SIRT1 as a Molecular Link Between Lifestyle Intervention and Ovarian–Metabolic Dysfunction in Experimental PCOS

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Polycystic ovary syndrome (PCOS) is a complex endocrine–metabolic disorder characterized by reproductive dysfunction, insulin resistance, chronic low-grade inflammation, oxidative stress, and altered energy homeostasis. Emerging evidence suggests that silent information regulator 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, plays a pivotal role in integrating metabolic signals with ovarian physiology. Through its regulatory effects on mitochondrial biogenesis, antioxidant defense, glucose and lipid metabolism, inflammatory pathways, and cellular survival mechanisms, SIRT1 has gained increasing attention as a potential molecular target in PCOS. Experimental models of PCOS have demonstrated dysregulation of SIRT1 expression in ovarian and peripheral tissues, potentially contributing to both metabolic and reproductive abnormalities observed in this condition. This review summarizes current evidence regarding the physiological role of SIRT1 in experimental PCOS and critically evaluates the impact of exercise training and caloric restriction on SIRT1 expression and related ovarian–metabolic pathways. Understanding these mechanisms may provide insights into the development of targeted non-pharmacological strategies aimed at mitigating the metabolic and reproductive consequences of PCOS.

Conclusion: SIRT1 has emerged as a promising molecular link connecting metabolic homeostasis with ovarian function in PCOS. Experimental evidence suggests that disturbances in SIRT1 signaling may contribute to insulin resistance, oxidative stress, inflammatory activation, and granulosa cell dysfunction, thereby promoting the ovarian–metabolic abnormalities characteristic of the syndrome.

Keywords: *SIRT1, Molecular , Lifestyle Intervention, Ovarian–Metabolic Dysfunction, Experimental PCOS*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age and is characterized by a heterogeneous combination of reproductive, metabolic, and psychological manifestations. According to current diagnostic criteria, PCOS encompasses varying phenotypes involving hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Beyond its effects on fertility, PCOS is increasingly recognized as a systemic disorder associated with insulin resistance, obesity, dyslipidemia, chronic low-grade inflammation, and increased cardiovascular risk. The multifaceted nature of the syndrome reflects the complex interactions between genetic predisposition, endocrine abnormalities, and environmental influences that contribute to its pathogenesis and clinical heterogeneity. [1]

A hallmark feature of PCOS is the close relationship between ovarian dysfunction and metabolic disturbance. Insulin resistance affects a substantial proportion of women with PCOS and contributes to compensatory hyperinsulinemia, which potentiates ovarian androgen production and suppresses hepatic synthesis of sex hormone-binding globulin. The resulting increase in circulating free androgens further aggravates follicular arrest and anovulation, establishing a vicious cycle linking metabolic impairment with reproductive dysfunction. Understanding the molecular pathways underlying this ovarian–metabolic interplay has therefore become essential for identifying novel therapeutic targets and improving disease management strategies. [2]

Among the ovarian abnormalities associated with PCOS, disrupted folliculogenesis remains central to the development of anovulation and subfertility. Excessive recruitment of early follicles, impaired selection of dominant follicles, and arrest of follicular growth at the small antral stage contribute to the characteristic polycystic ovarian morphology. These alterations are accompanied by dysregulation of granulosa and theca cell function, altered gonadotropin responsiveness, and disturbances in the intraovarian environment that collectively impair normal reproductive physiology. Experimental models of PCOS have facilitated the investigation of these mechanisms and have provided valuable insights into the cellular pathways involved in disease progression. [3]

Silent information regulator 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, has emerged as a critical regulator of cellular metabolism and stress adaptation. SIRT1 modulates several biological processes relevant to PCOS pathophysiology, including glucose and lipid metabolism, mitochondrial function, oxidative stress responses, inflammation, autophagy, and apoptosis. Through deacetylation of multiple transcription factors and co-regulators, SIRT1 integrates nutrient availability with cellular energy demands, thereby maintaining metabolic homeostasis. Increasing evidence suggests that alterations in SIRT1 signaling may contribute to both ovarian dysfunction and systemic metabolic disturbances observed in PCOS. [4]

Lifestyle interventions remain the cornerstone of PCOS management, with exercise training and dietary energy restriction representing two of the most effective non-pharmacological approaches for improving metabolic and reproductive outcomes. Recent experimental studies have proposed that activation of SIRT1-dependent pathways may mediate several of the beneficial effects induced by these interventions, including enhanced insulin sensitivity, reduced oxidative stress, improved mitochondrial function, and restoration of ovarian homeostasis. However, evidence regarding the effects of exercise training and caloric restriction on SIRT1 expression in experimentally induced PCOS remains fragmented. Therefore, this review aims to critically evaluate the current literature addressing the role of SIRT1 as a molecular link between lifestyle interventions and ovarian–metabolic dysfunction in experimental PCOS, while highlighting potential mechanisms and future research directions. [5]

SIRT1: Structure and Physiological Functions

Sirtuins constitute a highly conserved family of nicotinamide adenine dinucleotide (NAD^+)-dependent enzymes involved in regulating cellular adaptation to metabolic stress. In mammals, seven sirtuin isoforms (SIRT1–SIRT7) have been identified, each exhibiting distinct subcellular localization and biological functions. Among these, SIRT1 is the most extensively investigated and is predominantly

localized within the nucleus, although it can shuttle between the nucleus and cytoplasm depending on cellular conditions. The catalytic activity of SIRT1 relies on intracellular NAD^+ availability, enabling it to function as a metabolic sensor that links cellular energy status with transcriptional regulation. Through deacetylation of histones and numerous non-histone proteins, SIRT1 orchestrates adaptive responses that maintain cellular homeostasis under conditions of nutrient deprivation and environmental stress. [6]

The central role of SIRT1 in metabolic regulation is mediated through its interactions with multiple transcription factors and co-regulators involved in glucose and lipid metabolism. SIRT1 modulates hepatic gluconeogenesis, promotes fatty acid oxidation, enhances mitochondrial oxidative capacity, and improves insulin sensitivity in peripheral tissues. These actions occur through the deacetylation of key metabolic regulators, including peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), forkhead box O proteins, and peroxisome proliferator-activated receptors. Consequently, SIRT1 has emerged as a critical component of the nutrient-sensing network responsible for maintaining metabolic flexibility and energy balance. [7]

Beyond its metabolic functions, SIRT1 exerts potent cytoprotective effects through the regulation of oxidative stress, inflammation, autophagy, and apoptosis. SIRT1 enhances antioxidant defense mechanisms by influencing transcriptional pathways involved in reactive oxygen species detoxification while simultaneously suppressing pro-inflammatory signaling cascades. In addition, SIRT1 contributes to mitochondrial quality control and cellular survival through the modulation of autophagic processes, thereby preserving tissue function under conditions of physiological and pathological stress. These properties have generated considerable interest regarding the therapeutic potential of SIRT1 activation in disorders characterized by chronic inflammation and metabolic dysfunction. [8]

Recent evidence suggests that SIRT1 also plays an important role in ovarian physiology. SIRT1 expression has been identified in oocytes and granulosa cells, where it participates in the regulation of cellular metabolism, stress resistance, and maintenance of reproductive competence. Experimental studies have demonstrated that dysregulation of SIRT1 signaling within ovarian tissues may contribute to impaired follicular development and reduced cellular resilience in adverse metabolic environments. Therefore, alterations in SIRT1 activity may represent a mechanistic link between systemic metabolic disturbances and ovarian dysfunction, particularly in disorders such as PCOS where both pathways are profoundly disrupted. [9]

Ovarian–Metabolic Dysfunction in Experimental PCOS

Experimental models of PCOS have substantially advanced the understanding of the complex interactions between reproductive and metabolic disturbances that characterize the syndrome. Animal models induced by androgens, aromatase inhibitors, or other endocrine manipulations successfully reproduce many features observed in human PCOS, including anovulation, hyperandrogenism, polycystic ovarian morphology, insulin resistance, and adipose tissue dysfunction. These models have provided evidence that PCOS should not be viewed solely as a reproductive disorder but rather as a multifactorial condition involving profound metabolic dysregulation. The coexistence of ovarian abnormalities with systemic metabolic impairment underscores the importance of identifying common molecular pathways involved in disease pathogenesis. [10]

Insulin resistance represents one of the most extensively studied metabolic abnormalities in PCOS and is considered a major contributor to disease progression. Compensatory hyperinsulinemia enhances androgen biosynthesis by ovarian theca cells and amplifies luteinizing hormone-induced steroidogenesis. Simultaneously, insulin suppresses hepatic production of sex hormone-binding globulin, resulting in increased concentrations of biologically active androgens. The reciprocal relationship between hyperinsulinemia and hyperandrogenism establishes a self-perpetuating cycle that promotes both reproductive dysfunction and worsening metabolic status in experimental and clinical PCOS. [11]

Hyperandrogenism exerts direct effects on ovarian physiology by disrupting normal follicular

maturation and promoting follicular arrest. Excessive androgen exposure alters granulosa cell proliferation, impairs aromatase activity, and contributes to the accumulation of small antral follicles that characterize polycystic ovarian morphology. Consequently, dominant follicle selection fails to occur, leading to chronic anovulation and reduced fertility. Experimental studies have demonstrated that androgen excess also influences extra-ovarian tissues involved in metabolic regulation, further strengthening the concept of a bidirectional relationship between reproductive and metabolic dysfunction in PCOS. [12]

Accumulating evidence suggests that oxidative stress and mitochondrial dysfunction are important contributors to ovarian impairment in PCOS. Increased generation of reactive oxygen species and compromised antioxidant defenses adversely affect granulosa cell viability, steroidogenic activity, and oocyte quality. Furthermore, mitochondrial abnormalities impair cellular energy production and may aggravate insulin resistance and inflammatory responses. Since normal ovarian function requires substantial energy expenditure and effective redox regulation, disruption of these processes may represent a critical mechanism underlying follicular dysfunction in PCOS. [13]

In addition to oxidative stress, chronic low-grade inflammation has emerged as a key component of PCOS pathophysiology. Elevated concentrations of inflammatory mediators contribute to insulin resistance, alter ovarian steroidogenesis, and negatively influence follicular development. Experimental findings indicate that inflammatory signaling pathways interact closely with metabolic disturbances and oxidative stress, creating an unfavorable ovarian microenvironment that perpetuates disease progression. Understanding these interconnected mechanisms is essential for identifying therapeutic strategies capable of simultaneously targeting both metabolic and reproductive aspects of PCOS. [14]

Altered SIRT1 Expression in Experimental PCOS

Emerging evidence from experimental models suggests that SIRT1 signaling is disrupted in PCOS and may contribute directly to ovarian dysfunction. Ovarian exposure to hyperandrogenism, insulin resistance, and metabolic stress creates an environment that interferes with the normal regulatory functions of SIRT1. Since SIRT1 participates in the control of mitochondrial homeostasis, antioxidant defenses, and cellular survival pathways, alterations in its expression may compromise follicular development and ovarian resilience. Consequently, SIRT1 dysregulation has attracted considerable attention as a potential mechanistic link between metabolic abnormalities and impaired reproductive function in PCOS. [15]

Experimental investigations have demonstrated that ovarian glycative stress in PCOS is associated with disruption of the SIRT1 functional network. Using a mouse model of PCOS, Emidio and colleagues reported that methylglyoxal accumulation altered the expression of proteins involved in SIRT1-dependent pathways, suggesting that excessive glycative stress contributes to ovarian dysfunction through impairment of adaptive cellular responses. These findings indicate that SIRT1 may serve a protective role within the ovary by preserving cellular homeostasis under metabolically unfavorable conditions that characterize PCOS. [16]

Further support for the importance of SIRT1 in ovarian physiology has been provided by studies demonstrating its involvement in the ovarian response to oxidative and glycative insults. SIRT1 participates in defense mechanisms that maintain oocyte quality and ovarian function through modulation of stress-responsive pathways. Therefore, reduced SIRT1 activity may increase susceptibility of ovarian cells to apoptosis, mitochondrial dysfunction, and impaired folliculogenesis. Preservation of SIRT1 signaling may thus represent an essential requirement for maintaining reproductive competence in the presence of metabolic stress. [17]

Recent evidence has expanded the role of SIRT1 in PCOS by demonstrating its ability to regulate granulosa cell survival through inhibition of ferroptosis. Experimental data indicate that activation of SIRT1 attenuates iron-dependent lipid peroxidation and protects granulosa cells against cell death, thereby supporting follicular integrity and ovarian function. Given that granulosa cell dysfunction is a major contributor to follicular arrest and anovulation in PCOS, these observations further strengthen the

hypothesis that restoration of SIRT1 activity may provide therapeutic benefits for both ovarian and metabolic abnormalities associated with the syndrome. [18]

Effects of Exercise Training on SIRT1 Expression in Experimental PCOS

Exercise training is considered a cornerstone of lifestyle management in PCOS because of its beneficial effects on body composition, insulin sensitivity, cardiovascular health, and reproductive function. Systematic reviews have consistently demonstrated that structured exercise programs improve several cardiometabolic parameters in women with PCOS independent of substantial weight loss. Given the strong association between metabolic dysfunction and ovarian abnormalities in PCOS, exercise has attracted increasing interest as a non-pharmacological intervention capable of targeting the underlying pathophysiological mechanisms of the syndrome rather than merely alleviating its clinical manifestations. [19]

One of the principal molecular adaptations induced by exercise involves activation of nutrient-sensing pathways responsible for maintaining energy homeostasis. SIRT1 functions in close association with adenosine monophosphate-activated protein kinase (AMPK), and this interaction plays a pivotal role in the metabolic adaptations elicited by physical activity. Increased energy demand during exercise elevates intracellular NAD^+ availability, promoting SIRT1 activation and subsequent deacetylation of downstream metabolic regulators. Through this mechanism, exercise enhances mitochondrial biogenesis, improves oxidative metabolism, and facilitates efficient utilization of energy substrates, thereby promoting systemic metabolic flexibility. [20]

The interdependence between AMPK and SIRT1 provides an important physiological basis for the beneficial effects of exercise in disorders characterized by insulin resistance. Experimental evidence indicates that these signaling pathways cooperate to regulate the activity of PGC-1α, a master controller of mitochondrial function and oxidative metabolism. Activation of the AMPK–SIRT1–PGC-1α axis during exercise contributes to improved glucose uptake, enhanced fatty acid oxidation, and restoration of metabolic balance. Since insulin resistance represents a major contributor to hyperandrogenism and ovarian dysfunction in PCOS, exercise-induced activation of this pathway may indirectly ameliorate reproductive abnormalities through correction of metabolic disturbances. [21]

In addition to improving insulin sensitivity, exercise exerts anti-inflammatory effects that may be particularly relevant in PCOS. Clinical investigations have shown that regular aerobic exercise reduces circulating inflammatory markers and attenuates the chronic low-grade inflammatory state associated with the syndrome. Since inflammatory mediators adversely affect insulin signaling and ovarian function, their reduction may contribute to improvements in follicular dynamics and endocrine status. Although direct evidence linking exercise-induced reductions in inflammation to ovarian SIRT1 expression in experimental PCOS remains limited, the anti-inflammatory actions of exercise may support restoration of SIRT1-dependent protective pathways within ovarian tissues. [22]

Despite the growing recognition of exercise as a modulator of SIRT1 activity, studies specifically evaluating exercise-induced changes in SIRT1 expression in experimental PCOS models remain relatively scarce. Nevertheless, the available evidence supports the hypothesis that exercise improves ovarian and metabolic outcomes through mechanisms involving enhanced mitochondrial function, reduced oxidative stress, improved insulin responsiveness, and activation of nutrient-sensing networks in which SIRT1 plays a central role. Future experimental investigations integrating molecular analyses with reproductive and metabolic phenotyping are required to clarify the precise contribution of SIRT1 to exercise-mediated benefits in PCOS. [23]

Effects of Caloric Restriction on SIRT1 Expression in Experimental PCOS

Caloric restriction (CR), defined as a reduction in energy intake without causing malnutrition, has emerged as a powerful intervention capable of improving metabolic health and enhancing cellular stress resistance. Through its effects on body weight regulation, insulin sensitivity, lipid metabolism, and inflammatory status, CR has attracted considerable attention as a potential therapeutic strategy for

metabolic disorders. Since metabolic dysfunction is a major component of PCOS pathophysiology, dietary interventions that optimize energy balance may provide benefits extending beyond weight reduction alone. In this context, CR represents a physiologically relevant approach for modifying the ovarian–metabolic abnormalities characteristic of PCOS. [24]

The biological effects of caloric restriction are mediated, in part, through activation of SIRT1-dependent signaling pathways. Reduced nutrient availability increases the intracellular NAD^+/NADH ratio, thereby enhancing SIRT1 activity and promoting metabolic adaptation. Activated SIRT1 modulates several downstream targets involved in glucose homeostasis, mitochondrial biogenesis, oxidative stress resistance, and cellular survival. Consequently, SIRT1 has been proposed as one of the principal molecular mediators linking energy restriction with improved metabolic function and increased resilience to physiological stress. [25]

Experimental studies investigating caloric restriction have demonstrated favorable effects on longevity and protection against age-related metabolic deterioration, supporting the concept that nutrient-sensing pathways play a fundamental role in maintaining organismal homeostasis. Given that oxidative stress, chronic inflammation, and insulin resistance contribute significantly to PCOS progression, activation of SIRT1 through caloric restriction may theoretically attenuate these pathological processes. Improvements in insulin responsiveness could reduce ovarian androgen synthesis, whereas enhancement of antioxidant defenses may preserve granulosa cell function and follicular integrity. Although these mechanisms remain incompletely characterized in experimental PCOS models, they provide a compelling physiological rationale for further investigation. [26]

Despite the promising metabolic effects of caloric restriction, direct evidence evaluating its influence on ovarian SIRT1 expression in experimentally induced PCOS remains limited. Variability in dietary protocols, duration of interventions, and animal models complicates comparisons across studies and hinders definitive conclusions regarding optimal implementation strategies. Future experimental studies should integrate molecular analyses of ovarian SIRT1 signaling with assessments of reproductive function, insulin sensitivity, inflammatory status, and oxidative stress. Such investigations may clarify whether caloric restriction exerts direct ovarian actions or primarily improves reproductive outcomes through correction of systemic metabolic disturbances. [27]

Mechanistic Links Between Lifestyle Interventions and SIRT1 Signaling in Experimental PCOS

The metabolic adaptations induced by exercise training and caloric restriction converge on several nutrient-sensing pathways, among which the AMPK–SIRT1 axis has received particular attention. Under conditions of increased energy demand or reduced energy availability, activation of AMPK enhances intracellular NAD^+ biosynthesis, thereby facilitating SIRT1 activation. In turn, SIRT1 deacetylates multiple downstream targets involved in mitochondrial biogenesis, substrate utilization, and cellular stress resistance. This bidirectional interaction enables coordinated regulation of energy metabolism and may represent a central mechanism through which lifestyle interventions improve both systemic metabolism and ovarian function in PCOS. [28]

Improvement in insulin sensitivity is another important mechanism linking lifestyle interventions with SIRT1-mediated benefits. Since hyperinsulinemia contributes to excessive ovarian androgen production and disrupts normal folliculogenesis, restoration of insulin responsiveness may attenuate the reproductive consequences of metabolic dysfunction. Through modulation of genes involved in glucose uptake, fatty acid oxidation, and mitochondrial activity, SIRT1 promotes metabolic flexibility and reduces the burden of insulin resistance. Consequently, activation of SIRT1 signaling may interrupt the vicious cycle connecting hyperinsulinemia, hyperandrogenism, and ovarian dysfunction in PCOS. [29]

Oxidative stress and chronic low-grade inflammation are increasingly recognized as important contributors to the pathogenesis of PCOS, and both processes are influenced by SIRT1 activity. Experimental evidence suggests that SIRT1 enhances antioxidant defenses while suppressing pro-inflammatory pathways involved in tissue injury and metabolic deterioration. Lifestyle interventions capable of activating SIRT1 may therefore improve the ovarian microenvironment by reducing reactive

oxygen species accumulation and limiting inflammatory signaling. Such adaptations could preserve granulosa cell function, improve oocyte competence, and support normal follicular development in the setting of PCOS. [30]

Collectively, the available evidence supports the concept that SIRT1 functions as a molecular integrator linking nutritional status, physical activity, metabolic homeostasis, and reproductive physiology. Nevertheless, the relative contribution of direct ovarian effects versus secondary improvements resulting from enhanced systemic metabolism remains unclear. Future experimental studies should investigate tissue-specific changes in SIRT1 expression alongside comprehensive reproductive and metabolic assessments to determine the precise mechanisms through which exercise training and caloric restriction influence ovarian outcomes in PCOS. Elucidation of these pathways may facilitate the development of targeted lifestyle strategies aimed at maximizing both metabolic and reproductive benefits. [31]

Limitations and Future Perspectives

Despite increasing interest in the role of SIRT1 in PCOS, the available evidence remains limited by several methodological considerations. Most experimental studies have utilized different PCOS induction protocols, including androgen administration and aromatase inhibition, each reproducing specific aspects of the syndrome rather than its entire clinical spectrum. Furthermore, considerable heterogeneity exists regarding the type, intensity, and duration of exercise interventions as well as the degree and composition of caloric restriction employed across studies. These variations hinder direct comparisons and complicate the interpretation of findings related to SIRT1 expression and activity. Standardized experimental approaches incorporating comprehensive reproductive, metabolic, and molecular assessments are therefore required to strengthen the current evidence base. [32]

Another important limitation is the scarcity of studies directly evaluating ovarian SIRT1 expression in response to lifestyle interventions in experimentally induced PCOS. Much of the current understanding is extrapolated from investigations conducted in aging research, metabolic diseases, or non-PCOS reproductive models. Future studies should determine whether exercise training and caloric restriction exert tissue-specific effects on ovarian SIRT1 signaling or whether improvements in reproductive outcomes primarily result from enhanced systemic metabolism. Integrating assessments of insulin sensitivity, inflammatory markers, oxidative stress, mitochondrial function, and follicular dynamics with analyses of SIRT1-related pathways may provide a more comprehensive understanding of the mechanisms involved. Such insights may facilitate the development of individualized lifestyle strategies targeting both metabolic and reproductive dysfunction in PCOS. [33]

Conclusion

SIRT1 has emerged as a promising molecular link connecting metabolic homeostasis with ovarian function in PCOS. Experimental evidence suggests that disturbances in SIRT1 signaling may contribute to insulin resistance, oxidative stress, inflammatory activation, and granulosa cell dysfunction, thereby promoting the ovarian–metabolic abnormalities characteristic of the syndrome. Lifestyle interventions, particularly exercise training and caloric restriction, may ameliorate these disturbances through mechanisms involving activation of nutrient-sensing pathways, enhancement of mitochondrial function, and improvement of systemic metabolic status. However, direct evidence regarding the effects of these interventions on ovarian SIRT1 expression in experimental PCOS remains limited. Further well-designed experimental studies are needed to clarify the mechanistic role of SIRT1 and determine whether modulation of this pathway can be exploited to optimize non-pharmacological management strategies for PCOS.

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