/dl)	86.38	9.516	87.46	9.03	0.5
HOMAIR	2.25	1.1	2.91	1.28	0.008
Total testosterone (ng/ml)	1.2	0.5	1.1	0.4	0.78
TC(mg/dl)	199.77	14.70	203.67	14.57	0.59
HDL(mg/dl)	39.15	7.53	37.54	7.42	0.96

LDL(mg/dl)	119.21	21.60	125.54	21.82	0.89
VLDL(mg/dl)	42.37	8.84	41.54	10.15	0.15
TGL(mg/dl)	190.17	14.35	189.06	12.58	0.24

Table 5: Thyroid Status Vs HOMA IR

Thyroid Status (N=100)	HOMA IR					
	IS (12)		EIR (51)		IR (37)	
	No:	(%)	No:	(%)	No:	(%)
Euthyroid (52)	12	23	25	48	15	29
SCH(48)	0	0	26	54	22	46

Table 6: Age Distribution – Pcos

Study	Mean age (yrs)
El-Hafez H AA, et al ,2013	27
Sarama saha et al,2008	26
Omer Mohamed Shaoib,2015	29
Present study	26

Table 7: Mean Age - Euthyroid and SCH Groups (PCOS)

Study	Mean Age(Yrs.)		p value
	Euthyroid	SCH	
Enzevaei et al,2014	25	27	0.458
A Muller et al, 2009	29	26	0.02
Qun yu and jin Bei wang,2016	26	29	NS
Present study	26	26	0.79

Table 8: Mean Tsh- Euthyroid and SCH Groups (PCOS)

Study	Mean TSH(mIU/ml)		P Value
	Euthyroid	SCH	
Enzevaei et al,2014	1.8	6.8	0.006
Cemcelik et al,2012	3	7.4	< 0.001
Ganie et al,2011	2.51	7.1	0.03
Qun yu and jin Bei wang,2016	3.1	7.2	< 0.01
Present study	4.1	6.4	< 0.001

Table 9: Mean Fasting Serum Insulin - Euthyroid and Sch Groups (Pcos)

Study	Mean FSI(µIU/ml)		P value
	Euthyroid	SCH	
Enzevaei et al,2014	11.4	10.6	0.70
Cemcelik et al,2012	8.6	12.4	0.02
Ahmed Al syed et al,2006	10.8	12.5	<0.05
Present study	10.9	13.6	0.01;s

Table 10: Mean Homa Ir- Euthyroid and Sch Groups (Pcos)

Study	Mean homa ir		P value
	Euthyroid	Scht	
Enzevaei etal,2014	2.5	2.2	0.73
Cemcelik et al,2012	1.9	2.9	0.04
Qun yu and jin Bei wang,2016	2.8	4.2	0.01
Erini et al,2009	1.2	1.9	< 0.05
Sapna et al,2014	1	2	< 0.01
Present study	2.2	2.9	0.008;s

Table 11: Mean Tsh Vs Mean Homa Ir-Pcos

Study	r value	P value
El-Hafez H AA, et al ,2013	0.42	0.006
Shyam Rameshwar Adhau et al,2015	0.71	< 0.001
B.M Singh et al,2010	0.83	< 0.01
Sapna et al,2014	0.48	0.01
Present study	0.34	< 0.001