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REVIEW

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Decoding the significance of TERT gene in Polycystic Ovary Syndrome: From molecular mechanisms to emerging diagnostic and therapeutic strategies

Piyush Jagdish Balgote[1], Fathima Nowshad[2†], Avinash Patnaik[2†] and Jayanthi Sivaraman[1*]

Abstract

Polycystic Ovary Syndrome (PCOS) is a complex endocrine condition affecting women of reproductive age, characterized by hyperandrogenism, anovulation, and polycystic ovary morphology. It is influenced by environmental and genetic factors with high heritability and is associated with metabolic issues such as insulin resistance (IR), chronic inflammation, and oxidative stress. Despite extensive research, the molecular mechanism behind PCOS pathophysiology is still not fully understood. Recent studies highlighted the role of telomere biology and telomerase activity (TA), particularly that of telomere reverse transcriptase (TERT), in the development and progression of PCOS. Telomerase, a complex of ribonucleoprotein enzymes, is responsible for maintaining telomere length (TL). TERT promotes telomere stability, and its disturbance has been associated with reproductive diseases such as PCOS. This study critically examines the results of current studies on the TERT gene and its association with PCOS, as well as the mechanism underlying the reduction in TERT gene expression in women with PCOS. The review also highlights the key molecular discoveries related to TERT dysregulation in PCOS and its impact on clinical outcomes, suggesting that TERT expression levels can reflect disease severity, ovarian reserve, and the effectiveness of treatments in PCOS patients. TERT expression may be restored, and ovarian function may be enhanced by interventions focusing on oxidative damage, inflammation, or metabolic disorders. Future research may employ experimental methods such as telomerase activation, gene editing, and modification of TERT regulators. Elucidating the molecular mechanisms connecting TERT to ovarian dysfunction could enhance PCOS understanding and lead to the development of novel diagnostic markers and treatment strategies.

Keywords Polycystic Ovary Syndrome (PCOS), Ovarian Dysfunction, Infertility, TERT Gene, Telomerase, Telomere Length

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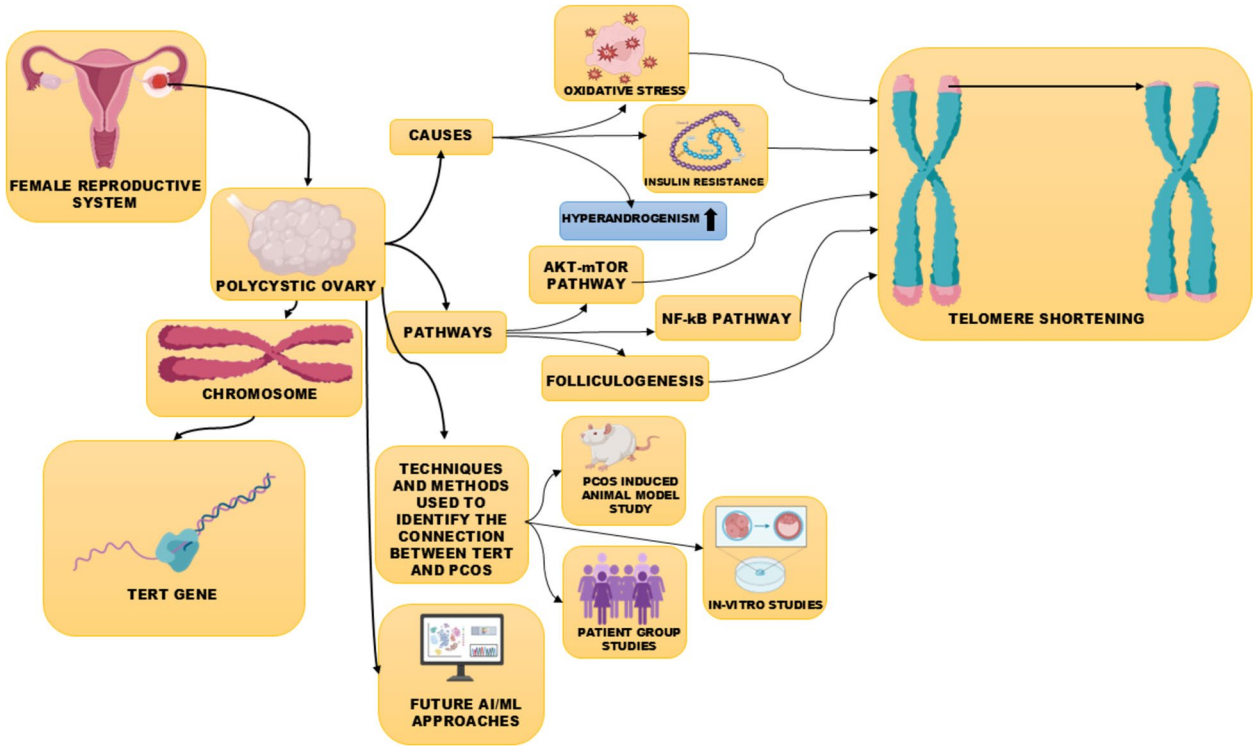
Graphical abstract



Introduction

Polycystic Ovary Syndrome (PCOS) is a hormonal disorder that affects women of reproductive age. Today, PCOS has become increasingly widespread among individuals due to our changing lifestyle [1]. PCOS is a hormonal imbalance characterized by excess hormone production by the ovaries, affecting 6–18% of women in their reproductive age [2]. PCOS involves the ovaries secreting excess androgens, disrupting the balance of reproductive hormones [3]. As an outcome, PCOS patients commonly experience inconsistent menstrual periods, skipped menstrual cycles, and ambiguous ovulation [4]. In 1935, Stein and Leventhal characterized 'PCOS' as a disorder of oligo-amenorrhea and polycystic ovaries that are frequently accompanied by hirsutism, acne, and obesity [5]. PCOS is one of the most prevalent causes of female infertility, insulin resistance (IR), obesity, type 2 diabetes, and cardiovascular risk factors; moreover, it might raise the risk of various health issues [6, 7]. Researchers reveal that the prevalence of PCOS is 8–13% in women and 6% in adolescent girls [8]. Researchers have started looking at whether cellular aging processes, such as telomere dynamics, may play a role in the development of PCOS because it is linked to metabolic disorders, long-term health risks, and reproductive dysfunction.

Telomeres are highly conserved nucleoprotein structures that serve as protective caps at the ends of eukaryotic chromosomes [9]. These structures are composed of tandem repetitions of a hexanucleotide sequence (TTAGGG), spanning 5 to 15 kilobases in length [10]. Their principal role is to protect the genetic material from degradation and instability during cell division. However, inadequate DNA repair systems and prolonged exposure to oxidative stress eventually cause telomeres to shorten, especially within granulosa cells (GCs) [11]. This progressive shortening has been identified as a key contributor to reproductive aging [12]. Telomere length (TL) is maintained by telomerase, a specialized reverse transcriptase enzyme that extends telomeres by adding TTAGGG repeats [13]. Telomerase plays a crucial role in preserving cellular function by preventing telomere degradation, which slows down the aging process, particularly in reproductive tissues [9]. Among several genetic determinants, the telomere reverse transcriptase (TERT) gene has garnered attention because of its critical involvement in cellular senescence, telomere maintenance, and ovarian function [14].

The TERT gene plays an important function in preserving cellular health via encoding the catalytic subunit of telomerase, an enzyme essential for preserving TL [14]. This gene has been widely studied for its involvement in key biological processes, including cellular aging, oxidative stress response, and reproductive health. It's activity is influenced by genetic and epigenetic factors that affect

expression and function, with the TERT gene being significant for delaying cellular senescence, ensuring proper telomere maintenance, and supporting ovarian function [9]. There are contradictions in the female reproductive system, as oocytes exhibit early aging while uterine tissues remain healthy and responsive. Additionally, meiotic dysfunction occurs more frequently with advancing age, leading to PCOS (Fig. 1), infertility, miscarriages, and children with congenital defects [15].

Researchers continue to explore its significance in aging and fertility, as alterations in this gene may have profound effects on overall cellular longevity and reproductive outcomes [16]. Oxidative stress in PCOS patients is linked to increased ROS markers, potentially impacting leukocyte telomere homeostasis, crucial for genome stability [17]. The underlying mechanism proposed is that chronic oxidative stress leads to increased telomeric friction, which in turn disrupts telomerase activity (TA) [18]. This impairment prevents the enzyme from effectively maintaining TL (Fig. 2), resulting in accelerated telomere shortening [12]. These results highlight the potential role of oxidative stress, which can lead to cellular aging and genetic instability in PCOS patients [18]. This review examines the relationship between TERT gene expression in females with PCOS and its implications for reproductive health.

Methodology

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar, covering all publications up to March 2025. The search utilized Medical Subject Headings (MeSH) and free-text keywords for extensive coverage and employed Boolean operators ("AND", "OR", and "NOT") to refine results related to Polycystic Ovary Syndrome and telomere biology. The primary search terms included: "Polycystic Ovary Syndrome," "PCOS," "telomerase reverse transcriptase," "TERT," "telomerase activity," "oxidative stress in PCOS," "ovarian aging," "inflammation," "telomere shortening," and even " TERT gene regulation in PCOS." Additionally, reference lists from key articles were manually screened to identify further relevant studies not captured in the initial database search. In this review formulation (Fig. 3), a total of 55 articles were screened, resulting in 8 exclusions for lack of relevance or methodological detail. The final dataset included 47 studies, from which data on research design, study population, methodological approaches, experimental assays (such as qPCR, TRAP, Western blot, RNA-seq), TERT expression levels, TA, telomere-related biomarkers, regulatory variables (including oxidative stress markers and inflammatory cytokines), and key outcomes were extracted and analyzed. A descriptive synthesis approach was utilized to integrate findings from several studies on telomere dynamics and TERT regulation in PCOS, addressing the heterogeneity in experimental designs, assay techniques, and population characteristics. The review examined both consistent and contradictory results, considering explanations for variability like tissue specificity and population heterogeneity, aiming to map current evidence and identify research gaps in the field.

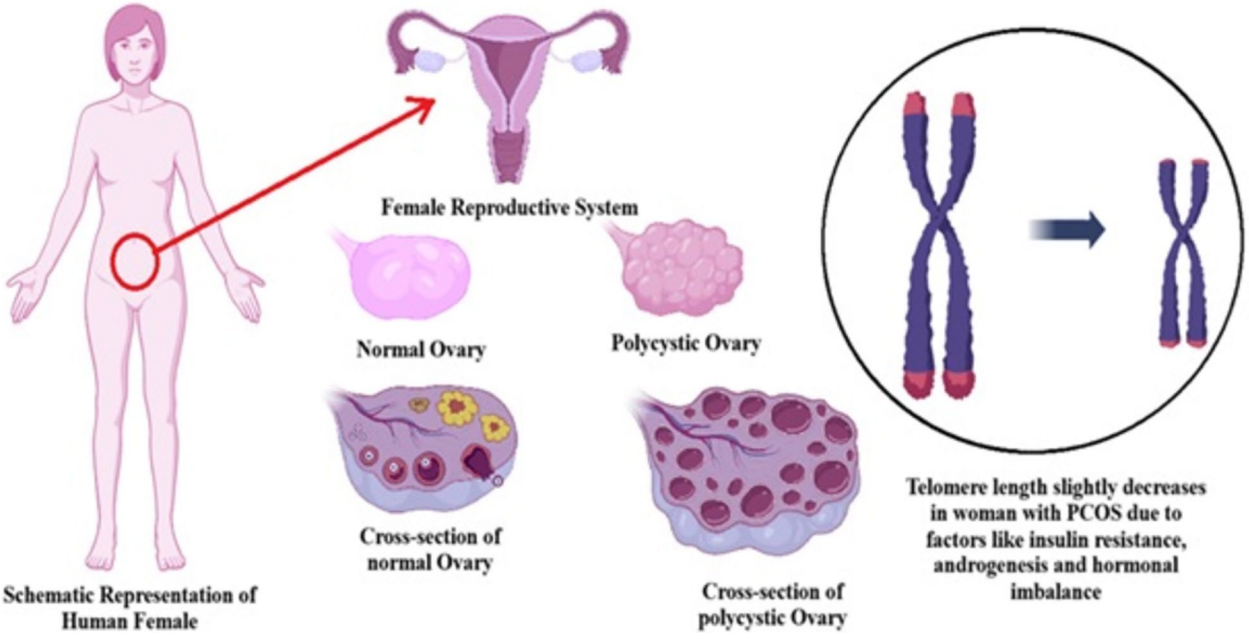


Fig. 1 An outline of PCOS in the female reproductive system, along with TL shortening

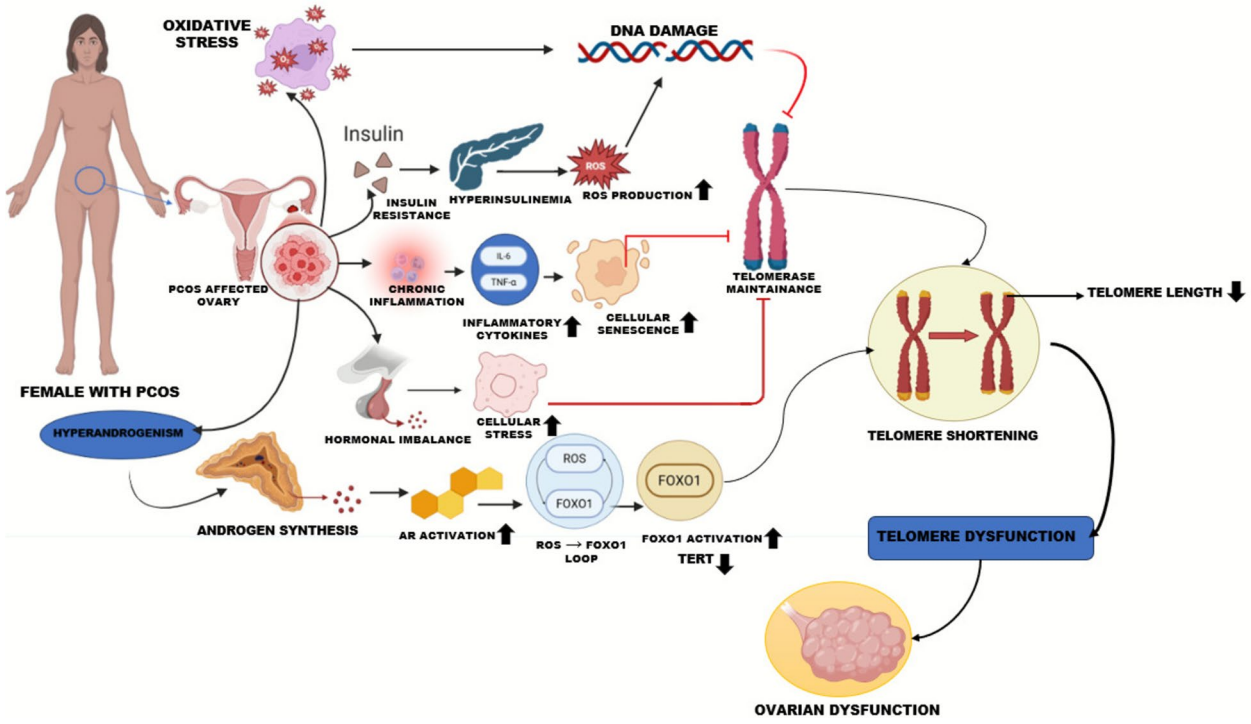


Fig. 2 A mechanistic link between PCOS and Telomere shortening leads to Ovarian Dysfunction (The schematic depicts that PCOS, characterized by oxidative stress, insulin resistance, inflammation, and hyperandrogenism, leads to ROS production, cellular senescence, and DNA damage, causing telomere shortening and ovarian dysfunction)

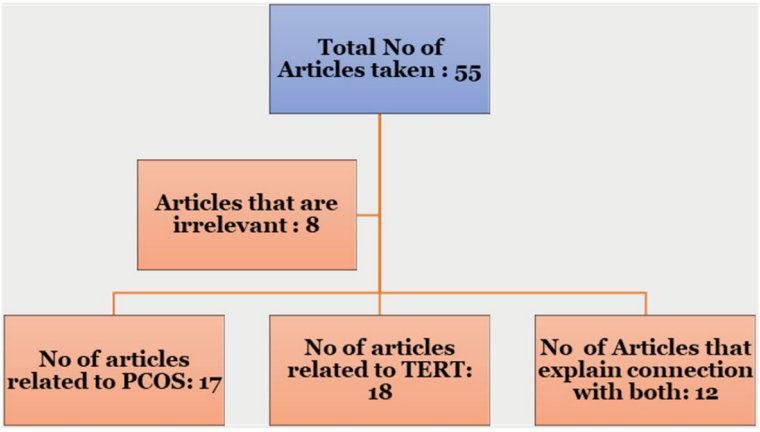


Fig. 3 A flow diagram of an article selection procedure for this study

PCOS: an inflammatory, hormonal, and metabolic stressor-driven multifactorial disorder

PCOS is a diverse endocrine-metabolic disorder marked by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. As a result of our evolving lives, it has been noted that girls' menarche rates have drastically changed over the past ten years [19]. In the last ten years, most girls aged nine to fifteen have reached puberty. Early maturing in girls is associated with a higher likelihood of reproductive disorders, particularly PCOS. Statistical analysis (Fig. 4) shows that the prevalence of PCOS in adolescent girls (ages 10–19) ranges from 5–15%, while in teenagers, it ranges from 11.04% at the age of 15–19. Among the adult women, the prevalence is between 5–18%, and a significant 70% of women with PCOS remain undiagnosed [20]. PCOS also correlates with systemic issues such as IR, increased insulin levels, chronic low-grade inflammation, and elevated oxidative stress [21]. It can cause significant hormonal imbalances, resulting in the formation of ovarian cysts that hinder ovulation [22]. The menstrual cycle is disrupted due to cysts preventing ovulation, with PCOS resulting from an

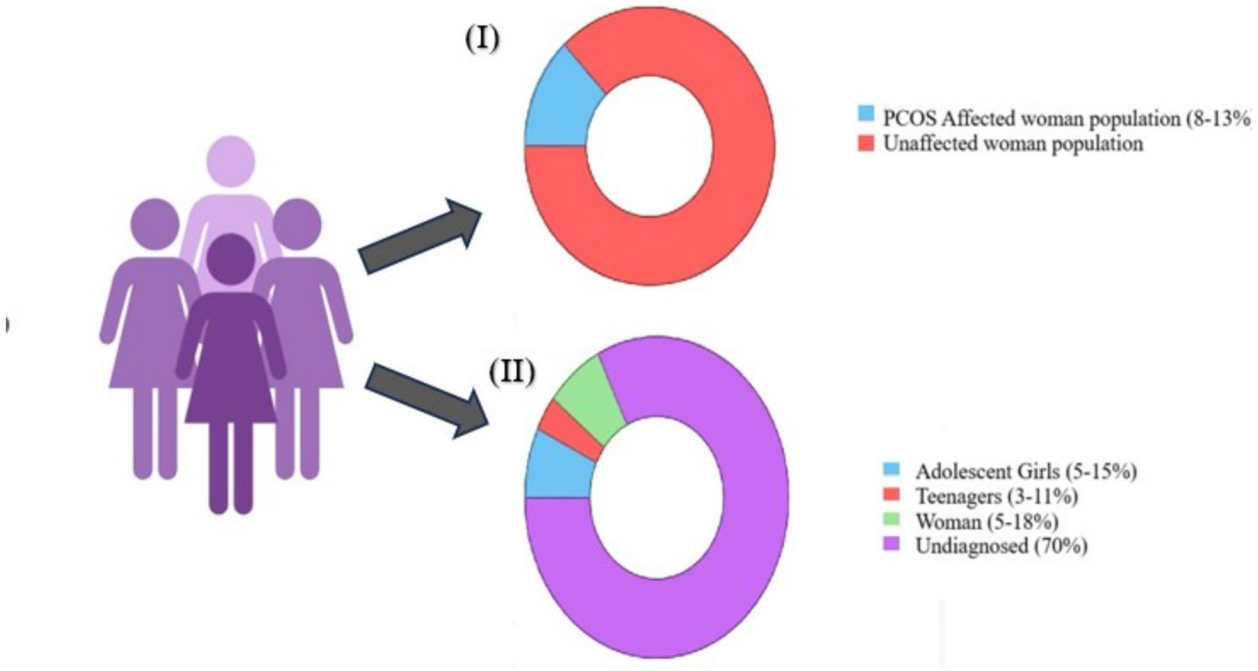


Fig. 4 An interpretation of statistical data of (I) women affected with PCOS, (II) Rate of prevalence of PCOS women with respect to age groups

increase in ovarian cysts caused by hormonal imbalance [23]. Together, these abnormalities foster conditions that lead to DNA damage, compromised mitochondrial function, and metabolic inflexibility.

IR is a prominent aspect of PCOS, leading to increased production of reactive oxygen species (ROS) due to mitochondrial overload and NADPH oxidase activation. Additionally, chronic low-grade inflammation characterized by elevated Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and other NF-κB-regulated cytokines exacerbates ROS generation and hinders cellular repair mechanisms [24]. Hyperandrogenism leads to oxidative stress and inflammation, negatively affecting GC function, follicle development, and ovarian hormone production. This hormonal imbalance can also result in hair loss, acne, hirsutism, and other issues in women [22].

Accelerated cellular aging in PCOS is primarily driven by metabolic and hormonal stressors, where prolonged oxidative stress causes telomeric DNA damage and inflammatory pathways, notably NF-κB, affect telomerase regulation. Emerging evidence indicates that ovarian tissues in PCOS may undergo premature senescence, disrupted folliculogenesis, and altered telomere maintenance, linking PCOS pathophysiology to telomere instability [25]. This supports further exploration of TERT regulatory roles in affected ovarian cells. PCOS-related metabolic, endocrine, and inflammatory disturbances affect pathways that regulate TL, TA, and TERT expression, suggesting that TERT dysregulation may contribute to reproductive aging in PCOS.

TERT and telomere biology: key modulators of cellular homeostasis and ovarian aging

Telomeres are specialized structures composed of proteins and repeating DNA sequences located at the ends of eukaryotic chromosomes [26]. Herman Muller combined the Greek terms "telos," meaning "end," and "meros," meaning "part," to form the word "telomeres," following their discovery in Drosophila melanogaster [27]. The single-stranded section at the 3' end of the telomere region has a guanine-rich stretch that is 50–500 nucleotides long and is referred to as the G overhang or G-rich region [28]. The G overhang region creates D-loop and T-loop structures at chromosome ends by invading double-stranded telomeric DNA, thus preventing single-stranded DNA from being recognized as a DNA break [29]. Telomeres are repetitive structures essential for chromosomal stability and genomic integrity during cell division. Their preservation is primarily managed by telomerase, which consists of the TERT catalytic subunit and the telomerase RNA component (TERC) [30]. Maintaining telomeres is crucial for ovarian function, especially in oocytes and GCs, due to their susceptibility to oxidative damage and ongoing proliferation.

TERT regulation is influenced by various biological factors that are disrupted in PCOS, such as oxidative stress, inflammation, metabolism, and hormonal signals. Oxidative stress leads to increased telomere shortening and represses TERT transcription. Inflammatory cytokines modulate TERT via NF-κB signaling, impacting its expression context-dependently [31]. Hyperandrogenism alters telomerase regulation through Wnt/β-catenin and

steroidogenic pathways, while insulin/IGF-1 signaling affects TERT via the PI3K/AKT pathway, which is crucial for cell survival and metabolism. The disruption of TERT expression or TA can result in premature GC senescence, impaired folliculogenesis, reduced ovarian reserve, and decreased oocyte competence in PCOS conditions. However, few studies show elevated TERT or TL in GCs of PCOS patients, suggesting compensatory activation due to chronic cellular stress [32]. These findings highlight the complexity of telomerase regulation and the importance of considering PCOS phenotypes, metabolic status, inflammation, and tissue specificity in telomere biology interpretation.

Overall, the sensitivity of TERT to oxidative, metabolic, and hormonal dysregulation makes telomere biology an attractive framework for explaining accelerated ovarian aging and GC dysfunction in PCOS. This provides a direct mechanistic bridge from the cellular stresses of PCOS to altered TA, telomere dynamics, and reproductive outcomes.

Understanding the molecular expression in the TERT gene

The TERT gene encodes the catalytic subunit of telomerase, crucial for TA in human cells. It's expression is regulated through transcriptional, epigenetic, post-transcriptional, and signaling pathways. Since TERT expression influences telomerase function, comprehending it's regulatory mechanisms is vital for understanding telomere dynamics in both physiological and pathological states.

Telomeres, once considered transcriptionally silent, are now transcribed into telomere repeat-containing RNAs (TERRAs), which have been characterized in rodents and humans [33–35]. TERRAs, containing UUAGGG repeats, are 100 bp-9 kb long and have multiple promoter regions at the subtelomeric site, primarily responsible for maintaining telomeric stability during the S phase of the cell cycle [34, 36]. A core catalytic reverse transcriptase domain (RT domain), a lengthy N-terminal (N-DAT) domain with conserved DNA and RNA-binding regions, and a C-terminal C-DAT domain comprise the three primary structural components of the TERT subunit of telomerase. The N-terminal region includes two subdomains involved in nucleic acid binding: the telomerase RNA-binding domain (TRBD) and the telomerase essential N-terminal (TEN) domain [37, 38].

Telomere-associated proteins, including telomere repeat binding factor 1 (TRF1) and 2 (TRF2), protection of telomeres 1a (POT1a), POT1, and TRF1 interacting nuclear protein 2 (TIN2), and repressor activator protein 1 (RAP1) form the Shelterin complex, which is crucial for regulating TL and maintaining chromosomal integrity. This complex prevents chromosomal fusion and protects chromosome ends from degradation [39, 40]. TRF1 and TRF2 bind to the double-stranded telomeric DNA within the Shelterin complex. TRF1 plays a key role in TL control by blocking telomeric activity (TA), but its overproduction can lead to excessive telomere shortening, which may hasten cellular aging [41]. Moreover, it recruits helicases like Bloom syndrome helicase (BLM) for DNA replication and anchors telomeres to the nuclear membrane, preventing chromosomal fusion during meiosis [42]. TRF2 acts as a negative regulator of telomere lengthening and inhibits DNA damage response activation by binding to the ataxia telangiectasia mutated (ATM) protein kinase. Its absence or overexpression can lead to chromosomal instability, telomere shortening, and elevated apoptosis in cells [40].

Unlike TRF1 and TRF2, which bind to the double-stranded section of telomeres, POT1 targets the single-stranded overhang. It is crucial for preventing DNA damage response activation by inhibiting ataxia telangiectasia and Rad3-related (ATR) protein kinase [43]. The absence of POT1 can lead to significant chromosomal pairing abnormalities and genome instability due to its role in controlling TL by positively influencing TA [44]. The end replication issue leads to the gradual shortening of telomeres with each DNA replication cycle. Factors such as oxidative stress, genotoxic exposure, underlying diseases, and biological aging can accelerate this process. When telomeres shorten significantly, cells may undergo apoptosis or enter senescence, resulting in reproductive aging and overall tissue degradation [45]. According to the cell type, shortened telomeres can be lengthened in two ways: TA or an alternative lengthening of telomeres (ALT) [46]. However, TA is limited to specific cell types, including lymphocytes, malignant cells, stem cells, germline cells, GCs, endothelial cells, and early embryonic cells [47].

The ribonucleoprotein enzyme telomerase consists of two main components: TERT, which provides catalytic activity through reverse transcriptase, and the TERC, which serves as a template for synthesizing new telomeric repeats at chromosome ends [9]. This extension process counteracts telomere attrition, ensuring genome stability and cellular longevity [48]. The overall structural components and function of telomeres are shown in Fig. 5. Telomerase and Shelterin proteins are vital for telomere maintenance; disruptions in their regulatory functions may lead to aging-related diseases, infertility, and cancer progression [39]. Understanding molecular pathways is vital for identifying potential treatment targets for diseases associated with aging and reproductive health [49].

Regulatory and Functional Interaction of the TERT Gene

Telomerase has been found to play a regulatory role in the NF-κB signaling pathways, leading to the activation

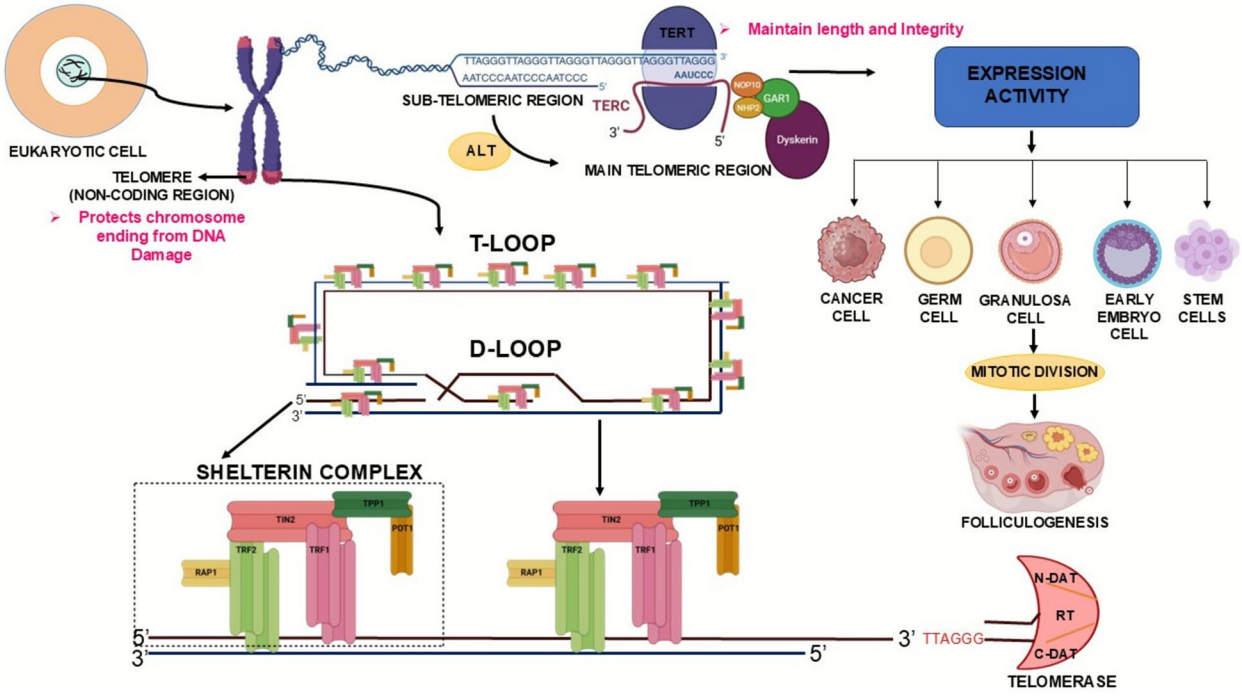


Fig. 5 A schematic view of Telomere structure and function in Eukaryotic Cells (This illustration depicts the structure of telomeres and their maintenance through the shelterin complex and TA. It emphasizes telomere roles in chromosomal protection, replication, and cell types that express telomerase, such as stem cells, germ cells, GCs, and cancer cells

of key inflammatory cytokines such as IL-6, IL-8, and TNFα [50]. This implies that telomerase affects cellular signaling networks, which can lead to inflammation and immunological responses, in addition to its role in telomere preservation [51]. Additionally, studies indicate that TERT, the telomerase catalytic component, can function as a transcriptional regulator of the Wnt/β-catenin signaling pathway [52]. TERT promotes the β-catenin-mediated epithelial-mesenchymal transition (EMT), essential for tissue regeneration, cellular plasticity, and cancer progression [53]. These findings indicate that telomerase has functions beyond elongating telomeres, affecting key pathways in inflammation, cellular differentiation, and disease progression [54].

The intricate web of molecular interactions and regulatory mechanisms involving TERT, by extending the repeated sequences at chromosome tips, counteracts the shortening that occurs during cell divisions [55, 56]. Telomerase dysregulation is linked to cancer and early ovarian aging, making its management crucial. Certain proteins act as negative regulators of TERT, preventing excessive telomere extension [57]. The POT1 is a protein in the Shelterin complex that binds to telomeres, preventing them from being identified as DNA damage. It regulates telomere extension by blocking telomerase access to the telomere ends, thereby suppressing TERT activity [44, 58]. Regulation is crucial to prevent oncogenesis caused by excessive cell proliferation [59]. BRG1, a transcription activator and component of the SWI/SNF chromatin remodeling complex, acts as a negative regulator of TERT expression. It achieves this by altering the chromatin structure at the TERT promoter, reducing accessibility for transcription factors. BRG1 plays a key role in cellular aging by inhibiting telomerase transcription, which is vital in differentiated cells to prevent unregulated proliferation associated with various malignancies [60].

However, in stem and some immune cells that continuously proliferate, various proteins enhance TERT activity to maintain telomere integrity [61]. TERT is directly activated by β-catenin, which is a key component of the Wnt signaling pathway, influencing embryonic development, stem cell maintenance, and cancer progression [62]. The notion that Wnt signaling maintains long-term proliferative capability in specific cell types is further supported by the indication that TA and cellular self-renewal are linked by the activation of TERT by β-catenin [63]. Adrenocortical dysplasia protein (ACD) is a crucial subunit of the Shelterin complex that enhances telomerase function by stabilizing it at chromosome ends, thus playing a vital role in telomere preservation and telomerase recruitment coordination. ACD enhances telomere extension in proliferative cells by facilitating telomerase access [64, 65].

Furthermore, TERT-mediated complex formation is improved by Telomerase Cajal Body Protein 1 (TCAB1) [66]. TCAB1 directs Telomerase to Cajal bodies, which

are subnuclear structures that helps in the movement and formation of ribonucleoprotein complexes [66]. TCAB1 is essential for the proper maturation and localization of the telomerase enzyme. Besides its main role in telomere extension, TERT modifies various proteins, impacting cellular functions beyond telomere maintenance [67]. The H/ACA both Ribonucleoprotein Homolog and Ribonucleoprotein Complex Subunit 2 are modified by TERT, indicating a broader involvement in ribonucleoprotein functionality or RNA processing [68, 69]. Telomerase may contribute to RNA stability or ribosome synthesis, which are vital for rapidly proliferating cells [70, 71].

Other essential elements of the telomerase holoenzyme are linked to TERT, indicating that Telomerase Protein Component 1 may act as a structural or functional cofactor vital for the enzyme's activity [72]. TERT's ability to prolong telomeres is guaranteed by this relationship [9]. The final example highlights the importance of RNA changes in telomerase function, specifically the interaction between dyskerin pseudo uridine synthase 1 and TERT. Dyskerin is a crucial component of the H/ACA small nucleolar ribonucleoprotein complex, responsible for the pseudo-uridylation of RNA [73, 74]. Its interaction with TERT (Fig. 6) implies that telomerase RNA undergoes essential changes required for its stability and functionality, guaranteeing effective elongation of the telomere [73]. Telomerase activation is essential for the regeneration of stem cells and certain immune cells; however, its overactivity is a hallmark of cancer [48]. On the other hand, poor TA causes telomere attrition, which exacerbates degenerative illnesses and aging [75]. Understanding the network of TERT regulators is vital for developing therapeutic strategies that target telomerase in age-related diseases and cancers [76].

Role of TL and TA in ovarian folliculogenesis

Telomeric shortening in GCs happens due to repeated mitotic divisions during folliculogenesis, influenced by the microenvironment of follicular fluid containing various substances. However, these cells also possess TA, which may repair shortened telomeres [77, 78]. The relationship between the TL, telomerase expression, and TA in human GCs and oocytes during folliculogenesis has been inadequately explored. The TERT gene's mechanism, including the impact of its upregulated and downregulated expression on TA, is depicted in Fig. 7. The expression levels of TERT protein and mRNA are crucial in regulating TA [79]. The telomeres of preantral follicles are shorter than those of primary, small-antral, and medium/large antral follicles [80]. TL regulation varies between GCs and oocytes, due to differing activation times of telomere lengthening processes during embryonic maturation. The study indicates that TA in GCs is a more reliable predictor of pregnancy success than factors such as TL, age, FSH, and estrogen levels [81]. Estrogen production during folliculogenesis is crucial for high-quality oocyte development and successful pregnancy [82]. Telomeres are essential for cellular processes such as meiosis, nuclear organization, and maintaining genomic integrity. The dysfunctional telomeres can contribute to diseases, including PCOS, infertility, and cancer.

Unveiling the connecting link between PCOS and the TERT gene

PCOS, linked to infertility, has become more prominent in medical and social discussions due to increased life expectancies. The existing laboratory indicators for PCOS are insufficient, and TERT has been utilized for identifying cellular aging. We need robust predictive indicators to improve the treatment of PCOS patients, potentially using TERT as a marker for reproductive potential in the context of advancing reproductive technology [83]. This review is notable for being the first compilation of findings from human epidemiological research on the relationship between various infertility variables and TL. This study, despite its limitations, may contribute to future research aimed at exploring connections and applications in medical settings.

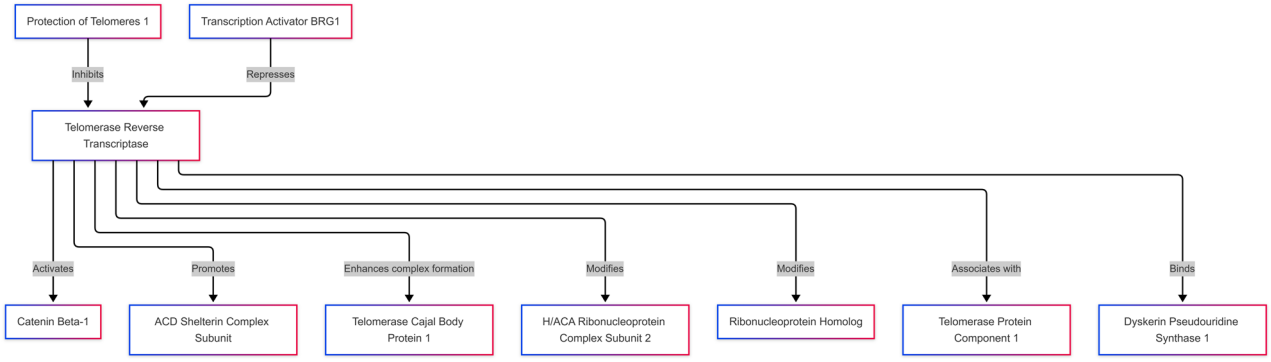


Fig. 6 An interactive network of functional partners involved in TERT activation (This diagram depicts the regulatory and functional relationships between TERT and its related proteins. It focuses on activators, repressors, and molecular complexes involved in telomerase control and telomere preservation)

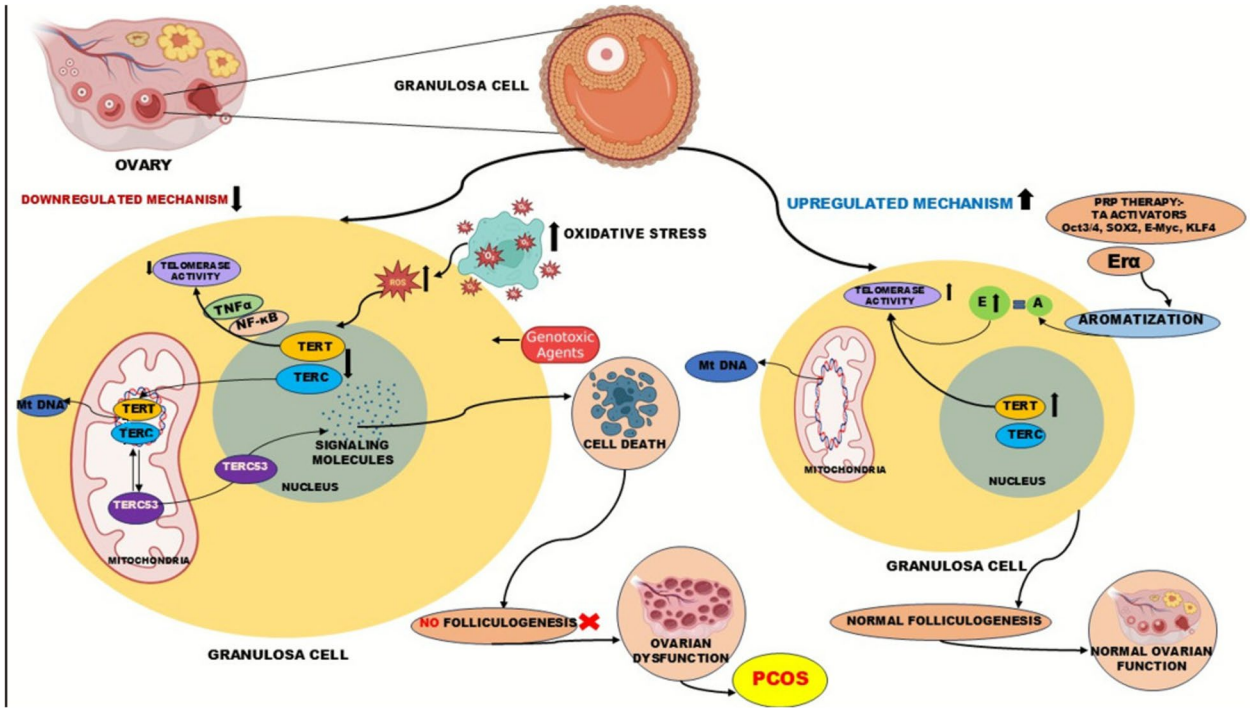


Fig. 7 A schematic representation of Telomerase modulation in GCs and its involvement in PCOS ovarian function and dysfunction (The left panel shows a downregulated mechanism in GC function in PCOS patients, causing oxidative stress, inflammation, and cell death. On the right panel, an elevated pathway, supported by increased TA and estrogen signaling, has been shown to restore ovarian function)

TERT Gene Expression in PCOS

The action of telomerase, primarily influenced by TERT expression rate, is essential for maintaining TL, ensuring genome integrity, and facilitating cell survival [55]. The activation of telomerase is essential for cellular immortalization and malignant transformation [84]. However, most human somatic cells lack TA, with exceptions in stem cells, tumor cells, and germ cells, which show varying levels of TA. Recent studies have explored the relationship between TA, TL, and PCOS.

According to one study, GCs from the PCOS group showed longer telomeres compared to the control group in a study involving 40 women with PCOS and 35 healthy women aged between 20 and 30. However, no significant difference in TL was observed in peripheral blood leukocytes between the two groups [85]. In a study involving 81 women without PCOS and 75 PCOS patients, there was no significant difference in leukocyte TL. However, PCOS patients exhibited significantly longer GC TL compared to controls, even after adjusting for age and BMI. This suggests that increased telomerase TERT activity may contribute to the retention of TL in cumulus cells of PCOS patients [86]. Telomerase regulates NF-κB signaling pathways, leading to the activation of inflammatory cytokines such as IL-6 and TNF-α [87]. According to studies, PCOS patients exhibit elevated TA levels in their cumulus cells, potentially contributing to the inflammatory processes associated with the disorder [88]. Examining the connection between NF-κB related low-grade chronic inflammation and elevated TERT expression in the ovaries of PCOS patients is vital, considering the established relationship between TERT and NF-κB [87, 89]. The variations in TL and TA are linked to the chronic inflammatory response of PCOS, where continual inflammation leads to oxidative stress and cell death [87].

TERT expression affects TA, and NF-κB activation promotes the secretion of TNF-α and IL-6. However, it is uncertain if TERT contributes to chronic inflammation and GC apoptosis through NF-κB signaling regulation. Further research is needed to understand the complex relationship between GC apoptosis, telomeres, and inflammation in PCOS [87]. Researchers aim to investigate the role of the communication network in affecting GC survival and its implications for follicular development in PCOS, utilizing a rat model [90]. Moreover, exploring these mechanisms may provide new insights into the root causes of PCOS and identify potential therapy targets for enhancing ovarian function [89].

Bridging the gap between TERT-PCOS interactive pathways

The cellular lifespan, proliferation, and systemic homeostasis are affected by the TERT pathway, which primarily influences the catalytic component of telomerase. This enzyme is crucial for maintaining telomeres, the protective cap at chromosome ends, addressing the

"end-replication problem" where DNA polymerase causes telomere shortening during cell division [91]. TERT uses an RNA template (TERC) to extend telomeres, which helps maintain genomic integrity and delays cellular senescence [92]. This action is essential for supporting tissue regeneration and repair in tissues with high turnover, including stem cells, germ cells, and rapidly renewing epithelia [93]. Cancer is marked by uncontrolled TERT activity, enabling cancer cells to bypass replication limits and proliferate indefinitely [94].

TERT plays a complex role in regulating the cell cycle, especially at the G1/S transition, which determines the initiation of DNA synthesis, alongside its function in telomere preservation [95]. TERT stimulates Cyclin D2 (CCND2) to phosphorylate the retinoblastoma (Rb) protein with CDK4/6, leading to the release of E2F transcription factors. This activation promotes genes necessary for S-phase progression and underscores TERT's role in cell proliferation, critical for tissue regeneration [96]. The hyper-proliferation due to dysregulation can contribute to tumor development [97]. Insufficient TERT activity can impede regeneration and accelerate tissue atrophy or aging [76, 98].

The TERT influences hormonal homeostasis by affecting ovarian function and altering steroidogenesis, the process of producing sex hormones from cholesterol [99]. CYP17A1 catalyzes androgen production, while CYP19A1 (aromatase) converts androgens to estrogens [100]. TERT inhibits CYP17A1, leading to an increased androgen-to-estrogen ratio that favors hyperandrogenism, a key feature of PCOS [101]. Follicle maturation is impaired by high levels of androgens, leading to ovarian cysts and anovulation [102]. A harmful cycle is formed as hyperandrogenism exacerbates IR simultaneously [103, 104]. Compensatory hyperinsulinemia, driven by the IR, enhances ovarian androgen production via CYP17A1, thereby perpetuating PCOS symptoms like metabolic dysfunction, hirsutism, and acne [105].

Insulin signaling is crucial for glucose homeostasis and also interacts with TERT. The binding of insulin to its receptor (INSR) activates phosphorylation of insulin receptor substrates like IRS1, which then activates the PI3K/AKT pathway [106]. GLUT4 transporters are activated by AKT, aiding in glucose absorption at cell membranes [107]. TERT enhances energy efficiency in growing cells, but chronic overexpression may desensitize insulin receptors, contributing to IR, a key factor in type 2 diabetes and metabolic disorders [108]. The dual function of TERT is emphasized, showcasing its role in balancing cell proliferation with the maintenance of metabolic health [109].

TERT influences adipogenesis in adipose tissue via the nuclear receptor Peroxisome Proliferator-Activated Receptor Gamma (PPARG), which regulates fat cell differentiation [110]. PPARG promotes lipid accumulation and adipokine production, leading mesenchymal stem cells to differentiate into adipocytes [111]. TERT enhances metabolic adaptability and telomere maintenance by increasing PPARG activity, potentially influencing obesity and related diseases [112]. This link shows that TERT integrates systemic energy management with cellular longevity, ensuring resources are accessible for rapidly regenerating tissues [113].

Figure 8 summarizes that the TERT coordinates a complex interaction involving metabolic homeostasis, hormone control, cell proliferation, and genetic stability [109]. It protects chromosome integrity and modifies related pathways are functions linked to obesity, diabetes, PCOS, and cancer [9, 114]. The mechanisms by which TERT influences the expression of genes like CYP19A1 and PPARG, along with the feedback loops connecting TA to metabolic conditions, remain poorly understood. Understanding these aspects is crucial for developing treatments that enhance TERT's protective roles while minimizing its risks.

Exploring the PCOS - TL reduction-associated pathways

PCOS is a complex endocrine disorder affecting metabolism, inflammation, and hormonal balance, among other bodily functions [105]. PCOS manifests variably across age groups, commonly associated with infertility, irregular menstrual cycles, and elevated testosterone levels [115]. Telomere shortening and cellular senescence are significant indicators of aging, resulting from interrelated processes including IR, chronic inflammation, and hormone imbalances [116].

IR is common in PCOS and is characterized by decreased cellular sensitivity to insulin, resulting in hyperinsulinemia. This condition, while not diabetes, increases the risk of developing type 2 diabetes and can impair cell health [117]. ROS are unstable chemicals that increase oxidative stress and damage biological structures, with their production rising when insulin levels are elevated [118]. Oxidative stress harms proteins, lipids, and DNA, disrupting normal cellular functions [119]. DNA damage is crucial as it triggers cellular repair mechanisms that, if excessive, can hasten cell aging [120, 121]. Telomeres protect genetic material from degradation and are affected by DNA damage [121]. The cells undergo apoptosis or senescence due to critically shortened telomeres, leading to tissue dysfunction and aging [122].

PCOS is linked to ongoing low-grade inflammation characterized by elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α [123]. These cytokines induce cellular stress and disrupt immune function through the activation of inflammatory pathways [124]. Chronic inflammation exacerbates insulin resistance and accelerates cellular senescence, hindering cells' ability to

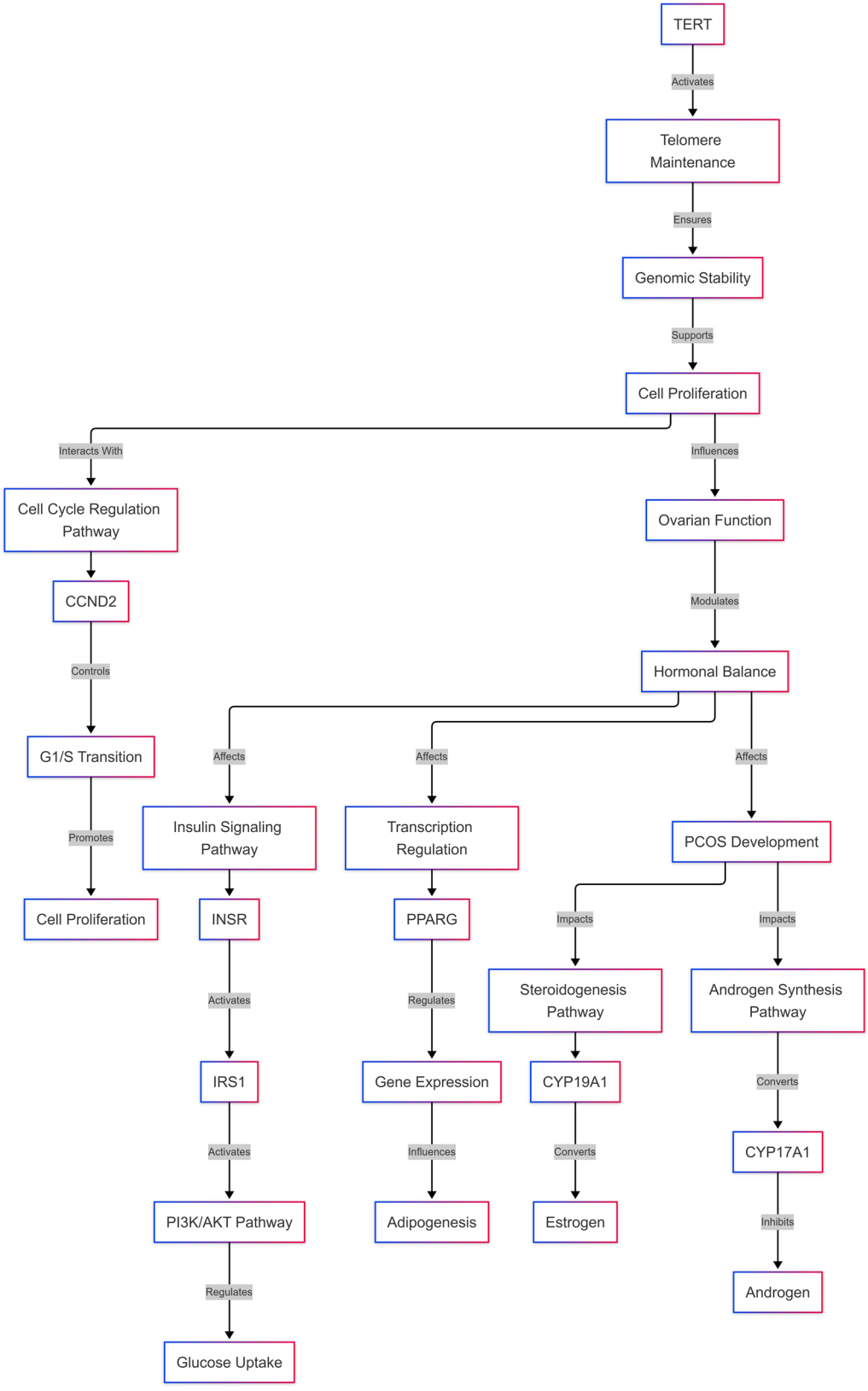


Fig. 8 An illustration showing TERT-regulated Pathways in PCOS (The figure illustrates how TERT impacts adipogenesis (PPARG), insulin signaling (INSR–IRS1–PI3K/AKT), cell cycle progression, and estrogen/androgen production (CYP17A1, CYP19A1), all of which are factors in the hormonal imbalance that characterizes PCOS)

proliferate and function normally [125]. The senescence-associated secretory phenotype (SASP) refers to the process by which senescent cells secrete inflammatory chemicals, creating a cycle of inflammation that worsens tissue aging and dysfunction [126]. Persistent inflammation inhibits telomerase, leading to a buildup of senescent cells that compromises telomere maintenance [122]. Telomeres shorten more quickly, leading to early cellular aging [9].

Increased androgen levels, particularly testosterone, disrupts cellular function and elevate cellular stress, marking a key feature of PCOS [127]. Elevated testosterone increases systemic inflammation and worsens insulin resistance by disrupting metabolic functions, leading to greater DNA damage and telomere shortening due to impaired oxidative stress regulation [128]. Mitochondrial dysfunction, involving ineffective energy production in cells, is linked to increased androgens [112]. The loop of oxidative stress, inflammation, and telomere degradation is exacerbated by mitochondrial dysfunction, which leads to increased ROS production [119, 129]. Cells exhibit diminished functionality when telomeres are excessively short, as shown in Fig. 9, leading to early-onset of age-related conditions like metabolic syndrome, cardiovascular disease, and neurological disorders [116].

The interplay of oxidative stress, chronic inflammation, and hormonal instability undermines telomere preservation [130]. In PCOS patients, telomeres shorten more

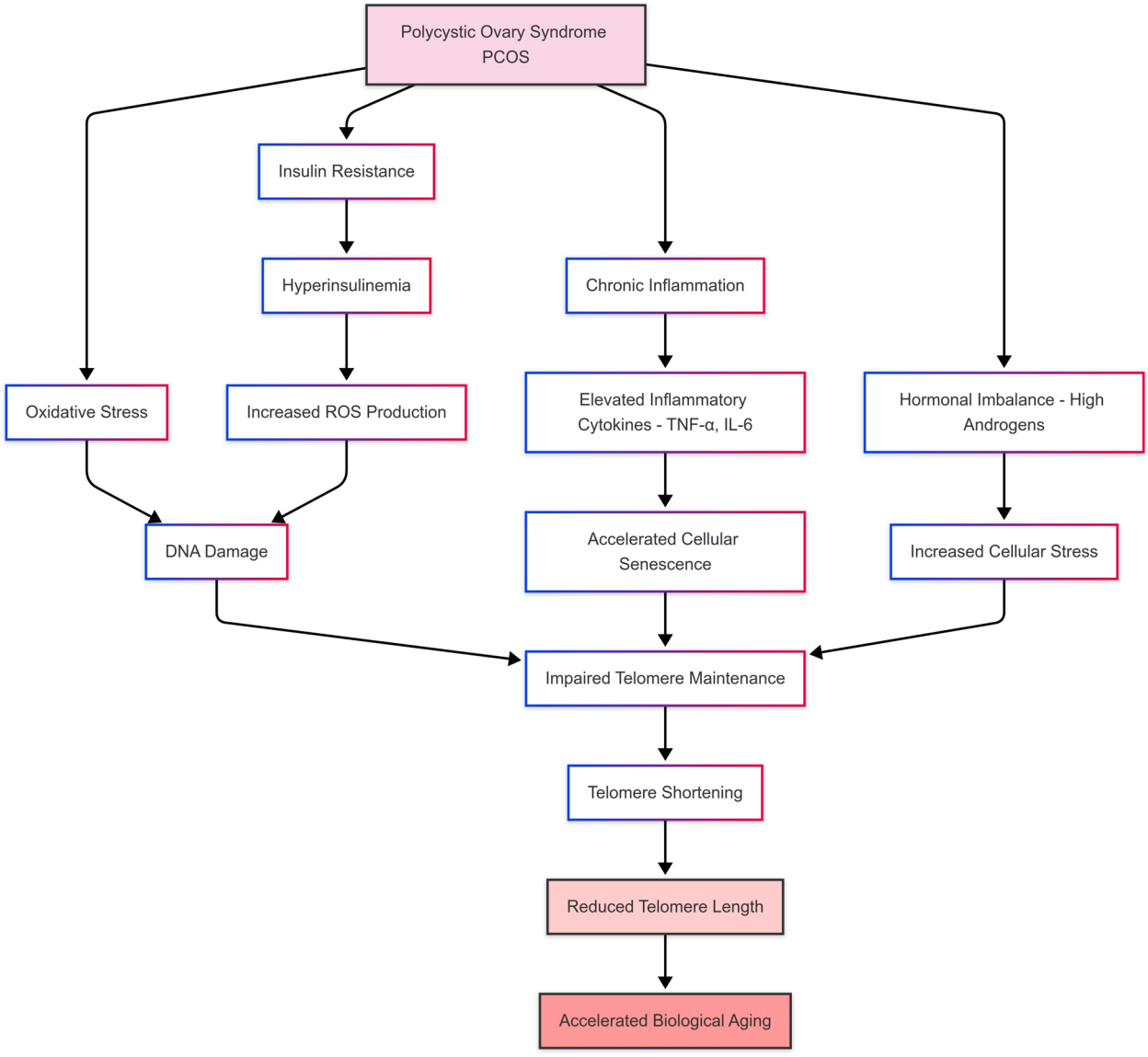


Fig. 9 A Schematic overview of PCOS-associated factors linked to the TL Reduction Pathway (This figure shows the molecular and cellular mechanisms that connect accelerated biological aging to PCOS. It demonstrates how insulin resistance, inflammation, and hormonal imbalance brought on by PCOS lead to oxidative stress, DNA damage, and telomere shortening)

rapidly with aging due to increased cellular stress [131, 132]. Short telomeres contribute to accelerated aging by restricting cell division and tissue regeneration, leading to earlier onset of age-related illnesses like diabetes, cardiovascular disease, and neurodegenerative disorders as telomeres degrade [116]. Telomere disruption in PCOS heightens the risk of infections and chronic diseases, affecting longevity and reproductive health, making early intervention essential due to accelerated aging [76].

Potential therapeutic implications

Lifestyle changes such as maintaining a balanced diet, engaging in regular exercise, and reducing stress can enhance insulin sensitivity and lower inflammation [133]. Anti-inflammatory treatment drugs like metformin may mitigate the long-term effects of PCOS [134]. A study suggests that antioxidants like vitamin C, vitamin E, and resveratrol can prevent oxidative stress and preserve telomere integrity [135]. Hormonal therapies may mitigate biological aging and telomere shortening. PCOS is a systemic condition that promotes telomere shortening and cellular senescence due to IR, chronic inflammation, and hormonal imbalances [136]. Early diagnosis and management are essential for mitigating long-term health impacts in individuals with PCOS. Tackling inflammation, oxidative stress, and metabolic dysfunction is key to slowing aging and enhancing overall health [129]. While these strategies benefit metabolic and reproductive outcomes in PCOS, there are no studies directly assessing their effects on TERT gene expression or TA in ovarian cells. The current evidence does not confirm a direct causal relationship between lifestyle, pharmacological, or nutritional interventions and specific changes in TERT expression or TA in women with PCOS. However, given that TERT is influenced by oxidative stress, inflammation, metabolic issues, and hormonal imbalances, which are the key characteristics of PCOS. It is plausible that interventions addressing these factors could indirectly affect telomere dynamics.

Figure 10 depicts the interrelated pathways through which medicine and lifestyle changes might improve results in PCOS women. Inflammation and oxidative stress contribute to telomere shortening, increasing health risks and accelerating cellular aging [137]. The following therapeutic considerations are, therefore, hypothetical until further experimental studies validate these implications. The recommended lifestyle changes to mitigate these effects include regular exercise, a Mediterranean diet rich in antioxidants and omega-3 fatty acids, and stress-reduction methods such as yoga, meditation, and adequate sleep [138]. Drugs and supplements such as metformin, myo-inositol, D-chiro-inositol, vitamin D, and omega-3 contribute to hormone regulation, enhance insulin sensitivity, and possess anti-inflammatory effects [139]. Collectively, these therapies promote TA, leading to longer telomeres, reduced cellular aging, extended lifespan, and improved outcomes for PCOS. Figure 11 shows the detailed strategies and approaches for telomere lengthening and PCOS management using a multimodal strategy for treating PCOS that includes pharmacological treatments, lifestyle modifications, nutritional supplements, and other therapies. It underscores how

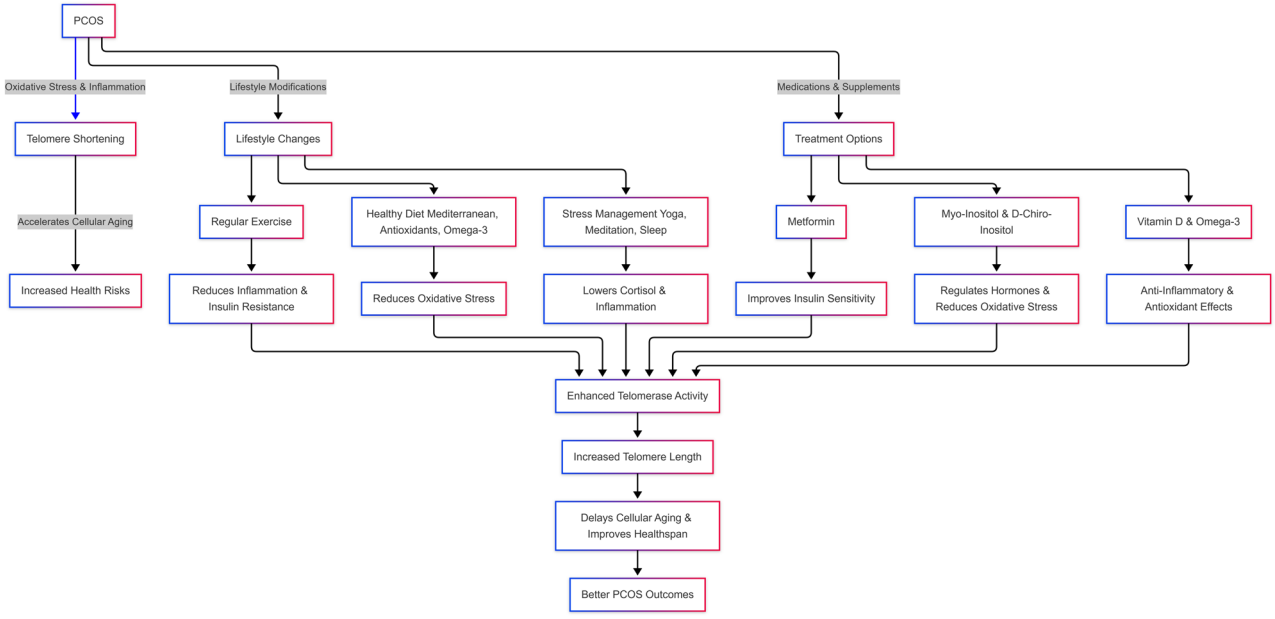


Fig. 10 An integrated Pathway for Telomere Activity Enhancement and PCOS Improvement (Lifestyle changes and medical treatments in PCOS can reduce oxidative stress, inflammation, and enhance TA, leading to increased TL, delayed cellular aging, and improved overall outcomes)

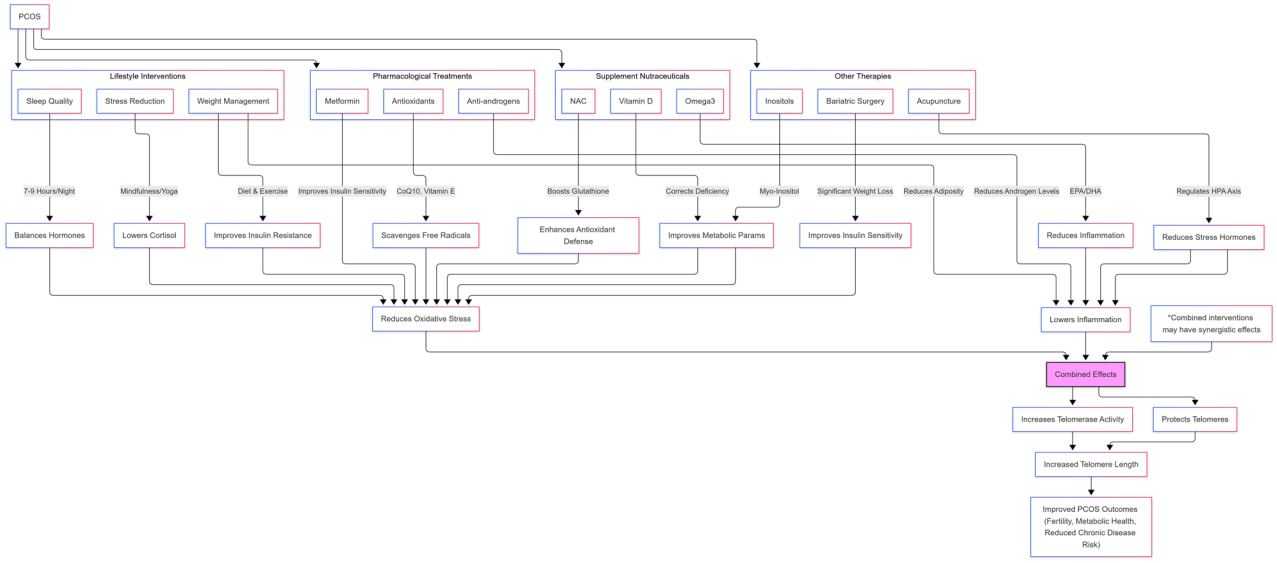


Fig. 11 The conceptual model illustrates the potential genetic, epigenetic, and therapeutic influences on telomere regulation in PCOS (This figure outlines a hypothetical framework on how genetic factors, such as TERT promoter variants and telomere-associated gene polymorphisms, along with epigenetic mechanisms like DNA methylation and histone modifications, may influence TA and TL in PCOS. It also discusses lifestyle, metabolic, and pharmacological interventions that could improve oxidative stress, inflammation, and insulin resistance in PCOS, though their direct impacts on TERT expression or telomere maintenance remain unproven. The pathways presented are conceptual and should guide future research rather than serve as facts)

treatments like inositol, omega-3, vitamin D, N-Acetyl Cysteine (NAC), metformin, antioxidants, stress reduction, restful sleep, and weight control improve insulin sensitivity, hormone balance, inflammation, and reduce oxidative stress. These approaches increase TA, TL, and protect telomeres. The synergistic effects of these strategies lead to improved metabolic health, lower chronic disease risk, and enhanced fertility related to PCOS.

Genetic and epigenetic factors significantly influence TERT expression in PCOS. Genetic variations, including single-nucleotide polymorphisms (SNPs) and promoter variants, affect TERT activity, though no specific PCOS-related SNPs have been identified [140]. Instead, variants impacting TERT promoter activity and regulatory domains may explain the variability in TA in PCOS [132]. Epigenetically, factors like promoter methylation and histone modifications also play a crucial role in TERT regulation [141]. Given that PCOS involves chronic inflammation, hyperinsulinemia, oxidative stress, and hormonal imbalance, these factors may alter TERT expression through epigenetic changes. Potential epigenetic factors in PCOS include oxidative or inflammation-induced DNA methylation changes in the TERT promoter, histone modifications, and dysregulated microRNAs (miR-21, miR-155, miR-126) or long non-coding RNAs that affect TERT transcripts [142]. However, direct evidence regarding these mechanisms in PCOS is currently lacking. Genetic and epigenetic pathways suggest a link between PCOS-related cellular stress and altered TA, but further rigorous mechanistic and interventional studies are required to assess the impact of modifying these pathways on telomere maintenance and ovarian aging in PCOS.

The current research highlights the need to address upstream disturbances like hyperandrogenism, insulin resistance, chronic inflammation, and mitochondrial dysfunction in relation to TA and related factors in PCOS [143]. However, the impact of these disturbances on TERT transcription and TL is yet to be examined in PCOS-specific models. While some studies in non-PCOS populations suggest that metabolic and inflammatory improvements may affect TA, caution is advised in generalizing these findings [144]. These intervention strategies for targeting TERT dysfunction in PCOS are potential avenues rather than established mechanisms. An urgent comprehensive mechanistic study, including longitudinal clinical trials and multi-omics analyses, is needed to ascertain the impact of modifying PCOS-related cellular stressors on TERT expression and telomere maintenance. TERT modulation in PCOS is considered a promising yet speculative therapy until further evidence is available.

The hyperandrogenism- IR-telomere senescence axis

Hyperandrogenism and CYP17A1 overexpression initiate the process [105]. An enzyme for steroidogenesis, CYP17A1, promotes 17,20-lyase and 17α-hydroxylase activity. The overexpression of this enzyme leads to excessive production of testosterone and androgens, resulting in hyperandrogenism [145]. The androgen receptor (AR) is activated in response to elevated androgens, translocating to the nucleus to modify gene expression and increase Wnt ligands. In ovarian theca cells, this

AR stimulation heightens androgen production, creating a feedforward loop that worsens hormonal imbalance [146]. The Wnt/β-catenin signaling pathway is activated when AR-induced Wnt ligands bind to Frizzled receptors, preventing the degradation complex and stabilizing β-catenin. Once in the nucleus, β-catenin collaborates with TCF/LEF transcription factors to enhance the transcription of TERT, an enzyme that extends telomeres [147]. The chronic Wnt/β-catenin activation aids in telomere maintenance but also promotes proliferative signaling, potentially leading to neoplastic transformation, despite temporarily slowing telomere shortening [148].

Metabolic stress and hyperandrogenism elevate NADPH oxidase activity and impair mitochondrial function, leading to ROS activation of the stress-responsive transcription factor FOXO1 [119]. FOXO1 regulates antioxidant genes to mitigate oxidative stress, but excessive FOXO1 activity inhibits TERT transcription, altering its role from pro-senescence to protective. Dysfunction in insulin receptors and insulin receptor substrate occurs due to TNF-α or ROS, leading to IRS-1 serine phosphorylation or lipotoxicity, which impede the activation of the PI3K/AKT pathway. This leads to telomere shortening and cellular senescence [149]. The single-stranded DNA exposure from telomere attrition activates the p53/p21 and p16/RB pathways, halting cell division. Senescent cells form senescence-associated heterochromatin foci (SAHF) that silence proliferation-promoting genes [150]. Additional SASP factors from these cells are matrix metalloproteinases (MMPs), TGF-β, and IL-6, which lead to tissue remodelling and inflammation via a "bystander effect," inducing senescence in nearby cells [151]. The activation of NF-κB and the inflammatory cascade exacerbate damage, as SASP-derived TNF-α and IL-6 activate NF-κB via TNFR1 and the IKK complex. This leads to a self-sustaining inflammatory loop, stimulating transcription of pro-inflammatory cytokines like IL-6, TNF-α, and cyclooxygenase-2 (COX-2) [50, 151].

Telomere dysfunction, worsened by ROS, leads to instability in TERT mRNA, while NF-κB inhibits TERT transcription. This creates a cycle (Fig. 12) involving hyperandrogenism, IR, telomere dysfunction, and inflammation. Inflammation, through INSR suppression and JNK activation, interferes with insulin signaling [152]. IR leads to hyperinsulinemia, which stimulates ovarian theca cells to overexpress CYP17A1 via INSR/IRS-2, resulting in elevated androgen levels [152, 153]. The dysfunction of adipose tissue due to visceral fat, which releases pro-inflammatory cytokines and free fatty acids, worsens hormonal and metabolic issues. Therapeutic strategies addressing this include CYP17A1 inhibitors (e.g., abiraterone) to reduce androgen synthesis, antioxidants (e.g., NAC) to neutralize ROS, insulin sensitizers (e.g., metformin) to restore PI3K/AKT signalling, and senolytics (e.g., dasatinib/quercetin) to eradicate senescent cells are a few examples of therapeutic strategies targeting various involved pathways [145, 154]. These therapies are crucial in conditions like PCOS and type 2 diabetes, where hyperandrogenism, IR, and inflammation occur together. They aim to break the cycle of oxidative stress, cellular senescence, and excess hormones linked to age-related and metabolic disorders [129].

Studies conducted to explore the connection between PCOS and the TERT gene

Recent research on PCOS has focused on cellular aging and telomere biology, indicating that shortened telomeres and reduced TERT expression in women with PCOS suggest accelerated cellular senescence [155]. The impaired TA may contribute to ovarian dysfunction, follicular atresia, and reproductive aging [156]. PCOS and the TERT gene are studied using molecular, cellular, computational, and clinical techniques (Fig. 13), including qRT-PCR and Western blotting for mRNA and protein expression measurements. TL assessment utilizes quantitative PCR, TRF assay, and TRAP assay. RNA sequencing reveals gene expression patterns, whereas CRISPR-Cas9 gene editing is employed to manipulate TERT expression in experimental studies (Table 1). Cell-based models, including cultured GCs from PCOS patients for genetic and observational studies (Table 2), enable researchers to study telomerase regulation under stress conditions. Flow cytometry, DNA methylation assays, and advanced models like induced pluripotent stem cells are used to study patient-specific telomere dynamics. Hormonal and metabolic profiling and histological analysis using an animal model (Table 3) support these findings, providing a comprehensive understanding of TERT dysfunction's role in PCOS pathophysiology.

Modern approaches and advanced tools

An advancement in bioinformatics methodologies, such as genome-wide association studies (GWAS), transcriptomic analyses, and molecular docking, has significantly deepened our understanding of the TERT gene's role in PCOS [170]. Computational techniques enable the analysis of large-scale genetic data to identify links between genetic variants and disease susceptibility, as well as to predict mutation impacts. Transcriptomic analyses facilitate the understanding of TERT's interactions with genes and pathways associated with PCOS, while molecular docking reveals its structural interactions with proteins, highlighting its regulatory roles in cellular processes [171]. The Telomere Length Database Project (TLDP), now available as "BIOTEL version 2.4," is a semi-automated tool that calculates various TL statistics. It is beneficial for biological age estimation and research in telomere biology [172].

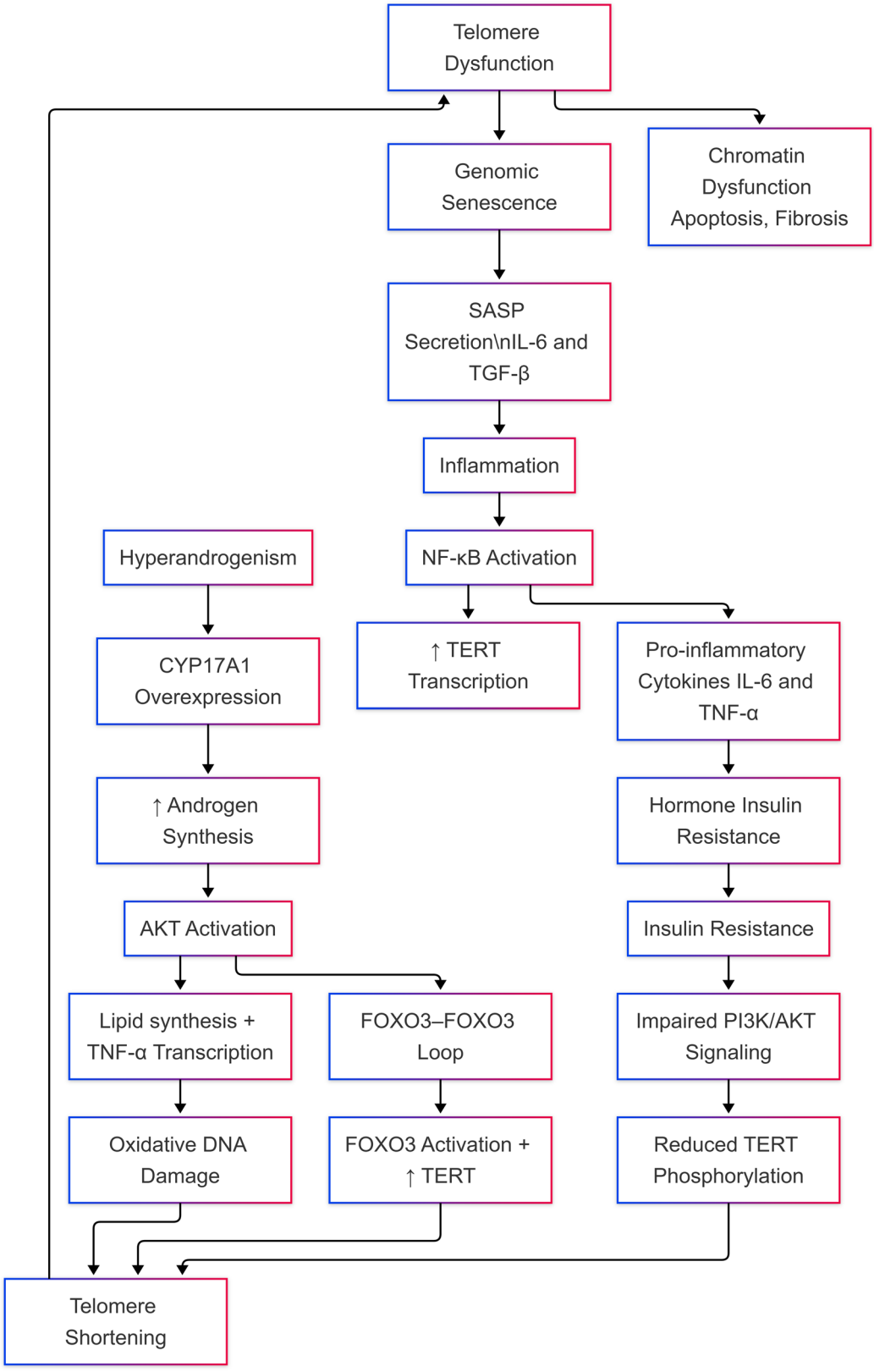


Fig. 12 A schematic representation of the Hyperandrogenism-IR-Telomere Senescence axis in PCOS (The figure demonstrates the link between hyperandrogenism, insulin resistance, telomere dysfunction, and inflammation, highlighting the detrimental effects of these factors on ovarian health)

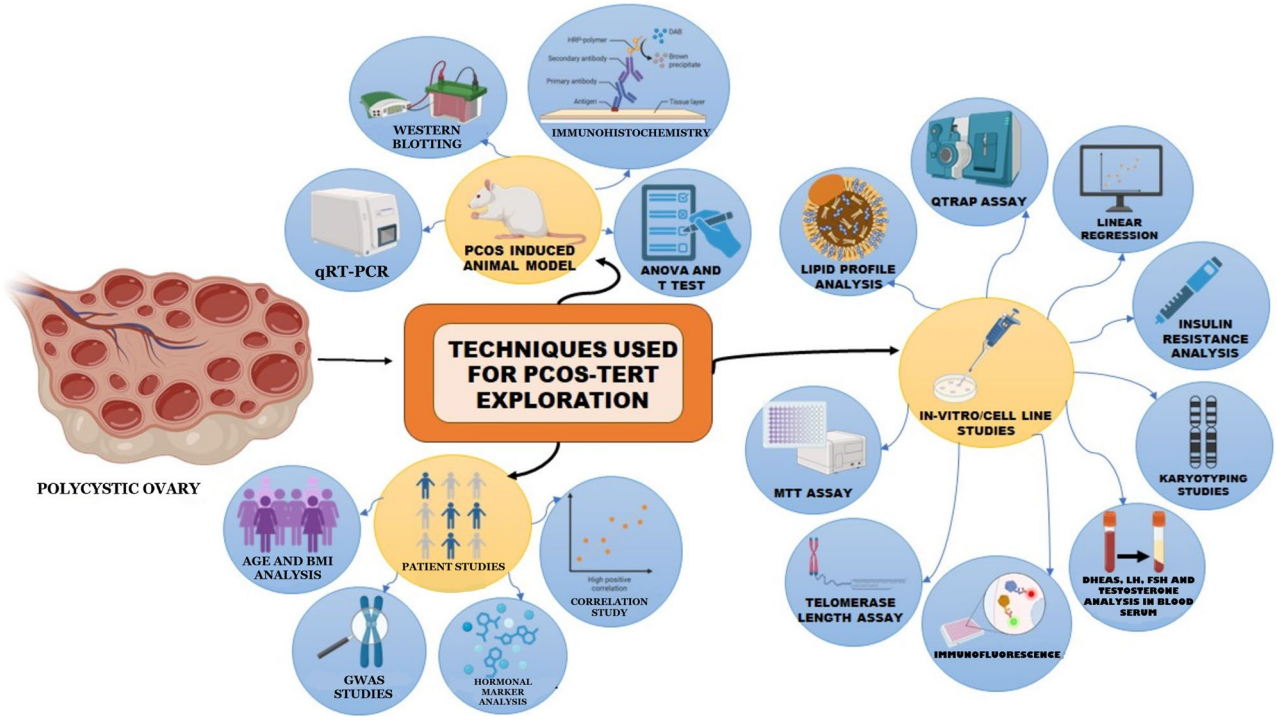


Fig. 13 A comprehensive representation of key techniques in PCOS-TERT research (It shows various methods used to study the PCOS-TERT axis, including molecular tools, cellular models, and patient-based studies, enabling a comprehensive exploration of telomere biology in PCOS pathophysiology)

Researchers can identify key genetic and epigenetic factors impacting PCOS pathophysiology, such as telomere maintenance, oxidative stress response, and reproductive aging, through these advanced tools, techniques, and databases. It is essential to comprehend these biological pathways to discover possible therapeutic targets and develop precision medicine strategies for PCOS. A thorough summary of the TERT gene's role in PCOS is provided, highlighting various approaches (Table 4) and innovative strategies (Table 5) to elucidate the intricate molecular pathways underlying the condition. Understanding the genetic foundations of PCOS and TERT is advancing through the integration of computational and experimental methods, leading to new treatment and diagnostic techniques. Telomeres shorten with each cell division until they reach a length that triggers cellular senescence, leading to a decline in cellular function. This shortening is recognized as a fundamental aspect of aging, significantly involved in age-related degenerative processes and serving as a key biological marker of cellular longevity and tissue aging [45].

Emerging Machine Learning for unveiling the role of the TERT gene in PCOS

The development of machine learning (ML) has significantly impacted genomic and biomedical research, enabling the analysis of high-dimensional data to identify patterns that standard statistical methods might miss. In the context of PCOS, ML models have been effective in predicting illness risk, categorizing molecular subtypes, and uncovering gene-disease relationships, with increasing focus on the TERT gene in PCOS research [188]. Transcriptomic and genomic datasets are utilized with various ML models, such as support vector machines (SVM), random forests (RF), and deep neural networks (DNN), to identify biomarkers associated with PCOS [189]. These algorithms can identify differentially expressed genes like TERT by analyzing complex nonlinear relationships between genetic variations and disease symptoms. Methods such as LASSO regression and recursive feature elimination (RFE) consistently highlight TERT's potential role in PCOS cohorts, suggesting its involvement in ovarian dysfunction and hormone imbalance [190].

An ML-based integrative study of multi-omics datasets, including genomes, epigenomics, and transcriptomics, gives a comprehensive understanding of TERT's role in PCOS (Table 6). An unsupervised clustering technique has identified subgroups of PCOS with distinct TERT expression patterns, correlating these patterns with clinical traits such as insulin resistance, hyperandrogenism, and ovarian shape, suggesting that TERT may serve as both a biomarker and a potential therapeutic target. The predictive ML models utilizing clinical and genetic data are incorporating TERT SNPs and expression levels to stratify the risk of PCOS. These models aim to improve

Table 1 Experimental research examining the possible link between PCOS and TERT gene expression

Authors & Publication Year	Study Objective	Experimental Methodology	Important Findings on TERT/PCOS	Limitations	Citations
(Velazquez et al., 2021)	• Association between TL and obesity • Impact of hyperandrogenism on TL	• aTL measured using RPLP0 and telomeric repeat primers • Clinical parameters like BMI, WC, Lipid profile, Testosterone, and IR were checked • Statistical tests, ANCOVA, and multiple variable regression were performed	• PCOS women show longer aTL than controls • In patients with obesity shorter aTL was observed • In patients with hyperandrogenism, longer aTL was observed • WC negatively affects aTL, whereas testosterone positively affects it	• Cross-sectional design • Small sample size • Limited insight into TERRA dysregulation • Potential confounders are not explored	[114]
(Wang et al., 2017)	Role of TERRA in Telomere Maintenance	• RNA-FISH for TERRA localization • LTL and TERRA measured via qPCR • Hormonal assays like insulin, DHEAS, LH, FSH, and testosterone were done	• In PCOS patients, lower TERRA expressions were found • The lower the TERRA level, the longer the LTL • Testosterone negatively correlates with TERRA and positively correlates with LTL	• Small sample size • Cross-sectional nature • Limited insight into TERRA dysregulation	[85]
(Wei et al., 2017)	Telomere lengthening in GCs of PCOS women	• 81 IVF controls and 75 PCOS cases • GCs and leukocytes were collected from follicular fluids and blood • Relative TL was measured using qPCR • Correlation with metabolic and hormonal markers	• PCOS GCs have longer telomeres (1.57 ± 0.67 vs. 1.00 ± 0.37) • It suggests elevated TA in PCOS GCs • It can be driven by hyperandrogenism or increased follicular density	• Smaller sample size • Cross-sectional nature • Limited insight into TERRA dysregulation • Potential factors are not explored completely	[51]
(Hashemian et al., 2020)	• Difference between PCOS and a normal human GC line • Establishment and Characterization	• Retroviral transfection for immortalization • Marker validation using western blotting and immunofluorescence was done • Hormone assays are performed using culture media • Karyotyping and STR profiling	• PCOS patients (n = 698) have shorter LTL compared to controls (n = 611), • Short LTL indicates accelerated aging • Higher PCOS risk is associated with shorter LTL (OR = 1.614), and LTL and DHEAS levels in controls are negatively correlated	• Immortalized cells may not reflect natural physiology • Ovarian microenvironment is not replicated • Limited functional validation • Lack of donor variability	[157]
(Song et al., 2018)	• Akt-mTOR Signaling in PCOS • Regulation of GC proliferation and apoptosis	• 25 healthy IVF/ICSI controls and 25 PCOS GC samples were taken • INSR siRNA and insulin simulation were done • MTT assay and apoptosis tests • Western blot and RT-PCR for TA	• Insulin increases apoptosis in PCOS GCs • Low Akt-mTOR activation • Reduced TA • Dysregulated pathways may contribute to PCOS pathogenesis	• Cross-sectional design • Small sample size • PCOS heterogeneity is underexplored • Long-term consequences are unclear	[158]
(Hao et al., 2023)	• TL and ovarian aging	• Retrospective IVF/ICSI study (n = 160) • RT-qPCR for TERT expression and TL • Logistic regression for IVF associations	• In older women, shorter telomeres but higher TERT in GCs • Oocyte yield negatively correlated with TERT • No link with pregnancy rates	• Cross-sectional • Limited sample size • Restricted IVF populations, so lower generalizability	[46]
(Sutterlüty et al., 2023)	Telomere transcript quantification for genetic risk	• Review of 25 qPCR TERRA studies • RT-qPCR and T/S-qPCR • ROS induced TERRA expression • Proposed high-throughput screening use	• TERRA protects telomeres from oxidative stress • TERRA levels fluctuate with ROS • TERRA and TL are useful for genotoxicity assessment • PCOS may alter TERRA dynamics	• No empirical data • Variability and reproducibility issues • Lack of confounder analysis	[159]
(Pedroso et al., 2020)	Telomere Activity in PCOS	• Compared LTL and cumulus cell TA in PCOS and controls	• PCOS leukocytes have shorter telomeres • Cumulus cells have higher TA • Suggest a compensatory telomere preservation mechanism	• Small sample size • Cross-sectional • Causal relationships are unclear	[160]
(X. Xu et al., 2017)	Link between telomere dysfunction and early ovarian aging	• LTL and GTL measured by qPCR • Q-TRAP for TA • IVF parameters like fertilization rate and embryo quality were analyzed • Southern Blotting was done for confirmation	• POI patients showed lower TA • Shorter LTL and GC Telomeres • IVF reduced Two Pronuclei (2PN) fertilization with low telomerase	• Cross-sectional design • Missing longitudinal data	[161]

Table 2 Experimental evidence from genetic studies conducted to find out the connection between PCOS and TERT

Authors & Publication Year	Study Objective	Experimental Methodology	Important Findings on TERT/PCOS	Limitations	Citations
(Cao & Chen, 2024)	Mendelian Randomization to check the causal distance between LTL and PCOS	• GWAS-based MR analysis in Chinese and European populations • Instrumental variable selection	• Shorter LTL increases PCOS risk in both cohorts • Lifestyle changes may help preserve TL	• Limited generalizability to other populations • MR may not account for all confounders • Telomere biology complexity is not fully addressed	[162]
(Cozzolino et al., 2022)	Transcriptomic profile of PCOS in GCs and PBMCs	• RNA sequencing GCs and PBMCs • qRT-PCR validation • Pathway enrichment analysis	• Sirtuin signaling, mitochondrial dysfunction, and oxidative phosphorylation dysregulation • Oxidative stress may disrupt telomerase function in PCOS	• Small sample size • Cross-section design • Less information about medication and lifestyle management	[163]
(Lee et al., 2015)	GWAS to identify PCOS Susceptibility loci	• GWAS in 976 cases and 946 controls • Replication study • Pathway analysis using KEGG	• New locus near KHDRBS3 associated with PCOS • Linked to insulin resistance and steroidogenesis pathways	• Only common variants studied • European population only • Functional consequences are not explored	[164]
(Ribeiro et al., 2021)	• Effect of aerobic exercise on TL and hormone profiles in PCOS	• 87 PCOS women in Control Group (CG), Intermittent Aerobic Training (IAT), and Continuous Aerobic Training (CAT) groups • 16 weeks of exercise • Telomere qPCR analysis	• Exercise reduced testosterone and obesity markers • No change in TL and inflammation	• Short intervention duration • No diet control • TL measured by qPCR with limited precision	[165]
(Yang et al., 2024)	Mendelian randomization analysis of TL and reproductive endocrine disorders	• GWAS data from FinnGen and UK Biobank • Univariable and multivariable MR • Sensitivity tests	• Longer LTL increases ovarian endometrioma and menorrhagia • No evidence linking LTL to infertility or PCOS	• Weak instrument bias possible • Residual confounding • No causal proof due to MR limitations	[166]
(Q. Li et al.,2014)	Association of LTL with PCOS pathophysiology	• LTL measurement in 698 PCOS and 611 controls • Hormonal correlation analysis	• LTL was considerably shorter in PCOS patients (n = 698) than in controls (n = 611), comparable to 6.16 years of accelerated aging • Shorter LTL increases PCOS risk (OR = 1.614)	• Observational study • Cross-sectional design	[167]
(Péntek et al.,2023)	• Evaluate the TL and TA in GCs and follicular fluid in IVF	• 102 IVF patients • TL, TA, DNA damage assays • Statistical correlation analysis	• No association between IVF outcomes and TA • Oxidative DNA damage negatively affects oocyte and embryo outcomes	• Single-center study • Observational design • Assay limitations	[168]
(Ying Li et al.,2017)	• TL and TA in PCOS GCs • Effect of contraceptive pretreatment	• 163 infertile women • TL and telomerase assays • Hormonal analysis and regression	• Shorter TL in PCOS GCs • Contraceptives do not alter Telomere and TA	• Small sample size • Cross-sectional • Limited generalizability	[169]

early diagnosis, especially in cases with mild symptoms, and demonstrate increased accuracy when TERT-related characteristics are included in ensemble models [196]. Despite advancements, challenges remain in applying ML in PCOS research, including reduced generalizability from heterogeneous data, small sample sizes, and genetic diversity. The critical steps for translating ML findings into therapeutic insights are strong model validation, cross-cohort replication, and the use of explainable AI methodologies. Future research (Table 7) should focus on interpretable models that elucidate TERT's biological significance and connections with other PCOS-associated genes.

Limitations of the PCOS-TERT research

The studies reviewed in this manuscript exhibit several methodological constraints that must be considered when interpreting the current evidence linking TERT, TA, TL, and PCOS. First, a substantial proportion of the available research relies on cross-sectional or observational designs, which restrict the ability to determine temporal relationships or draw causal inferences between telomere dysregulation and PCOS pathophysiology. This limitation is evident in many studies assessing leukocyte TL, granulosa and cumulus cell telomere dynamics, TA, and TERRA expression, all of which collect data at a single time point. Numerous studies on ovarian tissue and granulosa/cumulus cells often utilize small sample sizes,

Table 3 Preclinical data from animal models demonstrate the link between PCOS and TERT gene regulation

Authors & Publication Year	Study Objective	Experimental Methodology	Important Findings	Limitations	Citations
(Kosebent & Ozturk, 2021)	• Alterations in Telomere Expression in Aging Mice's Ovary Follicles • TERT protein level and TA	• qRT-PCR is used for telomere-associated genes • Western Blot for analyzing telomerase levels • Mechanical isolation of follicles from adult and aged mice • Statistical tests, ANOVA, and t-tests were performed	• Decreased TERT expression in aged ovarian follicles • Significant drop in TERT protein in elderly mice • TA remained the same across different age groups	• Species variation limits relevance to humans • May not capture dynamic telomere changes • Mostly observational in nature • Technical challenges in follicle isolation	[90]
(Xue et al., 2024)	• NF-κB-TERT Feedback Regulation in PCOS Rats • GC apoptosis mechanisms	• Letrozole treated, high-fat diet PCOS rat model • LPS-treated KGN cell model • Western blotting and RT-qPCR • Immunohistochemistry • TL assay • Flow cytometry	• PCOS rats showed elongated telomeres • Decrease in BCL-2, NF-κB, IL-6, TNF-α, TERT, BAX, Caspase 3 • NF-κB and TERT loop are linked to apoptosis • Inhibitors reduced inflammation in KGN cells	• Chronic inflammation alters TERT regulation • Hormonal imbalance can cause GC apoptosis • Overactivation of NF-κB disrupts TERT, leading to inflammation and anovulation	[87]

Table 4 Methodologies used to find the relationship between PCOS and TERT gene expression

Methods used	Methodology	Limitations observed	Citations
Genome-wide association studies (GWAS)	Scan complete genomes for genetic variants associated with certain disorders. GWAS have discovered genetic loci related to PCOS on chromosomes 2p16.3, 2p21, and 9q33.3	Requires huge sample sizes, GWAS only explains a part of the genetic contribution to a trait, and the possibility of creating additional false positives	[173]
DNA Methylation Profiling	Assessment of epigenetic alterations by methylation that leads to PCOS; methylation indicators serve as biomarkers for TERT gene changes in PCOS; it affects gene expression and cellular expression	Tissue specificity, imperfect conversion, DNA degradation, epigenetic variability, complexity in data processing, and difficulties in connecting gene expression to illness	[174]
Immunohistochemistry for TERT	Localizes TERT gene expression in PCOS, employs antibodies to visualize TERT genes in tissues, and detects TERT gene expression and function in PCOS and other cellular processes	Antibody specificity and sensitivity, tissue sample quality, difficulties with many targets, and issues in quantifying	[175]
Clinical exome sequencing	Targets the genome's protein-coding regions. Identify variations such as mutations and polymorphisms, with an emphasis on protein-coding areas that contribute to PCOS. Detecting possible PCOS concerns through pathophysiology	Incomplete coverage of gene areas, issues in defining the cause, difficulty in evaluating pathogenicity, and sequencing mistakes	[176]
TA assay	Telomeric repeat amplification assesses the activity of telomerase, which maintains TL and encodes the catalytic portion of the TERT gene. Altered TA has been detected in GCs of PCOS patients, which act as a biomarker	Requires high-quality samples with intact TA; reliable TA estimation is complicated, tissue-specific, and has a restricted dynamic range	[177]
TERT gene expression analysis (qRT-PCR)	Quantifies TERT mRNA levels in ovarian tissue and GCs, amplifies TERT cDNA using primers, and quantifies the expression levels, identifies changed gene expression, and corresponds with the severity of PCOS	RNA degradation affects the results, primer specificity, quantification, and interpretation challenges	[90]
TERT protein expression analysis (Western Blotting)	While immunofluorescence identifies and measures proteins in tissues, the detection of TERT protein levels in ovarian tissue illuminates the role of TERT in PCOS pathophysiology and provides information on TERT protein localization	High-quality specific antibodies are difficult to obtain due to sample integrity concerns, as well as difficulties with standardization and interpretation	[87]
Next Generation Sequencing	Analyzes the protein-coding area of the gene and numerous genomic regions, focusing on the specific target or gene, sequencing of the full exome, discovery of uncommon genetic variations and mutants in TERT genes	Complexity in data processing owing to enormous data collected; some alterations cannot be discovered by NGS; functional relevance and interpretation are difficult	[178]
Microarray analysis	Analysis of the TERT gene expression level, measurement of gene expression variations, identification of signaling networks, biological processes, and gene expression patterns that are altered by PCOS	Limited dynamic range, probe design, tiny changes cannot be detected, high expression leads to saturation, and quantification is challenging	[179]
Bioinformatics data analysis	Analyze gene expressions and regulation utilizing accessible datasets, sequence, pathways, identify genetic variations, and perform gene expression profiling	Algorithmic biases, low data quality, need for large-scale resources, limited comprehension, and difficulties in interpretation	[170]

Table 5 Innovative Methods for exploring the crosstalk between the PCOS and TERT

Strategies	Description	Scientific Rationale	Key Methodologies	Challenges	Citations
Analysis of TL in PCOS patients	Examining the potential correlation between PCOS characteristics (such as anovulation and hyperandrogenism) and telomere attrition in GCs, oocytes, or leukocytes	TL is maintained by TERT. One known characteristic of some PCOS patients is accelerated ovarian aging, which may be exacerbated by reduced TA	For measuring TL, use qPCR or Southern blot (TRF analysis) Flow-FISH for immune cell telomere dynamics	Age and tissue have an impact on TL. Confounding factors, such as lifestyle and BMI. There is frequently a paucity of longitudinal data	[88]
Profiling TERT expression in Ovarian Cells	Assessing the amounts of TERT mRNA and protein in PCOS ovarian granulosa, theca, and stromal cells	In PCOS, altered TERT expression may have an impact on cell survival, ovulation, and follicular development	For transcriptional analysis, use RT-qPCR and RNA-seq IHC and Western blot are used to quantify proteins For localization, immunofluorescence is used	Access to ovarian tissues is restricted. Inter-individual variability is high. The phenotypic subgroups of PCOS are diverse	[180]
TERT Promoter Epigenetic Regulation in PCOS	Examining histone changes and DNA methylation at the TERT promoter to see whether PCOS is associated with epigenetic activation or silencing	It is recognized that epigenetic dysregulation plays a role in PCOS. TA in ovarian cells may be impacted by TERT promoter methylation	Methylation via bisulfite sequencing. for histone markers (e.g., H3K27me3, H3K4me3), ChIP-qPCR or ChIP-seq. or a higher density of follicles	High-resolution, cell-specific epigenomic data are required. It's challenging to distinguish between cause and effect. Sample sizes are small	[181]
Transcriptome of Single Cells in PCOS Ovaries	Comparing the expression of TERT in PCOS with control ovaries for each kind of follicular cell, such as the granulosa, oocyte, and theca	Cell-type-specific changes in telomerase function may be a part of PCOS. These shifts can be identified via single-cell analysis	Platforms for scRNA-seq (10X Genomics, Smart-seq). Bioinformatic pipelines for the analysis of gene pathways and clusters	Expensive and technically complicated. The availability of fresh tissue. Cellular heterogeneity makes data interpretation challenging	[182]
GWAS and eQTL Research connecting PCOS and TERT Locus	Locating and evaluating the effects of SNPs in or close to the TERT gene linked to PCOS characteristics on TERT expression	Through telomere maintenance or hormone pathway control, common genetic variations at the TERT locus may affect a person's vulnerability to PCOS	GWAS, or genome-wide association studies. The mapping of expression quantitative trait loci (eQTL). Bioinformatics tools such as ENSEMBL and GTEx	Requires cohorts of at least 10,000 people. It is challenging to interpret polygenic risk in isolation. There is insufficient functional validation of SNPs	[183]
TERT modulated Animal models	Using TERT overexpression or knockout to create mouse models that resemble PCOS to investigate the effects on ovarian morphology and metabolic dysfunction	Enables the investigation of causality: whether TERT disruption resembles or lessens the symptoms of PCOS (such as insulin resistance and cystic follicles)	TERT knockout or transgenic mice. Letrozole induced PCOS models or DHEA models. Hormone tests, ovarian histology	Human and mouse telomere biology are different. Transgenic models raise ethical issues. Models might not accurately depict the intricacy of PCOS	[184]
PCOS Cell Culture models using TERT manipulation	Use CRISPR/Cas9 or siRNA to modify TERT expression and evaluate cellular results in granulosa or theca cells cultured from PCOS ovaries	In PCOS, TERT activity may have an impact on oxidative stress, hormone synthesis (such as androgens and estradiol), and cellular senescence	Ovarian tissue is the primary cell culture. Overexpression or silencing of TERT (CRISPR, siRNA). ELISA, senescence β-gal staining, and ROS tests	The quantity of viable primary cells is limited. Cultured cells can lose their in vivo properties. Effects of off-target gene editing	[185]
Therapeutics based on Telomerase in PCOS	Testing telomerase inhibitors or activators (like TA-65) in animal or cell models of PCOS to assess their impact on ovarian function	Telomerase modulation may help PCOS ovaries avoid hyperproliferation or revitalize ovarian cells	In vitro drug screening. Hormone tests (testosterone, FSH, and LH). Evaluation of Folliculogenesis	Tumorigenesis risk is associated with TERT activators. Long-term safety and efficacy research is required. Ethical and regulatory obstacles	[186]
Methods of Integrative Multi-Omics	Integrating data from PCOS patients' proteome, transcriptomics, epigenomics, and genomics to find networks that connect TERT to illness pathways	It is recognized that epigenetic dysregulation plays a role in PCOS. TA in ovarian cells may be impacted by TERT promoter methylation	Multi-omics pipelines, such as WGCNA and MOFA. Tools for network biology.—ML and AI for finding patterns	Data integration is difficult. Large datasets are needed. It is challenging to experimentally evaluate new findings	[187]

which compromises statistical power and generalizability of findings related to various PCOS phenotypes. These limitations hinder adjustments for confounders, with many studies involving only 25–80 participants, leading to increased variability and inconsistent results in the literature.

Many studies reviewed inadequately adjust for biological factors affecting TL and TERT expression

Table 6 ML Approaches used in TERT-PCOS Research

ML Approach	Applications in TERT-PCOS Research	Advantages	Disadvantages	Example	Citations
Feature Selection (for example, LASSO or RFE)	Detecting important genes such as TERT from high-dimensional genomic data	Reduces dimensionality, emphasizes the most relevant genes, and prevents overfitting	Non-linear interactions may be ignored, and outcomes vary depending on input attributes	LASSO regression found TERT among the main predictors of the PCOS phenotype in transcriptome data	[191]
Supervised learning (SVM, Random Forest)	Classifying PCOS vs. non-PCOS patients using TERT expression or SNP data	High classification accuracy and the ability to handle massive feature sets	Requires labelled data; model interpretability might be limited	SVM diagnosed PCOS patients with more than 85% accuracy when TERT expression was included as a feature	[190]
Unsupervised learning (e.g., k-means and hierarchical clustering)	Identifying PCOS subgroups using TERT-related expression patterns	No requirement for labeled data; beneficial for phenotypic subtyping	Sensitive to basic settings, may overlook small trends	Clustering revealed PCOS subgroups with elevated TERT expressions associated with metabolic abnormalities	[192]
Deep learning (such as DNNs and autoencoders)	Predicting complicated interactions of TERT and other genes	Captures non-linear, hierarchical connections; scalable	Risk of overfitting and is less interpretable	The autoencoder used TERT expression and methylation data to differentiate PCOS molecular markers	[193]
Integrative Multi-Omics ML	Using transcriptomic, epigenomic, and genomic data to investigate TERT's systemic involvement	Improved biomarker development through a more comprehensive understanding of gene-disease interactions	Complex integration is computationally demanding	RF model employing integrated omics data found TERT as key in PCOS inflammatory pathways	[194]
Explainable AI (e.g., SHAP and LIME)	Understanding the contribution of TERT characteristics in ML predictions	Promotes transparency and trust in ML outputs	Added complexity in model development; post-hoc explanation may not be completely true	SHAP values revealed that TERT expression greatly affected PCOS risk prediction in RF models	[195]

independently of PCOS, such as age, BMI, oxidative stress, insulin resistance, inflammation, and medication. In the absence of thorough confounder adjustment, reported associations may reflect these uncontrolled influences. The studies reviewed utilize various techniques for measuring TL and TA, such as qPCR T/S ratio, TRF, TRAP, and q-TRAP. This diversity in measurement methods, sample preparation, tissue types, and analytical protocols complicates cross-study comparisons. Variations in assay sensitivity, dynamic range, and tissue specificity may lead to inconsistent findings, hindering quantitative result synthesis.

These limitations emphasize the necessity for robust longitudinal cohort studies, standardized assays for telomeres and telomerase, thorough confounder adjustments, and mechanistic research utilizing patient-derived cells and animal models. Filling these gaps is crucial for elucidating the causal role of TERT and telomere biology in PCOS and applying these findings to clinical biomarkers or therapeutic strategies.

Lacunae/research gap

Despite extensive research linking PCOS to the TERT gene, its role in ovarian dysfunction remains unexplored, leaving significant gaps in understanding its contribution to telomere maintenance and cellular aging in relation to PCOS. The role of TERT in PCOS is expanding, yet substantial gaps exist in the current literature.

Most studies conducted are cross-sectional studies, which is a limiting factor in drawing causal inferences between TERT expression, TA, and PCOS clinical manifestations.

The regulatory mechanisms, such as hyperandrogenism, IR, and oxidative stress, are not yet fully understood.

Research has focused on GCs and leukocytes, leaving telomerase dynamics in other ovarian cell types unexplored.

The influence of lifestyle modifications and pharmacologic interventions on TERT expression is also poorly understood.

Ethnic and genetic variability in TERT-related polymorphisms contributes to PCOS susceptibility and heterogeneity.

Clinical implications of altered TA in PCOS remain unclear and underexplored in translational research.

Further research can provide more insights into TERT polymorphisms or epigenetic modifications that can cause PCOS.

Discussion

The review highlights a complex relationship between TERT regulation, telomere biology, and PCOS pathophysiology. Some studies indicate reduced TL and decreased TA, pointing to accelerated cellular aging in

Table 7 Future AI/ML-based strategies employed for predicting linked biomarkers associated with PCOS and TERT

Study Area	Focus	AI-ML Techniques	Key Outcomes	Future Research View	Citations
PCOS Diagnosis	Early and precise diagnosis of PCOS	Deep Learning, SVM, Decision Tree	Enhanced diagnosis accuracy with hormonal, metabolic, and imaging data	Combining transcriptomic and genomic information for accurate diagnosis	[190]
PCOS Phenotyping	To classify PCOS subtypes	Clustering Algorithms	Improved categorization according to Insulin resistance, symptoms, etc	Treatment regimens tailored to individual phenotype-genotype profiles	[197]
TERT expression in PCOS	Examining TERT expressions in PCOS patients' ovarian tissues	DNA data mining and ML classifiers	New evidence of TERT expression changes in ovarian dysfunction associated with PCOS	Longitudinal studies that link TERT expression and ovarian aging in PCOS	[198]
AI-driven Biomarker Discovery	Identifying indicators that connect telomere biology and PCOS	Feature Selection Algorithms and Neural Networks	Finding possible TERT-related indicators in tissue or blood samples	Multi-omics integration for biomarker panels, like TL and TERT	[199]
Genetic Risk Prediction	PCOS risk prediction using TERT and other genes	Polygenic Risk Scoring and Random Forest	Identify the genetic variants contributing to PCOS	Modelling the TERT gene environment interactions using AI	[200]
TL Prediction	To estimate the TL from health data	Ensemble Learning and Regression Models	Predicting the non-invasive TL as an indicator of PCOS aging	Using AI to connect telomere biology, lifestyle variables, and PCOS development	[198]

PCOS, while others show TERT upregulation in specific ovarian cells, particularly GCs [201]. These conflicting findings necessitate a nuanced understanding of telomere dynamics in the varied physiological context of PCOS.

A key source of variability in reproductive biology originates from cell-type specificity among GCs, theca cells, cumulus cells, leukocytes, and stromal cells, which exhibit differences in proliferation, metabolic stress, and hormonal environments. Notably, GCs experience significant proliferation during folliculogenesis, potentially leading to TERT upregulation as a compensatory response to oxidative stress, inflammation, and mitochondrial dysfunction prevalent in PCOS. This adaptive response can enhance TA to preserve chromosomal stability despite telomere shortening due to chronic oxidative stress [202]. However, leukocyte studies show shorter telomeres and reduced TA, indicating systemic metabolic and inflammatory stress as opposed to localized mechanisms in ovarian cells. Consequently, differences in findings between tissues stem from their unique biological roles and stress levels.

The variation in disease stage and phenotype in PCOS affects TERT regulation. Early-stage or hyperandrogenic phenotypes may show increased TERT as a protective response, while chronic, metabolically severe cases could experience telomere exhaustion and downregulated TERT, leading to impaired ovarian function. The phenomenon of an initial spike in TERT followed by telomere-driven senescence remains unexplored and could account for inconsistent findings across studies, indicating a need for longitudinal studies assessing TL, TA, and TERT expression in various PCOS subtypes.

The confounding factors such as age, BMI, insulin resistance, inflammation, and medication use significantly influence telomere biology. Many studies fail to fully adjust for these variables, complicating the distinction between PCOS-specific effects and other influences. The methodological variations, including assay choices and tissue sampling techniques, also contribute to inconsistent outcomes, thus hindering comparability and interpretation across studies. Mechanically, TERT effects in PCOS are influenced by various pathways. Oxidative stress and chronic inflammation accelerate TA and reduce telomerase function, while increased androgen signaling and Wnt/β-catenin activation may enhance TERT transcription. Additionally, metabolic dysregulation can affect TERT through insulin/IGF-1 pathways, mitochondrial stress responses, or NF-κB signaling. This interplay indicates that TERT behaviour in PCOS is context-dependent, shaped by both damaging factors and proliferative signals.

The overall current literature indicates that telomere regulation in PCOS involves a dynamic balance between accelerated cellular aging and compensatory

Table 8 Emerging Strategies in Linking TERT to PCOS

Strategies	Detailed Description	Scientific Rationale	Key Methodologies	Challenges
CRISPR-based functional screening [203]	Methodically altering TERT gene expression in PCOS models via CRISPR-Cas9 and CRISPRi/a techniques	Aids in locating TERT genetic regulators linked to PCOS, potentially revealing new treatment targets	Gene editing using CRISPR/Cas9, lentiviral transduction, pooled guide RNA libraries, and downstream transcriptomics	Delivery effectiveness, off-target effects, and the necessity for primary tissue validation are critical considerations in the assessment of therapeutic interventions
Ovarian Folliculogenesis in Organoid Models [204]	Development of three-dimensional ovarian organoids using induced pluripotent stem cells (iPSCs) derived from PCOS patients	Investigation of TERT in follicle development through the simulation of the natural ovarian microenvironment	RNA-seq, live imaging, hormonal stimulation, Matrigel-based culture, and iPSC differentiation	High cultural costs, technical complexity, and differentiation variability
Studies of Longitudinal Cohorts [205]	Prospective monitoring of PCOS traits, telomere dynamics, and TERT levels across time in various populations	Makes it possible to comprehend changes across time and possible causality	ELISA for TERT, TL assays, metabolic and reproductive profiling, and statistical modeling	Length of time, high incidence of attrition, and financial limitations
Spatial Transcriptomics [206, 207]	Mapping of gene expression, including TERT, while maintaining the spatial architecture of intact ovarian tissues	Aids in the connection between PCOS histopathology and tissue-specific TERT expression	Slide-by-slide, H&E staining, spatial clustering techniques, and Visium spatial gene expression	Requires complicated analysis, costly reagents, and fresh tissues
Single-Cell Multi-Omics [208]	Research utilizing proteomics, ATAC-seq, and single-cell RNA-seq aims to uncover regulatory networks associated with TERT	Analyzes TERT's cell-specific functions in ovarian dysfunction	Library preparation, single-cell separation, and multimodal data integration (Seurat, ArchR)	Interpretation of data, difficulties with integration, and high expense
AI-driven Predictive modeling [209]	Large-scale datasets are analyzed using ML to forecast the course of TERT-related PCOS illness	Permits the establishment of individualized therapy and risk stratification	Model validation, supervised learning (such as SVM and XGBoost), and feature selection	Requires transparent and reproducible algorithms, as well as clean, labeled data
TERT-targeted Nanotherapeutics [210]	Development of nanoparticles aimed at the direct transport of TERT modulators to ovarian cells	Potential for cell-specific TERT function modulation	Surface modification, in vitro and in vivo efficacy tests, and nanoparticle manufacturing	Off-target effects, immunological clearance, and delivery efficiency
Single-Cell Spatial Epigenomics [211]	Combining single-cell epigenetic profiling (e.g., histone code, methylome) with spatial transcriptomics	Demonstrates how TERT is regulated by chromatin status in the geographical environment of the ovaries	Data integration with spatial transcriptomics, spatial methylomics, and scATAC-seq	Requires sophisticated data and extensive tissue access
Multi-Organ Chip models [212, 213]	Systems that replicate endocrine signaling in vitro by combining pituitary, hypothalamus, and ovarian tissues	Reconstructs the role of systemic hormones in TERT expression	Hormone monitoring, co-cultivation methods, and microfluidic devices	Issues with bioengineering and instability over time
circRNA Functional Profiling [214]	Circular RNAs controlling TERT transcription and translation have been identified and validated	CircRNAs may use protein scaffolding or miRNA sponging to function as TERT regulators	Luciferase assays, circRNA prediction (CIRI, CircExplorer), and RNA-seq	Biology is not well understood and has a low abundance
High-Throughput Small-Molecule Screening [215]	Searching through compound libraries for TERT modulators in PCOS models	List of medications that target the telomerase pathway and are relevant to PCOS	Hit validation, reporter assays, and automated screening platforms	Clinical translation, cell-type effects, and compound specificity

mechanisms, emphasizing the need to view TERT and telomere changes within the wider cellular and hormonal context instead of as standalone biomarkers. Future research (Table 8) should utilize longitudinal study designs and multi-tissue, multi-omics approaches, as well as mechanistic perturbation experiments, to determine if TERT dysregulation is a cause or consequence of PCOS. The standardization of TL/TA measurement protocols and adjusting for confounders are vital for addressing current inconsistencies. It emphasizes the necessity of considering disease phenotypes, patient age, and metabolic profiles in telomerase system research related to PCOS. A better understanding of TERT biology in PCOS could lead to targeted interventions to reduce ovarian aging and enhance reproductive outcomes.

Conclusion and future perspective

This review highlights the intricate role of TERT, TA, and telomere regulation in the pathophysiology of PCOS. While some studies indicate shorter telomeres and reduced telomerase function, suggesting accelerated cellular aging, others show TERT upregulation in certain ovarian cells. These contrasting results highlight that telomere biology in PCOS is complex, involving a balance between degenerative factors like oxidative stress, inflammation, insulin resistance, and metabolic dysfunction,

and compensatory responses driven by androgen excess, growth-factor signaling, and follicular remodelling. The current evidence indicates that telomere dysfunction may impair ovarian function and oocyte quality in PCOS, alongside broader metabolic disturbances. However, limitations like cross-sectional designs, small sample sizes, tissue-specific variability, and heterogeneity in TL/TA assays hinder strong conclusions and the determination of causality, highlighting the need for standardized and rigorous study designs.

Future research on PCOS should focus on longitudinal cohorts, robust clinical studies, and mechanistic experiments with patient-derived cells and animal models to determine the role of TERT dysregulation. The multi-omics integration, genetic causal inference, and single-cell analyses are crucial for resolving cell-type-specific effects and understanding the molecular diversity of PCOS phenotypes. An advancement in understanding TERT and telomere pathways could result in new biomarkers for early detection, improved stratification of PCOS subtypes, and therapeutic strategies to reduce ovarian aging, enhance ovarian TA, and restore reproductive and metabolic health as a potential rejuvenation technique.

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Declarations

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NA.

Consent for publication
We ensure that this work has not been published in whole or in part, and it is not being considered for publication in any other language. After carefully reviewing the work, each author gave their approval and agreement for it to be submitted to the "Journal of Ovarian Research" journal.

Competing interests
The authors declare no competing interests.

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