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Review Article

An insight of association of insulin resistance with polycystic ovary syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS), a multifaceted condition, often has salient features like insulin resistance (IR). Abnormal alternation in insulin synthesis and function usually alters PCOS expressivity by deviating molecular and biochemical activity underlying this pathophysiology.

Aims: This review intends to unveil the molecular basis of the genetic polymorphism of IR and its correlation with PCOS. It also highlights the existing methods of IR estimation.

Material and Methods: Searching of different articles using keywords including PCOS, IR, and polymorphism in various databases was performed to illustrate the review article.

Conclusion: PCOS, and IR are complex and multifactorial conditions in terms of the contributing factors, their interactions, and expressivity. Further studies on diversified genotype responses to environmental and ethnic variances are required for precise understanding.

Key Messages: Insulin resistance (IR) and polycystic ovary syndrome (PCOS) are intricately interacted conditions that abnormally alter functions from genetic to organ system level. Complex gene-environment interactions make it difficult to understand the etiology and manifestation, and so diagnosis and management approaches of the heterogeneous pathophysiology are not foolproof. Further studies on genetic susceptibility related to ethnic distribution are essential for the implementation of personalized treatment of IR and PCOS.

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1. Introduction

Polycystic ovary syndrome (PCOS), an emerging endocrinopathy, affects 5-10% of reproductive-aged women with unspecified etiology.¹⁻³ Menstrual complications, hyperandrogenism, polycystic ovaries, excessive luteinized theca cells in ovarian stroma (hyperthecosis), and cutaneous manifestation like acanthosis nigricans indicate dysregulation of neuroendocrine axes in PCOS.^{1,4-7} Interactions of insulin resistance (IR) with hyperandrogenism and many confounding factors altered

the activities of the hypothalamic-pituitary-adrenal axis, sympathoadrenal medullary system, and hypothalamic-pituitary-gonadal axis in PCOS.^{1,4-7} In this review the possible genetic and molecular basis of IR and its relationship with PCOS were illustrated in an approach to fulfill the missing links.

2. Materials and Methods

Terms including “Insulin resistance, PCOS, single nucleotide polymorphism (SNP), molecular biology and genetics of IR” were used in databases of PubMed and PMC to search the articles (timeline: 1947-2021) for

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writing the review article.

2.1. Molecular basis of insulin resistance (IR)

The metabolic effect of insulin is mediated by binding it with the α -subunit of heterotetrameric insulin receptors. It activates the tyrosine kinase of the receptor's β -subunit triggering the phosphorylation of insulin receptor substrate (IRS) proteins and activation of phosphatidylinositol 3-kinase (PI3K).⁸ Protein kinase B (PKB) or Akt, a downstream molecule of the PI3K pathway, regulates insulin activities including glycogenesis and inhibition of glucose synthesis in the liver.⁸ In basal condition glucose transporter type 4 (GLUT4) often away from the cell membrane and resides in the endosomal system and "GLUT4 storage vesicles (GSVs)".⁹ Insulin translocates the GLUT4 from the GSV pool to the cell membrane for glucose import into muscle and adipose tissue (Figure 1).^{8,9} Studies suggest that PKB potentially phosphorylates AS160, a Rab-GAP (GTPase activating protein), and PtdIns3P 5-kinase (PIKfyve) which regulates insulin-stimulated GLUT-4 trafficking.⁹ PI3K can also regulate gluconeogenesis. Forehead box protein-o-1 (Foxo1) enters into the nucleus and activates transcription of few rate-limiting enzymes of gluconeogenesis like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase).^{8,10–14} PKB (Akt2) is responsible for phosphorylation of Foxo1 to restrict gluconeogenesis.^{8,10–14} Mutation of PKB (Akt2) results in a reduction of phosphorylation of Foxo1 protein leading to enhancement of transcription rate of PEPCK and G6Pase as well as gluconeogenesis in hepatocyte.^{8,10–14} This impairment is a key indicator of dysregulation of insulin action leading to IR, hyperglycemia, and type 2 diabetes mellitus (T2DM).^{8,10–14} Studies suggest that IRS-1 knockout mice may have a mild form of IR due to the compensatory behavior of pancreatic β cells. On the contrary null IRS-2 shows IR with impairment of pancreatic β cell compensation. The variation in IR expressivity indicates the diversified activity of IRS-1 and IRS-2 on the β cell mass and functionality.^{8,15} Intracellular serine kinases cause serine phosphorylation in IRS-1 that can lead to a decrement in the interaction of insulin receptor/IRS-1 and/or IRS-1/ PI3K and increment in IRS-1 dissociation.⁸ This deregulation is a key feature of IR and can be propagated in an inherited manner.⁸ Studies represent that adipokines like tumour-necrosis-factor (TNF) and circulating free fatty acids (FFA) can stimulate serine phosphorylation in IRS-1 leading to impairment in signal transduction of insulin.⁸ TNF- α can activate stress-induced enzymes, a c-Jun-NH2-terminal kinase that also stimulates the phosphorylation phenomenon.^{8,16} Class 1a of PI3K consists of a more regulatory subunit (p85) and a less catalytic subunit (p110) that leads to the formation of the heterodimer (p85- p110) and free p85 monomer. Imbalance

in these subunits of PI3K may lead to IR by negatively affecting the cell signaling cascade.^{8,17}

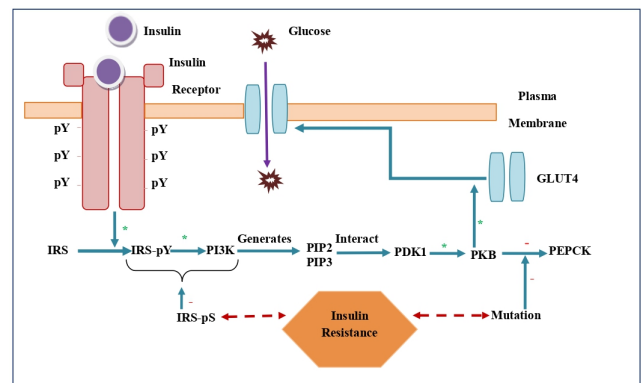


Fig. 1: Insulin signaling cascade and insulin resistance. pY=phosphorylated tyrosine; Glut4 =Glucose-transporter-tyhpe-4; IRS= Insulin receptor substrate; PI3K =Phosphatidylinositol 3 kinase; PIP2 = Phosphatidyl-inositol-3,4-bisphosphate; PIP3+ Phosphatidyl-inositol-3,4,5-trisphosphate; PDK1= Phosphatide-dependentkinase-1; PKB = Protein-kinase B; PEPCK = Phosphoenopyruvate carboxykinase; pS= Phosphorylated serine, *= stimulation, - = inhibition

2.2. Mitochondria and insulin resistance (IR)

Intramyocellular and intrahepatic lipid accumulation are associated with a reduction in mitochondrial function like oxidative phosphorylation and electron transport chain (ETC).¹⁸ Decrement of mitochondrial density and activity are indicators of IR and T2DM.^{18,19} Catabolism of oversupplied nutrients provides enhanced electron supply in ETC that induces proton gradient across the mitochondrial inner membrane.¹⁸ Failure in the coupling of this increased proton gradient and ATP synthesis leads to the generation of excess reactive oxygen species (ROS) resulting in oxidative stress.¹⁸ ROS as well as oxidative stress can damage various biomolecules including nuclear and mitochondrial DNA, lipid, and amino acids and cause dysfunctioning in signal transduction of insulin along with IR.^{18,19} The exact mechanism behind the interaction between mitochondria and IR is still unclear. Emerging studies on skeletal muscle demonstrate that mitochondrial dynamics along with immunoreactivity and insulin sensitivity are interconnected with diet.¹⁸ Proper dietary patterns can reduce mitochondrial dysfunction and regain oxidative capacity.^{18,20}

2.3. Proposed methods for estimation of insulin resistance (IR)

IR along with altered fat distribution and hyperinsulinemia are major etiological factors of T2DM, dyslipidemia, cardiovascular disease, and PCOS.^{21–25} There are several

Table 1: Methods to estimate insulin sensitivity and resistance^{23,26–28}

Methods	Measurement / advantage	Accuracy	Disadvantage (s)
HEC ⁱ	Insulin sensitivity	Body mass (g)	316 (Median value)
		Fasting glucose (mg/dl)	133 (Median value)
		Fasting insulin (μ U/ml)	52 (Median value)
		GIR ⁱⁱ ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	14.5 (Median value)
		R _d clamp	20 (Median value)
QUICKI ^{iv}	Insulin sensitivity (linear correlation)	Clamp HGP ⁱⁱⁱ ($\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	5.5 (Median value)
		QUICKI	0.263 (Median value)
HOMA-IR ^v	IR ^{vi} and functionality of pancreatic β cells. May detect high fat	Mean coefficient of variance	34.8%
		HOMA-IR and AUC-ITT ^{vii} (correlation)	p=0.0248
McAuley index	IR (in normoglycemic individuals)	Recorded ethnicity Black (n=13), brown (n=9), yellow (n=0), indigenous (n=3), undeclared (n=14)	Metabolic syndrome-Absent: 8.3 (7.5-9.7) and Present: 7.1 (6.3-8.3), P=0.001

ⁱHyperinsulinemic euglycemic clamp

ⁱⁱGlucose infusion rate

ⁱⁱⁱHepatic glucose production

^{iv}Quantitative insulin sensitivity check index

^vHomeostatic model assessment-insulin resistance

^{vi}Insulin resistance

^{vii}Area under curve-insulin tolerance test

proposed methods to estimate IR and sensitivity for clinical, epidemiological, and research purposes (Table 1).^{23,26–28} Estimation of insulin sensitivity depends on two methods — (1) calculation based on fasting plasma concentration of glucose, insulin, and triglycerides and (2) calculated by using plasma concentration of glucose and insulin involving oral glucose tolerance test (OGTT).²³

2.4. Crosstalk between insulin resistance (IR) and PCOS

Insulin is an essential hormone that regulates the metabolism of carbohydrates, lipids, and protein.⁴⁰ Abnormal activity of pancreatic β cells and decrement in cellular sensitivity for circulating insulin can lead to IR.^{1,8,22} This unusual condition alters fat distribution pattern, obesity, muscle mass, and hormonal function such as hyperandrogenism and induces multiple health complications including dysfibrinolysis, intravascular thrombosis, dyslipidemia, cardiovascular risks, and PCOS (Figure 2).^{1,8,22,41,42} Insulin stimulates gonadotrophin-releasing hormone (GnRH) secretion from the hypothalamus involving mitogen-activated protein kinase (MAPK) pathway and GnRH induces secretion of luteinizing hormone (LH) from adenohypophysis that augments ovarian steroidogenesis, specifically androgens.^{22,43} Insulin suppresses insulin-like-growth-factor binding protein-1 (IGFBP-1) via PI3K pathway in hepatocyte and ovary that induces insulin-like-growth-

factor-1 (IGF-1) availability.^{22,44} IGF-1 facilitates insulin-induced suppression of sex hormone-binding globulin (SHBG) level in the blood leading to increased availability of androgens, a key component of PCOS.²² Monosaccharides like fructose and glucose also participate in the inhibition of SHBG expression by down-regulation of hepatic-nuclear-factor-4- α (HNF-4 α).⁴⁵ Decrement in IGFBP-1 activity induces hyperandrogenism that triggers PCOS. Insulin can inhibit IGFBP-1 via regulating thymine-rich insulin response elements (TIRE) in DNA involving activation of PI-3K.^{22,46} Presence of IGF-1 receptor and insulin receptor (INSR) in granulosa cells (GC), stromal cells, and theca cell (TC) indicate insulin activity in ovarian function such as steroidogenesis.^{22,47,48} Insulin stimulates the excess synthesis of various steroids including testosterone, progesterone, and 17- α -hydroxyprogesterone by facilitating the activity of the steroidogenic acute regulatory protein (StAR) and enzymes such as 17 α -hydroxylase/17, 20-lyase (CYP17A1), 3 β -hydroxysteroid dehydrogenase (3 β -HSD), aromatase (CYP19A1) and CYP11A1 in polycystic-ovaries.^{22,49,50} The “selective insulin resistance” theory illustrates ovarian sensitivity to insulin and subsequent synthesis of androgen during systemic IR.⁵¹ Insulin and LH synergistically stimulates low-density lipoprotein cholesterol (LDL-C) receptors transcription in GC via PI3K, PKA, and MAPK pathways.²² Insulin also induces steroidogenesis by upregulating aromatase activity in GC cells that subsequently acts as a key component for transformation to androgen in TC

Table 2: Genetic basis of association between insulin resistance and PCOS^{i 29–39}

SNP ⁱⁱ	Method	Population
* ⁱⁱⁱ rs2252673 (INSR ^{iv})	Case-control association and discovery, and replication cohort	Unrelated 275 White PCOS individuals and 173 White control at University of Alabama at Birmingham (UAB)
*C1008T at exon 17 (INSR) and CC genotype (C1085T)	Pilot study, PCR-RFLP ^v	Equal number of PCOS patients in Safdarjung Hospital, New Delhi and control
*rs2059807 and rs1799817-INSR	Case-control study	Indian women-253 PCOS individuals and 308 age-matched control
*Mutation exon 19 (His1130Arg)-INSR	Literature screening	Two sisters
*Gly972Arg (IRS-1 ^{vi}) Gly1057Asp (IRS-2 ^{vii})	Literature screening	Odd ration and 95% confidence interval
*Exon 17 C/T SNP	Case-control study, PCR-RFLP	99 PCOS individuals and 136 healthy women, approved by Mount Sinai School of Medicine institutional review board-SNP or linkage disequilibrium to be further investigated
# ^{viii} rs2059806 and rs1799817 (INSR)	PCR-RFLP	Iranian population-186 PCOS individuals and 156 healthy women
#rs1799817, rs2059807, rs8108622, rs10500204-INSR	PCR	260 Hans Chinese family trios-Center for Reproductive Meidcine, Provicinal Hospital affiliated to Shadong University
*rs3786681, rs17253937 and rs2252673-INSR	PCR and automated sequencer for sequencing	224 Chinese family trios-approved by Institutional review board of Shandong University. Weak association in rs2252673
#rs1799817, and rs1799817 and rs2059806, *rs2059807	Meta-analysis	20 case control study (17460 PCOS patients and 23845 control), 98 SNPs (23 exons) and flanking regions of INSR
*Exon 17 C/T SNP of INSR	Case-control study, direct sequencing	Indian women-180 PCOS individuals and 144 age-matched control
*Gly972Arg (IRS-1) Gly1057Asp (IRS-2)	Literature screening-2975 PCOS patients and 3011 control	Odd ration and 95% confidence interval. PCOS associates with Gly972Arg (IRS-1) in Caucasian ethnicity and Gly1057Asp (IRS-2) in Asian ethnicity.
*rs1799817 (C/T His1058His)-INSR. Gly972Arg (IRS-1) and Gly1057Asp (IRS-2)	Review study	Caucasian (PCOS patients: 99 and healthy women: 136), Chinese (PCOS patients: 120 and healthy women: 40), Indian (PCOS patients: 180 and healthy women: 144) and Japanese (PCOS patients: 61 and healthy women: 99). Italian (PCOS patients: 65 and healthy women: 27), Greek (PCOS patients: 83 and healthy women: 88), Japanene (PCOS patients: 123 and healthy women: 380) and Turkish (PCOS patients: 60 and healthy women: 60).

ⁱ Polycystic ovary syndromeⁱⁱ Single nucleotide polymorphismⁱⁱⁱ Association^{iv} Insulin receptor^v Polymerase chain reaction- restriction fragment length polymorphism^{vi} Insulin receptor substrate-1^{vii} Insulin receptor substrate-2^{viii} No association

cells.²² Further study is required to understand the basis of ethnic, anthropometric, and genetic contribution for differential metabolic, endocrine and phenotypic expression of IR in the PCOS population.

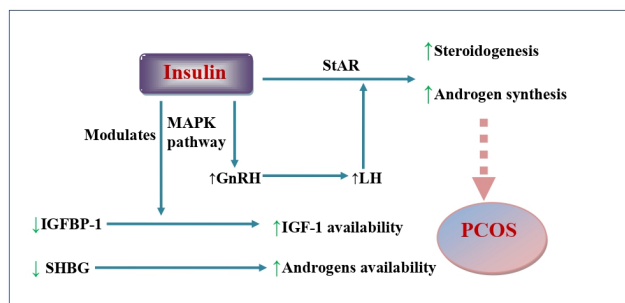


Fig. 2: Possible pathways of role of insulin in PCOS

PCOS = Polycystic ovarian syndrome, StAR = Steroidogenic regulatory protein, MAPK + Mitogen activated protein kinase, GnRH = Gonadotropin-releasing hormone, LH = Luteinizing hormone, IGFBP-1 = Insulin-like growth factor binding protein-1, IGF-1 = Insulin—like growth factor-1, SHBG = Sex hormone binding globulin

2.5. Insulin resistance (IR) and PCOS – Role of genetic polymorphism

PCOS and IR both are genetically regulated and the prevalence of IR with or without PCOS can be found in the first-degree relatives of women with PCOS.^{29,52} This phenomenon indicates crosstalk between PCOS, and genes of insulin signaling pathways that regulate the interaction of insulin with INSR and are associated with other signaling cascades which participate in the regulation of metabolism and cell proliferation.^{29,53} The twisting and meshing of different components of insulin signaling and PCOS are not clear. Analysis of genetic variation involving single nucleotide polymorphism (SNP) study is a cardinal approach to understand the association between PCOS and insulin signaling. IR polymorphism studies of the PCOS population were illustrated in (Table 2).^{29–39,54} Genome-wide association study (GWAS) along with genetic polymorphism study are implicated to understand the genetic background in association with epigenetic factors, ethnicity, and lifestyle alternations of disease and syndrome. Goodarzi et al. performed a study on components of an insulin signaling pathway to find out its interaction with PCOS where genotyping of INSR and 27 genes coding for different pathways including PI3K were incorporated.²⁹ In their study genotyping of 11 genes controlling glycogen synthase kinase 3 β reflected that INSR and IRS-2 are key factors of PCOS.²⁹ Another study of a meta-analysis involving 889 cases and 1303 controls, and 795 cases and 576 controls was performed where the results of the analysis suggest that IRS-1 Gly972Arg polymorphism is

a key component of PCOS development with enhanced insulin level.⁵³ This outcome also indicates the association between lowering of PI3K activity with impairment of insulin-stimulated signaling.⁵³

3. Conclusion

PCOS is intertwined with various pathophysiological conditions and IR might be the most important of them. Disruption in insulin action by different means such as pancreatic deregulation and declination in insulin signaling associates and/or induces the onset and progression of PCOS or vice versa. Females of the Asian population reported a higher prevalence of central adiposity that could be a silent contributor to PCOS and they are prone to fall under cardiometabolic threat in post-reproductive life. Rapidly changing lifestyle patterns, diet, and increasing exposure to stress promote to worsen the situation, and the heterogenic disorders like PCOS 'tends' to rise. Considering these facts, it is essential to pursue further studies combining all the possible associated areas of a particular ethnic population for a better understanding of the divergent nature of PCOS. To apprehend the causes and progression of PCOS, the genetic predispositions and their contribution in response to epigenetic factors, and differential manifestation are needed to be evaluated in a precise and individualistic manner.

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