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Review Article

OBESITY AS A PATHOGENIC FACTOR IN POLYCYSTIC OVARIAN SYNDROME: A NARRATIVE REVIEW

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Abstract: Polycystic ovary syndrome (PCOS) represents the most common endocrine disorder affecting reproductive-aged women, with prevalence estimates ranging from 6.63% to 17.8% depending on diagnostic criteria applied. Obesity affects 49-80% of women with PCOS and serves as both a comorbidity and significant pathogenic contributor. The interplay between obesity and PCOS intensifies metabolic dysfunction, hyperandrogenism, and reproductive impairment, creating a bidirectional relationship that complicates clinical management. This narrative review critically examines the pathogenic mechanisms linking obesity to PCOS development and progression, synthesizing current evidence on metabolic, endocrine, cellular, and genetic pathways. A comprehensive literature search was conducted across PubMed, MEDLINE, and Scopus databases. Studies were prioritized from SCIE-indexed journals, emphasizing systematic reviews, meta-analyses, prospective cohorts, and mechanistic investigations. Obese women with PCOS demonstrate significantly worse metabolic and reproductive outcomes compared to lean counterparts, with phenotype-dependent variations in insulin resistance severity. Obesity functions as a critical pathogenic amplifier in PCOS through interconnected metabolic, endocrine, inflammatory, and microbial mechanisms.

Keywords: Polycystic ovary syndrome, Obesity, Metabolic pathways, Genetic predisposition.

INTRODUCTION

Polycystic ovary syndrome (PCOS) constitutes the most prevalent endocrine-metabolic disorder among women of reproductive age, affecting approximately 8.7-17.8% of this population depending on diagnostic criteria employed.[1,2] The syndrome manifests as a heterogeneous constellation of reproductive, metabolic, and psychological disturbances characterized by ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound.[1,2] Three primary diagnostic frameworks exist for PCOS identification: the 1990 National Institutes of

Health (NIH) criteria requiring both hyperandrogenism and ovulatory dysfunction; the 2003 Rotterdam criteria mandating two of three features (hyperandrogenism, ovulatory dysfunction, polycystic ovaries); and the 2006 Androgen Excess and PCOS Society (AE-PCOS) criteria emphasizing hyperandrogenism plus ovulatory dysfunction or polycystic ovarian morphology.[3-5] High-quality epidemiological studies utilizing standardized assessment tools report PCOS prevalence of 10.89% (Rotterdam), 10.61% (AE-PCOS), and 6.63% (NIH), with Rotterdam criteria capturing the broadest phenotypic spectrum.[1]

The association between obesity and PCOS represents a critical clinical concern, with 49-80% of affected women classified as overweight or obese (BMI ≥25 kg/m²).[6] This prevalence substantially exceeds that observed in age-matched general populations, suggesting obesity functions not merely as a comorbidity but as an active pathogenic contributor.[3-4] Obese women with PCOS consistently demonstrate more severe hyperandrogenism, greater metabolic abnormalities including pronounced insulin resistance and dyslipidemia, increased visceral adiposity, and worse reproductive dysfunction compared to lean PCOS counterparts.[6-8] The clinical significance extends beyond reproductive health, encompassing elevated risks for type 2 diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, and psychological morbidity.[7-9]

Despite extensive research, the precise nature of the obesity-PCOS relationship remains incompletely understood, particularly regarding directional causality. Does obesity trigger PCOS development in genetically susceptible individuals, or does underlying PCOS pathophysiology predispose to weight gain through metabolic and neuroendocrine derangements? Emerging evidence suggests a bidirectional, reinforcing relationship wherein obesity amplifies pre-existing PCOS features while PCOS-related metabolic dysfunction facilitates further adipose tissue accumulation. This "vicious cycle" model integrates hyperandrogenism and hyperinsulinemia as central drivers of peripheral insulin resistance that perpetuates both conditions.[7,10]

This narrative review critically examines the multifaceted mechanisms through which obesity contributes to PCOS pathogenesis and phenotypic expression.

METHODS

A comprehensive literature search was conducted across PubMed, MEDLINE, and Scopus databases, with inclusion of seminal earlier studies. Search terms encompassed "polycystic ovary syndrome," "obesity," "insulin resistance," "hyperandrogenism," "adipokines," "gut microbiome," and related metabolic pathway descriptors. Studies were prioritized from SCIE-indexed journals, emphasizing systematic reviews, meta-analyses, prospective cohorts, and mechanistic investigations.

METABOLIC PATHWAYS LINKING OBESITY AND PCOS (Fig no. 1)

Insulin Resistance as Central Pathogenic Driver

Insulin resistance (IR) represents a unifying pathophysiological feature affecting 50-70% of women with PCOS, with substantially higher prevalence among obese compared to lean phenotypes. Obesity exacerbates insulin resistance through multiple mechanisms, primarily via excess adipose tissue secretion of free fatty acids (FFAs) and inflammatory cytokines that impair insulin signalling in peripheral tissues.[10,11] In skeletal muscle and hepatic tissues, elevated circulating FFAs activate protein kinase C isoforms and c-Jun N-terminal kinase (JNK), leading to serine phosphorylation of insulin receptor substrate-1 (IRS-1) rather than the functional tyrosine phosphorylation required for glucose transporter-4 (GLUT-4) translocation.[12] This molecular interference diminishes glucose uptake and utilization, necessitating compensatory pancreatic β-cell insulin hypersecretion to maintain euglycemia.[10,11]

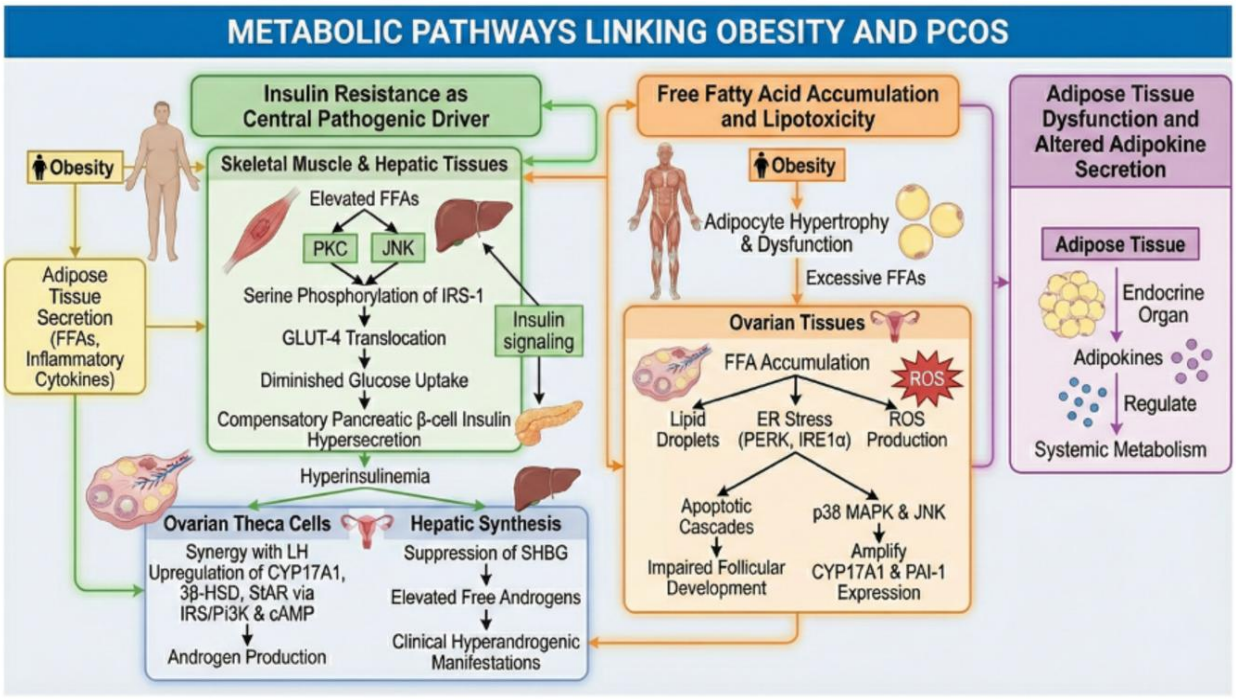

Fig no. 1: Metabolic Pathways linking Obesity and PCOS

The resulting hyperinsulinemia directly contributes to PCOS pathogenesis through multiple reproductive and metabolic consequences.[9,10] Insulin acts synergistically with luteinizing hormone (LH) to stimulate ovarian theca cell androgen production by upregulating steroidogenic enzymes including CYP17A1, 3β-hydroxysteroid dehydrogenase, and steroidogenic acute regulatory protein (StAR).[13-15] This occurs via activation of the insulin receptor substrate/phosphoinositide 3-kinase (IRS/PI3K) pathway and co-activation of cyclic adenosine monophosphate (cAMP) signalling cascades.[15] Additionally, hyperinsulinemia suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), the primary plasma carrier protein for testosterone and estradiol.[6,7] Reduced SHBG concentrations elevate free androgen fractions, intensifying clinical hyperandrogenic manifestations including hirsutism, acne, and androgenic alopecia even when total testosterone levels remain modestly elevated.[7-8,10]

Free Fatty Acid Accumulation and Lipotoxicity

Obesity-associated adipocyte hypertrophy and dysfunction lead to excessive release of non-esterified fatty acids into systemic circulation, creating a state of chronic lipid oversupply that particularly impacts ovarian tissues.[6,16] Elevated FFAs induce lipotoxic effects in granulosa and theca cells through several interconnected mechanisms. First, FFAs accumulate within ovarian cells when β-oxidation capacity becomes saturated, forming lipid droplets that disrupt normal cellular architecture and organelle function.[16] At the molecular level, excess FFAs activate endoplasmic reticulum stress responses by overwhelming protein folding machinery and disrupting calcium homeostasis. In granulosa cells, FFA-induced ER stress activates protein kinase RNA-like ER kinase (PERK) and inositol-requiring enzyme 1α (IRE1α) signalling pathways, triggering apoptotic cascades that impair follicular development and oocyte quality.[3] Simultaneously, FFAs stimulate reactive oxygen species (ROS) production through mitochondrial dysfunction and NADPH oxidase activation, establishing oxidative stress that damages cellular lipids, proteins, and DNA. This oxidative milieu activates p38 mitogen-activated protein kinase (MAPK) and JNK stress pathways, which further upregulate CYP17A1 and plasminogen activator inhibitor-1 (PAI-1) expression, amplifying both androgen synthesis and thrombotic risk.[6]

Adipose Tissue Dysfunction and Altered Adipokine Secretion

Beyond serving as a passive energy storage depot, adipose tissue functions as a dynamic endocrine organ secreting numerous bioactive molecules termed adipokines that regulate systemic metabolism, inflammation, and reproductive function.[17-20] In obesity, adipose tissue undergoes pathological remodelling characterized by adipocyte hypertrophy, macrophage infiltration, local hypoxia, and altered secretory profiles that collectively contribute to PCOS pathogenesis.[21]

Leptin, a 16-kDa protein hormone primarily produced by adipocytes in proportion to fat mass, exhibits markedly elevated concentrations in obese PCOS women compared to both lean PCOS and healthy controls.[20] At the reproductive axis, excessive leptin disrupts gonadotropin-releasing hormone (GnRH) pulsatility, alters LH/FSH secretion ratios favouring LH predominance, and directly impairs ovarian steroidogenesis and oocyte maturation. Recent diagnostic accuracy analyses demonstrate leptin achieves the highest predictive value for identifying obesity in PCOS patients (area under curve = 0.85, 95% CI: 0.79-0.91), underscoring its central role in the metabolic-reproductive interface.[20]

Conversely, adiponectin an insulin-sensitizing adipokine with anti-inflammatory properties shows significant reductions in obese PCOS populations.17-18 Adiponectin enhances insulin sensitivity through activation of AMP-activated protein kinase (AMPK) pathways in liver and muscle, suppresses hepatic gluconeogenesis, and promotes fatty acid oxidation. The combination of elevated leptin and reduced adiponectin creates a pro-inflammatory, insulin-resistant metabolic milieu that amplifies both metabolic and reproductive PCOS features.[17-20]

Impact on Sex Hormone-Binding Globulin Suppression

Sex hormone-binding globulin (SHBG), synthesized primarily by hepatocytes, serves as the principal transport protein for sex steroids in plasma, binding approximately 65% of circulating testosterone and 98% of estradiol under normal conditions.[6-7] Only unbound and albumin-bound androgens possess biological activity, making SHBG concentrations a critical determinant of effective androgen exposure at target tissues.[7] Obesity-related hyperinsulinemia potently suppresses hepatic SHBG synthesis through mechanisms involving insulin-mediated downregulation of hepatocyte nuclear factor-4α (HNF-4α), a key transcriptional regulator of the SHBG gene.[6]

This suppression creates a dual pathogenic effect in PCOS. First, reduced SHBG binding capacity elevates free androgen index (FAI) calculated as [total testosterone ÷ SHBG] × 100 thereby increasing bioavailable androgen concentrations that drive hirsutism and other virilizing features even when total testosterone measurements appear only modestly elevated. Second, lower SHBG levels further worsen insulin resistance through loss of its insulin-sensitizing effects in metabolic tissues, perpetuating the hyperinsulinemia-androgen excess cycle.[7,10]

ENDOCRINE DISRUPTIONS IN OBESITY-RELATED PCOS

Hypothalamic-Pituitary-Ovarian Axis Dysfunction

Obesity profoundly disrupts hypothalamic-pituitary-ovarian (HPO) axis regulation through multiple levels of neuroendocrine interference.[6,12] At the hypothalamic level, obesity-associated metabolic signals including hyperleptinemia, insulin excess, and inflammatory cytokines alter gonadotropin-releasing hormone (GnRH) neuronal function. While moderate leptin levels facilitate reproductive function by signalling adequate energy stores for pregnancy, the hyperleptinemia characteristic of obesity paradoxically impairs GnRH pulsatility through central leptin resistance mechanisms. This disrupted GnRH secretion pattern contributes to the characteristic alterations in pituitary gonadotropin release observed in PCOS.[6]

Adipose-derived inflammatory mediators including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) further compromise hypothalamic function by disrupting kisspeptin neurons critical regulators of GnRH pulsatility—and altering neuropeptide Y and pro-opiomelanocortin pathways that integrate metabolic and reproductive signals.[6,12] Chronic low-grade inflammation associated with obesity additionally influences the hypothalamic-pituitary-adrenal (HPA) axis, potentially contributing to adrenal androgen overproduction observed in approximately 50% of PCOS cases.[24] This neuroendocrine reprogramming establishes a metabolically driven disruption of reproductive

axis function that intensifies with increasing adiposity.[6]

Altered LH/FSH Ratio and Gonadotropin Secretion Patterns

A hallmark endocrine feature of PCOS involves elevated luteinizing hormone (LH) concentrations relative to follicle-stimulating hormone (FSH), typically manifesting as an LH/FSH ratio >2:1 in approximately 40-70% of cases depending on assay methodology and diagnostic criteria.[6,10] Obesity-related metabolic disturbances amplify this dysregulation through several mechanisms. First, obesity-induced hypothalamic GnRH pulse frequency acceleration preferentially stimulates pituitary LH secretion over FSH, as LH synthesis responds more robustly to rapid GnRH pulsatility. This altered secretion pattern drives theca cell androgen overproduction while simultaneously impairing FSH-dependent follicular maturation, creating the characteristic anovulatory phenotype.[6-7]

Second, hyperinsulinemia directly enhances pituitary responsiveness to GnRH, amplifying LH pulse amplitude and further skewing the LH/FSH balance toward LH predominance. Prospective studies utilizing bariatric surgery interventions have demonstrated that sustained weight loss achieves continuous LH reduction with corresponding improvement in ovulatory function, confirming obesity's causal contribution to gonadotropin dysregulation. Notably, this improvement in ovulatory dysfunction represents the most consistent and sustained benefit observed following surgical weight reduction, while other hormonal parameters show more variable responses.[24]

Third, elevated free fatty acids and adipokine imbalances modify pituitary gonadotrope cell function through inflammatory signalling pathways including JAK-STAT, HIF-1, and PI3K-Akt cascades. These molecular alterations amplify gonadotropin responses to GnRH stimulation and alter gonadotropin glycosylation patterns, potentially affecting bioactivity and clearance rates.[13] The convergence of hypothalamic, metabolic, and inflammatory signals creates a self-reinforcing endocrine environment favouring LH excess and FSH inadequacy, thereby perpetuating anovulation and follicular arrest characteristic of PCOS.[6,7]

Enhanced Androgen Biosynthesis from Ovarian and Adrenal Sources

Hyperandrogenism constitutes a defining feature of PCOS, with 60-80% of patients demonstrating biochemical or clinical evidence of androgen excess. Obesity amplifies androgen production through direct effects on ovarian and adrenal steroidogenic tissues.[13-14] In ovarian theca cells, the combination of elevated LH and hyperinsulinemia synergistically upregulates key steroidogenic enzymes responsible for androgen synthesis.[13,14-15] CYP17A1, encoding the cytochrome P450 enzyme 17α-hydroxylase, represents the rate-limiting step in androgen biosynthesis and shows significantly increased expression in PCOS ovaries.[13-15]

Insulin stimulates CYP17A1 expression through activation of the insulin receptor substrate/phosphoinositide 3-kinase (IRS/PI3K) pathway and cooperative enhancement of LH-mediated cAMP signaling.[15] Additionally, genetic polymorphisms in CYP17A1 (particularly rs74357) have been associated with PCOS susceptibility, with the polymorphic C allele and CC genotype showing higher frequency in PCOS populations.[13] This variant generates an additional Sp1 transcription factor binding site near the promoter region, enhancing CYP17A1 transcriptional activity and contributing to constitutional hyperandrogenism.[13] Overactivation of PI3K/AKT signalling in theca cells leads to androgen excess and ovarian dysfunction, with CYP17A1 serving as a direct downstream target.[15]

Beyond ovarian sources, adrenal androgen production contributes substantially to total androgen burden in PCOS, particularly dehydroepiandrosterone sulphate (DHEA-S).[25] Obesity-related chronic inflammation may dysregulate the HPA axis, leading to altered cortisol metabolism and enhanced adrenal androgen synthesis.[25] The inflammatory cytokines TNF-α, IL-6, and C-reactive protein (CRP) demonstrate elevated concentrations in obese PCOS women and correlate with both insulin resistance severity and androgen levels.[6,12] These pro-inflammatory mediators drive PCOS-IR (PCOS-associated insulin resistance) development through JAK-STAT, HIF-1, and PI3K-Akt signalling pathways, creating a positive feedback loop wherein inflammation worsens insulin resistance, which further amplifies inflammatory responses.[12]

Role of Hyperinsulinemia in Androgen Overproduction

Hyperinsulinemia functions as a critical mediator connecting metabolic dysfunction to reproductive pathology in PCOS.[6,7-8,10-11,15] Beyond its synergistic effects with LH on ovarian steroidogenesis, insulin directly stimulates theca cell androgen production through multiple molecular mechanisms.[15] In vitro studies demonstrate that insulin increases testosterone biosynthesis in cultured theca cells through IRS/PI3K pathway activation and cooperative enhancement of cAMP signalling cascades. This involves not only CYP17A1 upregulation but also increased expression of other steroidogenic enzymes including StAR protein and CYP11A1, which facilitate cholesterol transport into mitochondria and its conversion to pregnenolone, the common precursor for all steroid hormones.[15]

The insulin receptor in theca cells maintains normal function despite peripheral insulin resistance, creating a scenario termed "selective insulin resistance" wherein metabolic insulin actions are impaired while mitogenic and steroidogenic effects remain intact or enhanced. This paradox explains how hyperinsulinemia drives androgen overproduction even as glucose homeostasis deteriorates.10-11 Furthermore, insulin's suppression of hepatic SHBG synthesis independently increases free androgen concentrations, compounding the direct steroidogenic effects.[6,7]

CELLULAR AND MOLECULAR MECHANISMS

Endoplasmic Reticulum Stress in Granulosa and Theca Cells

Endoplasmic reticulum stress (ERS) has emerged as a central cellular mechanism linking obesity-related metabolic overload to ovarian dysfunction in PCOS. The ER serves critical functions in protein folding, calcium homeostasis, and lipid synthesis, becoming overwhelmed when cellular metabolic demands exceed its capacity a condition termed "ER stress". In obesity, elevated free fatty acids (FFAs) represent a primary upstream trigger of ERS in ovarian granulosa and theca cells. FFAs accumulate within these cells when mitochondrial β-oxidation capacity becomes saturated, leading to lipid droplet formation, membrane lipid composition alterations, and disruption of ER calcium channels.[16]

At the molecular level, FFA-induced ER stress activates three major transmembrane stress sensors: protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1α (IRE1α), and activating transcription factor 6 (ATF6). In granulosa cells, activation of PERK and IRE1α signalling pathways triggers the unfolded protein response (UPR), initially functioning as an adaptive mechanism to restore ER homeostasis. However, chronic or severe ER stress shifts this response toward pro-apoptotic signalling, inducing granulosa cell death that impairs follicular development and oocyte quality. Specifically, sustained PERK activation leads to phosphorylation of eukaryotic initiation factor 2α (eIF2α) and subsequent induction of C/EBP homologous protein (CHOP), a transcription factor that promotes apoptosis.[6]

In theca cells, ERS contributes to steroidogenic dysfunction and enhanced androgen production. FFAs upregulate CYP17A1 and plasminogen activator inhibitor-1 (PAI-1) expression through reactive oxygen species (ROS)/p38 MAPK and JNK signalling axes, amplifying androgen synthesis. This upregulation occurs concurrently with ER stress responses, suggesting coordinated mechanisms whereby metabolic overload simultaneously impairs normal cellular function while enhancing pathological steroidogenic output. The convergence of ER stress, oxidative stress, and inflammatory signalling in ovarian cells creates a self-reinforcing cycle of cellular dysfunction that perpetuates both metabolic and reproductive abnormalities.[7]

Autophagy Dysregulation Induced by Elevated FFAs

Autophagy, a conserved cellular degradation process that removes damaged organelles and protein aggregates, plays essential roles in maintaining ovarian cell health and function. Elevated FFAs associated with obesity dysregulate autophagy in granulosa and theca cells through multiple mechanisms. Under normal conditions, moderate autophagy supports follicular development by removing damaged mitochondria, reducing oxidative stress, and recycling cellular components to sustain energy-intensive steroidogenic processes. However, chronic FFA excess disrupts this balance, leading to either excessive autophagy (contributing to premature cell death) or insufficient autophagy (allowing accumulation of damaged cellular components).

At the molecular level, FFAs interfere with mammalian target of rapamycin (mTOR) signalling, a key autophagy regulator.

Hyperinsulinemia and nutrient excess typically activate mTOR, suppressing autophagy initiation through inhibition of ULK1 (unc-51-like kinase 1) complex formation. However, the lipotoxic stress induced by FFA accumulation can paradoxically trigger autophagic responses through AMPK activation and mTOR inhibition in an attempt to clear lipid droplets and damaged organelles. This dysregulated autophagy contributes to granulosa cell apoptosis, impaired steroidogenesis, and reduced oocyte quality observed in obese PCOS patients.

Furthermore, the interaction between ER stress and autophagy creates additional complexity. IRE1α activation during ER stress can stimulate autophagy through JNK-mediated phosphorylation of Bcl-2, releasing Beclin-1 to initiate autophagosome formation. When ER stress becomes chronic as occurs with persistent obesity-related metabolic overload this adaptive autophagy response becomes maladaptive, contributing to excessive granulosa cell loss and follicular atresia. The net effect is impaired folliculogenesis, reduced oocyte developmental competence, and worsened fertility outcomes in obese women with PCOS.[6-7]

Oxidative Stress and Reactive Oxygen Species Pathways

Oxidative stress, characterized by excessive reactive oxygen species (ROS) production overwhelming antioxidant defence capacity, represents a critical pathogenic mechanism in obesity-related PCOS.[26] Multiple sources contribute to elevated ROS in obese PCOS patients. First, mitochondrial dysfunction resulting from FFA oversupply leads to electron transport chain impairment and increased superoxide anion (O_2^-) generation. Second, NADPH oxidase enzymes in adipose tissue, immune cells, and ovarian cells become activated by inflammatory cytokines (TNF-α, IL-6) and FFAs, producing O_2^- and hydrogen peroxide (H_2O_2).6,12 Third, advanced glycation end products (AGEs) formed through non-enzymatic glycation of proteins and lipids in hyperglycaemic conditions activate receptor for AGEs (RAGE), triggering ROS generation through NADPH oxidase pathways.[26]

The consequences of oxidative stress in PCOS are multifaceted. ROS directly damage cellular macromolecules including lipids (causing membrane peroxidation), proteins (inducing carbonylation and aggregation), and DNA (creating strand breaks and mutagenic lesions). In granulosa cells, oxidative damage impairs steroid hormone synthesis, disrupts gap junction communication with oocytes, and triggers apoptotic pathways mediated by cytochrome c release from damaged mitochondria. In oocytes, ROS-induced damage compromises meiotic spindle organization, chromosome segregation, and developmental competence, contributing to increased miscarriage rates and reduced live birth rates in obese PCOS women.[6]

At the signalling level, ROS function as second messengers activating stress-responsive kinases including p38 MAPK and JNK. These kinases phosphorylate and activate transcription factors (AP-1, NF-κB) that upregulate pro-inflammatory cytokine expression, creating a positive feedback loop wherein oxidative stress promotes inflammation, which further generates ROS.12 Importantly, ROS/p38 MAPK and JNK axes directly upregulate CYP17A1 and PAI-1 expression in theca cells, linking oxidative stress to enhanced androgen biosynthesis. This connection explains how obesity-related oxidative stress not only damages cellular components but actively drives the hyperandrogenic phenotype characteristic of PCOS.

CYP17A1 Upregulation and Steroidogenic Enzyme Alterations

CYP17A1, encoding cytochrome P450c17α (17α-hydroxylase/17,20-lyase), represents the rate-limiting enzyme in androgen biosynthesis and shows consistently elevated expression in PCOS ovarian tissues. This enzyme catalyzes two sequential reactions: 17α-hydroxylation of pregnenolone and progesterone, followed by 17,20-lyase cleavage to generate dehydroepiandrosterone (DHEA) and androstenedione immediate precursors of testosterone.[13-15] Multiple obesity-related factors converge to upregulate CYP17A1 in theca cells.[6,15]

First, hyperinsulinemia stimulates CYP17A1 expression through IRS/PI3K pathway activation, which enhances both enzyme transcription and activity. This insulin effect synergizes with LH signalling, as LH-induced cAMP/protein kinase A (PKA) pathways cooperatively activate transcription factors including steroidogenic factor-1 (SF-1) that bind CYP17A1 promoter elements.15 Second, genetic polymorphisms in CYP17A1, particularly the rs74357 variant creating an additional Sp1 binding site, enhance

transcriptional activity and contribute to constitutional androgen excess in susceptible individuals. Meta-analyses confirm higher frequencies of the polymorphic C allele and CC genotype in PCOS populations compared to controls, supporting this variant's pathogenic role.[13]

Third, oxidative stress-activated p38 MAPK and JNK pathways directly upregulate CYP17A1 transcription and enzyme stability. FFAs stimulate these stress kinases through ROS generation, providing a direct mechanistic link between obesity-related lipotoxicity and androgen overproduction. Fourth, chronic inflammation associated with obesity increases CYP17A1 expression through inflammatory signalling cascades including NF-κB activation.12 Beyond CYP17A1, other steroidogenic enzymes show altered expression in obese PCOS, including increased StAR protein (facilitating cholesterol transport into mitochondria), elevated CYP11A1 (catalyzing cholesterol side-chain cleavage to pregnenolone), and enhanced 3β-hydroxysteroid dehydrogenase (converting DHEA to androstenedione). These coordinated changes create a steroidogenic milieu favoring excessive androgen synthesis from multiple enzymatic steps.[17]

Adipokines and Gut Microbiome Interactions

Leptin Resistance and Reproductive Axis Suppression

Leptin, the prototypical adipokine discovered in 1994, regulates energy homeostasis and reproductive function through actions on hypothalamic neurons. In normal physiology, leptin signals adequate energy reserves to hypothalamic centers, permitting reproductive function by stimulating kisspeptin neurons that drive GnRH pulsatility. However, obesity characteristically produces hyperleptinemia alongside central leptin resistance, wherein hypothalamic leptin signalling becomes impaired despite elevated circulating concentrations.[17-18]

In obese PCOS women, serum leptin levels are substantially elevated compared to both non-obese PCOS and healthy controls, with concentrations correlating strongly with BMI, waist circumference, and insulin resistance severity.20 Recent multi-ethnic studies from 2022-2024 confirm hyperleptinemia as characteristic of the metabolically dysfunctional PCOS phenotype.[17-18] Diagnostic accuracy analyses demonstrate leptin achieves the highest predictive value for identifying obesity in PCOS (AUC = 0.85, 95% CI: 0.79-0.91, $p<0.001$), outperforming other adipokines and metabolic markers.[20]

Despite elevated concentrations, leptin's reproductive effects become paradoxically impaired in obesity. Mechanisms underlying leptin resistance include downregulation of hypothalamic leptin receptors (ObRb), increased suppressor of cytokine signalling 3 (SOCS3) expression that blocks leptin receptor signalling, impaired leptin transport across the blood-brain barrier, and ER stress in leptin-responsive neurons. The resulting disruption of GnRH pulsatility contributes to altered LH/FSH ratios and ovulatory dysfunction. Additionally, elevated leptin directly affects ovarian function, with studies showing leptin inhibits insulin-like growth factor-1 (IGF-1) actions in granulosa cells, impairs aromatase activity, and promotes granulosa cell apoptosis. These direct ovarian effects compound the central neuroendocrine disruption, creating multilevel reproductive impairment.[6]

Adiponectin Deficiency and Insulin Sensitivity

Adiponectin, a 30-kDa protein secreted exclusively by adipocytes, demonstrates insulin-sensitizing, anti-inflammatory, and anti-atherogenic properties.[22] Unlike most adipokines, adiponectin shows an inverse relationship with adiposity, with concentrations markedly reduced in obesity. In obese PCOS women, adiponectin levels are significantly lower compared to both non-obese PCOS patients and healthy controls, with this reduction strongly associated with insulin resistance severity.[17-18]

Adiponectin enhances insulin sensitivity through multiple mechanisms. Binding to its receptors (AdipoR1 and AdipoR2) on skeletal muscle and liver activates AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-alpha (PPARα) pathways. AMPK activation increases glucose uptake, enhances fatty acid oxidation, and suppresses hepatic gluconeogenesis. Adiponectin also exerts anti-inflammatory effects by inhibiting NF-κB activation and reducing pro-inflammatory cytokine secretion from macrophages and adipocytes. The combination of improved insulin sensitivity and reduced inflammation makes adiponectin deficiency a critical contributor to metabolic dysfunction in obese PCOS.[17-18]

Genetic studies have identified ADIPOQ polymorphisms associated with PCOS

susceptibility.[2] The rs182052 variant shows increased frequency in small-for-gestational-age individuals who subsequently develop PCOS, suggesting developmental programming of adiponectin-mediated metabolic function. Protein interaction network analyses reveal adiponectin's key interactions with ERP44, PPARγ coactivator-1α (PGC-1α), and cadherin-13 (CDH13), linking adiponectin signalling to mitochondrial biogenesis, oxidative metabolism, and vascular function.[22] Interventions that raise adiponectin levels—including weight loss, thiazolidinedione medications, and possibly gut microbiome modulation represent promising strategies for improving metabolic and reproductive outcomes in PCOS.[27]

Gut Dysbiosis Contribution to Metabolic Endotoxemia

The gut microbiome has emerged as a critical regulator of metabolic health, with profound implications for PCOS pathogenesis.[21,25,28-29] Obese PCOS women exhibit more severe gut microbiota dysbiosis compared to those with PCOS alone or obesity alone, suggesting synergistic effects of these conditions on microbiome composition. Characteristic alterations include increased abundance of Gram-negative bacteria from Escherichia/Shigella and Bacteroides genera, which produce lipopolysaccharide (LPS), alongside decreased beneficial bacteria including Akkermansia species that maintain gut barrier integrity.[21,28]

This dysbiotic profile contributes to "metabolic endotoxemia" a state of chronic low-grade elevation in circulating LPS resulting from increased intestinal permeability. High-fat diets associated with obesity impair tight junction proteins between intestinal epithelial cells, allowing LPS translocation into portal and systemic circulation.[21,28] Once in circulation, LPS binds Toll-like receptor 4 (TLR4) on immune cells, adipocytes, hepatocytes, and potentially ovarian cells, triggering NF-κB-mediated inflammatory responses. This microbiome-derived inflammation exacerbates insulin resistance, promotes adipose tissue dysfunction, and may directly interfere with ovarian steroidogenesis.[21,25,28]

Beyond inflammatory effects, gut microbiota influence energy harvest, with dysbiotic communities demonstrating enhanced capacity for extracting calories from dietary substrates, thereby promoting weight gain. The interplay between obesity and gut dysbiosis creates a vicious cycle wherein excess adiposity alters microbiome composition, which further promotes metabolic dysfunction and weight gain. Additionally, gut microbiota modulate the hypothalamic-pituitary-adrenal (HPA) axis through the gut-brain axis, potentially affecting stress responses and neuroendocrine function relevant to PCOS.[25,27]

Short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate produced by beneficial gut bacteria through fermentation of dietary fiber demonstrate reduced concentrations in dysbiotic states. SCFAs exert beneficial metabolic effects by improving insulin sensitivity, reducing inflammation, maintaining gut barrier function, and regulating appetite through effects on enteroendocrine cells. Their deficiency in obese PCOS contributes to metabolic dysfunction and inflammatory tone.[25]

GENETIC AND EPIGENETIC FACTORS

Obesity-Related Genes in PCOS Pathophysiology

Genetic susceptibility plays a substantial role in both PCOS and obesity, with certain gene variants conferring increased risk for both conditions simultaneously. Genome-wide association studies (GWAS) have identified multiple loci associated with PCOS development, many of which regulate steroid hormone biosynthesis, glucose and insulin metabolism, follicular growth, and body weight regulation. Among obesity-related genes, FTO (fat mass and obesity-associated gene), ADIPOQ (adiponectin), and MC4R (melanocortin-4 receptor) demonstrate particular relevance to PCOS pathogenesis.[22,26]

The FTO gene, located on chromosome 16q12.2, represents one of the most robust genetic determinants of BMI and obesity risk in population studies. While FTO's precise molecular function remains debated, evidence suggests roles in appetite regulation, energy expenditure, and adipocyte differentiation. FTO variants show associations with PCOS risk in multiple populations, though effect sizes vary by ethnicity. Mechanistically, FTO may influence PCOS through effects on weight gain and adipose tissue accumulation, thereby amplifying insulin resistance and metabolic dysfunction. However, some studies report FTO associations with PCOS independent of BMI, suggesting possible direct effects on reproductive function or metabolic pathways.[26]

The ADIPOQ gene encodes adiponectin, with multiple polymorphisms affecting circulating adiponectin concentrations and PCOS susceptibility. The rs182052 variant shows increased frequency in small-for-gestational-age individuals who later develop PCOS, suggesting developmental programming of adiponectin function. Given adiponectin's insulin-sensitizing and anti-inflammatory properties, genetic variants reducing its expression or activity predispose to metabolic dysfunction characteristic of PCOS. Protein interaction networks reveal adiponectin's connections to PPARγ coactivator-1α (PGC-1α), linking genetic adiponectin variation to mitochondrial function and oxidative metabolism.[22]

MC4R, encoding the melanocortin-4 receptor critical for hypothalamic regulation of appetite and energy balance, shows associations with both obesity and PCOS in multiple populations. MC4R loss-of-function variants increase food intake and reduce energy expenditure, promoting weight gain. Additionally, melanocortin signalling influences reproductive function through effects on kisspeptin neurons and GnRH pulsatility, potentially creating direct reproductive effects beyond weight regulation. The convergence of metabolic and reproductive effects makes MC4R variants particularly relevant to understanding obesity-PCOS relationships.[26]

Gene-Environment Interactions

While genetic variants contribute to PCOS susceptibility, environmental factors substantially modulate genetic risk through gene-environment interactions. Obesity itself represents a critical environmental factor that unmasks or amplifies genetic predisposition. For instance, individuals carrying PCOS-susceptibility alleles may remain asymptomatic at normal weight but develop full syndrome manifestation following weight gain. This interaction explains phenotypic heterogeneity and variable age of onset observed in PCOS populations.[26]

Dietary factors interact with genetic background to influence PCOS risk. High glycemic index diets, excessive saturated fat intake, and advanced glycation end products (AGEs) can exacerbate metabolic dysfunction in genetically susceptible individuals. AGEs, formed through non-enzymatic glycation reactions between sugars and proteins or lipids, accumulate in obesity and high-sugar diets, activating RAGE (receptor for AGEs) and promoting oxidative stress and inflammation. This AGE-RAGE axis may particularly impact individuals with genetic variants affecting antioxidant systems or inflammatory pathways.[26]

Epigenetic Modifications from Metabolic Stress

Epigenetic mechanisms including DNA methylation, histone modifications, and non-coding RNA expression provide molecular links between environmental exposures and altered gene expression patterns.[22] Obesity and associated metabolic stresses induce epigenetic changes that may contribute to PCOS pathogenesis and potentially transmit risk across generations. DNA methylation alterations have been documented in adipose tissue, peripheral blood, and ovarian cells from PCOS women, affecting genes involved in steroidogenesis, insulin signalling, inflammation, and lipid metabolism.[26]

Epigenetic modifications may enable transgenerational transmission of PCOS risk. Maternal obesity, metabolic dysfunction, and hyperandrogenism during pregnancy create an altered intrauterine environment that epigenetically programs fetal development. Studies in both humans and animal models demonstrate that daughters born to PCOS-affected mothers show increased PCOS risk, with evidence suggesting this transmission occurs partly through epigenetic mechanisms rather than solely through genetic inheritance. Understanding these developmental programming effects has implications for preventing PCOS through optimizing maternal metabolic health during pregnancy.[26]

DISCUSSION

The relationship between obesity and PCOS represents a complex bidirectional interaction wherein obesity amplifies PCOS pathogenic mechanisms while PCOS-related metabolic dysfunction predisposes to weight gain and adipose tissue accumulation.[6-8,10] This review has synthesized evidence across multiple pathophysiological domains, revealing interconnected metabolic, endocrine, cellular, and inflammatory mechanisms through which obesity intensifies PCOS phenotypic expression. Despite substantial research, several areas of inconsistency and controversy persist. First, the magnitude of insulin resistance attributable to PCOS itself versus secondary to obesity remains debated, with studies reporting conflicting findings regarding insulin

sensitivity in lean PCOS women.[7,10] Methodological differences in insulin resistance assessment (HOMA-IR versus euglycemic-hyperinsulinemic clamp), heterogeneous PCOS phenotypes included in studies, and variable matching for confounders (adipose tissue distribution, physical activity) likely contribute to discrepant findings.

Second, the effectiveness of metformin in obese PCOS shows substantial heterogeneity across studies, with some reporting significant reproductive benefits while others demonstrate minimal effects beyond lifestyle modification. This variability may reflect differences in baseline insulin resistance severity, genetic polymorphisms affecting metformin pharmacokinetics or pharmacodynamics, concurrent dietary factors, and publication bias favoring positive results. Meta-analyses accounting for study quality and individual patient data could help resolve these inconsistencies.[30-31]

Third, optimal dietary macronutrient composition for PCOS management remains controversial, with proponents of low-carbohydrate, low-glycemic-index, Mediterranean, and other dietary patterns each citing supporting evidence. The relative lack of large head-to-head comparative trials examining equivalent caloric restriction with different macronutrient distributions limits definitive conclusions. Emerging evidence suggests dietary responses may be individualized based on genetic background, baseline metabolic parameters, and gut microbiome composition, potentially explaining inconsistent findings across populations.[32]

A fundamental question in PCOS pathophysiology concerns directional causality between obesity and reproductive dysfunction. Evidence supporting obesity as causal includes: dose-response relationships between BMI and symptom severity; temporal observations of weight gain preceding symptom onset or exacerbation; intervention studies showing weight loss improves outcomes; and bariatric surgery data demonstrating sustained reproductive improvement with maintained weight reduction.[33] These observations support obesity as an active pathogenic contributor rather than merely a comorbid condition.

Conversely, evidence supporting PCOS as predisposing to obesity includes: intrinsic insulin resistance in lean PCOS women suggesting metabolic defects independent of adiposity; observations that PCOS-related metabolic abnormalities including reduced resting energy expenditure and impaired lipid oxidation may facilitate weight gain; neuroendocrine disruptions affecting appetite regulation and satiety signalling; and psychological factors including depression and stress-related eating that cluster with PCOS.[16,34] These observations suggest PCOS itself may create vulnerabilities promoting weight accumulation.

The preponderance of evidence supports a bidirectional, synergistic relationship best described by integrative models recognizing multiple entry points into PCOS pathogenesis. Genetic predisposition, developmental programming (intrauterine androgen or metabolic exposure), environmental factors (diet, endocrine disruptors, stress), and behavioral influences interact to establish initial PCOS features in lean or normal-weight individuals.[22,26] Subsequent weight gain whether driven by lifestyle factors, PCOS-related metabolic alterations, or psychosocial influences amplifies pre-existing reproductive and metabolic dysfunction through the mechanisms detailed in this review.[6-8,10] This framework explains phenotypic heterogeneity, variable age of onset, and differential treatment responses observed in clinical practice.

This narrative review methodology offers advantages including comprehensive scope, thematic organization, and critical synthesis but also limitations compared to systematic review approaches. Narrative reviews lack explicit systematic literature search protocols, pre-specified inclusion/exclusion criteria, and formal quality assessment of included studies, potentially introducing selection bias. Additionally, narrative reviews do not employ quantitative meta-analytic techniques to pool effect sizes across studies, limiting precision of conclusions regarding intervention efficacy.

These limitations were partially mitigated through structured search strategies targeting major biomedical databases, prioritization of SCIE-indexed journals and high-quality study designs (systematic reviews, meta-analyses, prospective cohorts, randomized trials), and emphasis on recent publications supplemented by seminal earlier studies. However, readers should recognize that conclusions represent interpretive synthesis rather than quantitatively derived pooled estimates, and alternative interpretations of the literature remain possible.

Despite substantial progress, critical knowledge gaps warrant future investigation. First, longitudinal studies tracking women from PCOS diagnosis through decades of follow-up are needed

to clarify natural history, identify trajectories of metabolic progression, and determine optimal timing and intensity of interventions across the lifespan. Second, mechanistic studies elucidating the molecular basis for heterogeneous treatment responses could enable precision medicine approaches. Third, intervention trials examining gut microbiome modulation through prebiotics, probiotics, synbiotics, or fecal microbiota transplantation could determine whether targeting gut dysbiosis improves metabolic and reproductive outcomes. Fourth, comparative effectiveness research directly comparing dietary approaches (low-carbohydrate, low-glycemic-index, Mediterranean, intermittent fasting) under controlled isocaloric conditions would clarify whether macronutrient composition matters beyond caloric restriction. Fifth, investigations into developmental programming and transgenerational transmission of PCOS risk could inform prevention strategies.

CONCLUSION

Obesity represents a critical modifiable pathogenic factor in the PCOS, amplifying the metabolic dysfunction, hyperandrogenism, and the reproductive impairment through an interconnected mechanisms spanning cellular, endocrine, inflammatory, and the microbial pathways. Weight reduction through the comprehensive lifestyle modification produces clinically meaningful improvements in metabolic and reproductive outcomes, supporting its prioritization as first-line therapy for overweight and obese PCOS women.

Continued research elucidating mechanistic details, identifying predictive biomarkers of treatment response, and developing novel targeted therapies will advance precision medicine approaches that optimize individualized care and improve long-term health outcomes for women with this prevalent and complex disorder.

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