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ABNORMAL EXPRESSION OF MIRNA-21 AND OTHER MIRNAS INVOLVED IN POLYCYSTIC OVARY SYNDROME AND THE IMPLICATIONS FOR PUBLIC HEALTH ESPECIALLY IN LOW- AND MIDDLE-INCOME COUNTRIES

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ABSTRACT

Background: MicroRNAs are small non-coding RNA molecules crucial in regulating gene expression. In Polycystic Ovary Syndrome (PCOS), a common endocrine disorder in women of reproductive age, miRNA-21 and other miRNAshave been consistently reported as dysregulated, contributing to its pathophysiology. In PCOS, these are commonly altered (either raised or lowered) in ovarian cells and blood and this alteration can lead to the abnormal development of follicles, inflammation and hormone imbalance, which are major issues in PCOS. As a result, a potential biomarker for this condition that is associated with considerable morbidity. The development of potential biomarkers is important in developing countries such as Pakistan with high prevalence rates of up to 52% in Pakistani women of reproductive age as well as high co-payments impacting on seeking care. This is a key public health consideration in developing countries where multiple visits may be needed before a diagnosis of PCOS is made. Consequently, there is a need to consolidate current evidence to provide future direction. **Materials and Method**: A systematic review including studies showing that miRNA-21 and other miRNAs are involved in dysregulation in women with PCOS, including studies analyzing ovarian tissue and blood samples, and providing public health guidance building on co-author experience. **Results**:52 studies were involved in the review. The dysregulation of miRNA-21 in PCOS is associated with altered hormonal levels, particularly elevated androgens, and insulin resistance. The over expression of miRNA-21 is believed to contribute to metabolic disturbances commonly observed in PCOS patients. Overall, miRNAs have emerged as potential biomarkers for diagnosing PCOS due to their significant role in associate metabolic and hormonal alterations. **Conclusion**: The findings from this study provide valuable insights into the mechanisms of PCOS and the potential for miRNA-21as a biomarker and therapeutic target. This is crucial in developing countries such as Pakistan to address the challenges associated with diagnosing and managing PCOS. Other approaches are also needed to improve the mental health, and reduce morbidity, in this vulnerable group.

Key words: Polycystic Ovary Syndrome, MicroRNA-21, Biomarkers, Non-Invasive Diagnosis, Pakistan, Public Health.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a highly prevalent endocrine condition that affects women in their reproductive years[1-3]. It is a complex endocrine disorder typically affecting between 4 up to 20% of women of reproductive age globally depending on the diagnostic criteria[3-8]. However, prevalence rates vary by ethnicity with higher estimates in women who are black or of Middle-Eastern origin versus for instance Chinese women or white populations[6,9,10]. Published studies have also reported high prevalence rates up to 52% among Pakistani women of reproductive age versus appreciably lower rates among Western women[11,12]. Similar high prevalence rates have also been seen among Asian women from the Indian subcontinent living in the United Kingdom[13]. Increasing obesity also directly impacts on female reproductive health, particularly for conditions including PCOS[14].

PCOS is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology[1,5,15,16]. The etiology of PCOS is also multifactorial, involving genetic, environmental, and lifestyle factors[6,12,17]. However, the exact aetiology as well as the underlying mechanisms regarding the neuroendocrine and metabolic traits of PCOS are still unclear[4,6,18,19]. Currently, clinical diagnosis depends upon a number of factors. These include irregular menstrual cycles, excess facial hair growth along with acne, weight gain and infertility[4,5,9,20]. Alongside this, radiological assessments demonstrating multiple cysts in the ovaries[1,5,9]. These signs and symptoms are also seen in women in Pakistan with diagnosed PCOS, e.g. 80% are obese, 42% have trouble losing weight, between 49.2% and 71.8 % have irregular periods, between 53.8% to 67.3 % have acne and 50% have extreme hair loss[12,21].

However, before a diagnosis of PCOS can be made other causes of these clinical features need to be excluded[5]. These include hyperprolactinemia alongside potential tumours including ovarian or adrenal tumours[5,22]. As a result, a systematic approach towards diagnosis and treatment is important. This especially with the underlying mechanisms regarding the neuroendocrine and metabolic traits of PCOS still unclear alongside the exact aetiology[6,23,24]. The diagnostic criteria for PCOS have recently incorporated the measurement of Anti-Mullerian hormone (AMH) levels as an alternative to ultrasound[6,9,25,26]. In addition, peripherally generated 11-oxygenated androgens are also being seen as important predictors of metabolic risk[7]. However, a systematic approach to diagnosis and management is still normal practice.

Early diagnosis is important since PCOS has an appreciable impact on the health of women, including their mental health and quality of life, as well as considerable economic consequences[7,8,27-30]. Long term complications, incorporating long-term metabolic health consequences, include insulin resistance and type 2 diabetes, hypertension, coronary vascular disease, obstructive sleep apnea, anxiety and depression as well as infertility[5,14,15,31-35]. These complications are also seen among women with PCOS in Pakistan, where the symptoms of anxiety and depression are common, exacerbated by sexual dysfunction, which adversely affects their quality of life[11,21,36-39]. In addition, PCOS enhances the infertility rate among women in Pakistan, with rates as high as 38.5% reported[36,40,41].

As a result of potential morbidity issues, as well as current prevalence rates, the financial burden of PCOS can be considerable[3,42]. It has been estimated that the annual burden of PCOS in the UK is at least GB£237 million, enhanced by high prevalence rates of diabetes (26.5%) in this population[42]. Riestenberg et al. (2022) in the United States estimated that the total annual costs of PCOS, including the additional total healthcare-related

economic burden due to pregnancy-related and long-term morbidities, was $4.3 billion (2020 USD)[43]. More recently, Yadav et al. (2023) estimated that the direct annual healthcare costs for the most common mental health disorders in patients with PCOS in the USA, including anxiety, depression, and eating disorders, exceeded $4 billion (2021 USD)[44]. Taken together with their previous research, Yadav et al. (2023) believed overall that the healthcare-relatedeconomic burden of PCOS in the USA now exceeds $15 billion annually[44]. This takes into account the costs of diagnosis as well as the costs of complications, which includes PCOS-associated mental health, reproductive, vascular, and metabolic disorders[44]. Consequently, diagnosis and management of women with PCOS needs to improve to reduce the public health burden and associated costs.

In view of these current concerns, it is important to try and diagnose PCOS as early as possible, and treat effectively, especially in low- and middle-income countries (LMICs) where the burden of healthcare can be considerable with high patient co-payments[45-47]. This includes measures to reduce CVD risk including lifestyle changes and pharmacotherapy as well as medicines such as metformin to treat insulin resistance in PCOS patients[7,9,15,48-50]. Such measures are important in Pakistan with patients with untreated PCOS exhibiting high prevalence rates of hyperandrogenism (77.7%), diabetes (60.9%), infertility (33.2%), hypertension (19.8%), miscarriages (15.5%), high cholesterol levels (19.3%) and hyperandrogenism[21]. This is perhaps not surprising with high rates of obesity among women with PCOS in Pakistan[39]. Limited self-knowledge as well as issues of shyness can exacerbate the problem,creating public health pressures[39,41].

One area of growing interest in helping with diagnosis and management of PCOS is the role of microRNAs in its pathogenesis[18,51-53]. miRNAs are small, non-coding RNA molecules that regulate gene expression post-transcriptionally and are involved in numerous physiological and pathological processes, including metabolic and endocrine regulation[18,54-56]. miRNA-21, has garnered significant attention due to its broad regulatory roles and dysregulation in various diseases including PCOS[18,57,58]. miRNA-21 is also known to be involved in cell proliferation, apoptosis, and differentiation, and its dysregulation has been linked to inflammatory responses and metabolic disorders[59]. In PCOS, miRNA-21expression changes have been very much associated with the onset of insulin resistance, lipid metabolism disorders and hormonal homeostasis[60-63].

Previous studies have compared the expression of miRNA-21 in different tissues and biological fluids in women with PCOS[57,62]. It has been suggested that high circulation of miRNA-21 inserum can be proposed as good non-invasive biomarkers representing underlying metabolic and endocrine disorders[62,63]. In addition, a series of studies on profiling follicular fluid has shown specific miRNA-21 standards that regulate both the microenvironment and follicular progression in the ovaries[62,64-66]. These combined studies support the idea that the aberrant miRNA-21expression is not only the reflection of the systemic inflammation and metabolic maladjustment but also a key mediator in ovarian dysfunction in PCOS.

This is a systematic review that will summarize evidence on the distribution, expression patterns, and regulatory implications of miRNA-21 specifically and also other miRNAs that have been already reported in the PCOS women. The review aims to explain the role of altered miRNA-21 expression in leading to hormonal disequilibrium, insulin resistance and metabolic dysfunction in the presence of their upregulation or down-regulation in various biological settings[18,51,62,67-69]. By so doing, it builds on the previous studies to

bring about a modern and comprehensive insight into how miRNA-21 mediated pathways in PCOS occur, and may be used in future diagnostic and therapeutic innovations. This is very important in LMICs such as Pakistan which, as mentioned, have high prevalence rates of PCOS among women of reproductive age. Alongside this, concerns with affordability among patients needing to regularly seeking help from physicians as part of any lengthy diagnosis and management of PCOS. There are also issues of shyness and knowledge which also need addressing to address the health issues and concerns in this vulnerable population[41].

MATERIALS AND METHOD

Studies in this systematic review had to meet a number of criteria to be incorporated into the review. These included:

- Articles involving human subjects diagnosed with PCOS.
- Studies that investigated the expressions of miRNA-21 and other miRNAs involved in PCOS.
- Articles published in peer-reviewed journals.
- Studies providing clear data on the methods used to quantify miRNAs levels.
- Papers written in English with English recognized as the principal scientific language[70,71]

Exclusion criteria included any meta-analyses, editorials, case reports, animal studies, and studies with insufficient data.

The research question was established in order to investigate the difference in the expression of microRNAs in women with polycystic ovary syndrome (PCOS) and healthy controls. This study was aimed at discovering that miRNA-21sign up-regulated or down regulated in PCOS and how they may be involved in the diagnosis and pathophysiology of the disease.

We conducted a comprehensive search of electronic databases including PubMed, Scopus, Web of Science and Google Scholar using defined search terms (Table S1). The search strategy was developed to ensure maximum sensitivity and comprehensiveness. It combined both Medical Subject Headings and free-text terms related to “microRNAs, miRNA-21” and “polycystic ovary syndrome”. The search was conducted across databases including PubMed, Scopus, and Web of Science from January 2014 to April 2024 and the reference lists of relevant studies were also screened to identify additional eligible publications.

The search was limited to articles published from January 2014 to April 2024 as we wanted to include only the latest information. The review has considered the latest ten years as it was chosen due to the rapid development of miRNA-21research and capture up-to-date evidence. The reference lists of all included articles were also manually searched to identify any further relevant studies that may have been missed to enhance the robustness of the findings. The last search was conducted on April 30, 2024.

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency and reproducibility[44,72-77].

A reference management software was used to remove duplicates of all search results. Selection of the studies was done in two phases. (1) title and abstract first and (2) subsequently full-text review by three reviewers each for pertinent papers. Differences were sorted out by consensus or the intervention of a third reviewer. Data mining was also conducted twice in a standardized Excel sheet, whereby, details like the name of the author, the year of publication, country or region, study design, sample size, miRNAs that are being studied, method of detection and major findings were collected. Three reviewers were used to evaluate the quality of the studies and a consensus was reached to eliminate bias.

The papers in the Tables in the Results Section have been documented in year order starting with the earliest papers. In this way, demonstrate any progression with miRNA-21as a possible marker. If there is more than one paper published in any year, the authors will be cited in alphabetic order.

Finally, the health policy and educational guidance to improve the management of women with PCOS will be based on the considerable experience of some of the co-authors working for many years with health authority personnel and their advisers across multiple disease areas, countries and continents including LMICs[78-86].

RESULTS

Our initial search yielded 4670 results. After removing duplicates and screening titles and abstracts, 4619 studies were subsequently excluded for not meeting the inclusion criteria. Figure 1 depicts the Prisma flow chart of our systematic literature search. We subsequently retrieved and examined the full texts of 52 studies for detailed assessment (Figure 1).

The studies included in this review were conducted across various geographical regions, predominantly though in Europe, Asia, and North America, and encompassed a range of study designs including cross-sectional, case-control and cohort studies. The sample sizes varied appreciably between the studies, with participant numbers ranging from 20 to over 300 women diagnosed with PCOS. Diagnostic criteria for PCOS included the Rotterdam criteria, NIH criteria, and AE-PCOS Society criteria.

Figure 1: PRISMA flow diagram of the systematic literature search.

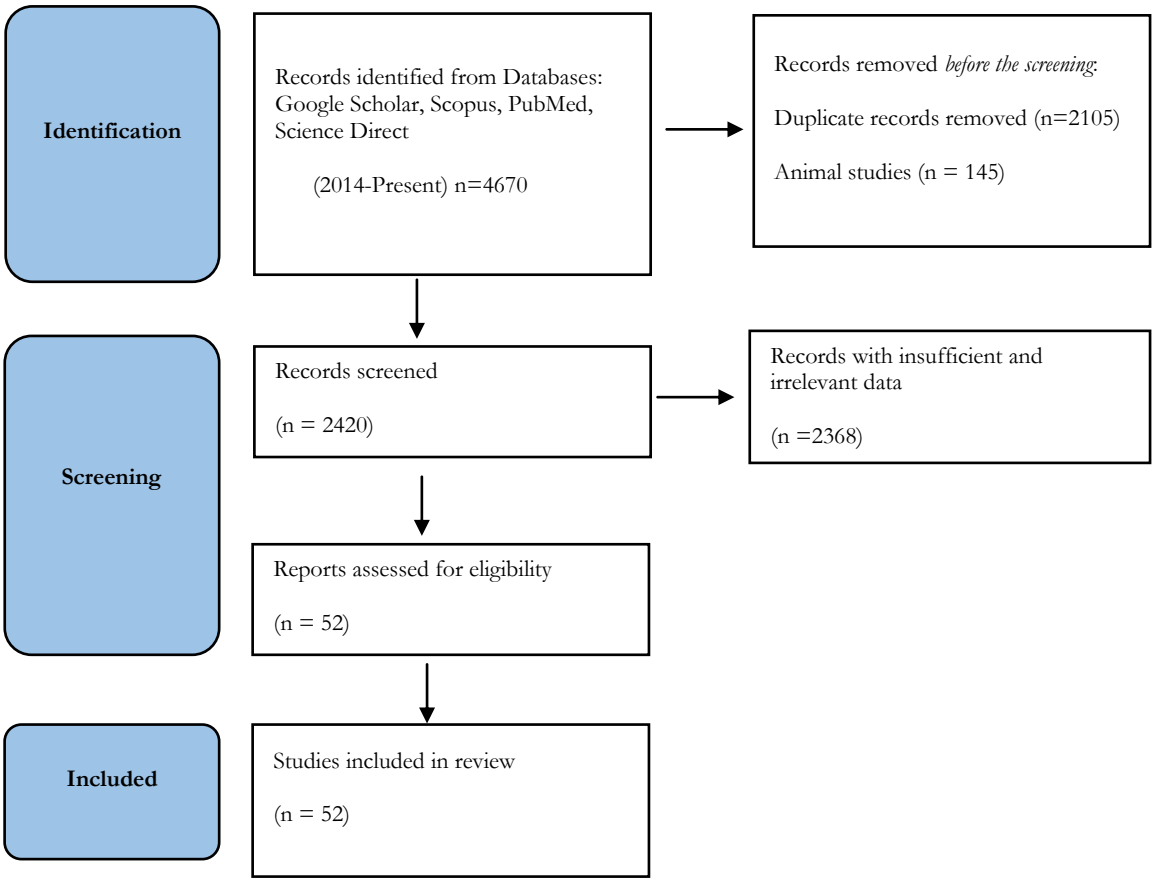

Table 1 provides a summary of the expression levels ofmiRNA-21 in the included studies.

Table 1: Summary of miRNA-21 Expression Levels in PCOS Patients

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (up regulated or down regulated)	Detected in Cells/Tissues
Jiang et al., 2015 (57)	Retrospective case-control	60 (30 PCOS, 30 control)	23.8-29.4 (PCOS), 24.5-31.3 (control)	Up regulated: miR-21	Serum
Naji et al., 2017 (99)	Case-control study	*N* = 66 (19 with normoandrogenic PCOS, 22 with hyperandrogenic PCOS, 25 controls)	28.89 ± 1.07/ 28.24 ± 0.82	Down regulated in follicular fluid: miR-21	Follicular fluid, granulosa cells
Dhaded & Dabshetty, 2018 (100)	Case-control	235 (110 PCOS, 125 control)	Not specified	Up regulated: miR-21	Serum
Sørensen et al., 2019 (101)	Case-control study	*N* = 62 42 PCOS patients and 20 Controls	27.0 ± 7.5/ 27.0 ± 6.3	Down regulated: miR-21-3p	Follicular fluid
De Nardo Maffazioli et al., 2022 (102)	Cross-sectional study	N= 52 (36 PCOS and 16 controls)	Not specified	Upregulated: *miR-21-5p*	Serum
Rashid et al, 2024 (62)	Systematic Review	200 (100 PCOS, 100 control)	21-30(PCOS), 24.5-31.3 (control)	Upregulated: miR-21	Granulosa cells, blood, follicular fluid
Naredi et al., 2024 (90)	Case-control study	Patients: 295		Upregulated: miR-21	Serum
Sabry et al., 2024 (92)	Case-control study	Not specified	25-40	Upregulated: miR-21	Human granulosa cells

Several studies identified and validated target genes of miRNA-21involved in metabolic and endocrine pathways. These genes include PTEN, RECK, and PDCD4, which are implicated in cell proliferation, apoptosis, and insulin signaling. This shows the miRNA-21identified in the reviewed studies and their expression in PCOS.Table 2 lists the other MiRNA identified in the reviewed studies and their expression in PCOS.

Table 2 : Summary of Other MiRNA Involved in PCOS

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (upregulated or downregulated)	Detected in Cells/Tissues
Long et al., 2014 (103)	Case-control study	N = 136 (68 with PCOS, 68 controls)	26.6 ± 2.8/ 27.9 ± 3.4	Upregulated: miR-222, 146a and 30c	Serum
Roth et al., 2014 (104)	Case-control study	Not specified	33.1 ± 4.4/ 27.1 ± 3.6	Upregulated: miR-32, 34c, 135a, 18b, and 9	Follicular fluid

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (upregulated or downregulated)	Detected in Cells/Tissues
Wu et al., 2014 (104)	Case-control study	*N* = 31 16 women with PCOS (8 with and 8 without IR) and 15 non-PCOS (9 with and 6 without IR).	32.33 ± 5.03/ 25.49 ± 5.56	Upregulated: miR-93, and 25	Adipose tissue
Ding et al., 2015 (63)	Case-control study	Screening cohort (N = 18, 9 PCOS, 9 controls) Verification cohort (N = 18, 9 PCOS, 9 controls)	27.9 ± 4.3/ 28.7 ± 5.2	Upregulated: miR-5706, let-7i-3 pm, 4463, 3665 and 638 Downregulated: miR-124-3p, 128, 29a-3p and let-7c	Serum
Jiang et al., 2015 (106)	Case control	24 (16 PCOS, 8 control)	29.69±2.39/31.75 ±4.40	Upregulated miR93, 107	Granulosa cell
Lin et al., 2015 (107)	Case-control	N= 18 (10 PCOS, 8 control	28.80±3.97/32.00 ±2.16	miR-19b, 92a, 92b,141, and 200a Downregulated	Ovarian Theca internal tissue
Liu et al., 2015 (108)	Case control Study	N=20 (10 PCOS, 10 control	27.4 ± 2.6/ 29.4 ± 3.0	Upregulated: miR-513a-3p, 508-3p, 513b, 514, 509-5p, 513c, 144, 510, 509-3p and 508-5p Down regulated: miR-151-3p, 720, 615-3p, 127-3p, 455-3p, 342-3p and 654-3p	Cumulus cells
Sathyapalan et al., 2015 (109)	Case-control study	*N* = 49 (25 with PCOS, 24 controls)	32.1 ± 9.0/ 32.2 ± 7.7	Up regulated: miR-93 and 223	Plasma
Shi et al., 2015 (110)	Case-control study	*N* = 48 (24 with PCOS, 24 controls)	28.3 ± 3.3/ 28.5 ± 3.6	Down regulated: miR-483–5p and 486–5p	Cumulus cells
Song et al., 2015 (111)	Case-control study	*N* = 134 (67 with PCOS, 67 controls)	26.7 ± 2.7/ 27.6 ± 3.3	Down regulated: miR-592,124-3p, 128, 29-3p, 16, 106b, 19a, 24, 186, let-7c and 1228	Serum
Xu et al., 2015 (112)	Case-control study	*N* = 41 (21 with PCOS, 20 controls)	N/A	Upregulated: miR-423-3p, 3651, 3653, 151b, 1273 g-3p, 590-5p, 3648, 7845-5p, 27a-5p, 1275, 483-3p, 7-5p, 483-5p, 10a-5p,	Cumulus granulosa cells

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (upregulated or downregulated)	Detected in Cells/Tissues
				184, 619-5p, 513b-5p, 1307-5p, 4516, 1307-3p, 514b-5p Down regulated: miR-3529-3p, 7974, 3065-5p, 214-3p, 200a-3p, 203a, 4732-5p, 423-5p, 3184-5p, 548n, 221-3p, 149-5p, 1298-5p, 193a-3p, 365a-3p, 219a-1-3p, 550b-2-5p, 144-5p, 660-5p, 548e-3p, 652-3p, 222-3p,506-5p, 193a-5p, 210-5p, 365b-5p, 330-3p, 223-3p, 186-5p, 185-5p, 92b-3p, 199b-3p, 766-5p, 15b-3p, 339-5p, 3960, 766-3p, let-7a-3p	
Huang et al., 2016 (113)	Case-control study	N = 36 (18 with PCOS, 18 controls)	32.6 ± 3.1/ 34.6 ± 2.2	Upregulated: miR-135b-5p, 152, 193a-3p, 194-5p, 196a-5p, 200b-3p, 423-3p, 454-3p, 455-5p, 4659a-3p, 509–3-5p, 509-3p, 513b-5p, 652-5p, 95, 1273e	Cumulus cells
Scalici et al., 2016 (114)	Case-control study	*N* = 121 (30 with PCOS, 91 controls)	Mean age for cohort 33.7 ± 4.5	Upregulated: miR-30a Downregulated: miR-140 and let-7b	Follicular fluid
Song et al., 2016 (115)	Case-control study	*N* = 42 (21 with PCOS, 21 controls) with preceded pilot study (*N* = 17)	23 ± 4/ 24 ± 6	Downregulated: miR-4522, 324-3p, and 6767-5p	Serum
Sorensen et al., 2016 (116)	Case-control study	*N* = 70 (49 PCOS women and 21 healthy matched women)	28.1 ± 4.3/ 27.8 ± 3.8	Upregulated: miR-518f-3p, Downregulated: miR-24-3p, -29a, -151-3p, and -574-3p	Follicular fluid

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (upregulated or downregulated)	Detected in Cells/Tissues
Xiang et al., 2016 (117)	Case-control study	*N* = 40 (20 with PCOS, 20 controls)	27.3 ± 2.5/ 28.2 ± 3.7	Downregulated: miR-483	Ovarian cortex
Cai et al., 2017 (118)	Case-control study	N = 50 (25 married women with PCOS and 25 controls	N/A	Downregulated: miR-145	Granulosa cells
Eisenberg et al., 2017 (119)	Case-Control	N = 40 (7 normally ovulating, 15 normally ovulating with pure male infertility factor, and 18 with PCOS)	26.9 ± 4.3/ 26.8 ± 4.7	Upregulated: miR-200b and 429	Serum
Hosseini et al., 2017 (120)	Case-control study	N = 410 (205 with PCOS, 205 controls)	31.2 ± 5.5/ 28.5 ± 5.0	Upregulated: miR-146a and 222	Plasma
Xiong et al., 2017 (121)	Case-control study	*N* = 48 (18 with PCOS, 30 controls)	N/A	Downregulated: miR-23a and 23b	Serum
Zhang et al., 2017 (122)	Case-control study	N = 33 (21 with PCOS, 12 controls)	Not specified	Downregulated: miR-320a	Cumulus cells
Ebrahimi et al., 2018 (123)	Case-control study	N = 372 (180 with PCOS, 192 controls)	26.8 ± 5.5/ 27.0 ± 4.38	Upregulated: miR-146a	Whole Blood
He et al., 2018 (124)	Case-control study	N = 123 (62 with PCOS, 61 controls)	28.27 ± 3.10/ 28.71 ± 2.46	Downregulated: miR-141 and 200c	Granulosa cells
Mao et al., 2018 (125)	Case-control study	*N* = 69 (43 with PCOS, 26 controls)	30.2 ± 2.8/ 31.1 ± 2.1	Downregulated: miR-126-5p and 29a-5p	Granulosa cells
Murri et al., 2018 (126)	Case-control study	*N* = 35 (12 with PCOS, 11 healthy women, 12 men)	27 ± 4/ 28 ± 3	Upregulated: miR-34c-5p and 548d-3p Downregulated: miR-26a-5p, 30c-5p, 107 and 199a-3p	Serum
Naji et al., 2018 (127)	Case-control study	*N* = 41 (20 with PCOS, 21 controls)	29.25 ± 0.84/ 28.42 ± 0.91	Upregulated in follicular fluid: miR-182 Downregulated in granulosa-lutein cells: miR-145 and 182	Serum, granulosa-lutein cells, follicular fluid
Wang et al., 2018 (128)	Case-control study	*N* = 30 17 PCOS patients and 13 controls	28.7 ± 0.7/ 30.0 ± 0.7	Upregulated: miR-27a-3p	Granulosa cells
Xue et al., 2018 (68)	Case-control study	*N* = 6 (3 with PCOS, 3 controls)	N/A	Upregulated: miR-200a-3p, 10b-3p, 200b-3p,29c-3p, 99a-3p and 125a-5p Downregulated:	Follicular fluid

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (upregulated or downregulated)	Detected in Cells/Tissues
				miR-105-3p	
Yao et al., 2018 (129)	Case-control study	N = 106 (55 with PCOS, 51 controls)	28.13 ± 0.41/ 27.37 ± 0.46	Downregulated: miR-335-5p	Follicular fluid
Zhang et al., 2018 (130)	Case control study	N= 40 (20 PCOS, 20 control)	Not specified	Upregulated: miR-873-5p	Follicular fluid
Geng et al., 2019 (131)	Case-control study	N=30 (15 married women with PCOS and 15 controls)	27.23 ± 1.83/ 28.53 ± 1.85	Upregulated: miR-99a	Granulosa cells
Hou et al., 2019 (132)	Case-control study	N = 28 (15 with PCOS, 13 controls)	29.60 ± 0.66/ 29.66 ± 0.82	Upregulated: miR-3188 and 3135b	Granulosa cells
Li et al., 2019 (56)	Case control study	N = 78 (46 with PCOS, 32 controls)	29.21 ± 4.78/ 29.43 ± 3.82	Upregulated: miR-33b and 142 Downregulated: miR-423	Granulosa cells
Luo et al., 2019 (133)	Case-control study	*N* = 12 (4 with POR, 4 with PCOS, 4 controls)	PCOS (27.00 ± 3.26) POR (37.00 ± 3.16) Controls (29.00 ± 3.22)	Upregulated: miR-23a	Granulosa cells
McAllister et al., 2019 (134)	Case-control study	*N* = 14 (7 with PCOS, 7 controls)	Non specified	Upregulated: miR-100-5p, 99b-5p, 1271-5p, 409-5p, 744, 410-3p, 127-3p, 654-5p, 494-3p, 1301-3p, 502-3p, 501-3p and 1293 Downregulated: miR-125a-3p,148b-5p, 195-5p,130b-3p and 4542a-5p	Ovarian theca cells
Rashad et al., 2019 (135)	Case-control study	*N* = 100 (60 with PCOS, 40 controls)	N/A	Downregulated: miR-320	Serum
Song et al., 2019 (136)	Case-control study	*N* = 83 (63 with PCOS, 20 controls)	28.21 ± 2.78/ 27.43 ± 3.62	Upregulated: miR-186 and 135a	Granulosa cells
Wang et al., 2019 (137)	Case-control study	*N* = 45 24 PCOS patients and 21 controls	28.7 ± 0.8/ 29.6 ± 1.0	Upregulated: miR-3188 and 3135b	Granulosa cells
Butler et al., 2020 (138)	Prospective pilot study	48 (24 PCOS, 24 control)	Not specified	miR-1260a, miR-18b-5p, miR-424-5p, miR let-7b-3p upregulated	Blood

Authors and Year	Study Type	Sample Size	Age (years)	Main Results (upregulated or downregulated)	Detected in Cells/Tissues
Nanda et al., 2020 (139)	Case-control study	*N* = 40 (20 with PCOS, 20 controls)	28.35 ± 7.45/ 25.15 ± 4.12	Upregulated: miR-122, 194, and 193b Downregulated: miR-199b-5p	Serum
Soyman et al., 2022 (140)	Case-Control	N= 100 (50 PCOS, 50 control)	Not specified|	miR-132, miR-146a, and miR-222 downregulated	Blood samples
Naseri et al., 2023 (141)	Case-control study	N=50 (25 PCOS, 25 Healthy)	28.08±4.40/28.72 5.38	Downregulated: miR-103	Serum
Udesen et al., 2023 (142)	Follow up study	N= 55 (46 PCOS and 9 control)	Not specified	Women with PCOS; miR-103-3p, miR-139-5p, miR-28-3p, and miR-376a-3p, which were decreased in PCOS. After follow-up, miR-28-3p, miR-139-5p, and miR-376a-3p increased in PCOS women to the levels observed in healthy controls	Serum

The studies reviewed have all indicated that there were significant correlations between microRNA-21 (miRNA-21) and several hormonal and metabolic parameters in patients with polycystic ovary syndrome (PCOS). A shift in miRNA-21 expression patterns was also mostly related to hyperandrogenism, insulin resistance, and dyslipidemia, suggesting that they might be involved in the metabolic dysfunctions associated with PCOS. Moreover, some studies have identified the connections between particular miRNA-21 and markers of inflammation, which serves as arguments in favor of the hypothesis that miRNA-21 may be the cause of the chronic inflammation of the low grade, which is a hallmark of PCOS. Together, these results are indicative of a potential integrated role of dysregulated miRNA-21expression in the pathophysiology of PCOS in affecting metabolic, endocrine, and inflammatory pathways[87].

A number of these studies have observed circulating miRNA-21as having the potential of being the non-invasive biomarkers of early detection, diagnosis, and monitoring of PCOS due to its stability in body fluids and reflecting the underlying molecular changes associated with the disease[63,80]. Its expression levels in circulating blood samples (serum and plasma) showed significant differences between PCOS patients and healthy controls, indicating its utility in diagnosing and monitoring the syndrome.

DISCUSSION

We believe our updated systematic review highlights the significant role of miRNA-21in the pathophysiology of PCOS, with our findings consistent with other previous studies[18,51,62,88,89]. For instance, Naredi et al. (2024) reported that miRNA-21isdifferentially expressed in the serum of PCOS patients, correlating with insulin resistance and hyperandrogenism[90]. Alongside this, it was identified that miRNA-21acts as a potential biomarker due to its elevated levels in the blood of women with PCOS, aligning with our findings of its diagnostic potential[90,91].

The upregulation of miRNA-21 was observed in various tissues and bodily fluids of women with PCOS again suggests its involvement in the syndrome's complex metabolic and endocrine disruptors[92]. miRNA-21 appears to target key genes involved in insulin signaling, cell proliferation, and apoptosis, contributing to the characteristic features of PCOS such as insulin resistance, hyperandrogenism, and chronic inflammation[2,53]. The dysregulation of miRNA-21 in PCOS opens avenues for their potential application in clinical settings[91,93]. As a non-invasive biomarker, miRNA-21 could potentially enhance early diagnosis and monitoring of PCOS, offering a simpler alternative to current methods that often require imaging and extensive hormone profiling, which can be expensive for women in countries with high co-payment levels such as Pakistan[94-96]. This is particularly important in countries with high PCOS prevalence rates and concerns with accessing relevant health services if multiple visits are needed for diagnosis and management and where affordability is a critical barrier along with issues of shyness[41,97]. Issues of affordability are exacerbated if women remain undiagnosed even after multiple visits to healthcare providers, which is often the case. Such barriers can potentially be addressed by well proven non-invasive markers. Once available, these need to be a low or no cost to patients to help address this appreciable public health challenge.Clarifying the gene networks and molecular pathways that dysregulated miRNA-21 modulate may also open the door to the creation of innovative, focused therapeutic approaches meant to address the endocrine and metabolic abnormalities associated with PCOS and, eventually, lower morbidity from the condition[93].

However, in order to be able to routinely use miRNA-21further research must first confirm its effectiveness as a PCOS biomarker, building on the its identified role in this updatedreview. This should be followed by clinical trials in LMICs such as Pakistan to assess the effectiveness of non-invasive tests such as miRNA-21 in the early diagnosis of PCOS before any full roll-out. Such trials could be facilitated by Governments and donors interested with improving the management of this condition among this vulnerable population in LMICs.

In the meantime, there needs to be enhanced training of physicians and other healthcare professionals (HCPs) in LMICs including Pakistan to improve identification and management of PCOS given current concerns[8,10,39,97]. This starts in Universities with HCP training to address current challenges associated with a diagnosis of PCOS alongside issues of shyness, embarrassment and reluctance among women to seek help from HCPs for their condition[39,41]. This includes training future HCPs to sensitively question women about their problems given their possible shyness as well as potentially lack of knowledge when they eventually seek help from HCPs for their problems[41]. This is especially important in LMICs with many women undiagnosed even after visiting many HCPs[8,10]. Alongside this, HCPs should learn to routinely check women exhibiting signs of hyper-androgenism or menstrual irregularities for possible PCOS. Post qualification, Gynecologists and other HCPs could coordinate with

physiotherapists to ensure that potential PCOS patients are provided with strategies to address issues of weight and obesity to reduce potential future complications.
Universities could also educate non-healthcare students, especially female students, about PCOS. This includes its risk factors, causes, prognosis, symptoms and available treatment options. Conducting awareness campaigns within academic institutions could include promoting disease education, arranging talks, as well as distributing material with disease awareness signage. In addition, instigating social media campaigns within universities to appreciably enhance awareness and lower current stigma associated with PCOS[41].

Alongside this, the Government and others could instigate campaigns advising women of reproductive age with BMIs above 23 about the risks and dangers of PCOS including its long-term complications. In addition, provide more specialist centers for women given the long-term morbidity and costs associated with PCOS and concerns with the length of time often taken to diagnose PCOS[8,11,37-39,44]. In conjunction, there also needs to be more educational campaigns among women generally as we have seen that the instigation of private social networks in Saudi Arabia enhanced awareness of PCOS and improved subsequent care[98].

The current lack of personalized care and practical advice on lifestyle modifications also contributes to current dissatisfaction with healthcare services in Pakistan and other LMICs[8,97]. Patients can frequently encounter repetitive and ineffective medical advice, leading to frequent changes in HCPs and treatment approaches[1], as well as face obstructions regarding their access to HCPs in the first place when developing PCOS symptoms. As part of this, Governments, donors and others should fund research in LMICs such as Pakistan regarding optimal ways that HCPs can empower women with suspected or actual PCOS on knowledge about their condition as well as practical advice on lifestyle modifications. Enhanced training for qualified HCPs, coupled with awareness campaigns among both HCPs and women, could also help reduce cultural barriers and improve the timely diagnosis and management of PCOS. We will be monitoring this in the future.

We are aware of a number of limitations with our review. These include the relatively small number of studies included compared with the initial papers sourced. However, one of the strengths of this review is the comprehensive search strategy and rigorous selection process, which ensured the inclusion of relevant and high-quality studies. This though may have reduced the power of detection and relevance for this non-invasive biomarker. We also only included published papers from 2015 onwards for the reasons stated. Despite these limitations, we believe our findings are robust and provide direction for the future to key stakeholder groups especially in LMICs such as Pakistan.

CONCLUSION

In conclusion, we believe this systematic review underscores the pivotal role of miRNAs (specifically miRNA-21) in the pathogenesis of PCOS. The consistent upregulation of miRNA-21across various studies, and its association with key metabolic and endocrine parameters, highlights its potential as a diagnostic biomarker and a therapeutic target. However, further clinical research is needed to validate these findings. In addition, explore the clinical applications of miRNA-21 in PCOS management and how they could be used as diagnostic markers. This is especially important in LMICs such as Pakistan with high co-payment levels and issues with women accessing pertinent healthcare services in the first place.

CONFLICTS OF INTEREST

There is no conflict of interest.

FUNDING

This research received no external funding.

ETHICAL APPROVAL

There was no need for ethical approval as this review concentrated only on published papers. Consequently, there was no direct involvement of patients.

DATA AVAILABILITY STATEMENT

All papers contained within the Tables are referenced. However, additional information is available upon reasonable request from the corresponding author.

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SUPPLEMENTARY TABLES

Table S1 – Search Terms including Boolean Operators

Boolean Operator	Other Search Words
MiRNA-21**OR** miR	MiR-21(to narrow)
MiR-21 **AND** other MiRNA-21s	MiRNA-21s involve in PCOS (to expand)
MiR-21 **AND** PCOS	Expression analysis (to narrow)
	Human Studies (to narrow)
	Case-Control studies
	PCOS

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