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Original Article

Metabolic Syndrome Severity Score in Subjects with and without Poly Cystic Ovarian Syndrome

Sikandar Hayat Khan, Ayesha Hafeez*, Rahat Shahid, Chaudhry Qamar Ul Haq Noor***, Javeria Hafeez****, Mehreen Gillani**

Department of Pathology, Pakistan Navy Ship Hafeez Hospital, Islamabad Pakistan, *Department of Pathology, Combined Military Hospital Multan/National University of Medical Sciences (NUMS) Pakistan, **Department of Radiology, Pakistan Navy Ship Hafeez Hospital, Islamabad Pakistan, ***Medical Directorate, Naval Headquarters, Islamabad Pakistan, ****Department of Dermatology, Combined Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To compare polycystic ovarian syndrome and their defining criteria with metabolic syndrome severity score among females with and without polycystic ovarian syndrome.
Study Design: Comparative cross-sectional study.
Place and Duration of Study: Naval Hospital Islamabad, from Jan 2018 to Dec 2021.
Methodology: We evaluated 293 female subjects for Poly Cystic Ovarian Syndrome after several exclusions who presented with an initial complaint of disturbances in menstrual cycles. These subjects underwent clinical examination including blood pressure and anthropometric indices and measurements of modified Ferriman Gallway score. Biochemical measurements included fasting plasma glucose, HDL cholesterol, triglycerides and insulin measurement. These parameters were measured for various components included in defining the Poly Cystic Ovarian Syndrome as per Rotterdam criteria and Metabolic Syndrome Severity Score equation to compare metabolic syndrome severity and insulin resistance among subjects with Poly Cystic Ovarian Syndrome and without Poly Cystic Ovarian Syndrome.
Results: Mean age among participants were 29.46±6.74 years. Disturbances in menstrual cycle reporting oligo/anovulation was reported by (181/293) 61.8% in comparison to (112/293) 38.2%. Hirsutism (modified Ferriman Gallway score>8) was present in (142/293) 48.5%. Radiological findings pointing towards Poly Cystic Ovarian Syndrome diagnosis were found in (72/293) 24.6%. Metabolic Syndrome Severity Score showed higher correlation with age, and insulin resistance in contrast to hirsutism and free androgen indices. Hirsutism was higher among oligo/anovulation females than participants without menstrual complaints (14.17+8.99 vs. 11.16+7.88, p=0.004). Similarly, biochemical hyperandrogenism Free Androgen Index was higher among oligo/anovulation subjects vs. those without oligo/anovulation females (5.24+4.52 vs 3.66+2.97, p=0.001). Metabolic Syndrome Severity Score and insulin resistance were not found to be significantly different among females having oligo/anovulation or hirsutism. We observed that Body Mass Index was significantly associated with Metabolic Syndrome Severity Score and insulin resistance than Rotterdam defined Poly Cystic Ovarian Syndrome criteria.
Conclusion: Metabolic Syndrome Severity Score equation does not associate with Poly Cystic Ovarian Syndrome criteria as defined by Rotterdam. Insulin resistance was mildly raised among Poly Cystic Ovarian Syndrome females. We interpret that obesity wherever associated with Poly Cystic Ovarian Syndrome was the reason behind mildly raised insulin resistance or relationship with Metabolic Syndrome Severity Score equation.

Keywords: Homeostasis Model Assessment of insulin resistance (HOMA-IR), Metabolic Syndrome Severity Score (MSSS), Modified Ferriman Gallway Scoring (mFG score), Polycystic ovarian syndrome (PCOS), Rotterdam PCOS criteria.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS), also sometimes termed as polycystic Ovarian Morphology has surfaced over last couple of decades as one of the major ailments affecting female reproductive system to cause varying types of clinical manifestations.[1] These manifestations even move beyond the reproductive tract to include dermatological manifestations, associations with metabolic disorders like diabetes and certain cancers.[2] Attempts to define a specific criteria or definition dates backs to the earlier efforts by Late American gynecologists Irving F. Stein and Michael Leo Leventhal, from where the term was coined as" Stein-Leventhal syndrome.[3] However, with further insight into clinical presentations and pathological associations by researchers' incoming years saw multiple criteria and phenotypic variations emerge to make things more variable along with differences in later definitions of PCOS.[4]

Literature review has highlighted an association of PCOS with metabolic syndrome where the criteria usually include obesity, hyperglycemia with dyslipidemia and hypertension which are not

Correspondence: Dr Sikandar Hayat Khan, Department of Pathology, Pakistan Navy Ship Hafeez Hospital, Islamabad Pakistan
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included in the diagnosis of PCOS diagnosis.[5] Likewise Nolan *et al*. reviewed PCOS pathogenesis and provided a recent framework associating metabolic abnormalities including insulin resistance with PCOS.[6] These studies highlight insulin resistance and resulting metabolic diseases to be essential in causation of PCOS but surprisingly there is no criteria which incorporates any of the metabolic derangements being included in any criteria for defining metabolic syndrome. The questions therefore arise that how strong these metabolic associations remain in the buildup of polycystic ovarian morphology. Secondly, if there is a role of metabolic derangements in causation of PCOS then the components included in the definition of metabolic syndrome must provide varying contribution towards the development of PCOS. Interestingly there are few studies which downsize the metabolic components in PCOS or insulin resistance possibly follow later or with appearance of hyperandrogenemia.[7] While the "Chicken vs Egg theory" remains the recent data dissecting deeper into the PCOS identifies multiple epigenetic triggers with preexisting genetic propensities which stays as the linchpin to future progression of disease towards differential phenotypes with some showing marked insulin resistance and vice versa.[8,9] Apart from molecular defects the phenotypic variations between PCOS phenotypes based upon symptoms do mention insulin resistance and metabolic components occurring in differing proportion among PCOS subjects.[10]

We therefore felt the need to assess a metabolically dangerous PCOS type from metabolically non compromised PCOS phenotype. In order to evaluate metabolic derangement in PCOS subjects we planned to propose "Metabolic Syndrome Severity Index" (MSSS equation) for measuring metabolic functional status PCOS and non-PCOS subjects and also attempt to assess the MSSS with regards to contribution from BMI, hyperandrogenemia, ultrasound presence/absence of PCOS and ovulation status with a yardstick measuring disease severity.

METHODOLOGY

The comparative cross-sectional study was carried out from Jan 2018 to Dec 2021 conducted Naval Hospital, Islamabad after approval from Ethical Review Board (letter no: 2018/Haf/1 dated 01-Jan-2018).

Inclusion Criteria: All female subjects in reproductive age group presenting at Gynecology Department with history of menstrual irregularity were included.

Exclusion Criteria: Subjects who were known diabetics, hypertensive on treatment, having infectious disorder, autoimmune ailment, having less than 2 years of menarche, suffering from some chronic form of ailment, using oral contraceptives of any type in the last 2-3 months, on hormonal treatment or fertility treatment, weight loss medication and other routine drugs or supplements for any reason were excluded.

Female subjects in reproductive age group presenting at gynecology department with history of menstrual irregularity were considered as "target population" and were offered to participate in the study based "upon non-probability convenience sampling". Subjects were advised to report to department of pathology on the second day of their menstrual cycle in "exact medical fasting status". On the day of reporting in morning subjects were explained in detail about the study project, radiological and lab testing involved and on agreeing they were asked to sign a written consent form. There were certain exclusion. We were able to finally include 293 subjects after excluding participants with age less than 19 years as per the requirements of MSSS definition criteria.

All participants were interviewed for the presence of amount and duration of cycle. Patient were generally examined for signs of any chronic disease. Anthropometric measurements were made as per laid own criteria. Ferriman-Gallway scoring was calculated as per modified criteria.[11,12] The diagnosis of clinical hyperandrogenism, oligoanovulation was made as per Kollmann et al criteria. Subjects were labeled to have "Oligo-anovulation" once menstrual cycle length was greater than 35 days.[13]

After history and clinical examination, we collected almost 10 ml of blood for various analysis including fasting plasma glucose, triglyceride, HDLc, total testosterone, Sex Hormone Binding Globulin (SHBG) and serum insulin. Patient were sent to radiology department for radiological examination for diagnosis of ovarian cysts. A diagnosis of "Polycystic ovarian Syndrome (PCOS)" was made by the radiologist only as per the Rotterdam criteria where presence of 12 or more ovarian cysts with size ranging between 2-9 mm diameter either with or without finding ovarian volume of less than 10 ml. Fasting plasma glucose was analyzed by Selctra-ProM for measuring glucose by GPO-PAP method. Total testosterone, SHBG were analyzed by Chemiluminescent microparticle Immunoassay (CMIA) on ARCHITECT iSystem, by Abbot Diagnostics. Serum insulin was

analyzed by chemiluminescence method on Immulite® 1000. Insulin resistance was calculated by Homeostasis Model Assessment of Insulin resistance (HOMAIR).[14] Free Androgen Index (FAI) was calculated using following formula: FAI (Total testosterone/ SHBG) x 100. Biochemical hyperandrogenism was labeled once FAI was greater than 5%.[15] MSSS score was measured as per criteria of previous study.[11]

We loss some patients with half work up done due to requirement of re-analysis and non-follow up from patient side, not attending the ultrasound clinic, not reporting in appropriate medical fasting state and inappropriate day of menstrual cycle and then not maintaining follow-up.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Descriptive data was analyzed for age, no of diagnosed cases with PCOS and no of diagnosed cases having menstrual abnormalities. Inferential statistics included calculation of correlation by using Pearson's correlation from age, modified FG score, free androgen index, insulin resistance and MSSS equation.

RESULTS

Major outcomes assessed for frequency were oligo/anovulation, hirsutism (mFG score), presence or absence of radiological and Rotterdam defined PCOS. Correlation was measured between age, FAI, mFG score, HOMA-IR and MSSS. Age, FAI, mFG score, HOMA-IR and MSSS were compared for presence or absence of oligo/anovulation and hirsutism. Finally, MSSS and insulin resistance were compared between PCOS and non-PCOS participants along with effect of BMI.

Mean age among participants were 29.46±6.74 years. Disturbances in menstrual cycle reporting oligo/anovulation was reported by (181/293) 61.8% in comparison to (112/293) 38.2%. Hirsutism (mFG score>8) was present in (142/293) 48.5%. Radiological findings pointing towards PCOS diagnosis were found in (72/293) 24.6%. Finally, 50.2% were diagnosed to have Rotterdam defined PCOS and 49.8% were not having PCOS as per the criteria. Table-I showed highest correlation MSSS with age, and insulin resistance while hirsutism and free androgen indices depicted minimal correlation with insulin resistance and MSSS. Hirsutism as measured by mFG score was higher among oligo/anovulation females than participants without menstrual complaints (14.17+8.99 vs 11.16±7.88, p=0.004) and similarly biochemical hyperandrogenism (FAI) was higher among oligo/anovulation subjects vs those without oligo/ anovulation females (5.24+4.52 vs 3.66+2.97, p=0.001) as shown in Table-II. Similarly, FAI levels were higher among hirsute females in comparison to females without hirsutism as 5.62+4.59 vs 3.71±3.27, p<0.001 [Table-III]. MSSS and insulin resistance were not found to be significantly different among females

Table-I: Correlation between Age, mFG Score (Hirsutism), Free Androgen Index (FAI), Insulin Resistance (HOMA IR) and Metabolic Syndrome Severity Score (MSSS) (n=293)

Parameters		Age (years)	Free Androgen Index (FAI)	Modified Ferriman- Gallwey (mFG) score	HOMA-IR	Metabolic Syndrome Severity Score {MSSS)
Age (years)	Pearson Correlation	1	-0.120*	-0.115	0.065	0.391**
	Sig. (2-tailed)		0.041	0.050	0.268	<0.001
Free Androgen Index (FAI)	Pearson Correlation	-0.120*	1	0.275**	0.169**	0.155**
	Sig. (2-tailed)	0.041		<0.001	0.004	0.008
Modified Ferriman Gallwey (mFG) score	Pearson Correlation	-.0115	0.275**	1	0.103	0.012
	Sig. (2-tailed)	0.050	<0.001		0.079	0.831
HOMA-IR	Pearson Correlation	0.065	0.169**	0.103	1	0.323**
	Sig. (2-tailed)	0.268	0.004	0.079		<0.001
Metabolic Syndrome Severity Score	Pearson Correlation	0.391**	0.155**	0.012	.323**	1
	Sig. (2-tailed)	<0.001	0.008	0.831	<0.001	

*. *Correlation is significant at the 0.05 level (2-tailed)*

**. *Correlation is significant at the 0.01 level (2-tailed)*

Independent sample t-statistics were used to compare between (HOMAIR), age, BMI, free androgen index (FAI), modified Ferriman-Gallwey score (hirsutism), insulin resistance and metabolic syndrome severity score (MSSS) between subjects with oligo/anovulation and normal menstrual cycles and later by evaluating groups formulated by modified FG score groups. General Linear Model was used to evaluate to compare Metabolic Syndrome Severity Score (MSSS) index and insulin resistance (HOMAIR) as continuous variable and BMI and presence of PCOS as fixed variables. The p-value of ≤0.05 was considered statistically significant.

having oligo/anovulation or hirsutism. We, therefore went further to evaluate the role of BMI and presence or absence of PCOS on insulin resistance and severity measure of metabolic syndrome i.e., MSSS. We observed that BMI was more strongly and statistically significant associate with MSSS than Rotterdam defined PCOS females [Figure-1]. We also observed that BMI was statistically significant for insulin resistance than Rotterdam defined PCOS females identifying PCOS related changes including hirsutism, biochemical hyperandrogenism and oligo/ anovulation may not be directly related with metabolic derangements including insulin resistance except obesity [Figure-2].

Table-II: Comparison between (HOMAIR) Age, BMI, Free Androgen Index (FAI), modified Ferriman-Gallwey score (Hirsutism), Insulin Resistance and Metabolic Syndrome Severity Score (MSSS) between subjects with Oligo/Anovulation and Normal Menstrual Cycles (n=293)

Parameters	Oligo/Anovulation (Mean+SD)		*p*-value
	Yes	No	
Age (Years)	29.18+6.89	29.92+6.48	0.360
Free Androgen Index (FAI)	5.24+4.52	3.66+2.97	0.001
Modified Ferriman Gallwey (mFG) score	14.18+8.99	11.16+7.89	0.004
Body mass index (BMI)	29.38+5.54	28.76+5.60	0.355
Insulin resistance (HOMA-IR)	3.60+3.23	3.32+3.01	0.453
Metabolic Syndrome Severity Score (MSSS)	1.16+1.05	1.10+1.14	0.652

Table-III: Comparison between Age, BMI, Free Androgen Index (FAI), Insulin Resistance (HOMAIR) and Metabolic Syndrome Severity Score (MSSS) Between Subjects with Hirsutism and no Hirsutism as Defined by Modified FG scale (n=293)

Parameters	Hirsutism as measured by mFG8 (Mean+SD)		*p*-value
	Hirsutism present	Hirsutism absent	
Age (years)	29.03+6.19	29.87+7.23	0.289
Free Androgen Index (FAI)	5.62+4.59	3.71+3.27	<0.001
Body Mass Index (BMI)	29.59+5.76	28.70+5.36	0.175
Insulin resistance (HOMAIR)	3.63+3.52	3.38+2.76	0.499
Metabolic Syndrome Severity Score (MSSS)	1.09+0.96	1.19+1.19	0.371

DISCUSSION

We observed that insulin resistance in general and metabolic syndrome severity score index were not significantly associated with PCOS patients. However, we as authors believe that this finding, provided limitations is important to appreciate in terms of underlying heterogeneity associated within the pathogenesis of PCOS along with the fact that how criteria for PCOS and metabolic syndrome have been defined. We do appreciate the conventional definition of PCOS relies on criteria which do not incorporates any of the components included in defining metabolic syndrome nor all factors for defining PCOS may possibly be related with metabolic syndrome. While studies have associated metabolic syndrome with PCOS,[15,16] still the criteria of National Cholesterol Education Program and International Diabetic Federation (IDF) are not based upon any factorial analytics unlike MSSS equation which incorporates a mathematical formula which seems more statistical and focused.[11] Furthermore, the conventional metabolic syndrome criteria by WHO, IDF and NCEP not only have differences in terms of included components but considerable variations have been acknowledged in various population groups.[16]

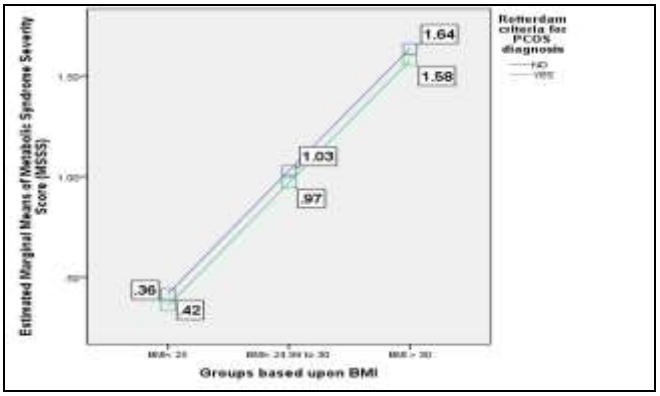

Figure-1: Difference between Metabolic Syndrome Severity Score (MSSS) index as continuous variable and BMI and presence of PCOS as fixed variables indicated PCOS vs no PCOS to have non-significant differences (p=0.607) and BMI showing significant differences

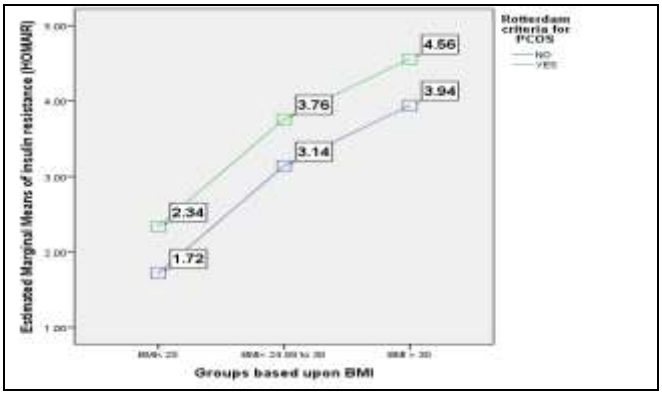

Figure-2: Difference between insulin resistance as measured by HOMAIR as continuous variable and BMI and presence of PCOS as fixed variables indicated PCOS vs no PCOS to have

non-significant differences and BMI showing significant differences

Dissecting deeper into the pathogenesis of components included in defining PCOS, we can find certain pertinent explanations supporting our findings: Firstly, PCOS as of now is differentially defined and possibly multifactorial triggers may be involved in pathogenesis. Lim *et al*. in a meta-analysis of 4530 studies have highlighted that obesity measures as also observed in our data and not biochemical hyperandrogenism or hirsutism are only related with insulin resistance.[17] Jamil *et al*. in 263/526 reproductive age females identified different phenotypes of PCOS including PCOS with oligo-anovulation (O), Radiological PCO morphology (P), PCOS with hyperandrogenism (H) and thus classified 4 phenotypes in different combinations. The authors in this study observed that there were few abnormalities relating to metabolic derangements but still oligo-anovulation and radiological presence of PCOS morphology were not associated with underlying insulin resistance.[18] Furthermore, there is evidence which supports the differential and yet to be explored reasons needing us to dip deeper down the PCOS phenotypes, which questions the reasons why it has been termed a "singular disease" or not as a group with different tentacles with each needing a differing diagnostic and therapeutic approach.[19,8-10] Noteworthy here is the fact the molecular pathological triggers in terms of genetics and later life epigenetic insults can be the reason underlying many of the different presentation under the umbrella definition of PCOS.[20,21] We, therefore feel that our findings truly depict the ground situation in terms of PCOS not only in terms of the differences observed with regards to association with MSSS or link with insulin resistance. We feel that the different phenotypes as highlighted above may lead us to an understanding about heterogeneous nature of the disease which seems to be aligning well with new publications on the PCOS.

Provided insignificant differences for various factors included in the PCOS criteria and metabolic syndrome criteria, it seems that obesity could be one reason increasing insulin resistance or association to some degree with MSSS in PCOS. Provided our findings are not in accordance with some data where lean PCOS were also observed to have higher insulin resistance,[22] still above references depict most factors included in PCOS criteria suggest less role of insulin resistance with PCOS than contribution by androgens. A comparative study on Chinese Han females suggested that HOMAIR underestimated insulin resistance in PCOS population in comparison to euglycemic clamp test.[23] Thus it seems that provided some supportive evidence favoring a generalized increase in insulin resistance among all PCOS group, the major contribution to insulin resistance results from obesity.

While there were limitations the clinical significance of our findings can't be undermined. The study emphasizes that all PCOS patients may not have insulin resistance, especially the group without obesity. Anti-insulin resistance therapy may only be started after prior evaluation of insulin resistance and the specific symptoms included in the criteria needs differential treatment. Provided limitations the local study has generated sufficient evidence for planning long-term epidemiological reasons to study the PCOS pattern prevailing in our community to explore underlying pathogenesis. Furthermore, the study also highlighted both genetic and epigenetic triggers which impact ovarian morphology and thus a molecular level study must be conducted to understand causative triggers for PCOS in our community.

LIMITATION OF STUDY

Study had faced disruptions due to including due to closure of OPDs during peak COVID-19 cases and took a longer time in completion and sample size achievement than desired. We also felt that measures and methods of insulin resistance vary and HOMAIR is known as surrogate screening marker with inherent weakness while euglycemic clamp test remains a difficult ask to conduct in general hospital settings in every patient.

CONCLUSION

Metabolic syndrome severity score (MSSS) equation does not associate with PCOS criteria as defined by Rotterdam. Insulin resistance was mildly raised among PCOS females. We interpret that obesity wherever associated with PCOS was the reason behind mildly raised insulin resistance or relationship with MSSS equation.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SHK & AH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

RS & CQUHN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

JH & MG: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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