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MicroRNAs as Biomarkers for Metabolic Disorders in Polycystic Ovary Syndrome (PCOS): A Review

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Polycystic ovary syndrome (PCOS) is associated with several mild metabolic disorders, including insulin resistance (IR), obesity, and dyslipidemia, as well as with some more severe ones, including type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease. Clinically, mild metabolic complications of PCOS such as IR or lipid metabolism disorders are the predictors of these more severe ones. So far, there is no reliable single marker that enables defining metabolic risk in patients with PCOS. Therefore, novel independent markers of metabolic disturbances are needed. Most reports have focused on microRNA (miRNA, miR) assessment in blood serum or granulosa cells, suggesting the high potential clinical utility of such management. The greatest number of studies focused on the association between miRNAs and IR, obesity, or lipid disorders, and some miRNAs were characteristics of all these processes concomitantly. The altered expression of miR-222, miR-223, miR-320, and miR-122 has been most commonly mentioned as the regulator of these metabolic distortions and seems to result from common regulation pathways of metabolic disturbances. In turn, the current literature lacked the miRNA which could be identified as a reliable marker of type 2 diabetes mellitus or NAFLD accompanying PCOS. Therefore, the main objective of future studies should be determining miRNA markers of these most serious metabolic complications. This article aims to review the role of microRNAs as biomarkers for metabolic disorders in PCOS.

Keywords: Insulin Resistance • Metabolic Diseases • MicroRNAs • Obesity • Polycystic Ovary Syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is a complex disorder characterized by hormonal and metabolic imbalances, which affects approximately 6% to 20% of women of reproductive age [1-3]. Mounting evidence suggests that environmental and genetic factors together with inflammation and microbiome alterations are of fundamental importance in the development of PCOS [4-7].

Among the wide range of dysfunctions and symptoms, affected women most frequently display hirsutism, acne, hyperandrogenemia, oligo- or amenorrhea, infertility, polycystic morphology of the ovaries, and insulin resistance (IR) [8,9]. Some of the above-mentioned symptoms were included in the revised Rotterdam criteria, which allow for diagnosing PCOS with a high degree of certainty after excluding other possible causes. According to the criteria, for PCOS diagnosis the patients must present at least 2 of the following symptoms: clinical or biochemical hyperandrogenism, chronic oligo- or an-ovulation, and polycystic ovarian morphology, or elevated levels of anti-Müllerin hormone (AMH) [10]. Nevertheless, despite diagnostic guidelines, years of research on the etiology of PCOS have revealed that even the diagnostic criteria insufficiently cover the complexity of biological alterations accompanying the disease [11].

These endocrine and metabolic disorders underlying PCOS form a network of interacting connections that further entail metabolic complications of this condition [12]. Hyperandrogenemia, which is the flagship biochemical disorder characteristic for patients suffering from PCOS, predisposes to disruption in insulin metabolism, leading to IR and hyperinsulinemia [13]. Further, all these disturbances substantially contribute to the occurrence of metabolic syndrome (MetS) components, including impaired glucose metabolism, as well as obesity, hypertension, and lipid metabolism disruption [14,15]. Accumulating data suggest that MetS fosters the development of type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD), and other related metabolic disorders [16-18]. Such links between metabolic complications and PCOS are directly reflected in statistics reporting a significantly higher incidence of metabolic disorders in patients with PCOS in comparison to healthy women [19].

In response to this phenomenon, guidelines elaborated by the European Society of Human Reproduction and Embryology (ESHRE) [10] and the American College of Obstetricians and Gynecologists (ACOG) [20] are consistent with the urgency of screening for cardiovascular disease, glucose metabolism disorders, and type 2 diabetes mellitus in patients with PCOS to avoid the development of more severe forms of these complications. Although the recommendations are generally not entirely in agreement, the screening schemes regarding metabolic risk share many similarities. Firstly, the screening tools, aimed to predict these disorders, are limited to the clinical features, including body mass index (BMI) and blood pressure, and the utility of some laboratory tests, including fasting glucose, cholesterol, lipoproteins, and triglycerides. Secondly, the recommended screening methods do not allow for identifying the cohort at risk of developing IR, the individual components of MetS, or NAFLD. Thus, the recommendations assume that the occurrence of some metabolic discrepancies will be a predictor of the occurrence of others more complex. Since it implies the initial presence of some pathological process, risk cannot be estimated in patients who have not yet developed any metabolic pathologies [10,20].

Many recent studies have investigated clinical features or metabolic markers for estimation of metabolic risk [21-23]. In addition, some authors have also proposed other indicators of metabolic abnormalities in patients with PCOS, such as oxidative stress [24-26] or inflammatory biomarkers [27,28]. Nevertheless, as the studies were most often the only ones to investigate the effectiveness of these markers, these results are difficult to interpret and should be further validated [24-28].

During the last decade, the role of microRNA (miRNA, miR) in PCOS has been the subject of extensive scientific research [29]. One of the most novel reviews concerning this issue has emphasized the crucial role of miRNAs in regulating pivotal pathways involved in the pathogenesis of PCOS, and proposed the utility of miRNAs as therapeutic targets [30]. According to the current literature, miRNAs are also molecules associated with metabolic disorders, including IR, MetS, and NAFLD in the normal population [31-33]. Therefore, this article aims to review the role of microRNAs as biomarkers for metabolic disorders in PCOS.

miRNAs in Insulin Resistance (IR)

IR is a condition involving decreased sensitivity of an organism's tissues to insulin [34]. In addition to being one of the central features of PCOS, IR has been also identified as a risk factor predisposing to numerous PCOS complications such as MetS, NAFLD, or type 2 diabetes mellitus [35]. Moreover, the most recent research suggests that IR is a risk factor for poor in vitro fertilization (IVF) outcomes [36]. Although have tools to diagnose IR, including Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), or insulin resistance index (IRI), it has been shown that available markers have limitations and novel ones are needed [37-39].

Among all metabolic disorders associated with PCOS for which links with miRNA expression have been evaluated, IR was most extensively analyzed (**Table 1**). Numerous studies have

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Table 1. Associations between dysregulated microRNAs (miRNAs) and insulin resistance (IR) in patients with polycystic ovary syndrome (PCOS).

Authors	Year	Collected material	Upregulated miRNA	Downregulated miRNA
Chen et al [40]	2013	Adipose tissue	miR-223; miR-133	–
Murri et al [41]	2018	Serum	miR-197-3p; miR-378a-5p; miR-223-5p; miR-122-5p; miR-203a; miR-16-1-3p; miR-193a-5p; miR-378a-3p; miR-24-3p; miR-361-5p; miR-365a-3p; miR-192-5p; miR-1468; miR-425-3p	miR-151a-5p/3p; miR-199a-5p/3p; miR-98-5p; miR-103a-3p; miR-107; miR-30c-5p; miR-18a-5p; miR-326; miR-30b-5p; let-7f-5p
Huang et al [42]	2023	Serum	miR-21; miR-27a; miR-93; miR-221; miR-222; miR-223	–
Huo et al [43]	2022	Serum	miR-486-5p; miR-6088; miR-122-5p	miR-223-3p
Chuang et al [45]	2015	Adipose tissue	miR-223	–
Wang et al [48]	2022	Serum	miR-222-3p	–
Jiang et al [50]	2016	Serum	miR-122; miR-193b; miR-194	–
Hu et al [51]	2020	Granulosa cells	hsa-miR-612; hsa-miR-4449; hsa-miR-4488; hsa-miR-6510-5p; hsa-miR-548ar-3p; hsa-miR-3656; hsa-miR-7110-5p; hsa-miR-4516; hsa-miR-4492; hsa-miR-3162-3p; hsa-miR-3141; hsa-miR-3195; hsa-miR-6087; hsa-miR-1273g-3; hsa-miR-3196	hsa-miR-548aq-3p; hsa-miR-122-5p; hsa-miR-548t-5p; hsa-miR-3591-3p; hsa-miR-204-3p; hsa-miR-767-5p; hsa-miR-107; hsa-miR-33a-5p; hsa-miR-802; hsa-miR-548aj-5p; hsa-miR-190b; hsa-miR-103a-2-5p; hsa-let-7g-3p; hsa-miR-548g-5p; hsa-miR-590-5p; hsa-miR-105-5p; hsa-miR-585-3p; hsa-miR-144-3p; hsa-miR-199b-3p; hsa-miR-1298-5p; hsa-miR-20b-5p; hsa-miR-181c-5p; hsa-miR-6511b-3p; hsa-miR-126-5p; hsa-miR-378d; hsa-miR-29b-2-5p; hsa-miR-18b-5p; hsa-miR-3144-3p; hsa-miR-1255b-5p; hsa-miR-144-5p; hsa-miR-16-1-3p; hsa-miR-9-3p; hsa-miR-196b-5p; hsa-miR-34a-3p; hsa-miR-7114-5p; hsa-miR-3135b; hsa-miR-592
Krentowska et al [55]	2024	Serum	miR-27a	miR-320
Liu et al [56]	2023	Serum	miR-4488	–
Rashad et al [58]	2019	Serum	–	miR-320
Wander et al [60]	2022	Serum	miR-132-3p	miR-486-5p; miR-503-5p; miR-16-5p; miR-4732-5p/3p; miR-363-3p; miR-25-3p; miR-451a; miR-20b-5p; miR-15a-5p; miR-92-3p; miR-144-3p; miR-7-5p
Sang et al [61]	2023	Serum	–	miR-363-3p
Díaz et al [62]	2020	Serum	–	miR-451a; miR-652-3p; miR-106b-5p; miR-206
Wu et al [65]	2014	Adipose tissue	miR-25; miR-106b	–

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Table 1 continued. Associations between dysregulated microRNAs (miRNAs) and insulin resistance (IR) in patients with polycystic ovary syndrome (PCOS).

Authors	Year	Collected material	Upregulated miRNA	Downregulated miRNA
Xu et al [66]	2023	Granulosa cells	miR-1298-5p	–
Gao et al [67]	2022	Serum	miR-184; miR-326	–
Nanda et al [68]	2020	Serum	–	miR-24
Udesen et al [69]	2023	Serum	–	miR-342-3p
Zhang et al [70]	2023	Serum	–	miR-335-5p
Mu et al [71]	2021	Ovarian tissues of rats	miR-103	–
Soyman et al [72]	2022	Serum	–	miR-132
Sørensen et al [73]	2019	Serum	–	miR-1225-5p
Yang et al [74]	2018	Ovarian tissues of rats	miR-33b-5p	–

miRNA, miR – microRNA; hsa-miR – *homo sapiens* microRNA.

observed a substantial role of miR-223 in the pathogenesis of IR associated with PCOS, and almost all were in line with miR-223 overexpression both in serum and adipose tissue of IR-affected patients with PCOS compared to patients with PCOS without IR [40-42]. Besides these encouraging results, some discrepancies regarding the usefulness of miR-223 were also noted. Huo et al observed reduced expression of miR-223 in patients with PCOS and IR [43]. Although they did not indicate the possible causes, we hypothesize that this effect could have resulted from the ability of miR-223 to reduce IR by inhibiting macrophages with pro-inflammatory properties [44].

In contrast to the above-mentioned reports, Chuang et al found that use of this miRNA did not allow for differentiation between patients with and without IR in women with PCOS, despite the presence of a positive association between miR-223 and HOMA-IR values patients with PCOS and in healthy women [45], which might reflect the limited usefulness of this miRNA in the diagnosis of IR in patients with PCOS. Nevertheless, as the available literature has overall widely implicated the role of miR-223 in IR pathogenesis via identifying miR-223 interaction with type 4 glucose transporter (GLUT-4) and insulin substrate receptor-1 (IRS-1), involved in the insulin signaling pathway, miR-223 seems to be a reliable miRNA candidate to predict IR in patients with PCOS [46,47]. Further, elevated levels of the miRNAs of the 221 family, including miR-221 and miR-222, were linked to enhanced risk of IR in patients with PCOS [42,48]. Their multi-faceted role in pathways controlling insulin metabolism has long been debated and the regulation of GLUT-4 and the receptors for adiponectin has been described [49]. Several studies have also highlighted the importance of higher miR-122 expression in the pathogenesis of IR associated with PCOS [41,43,50]. Although most researchers agreed that elevated levels of this miRNA corresponded with an enhanced risk of IR [41,43,50], Hu et al found that in patients with PCOS who were diagnosed with IR, miR-122 was downregulated in comparison to the PCOS group without IR [51]. Analysis of studies describing the pathways in which this miR-122 is involved does not let us draw clear conclusions regarding a more relevant pattern of miRNA action. Thus, on the one hand, it was postulated that in the non-PCOS model, enhanced expression of miR-122 corresponded with intensified IR [52,53]. On the other hand, it was found that inhibition of this miRNA can modulate the expression of GLUT-4, IRS-1, and Forkhead Box A2 (FOXA2), which subsequently resulted in IR enhancement [54]. Also, some other miRNAs, whose increased expression was associated with the presence of IR in patients with PCOS, have been described by independent research teams, including miR-27a [42,55] and miR-4488 [51,56]. All these miRNAs have also previously been to some extent investigated in terms of association with the pathogenesis of insulin metabolism disturbances. The role of miR-27 has been well characterized and was observed to affect the PIK3/AKT pathway [57]. In contrast, although miR-4488 was found to be a regulator of genes participating in insulin metabolism, the details of the crosstalk are poorly understood [56].

A great number of studies have also pointed to the existence of miRNAs, whose reduced expression corresponded with IR. Krentowska et al, consistent with Rashad et al, found lower miR-320 expression to be linked with higher IR risk [55,58]. Nevertheless, these results should be treated cautiously, as in non-PCOS cohorts miR-320 has displayed different patterns of associations with IR [59]. Other miRNAs mentioned by at least

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2 researchers as negatively correlated with impaired insulin metabolism include miR-199-3p [41,51], miR-20b-5p [51,60], miR-363-3p [60,61], miR-107 [41,51], miR-144-3p [51,60], and miR-451a [60,62]. The role of these miRNAs seems to result from different mechanisms of action; eg, miR-363-3p regulates the PI3K-Akt pathway [63], miR-107 affects insulin secretion and pancreatic beta cell development [46], and miR-144-3p acts via the regulation of IRS-1 [64]. There were also several miRNAs, including miR-106b-5p [62,65], miR-486-5p [43,60], miR-1298-5p [51,66], miR-326 [41,67], miR-16-1-3p [41,51], and miR-378 [41,51], in which altered expression was noticed by different research teams. Nevertheless, as the obtained results were contradictory, the role of these miRNAs should be further thoroughly analyzed.

Hu et al found correlations between IR and both increased and decreased expression of different miRNAs, but most of their findings have yet to be confirmed by other researchers, and exploring these observations is required to draw any firm conclusions [51], and this is also needed for many other analyzed miRNAs for which the links with IR have been described only once [40-43,50,55,60-62,65-74] including dysfunctional glucose metabolism in adipose tissue (AT) (**Table 1**). Taking together the results from our research and data from the literature, it now appears that further efforts should rather focus on the investigation of miRNAs for which correlations with IR were found in multiple studies and for which pathways of action are relatively well known.

miRNAs in Obesity

Excess body weight is another metabolic disorder specific to PCOS that has been extensively discussed in terms of its association with miRNA expression. Obesity is a crucial factor in the development of a broad range of PCOS-related symptoms. Moreover, it has been postulated that the relationship between PCOS and obesity is reciprocal [9]. Research has shown many correlations between the level of specific miRNAs and obesity in patients with PCOS (**Table 2**).

Similarly, as in the case of IR, miRNA-223 was the most often mentioned obesity predictor and it has been revealed to positively correlate with higher BMI values [41,75,76]. These observations are inconsistent with reports regarding links between miR-223 and obesity in the general population, as a recent meta-analysis conducted by Veie et al has proven that elevated miR-223 levels correlated with weight reduction [77]. Thus, we hypothesize that patients with PCOS may display different regulatory patterns of obesity-associated miRNAs. A potential example of this phenomenon was described in the study by Murri et al, in which other miRNAs such as miR-21, miR-27b, miR-103, and miR-155 tended to present opposing links with BMI values between patients with PCOS and control groups [78]. Besides miR-223, the association between heightened expression of several other miRNAs, including miR-326 [60,67], miR-23a [79,80], and miR-122 [41,75], and greater obesity risk was confirmed by several researchers. The involvement of miR-122 in obesity development seems well-established in the literature, as several studies conducted on non-PCOS groups have shown obesity-related overexpression of this miRNA [81-83]. Nevertheless, there are many discrepancies regarding the action of other above-described miRNAs. A study conducted on non-PCOS cohorts indicated that lower miR-23a levels were associated with obesity [84]. Therefore, based on this observation, different mechanisms of miR-23a action in the pathogenesis of obesity cannot be excluded. Further, although Vega-Cardenas et al found that the role of miR-326 in obesity development results from this microRNA's ability to enhance inflammation in adipose tissue [85], Murri et al found that lower miR-326 concentrations corresponded with higher waist-hip ratio (WHR) in patients with PCOS [41]; therefore, details of the activity of this molecule should be further examined.

In turn, many other miRNAs mentioned in **Table 2** displaying positive associations with obesity were only once described in this context [25,41,60,66,67,69,78,86,87], which requires further research.

On the contrary, the evaluation of associations between downregulated miRNAs and greater risk of excess body weight in patients with PCOS has not led to clear conclusions. Only Wander et al [60] and Cirillo et al [88] consistently noticed the lowering levels of miR-486, probably contributing to obesity development through PI3K/Akt pathway targeting [89,90]. Some other miRNAs, including miR-151a-3p/5p, miR-199a-3p/5p [41], miR-4732-3p/5p, miR-451a, miR-486-5p, miR-16-5p [60], miR-24 [68], and miR-335-5p [70], for which lower regulation was proven to be associated with obesity development, have also been mentioned above to be underregulated in individuals with IR, showing potential common pathways underlying obesity and IR. Unfortunately, these links have only been described by single research teams; therefore, without additional confirmation of their role in the pathogenesis of obesity, these possible associations are unclear.

Lipid Metabolism Disorders Characteristic of Polycystic Ovary Syndrome (PCOS)

The characteristic picture of lipid metabolism disorders in patients with PCOS includes increased triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C), as well as an accompanying tendency for decreased high-density

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Table 2. Associations between dysregulated microRNAs (miRNAs) and various indicators of excessive body weight including body mass index (BMI), waist-hip ratio (WHR), and waist circumference in patients with polycystic ovary syndrome (PCOS).

Authors	Year	Collected material	Assessed parameter of obesity	Upregulated miRNA	Downregulated miRNA
Murri et al [41]	2018	Serum	BMI	miR-24-3p; miR-122-5p; miR-1537; miR-140-5p; miR-148a-3p; miR-223-5p; miR-23a-3p; miR-29c-3p; miR-30e-5p; miR-338-3p; miR-361-5p; miR-365a-3p; miR-378a-5p; miR-424-5p; miR-425-3p; miR-425-5p; miR-877-5p; miR-197-3p; miR-223-3p	miR-151a-3p; miR-151a-5p; let-7d-5p; miR-199a-3p; miR-199a-5p; miR-199b-5p; miR-379-3p
			WHR	miR-192-5p; miR-193a-5p; miR-203a; miR-122-5p; miR-378a-5p; miR-877-5p	miR-151a-3p; miR-151a-5p; miR-199a-3p; miR-199a-5p; miR-181a-2-3p; miR-30d-3p; miR-331-3p; miR-98-5p; miR-30b-5p; miR-326; miR-126-5p
Wander et al [60]	2022	Serum	Waist circumference	miR-326; miR-339-5p	miR-1294; miR-4732-5p; miR-451a; miR-486-5p; miR-16-5p; miR-15a-3p; miR-451b; miR-4732-3p; miR-1180-3p
Xu et al [66]	2023	Granulosa cells	BMI	miR-1298-5p	–
			WHR		
Gao et al [67]	2022	Serum	BMI	miR-184; miR-326	–
Nanda et al [68]	2020	Serum	BMI	–	miR-24
Udesen et al [69]	2023	Serum	WHR	miR-376-3p	-
Zhang et al [70]	2023	Serum	BMI	–	miR-335-5p
Udesen et al [75]	2020	Serum	BMI	miR-122; miR-223	–
Zhao et al [76][71]	2015	Serum	BMI	miR-223	–
Murri et al [78]	2013	Serum	BMI	miR-21; miR-27b; miR-103; miR-155	–
Xiong et al [79]	2017	Serum	BMI	miR-23a	–
Lin et al [80]	2020	Serum	BMI	miR-23a	–
Romero-Ruiz et al [86]	2021	Serum	BMI	miR-33a-5p; miR-143-3p	–
Yang et al [87]	2022	Granulosa cells	BMI	miR-133a-3p	–
Cirillo et al [88]	2019	Granulosa cells	BMI	–	miR-486

miRNA, miR – microRNA; hsa-miR – *homo sapiens* microRNA; BMI – body mass index; WHR –waist-hip ratio.

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lipoprotein cholesterol (HDL-C) serum concentrations [91]. Lipid disorders in PCOS have a genetic basis and are determined by the presence of IR and excess androgens. It is estimated that lipid disorders affect approximately 70% of PCOS patients, which indicates a significant population-level concern [92]. Among individuals affected by PCOS, such unfavorable serum lipid profiles can be observed throughout their whole lifetime [91] and contribute to deteriorated outcomes of assisted reproductive technology (ART) procedures and a higher risk of future cardiovascular complications [36,93].

microRNAs in Triglycerides (TG) Metabolism Disorders

The overwhelming majority of correlations between miRNAs and TG concentrations agree with the associations identified for IR. Thus, the reduced expression of miR-24 [68], miR-320 [58], and miR-361-3p [73], as well as enhanced expression of miR-184 [67], miR-326 [67], and miR-4488 [56], were noted to be predictors of higher TG concentrations. This strongly supports the hypothesis that the pathomechanisms of metabolic disorders in PCOS overlap. Moreover, according to Wang et al, miR-222-3p is inversely linked to TG concentrations but only in the group of obese women with PCOS, which further confirms that metabolic disorders in PCOS are inextricably linked [48]. The most correlations between the expression of various miRNAs and TG were found by Murri et al [41], most of them revealed for the first time. However, thorough analysis allowed us to observe some discrepancies between the results of this study and those obtained by other authors; the contradictory results regarded the concentrations of miR-24 [41,68] and miR-151a-5p [41,56]. While Murri et al noted a positive correlation between miR-24 and TG concentrations [41], Nanda et al obtained contradictory results [68]. In the same study by Murri et al, a negative correlation between miR-151a-5p and TG was found [41], but Liu et al found that elevated miR-151a-5p levels corresponded with higher TG concentrations [56].

microRNAs in Total Cholesterol (TC) Metabolism Disorders

Overall, the association between TC and miRNA expression in patients with PCOS has been less frequently described compared to other lipid fractions. Some of the miRNAs for which negative correlations with TC have been found, including miR-361-3p [41], miR-222-3p [48], and miR-363-3p [61], were also mentioned to be associated with IR in the same studies. In addition, some novel miRNAs were investigated and while miR-598 and miR-433-3p presented a positive link with TC, enhanced miR-429 expression was a predictor of lower TC concentrations [41,73]. The action of all of these 3 miRNAs on cholesterol metabolism regulation could be hypothetically explained by their influence on the PI3k/Akt pathway [94-97]. Interestingly, these miRNAs have not been proven in other studies to be the markers of IR in PCOS patients, the occurrence of which is also related to this pathway [98]. Hence, on the one hand, these miRNAs may be particular specific TC biomarkers. On the other, taking into consideration the aforementioned common regulation of both processes, they may have negligible diagnostic value. Therefore, additional research is needed.

microRNAs in Low-Density Lipoprotein Cholesterol (LDL-C) Disorders

Overall, the current literature draws attention to the similar predictive capabilities of TC and LDL-C in indicating patients are at high risk of CVD development. Following this relationship, some miRNAs, including miR-598 and miR-361-3p, displayed associations with LDL-C, which is also referred to as TC [41]. However the analysis of miRNA's usefulness in LDL-C level prediction conducted by Wang et al brought some inconsistencies in this regard and revealed that enhanced miR-222-3p expression was simultaneously linked to higher LDL-C and lower TC levels [48]. There is also a group of miRNAs that showed correlations with both LDL-C and IR. Some of them, including miR-107 or miR-320, were associated with LDL-C in the same manner as with IR, but others, including miR-223-3p or miR-151a-5p, displayed opposite relationships [41,56,99].

In addition, a new approach to the prediction of lipids' fraction via miRNA concentrations was proposed by Yu et al, who found a correlation between miR-4644 and LDL-receptor (LDLR) participating in LDL metabolism and enhanced expression of this miRNA corresponded with lower expression of LDLR. Although this study evaluated LDLR concentrations in follicular fluid and the authors emphasized the potential importance of these results in folliculogenesis, the described regulation should also be studied in the context of its role in development of systemic dyslipidemias [100].

microRNAs in High-Density Lipoprotein Cholesterol (HDL-C) Disorders

The available literature also shows numerous links between miRNAs and HDL-C concentrations [41,48,67,68,73]. The most prominent of these associations was again pointed out by Murri et al [41]. Nevertheless, it remains challenging to demonstrate any consistent results, as none of the other authors has reached the same conclusions. Only miR-361-5p was mentioned twice as a potential biomarker of HDL-C levels, but researchers disagreed on the type of this regulation [41,73]. While Murri et al have observed under-expression of this miRNA associated

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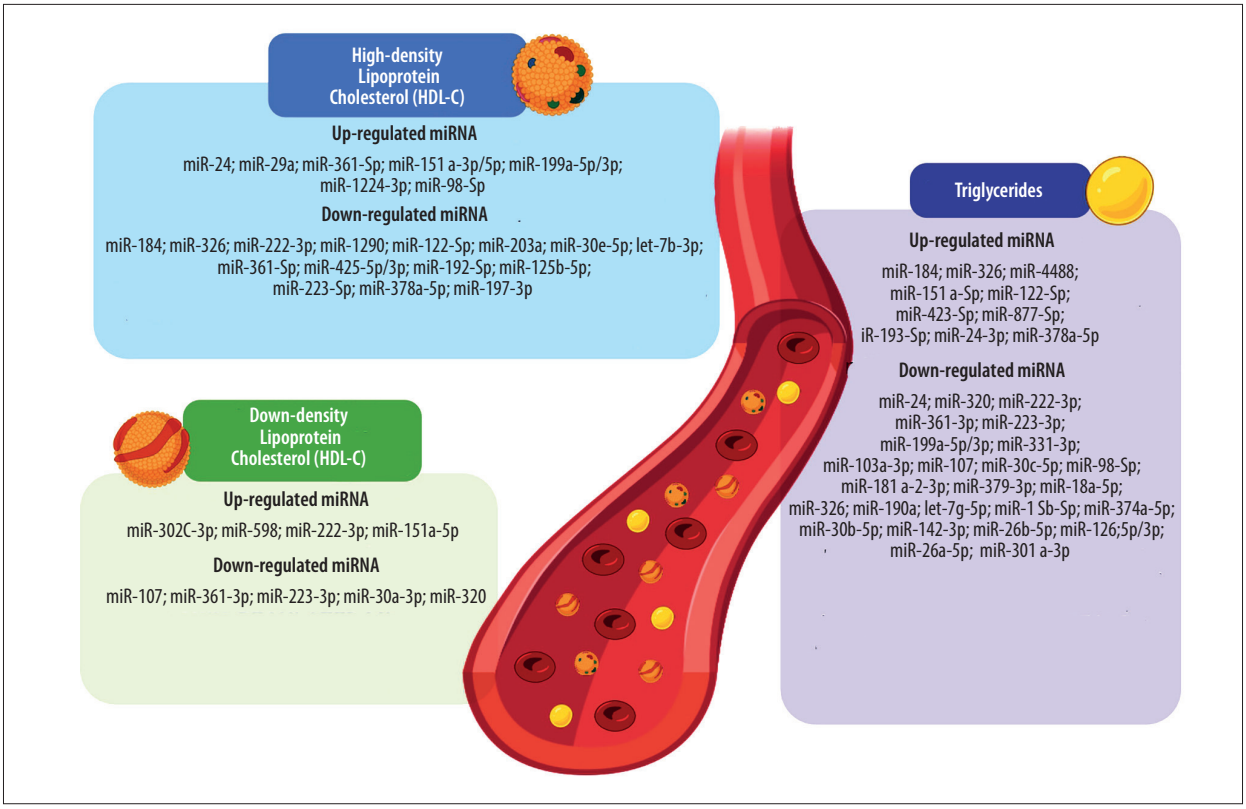

Figure 1. The graphic summary of alterations of microRNAs (miRNAs) concentrations associated with lipid profile parameters in patients with polycystic ovary syndrome (PCOS). Lipid metabolism disorders characteristics for PCOS include altered high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride serum concentrations. Each alteration of lipid molecule serum level is regulated by a down- or overexpression of a range of different miRNAs. Based on: [41,48,56,58,67,68,73,99]. *Created with BioRender software version 04.* HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; miRNA, miR – microRNA.

with higher HDL-C values [41], Sørensen et al found high miR-361-5p values predicted high HDL-C levels [73]. Considering the associations between IR and the development of HDL-C metabolism disturbance [101], the fact that in PCOS individuals' HDL-C concentrations were negatively correlated with the expression of miR-222-3p, miR-223-5p, and miR-326 seems important [41,48,67]. However, to consider these miRNAs as significant biomarkers of the levels of this lipid fraction, further studies demonstrating the association of these miRNAs with HDL-C are required.

A schematic summary of the relationships between various miRNAs and concentrations of TG, LDL-C, and HDL-C is depicted in **Figure 1**.

microRNAs in Hypertension

The risk of hypertension poses another important challenge in PCOS patients. The meta-analysis by Wekker et al revealed approximately twice as much hypertension risk among patients with PCOS, in comparison to the population of healthy women [102]. Persistently elevated blood pressure in women of reproductive age may lead to development of other cardiovascular disturbances; therefore, early prediction of this disorder seems crucial in prevention of more severe PCOS complications [103,104].

Despite such a high prevalence of hypertension in patients with PCOS, only a few studies have searched for candidate miRNAs for the prediction of this metabolic dysfunction. Wang et al attempted to find correlations between miR-222-3p and cardiovascular disease (CVD), to which the diagnostic criterion hypertension was included. They discovered that higher miR-222-3p serum levels corresponded with enhanced CVD risk. Overall, it is the only study that revealed miRNA expression can directly reflect the occurrence of the condition, in which higher blood pressure can occur [48].

Zhang et al assessed the impact of miR-339 on functioning of endothelial progenitor cells (EPC), showing that impaired action was involved in the initiation and development of hypertension

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and other CVD components. They found that PCOS was associated with diminished migration and proliferation of EPC and increased miR-339 serum expression. The researchers observed that higher miR-339 expression contributed to reduced migration and proliferation of EPC and hypothesized that this effect occurred through PI3K/AKT and SIRT1/PGC-1-alpha pathways [105].

In summary, it is surprising that PCOS-related hypertension has received little research attention, especially considering that the authors have often focused on the relationship between miRNA expression and hypertension of various etiologies unrelated to PCOS in the literature [106].

microRNAs in type 2 Diabetes Mellitus

Patients with PCOS who have IR display a significantly greater risk of type 2 diabetes mellitus development [107,108]. Similarly, in patients previously diagnosed with type 2 diabetes mellitus, the occurrence of PCOS and even its more severe forms is also more prevalent [109,110]. Considering such reciprocal influences, these disorders seem to share a common causal background. In clinical practice, multiple clinical signs are useful in predicting the onset of type 2 diabetes mellitus in patients with PCOS. To be able to predict the risk of diabetes at an early stage before any clinical symptoms appear, a single marker is desirable [111].

Using reverse transcription-quantitative polymerase chain reaction (RT-qPCR), Wang et al evaluated the association between serum expression of miR-222-3p and type 2 diabetes mellitus in PCOS patients. Their study included 111 patients with PCOS, 57 of whom were diagnosed with type 2 diabetes mellitus, and 94 women who served as healthy controls. Increased expression of miR-222-3p was a predictor of the complication of PCOS with type 2 diabetes mellitus. As this relationship concerned both overweight and normal-weight PCOS patients, miR-222-3p can be considered a highly useful marker for patients with different body weights [48].

Wu et al also focused on the role of microRNA in type 2 diabetes mellitus in patients with PCOS. Based on the assessment of the microRNA profile of 44 patients with PCOS and type 2 diabetes mellitus, miR-32-3p appears to be involved in the pathogenesis of this complication of PCOS through the PLA2G4A pathway. Unfortunately, the authors did not include patients with PCOS unaffected by type 2 diabetes mellitus; therefore, comparison of miR-32-3p expression between these groups was not possible [112].

An attempt to establish a common genetic background of PCOS and type 2 diabetes mellitus based on the bioinformatic analysis was also performed by Zhang et al. As a result of the research, 4 genes contributing to the pathophysiology of these diseases were identified. The subsequent evaluation of gene regulators revealed 28 miRNAs involved in post-transcriptional modifications. Nevertheless, as the authors did not determine whether upregulation or downregulation of miRNA expression is linked to enhanced risk of type 2 diabetes mellitus development in patients with PCOS, further investigation is needed [113].

Another interesting study, conducted by Hocaoglu et al, focused on assessment of miRNA expression in pregnant women with PCOS who had gestational diabetes mellitus (GDM). The expression of miR-16-5p and miR-155-5p was evaluated in leukocytes from the peripheral blood. The authors observed higher miR-16-5p expression in pregnant patients with PCOS and GDM in comparison to pregnant women with PCOS without this metabolic complication [114]. Understanding the significantly higher risk of GDM development in patients with PCOS [115] and increased prevalence of many GDM complications affecting women and their offspring, including type 2 diabetes mellitus [116], may improve clinical utility [114].

microRNAs in Non-Alcoholic Fatty Liver Disease (NAFLD)

Among all the metabolic symptoms and early complications of PCOS, NAFLD is one of the most frequently disregarded complications of the disease. NAFLD is caused by metabolic disorders characteristic of PCOS and is also triggered by some microbiome alterations or genetic disturbances [117,118]. Although NAFLD can result in severe complications, currently, due to the lack of optimal screening methods, routine tests in patients with PCOS are usually not recommended [117].

To the best of our knowledge, only 1 published study has evaluated the role of miRNA in NAFLD and PCOS. Chen et al used microarray analysis to find differentially expressed genes (DEGs) in PCOS and NAFLD samples. First, 61 genes were characterized as differentially expressed and the next step of the study included the identification of miRNAs that become targets for DEGs. They observed that miR-20a-5p, miR-101-3p, miR-129-2-3p, and miR-124-3p participated in the regulation of DEGs, but no detailed data on the nature of this regulation was mentioned. Thus, these results should be considered a foundation for further research [119].

Future Directions

The growing number of research studies that focus on miRNAs as markers for various diseases creates new prospects for

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these non-coding RNAs to predict the risk of metabolic complications of PCOS. The prominent question that results from our review concerns the desired character of metabolic disorder markers in patients with PCOS. Hence, it is crucial to determine whether a single marker for all metabolic disturbances or rather separate one for each will be more useful in everyday clinical practice. The analysis of the links between miRNAs and all metabolic disturbances revealed several miRNAs (eg, miR-222, miR-223, miR-320, or miR-122) which were found to be potential markers of various metabolic disturbances in PCOS. The physiological roles of these miRNAs partially explain the wide range of metabolic pathologies with which miRNAs have been described to be associated. miR-222 and miR-223, through their influence on immune cells, regulate the inflammatory response [120,121]. Thus, the fact that metabolic disorders are associated with inflammation confirms the role of these miRNAs in metabolic state regulation [122]. Another non-coding RNA – miR-320 – alleviates oxidative stress [123], which is another process involved in metabolic disturbances [124,125].

Moreover, the involvement of aforementioned miRNAs in various metabolic pathologies indicates common biological pathways underlying their background. Overall, it can be concluded that selection of miRNA characterizing a multitude of metabolic parameters is relatively easy to conduct. On the other hand, these miRNAs linked to a wide range of metabolic disturbances accompanying PCOS were also reported to be simply the markers of PCOS occurrence [55,56,72]. Therefore, there is a risk of the lack of marker sensitivity, which may manifest as the elevated levels of these miRNAs in most women with PCOS. The opposite research strategy involves the establishment of separate markers for each metabolic disorder. Although it requires more extensive scientific investigation, it seems more valuable, especially for the prediction of more severe PCOS complications, including type 2 diabetes mellitus or NAFLD.

When debating the above-mentioned issues, it also seems important in this context that future studies should evaluate the pathways in which selected miRNAs are involved, as well as identification of the genes targeted by the selected miRNAs. We hypothesized that such a research strategy could elucidate the mechanisms leading to involvement of selected miRNA in several different metabolic processes. Furthermore, this would allow an understanding of the discrepancies in the levels of the same miRNA found for the same metabolic disorder.

Another crucial issue is selection of the most optimal tissues or fluids for miRNA detection. The greatest diversity of biological materials was particularly evident in studies performed to search for correlations between miRNAs and IR. In addition to using serum samples, researchers collected granulosa cells, as well as adipose tissue fragments. The heterogeneity of various tissues could also be observed while investigating the relationships between miRNA and other metabolic impairments. Among all these biomaterials, the measurements performed in serum seem to have the highest diagnostic potential due to the simplicity of material collection. Similarly, granulosa cells derived from follicular fluid can also be easily obtained during follicular puncture before ART procedures; however, this method seems to be limited to patients displaying PCOS-related infertility. On the contrary, obtaining adipose tissue involves invasive techniques; therefore, the utility of this tissue in miRNA detection is lower.

Conclusions

The occurrence of even mild forms of metabolic disorders in patients with PCOS has negative health consequences and is a harbinger of more serious metabolic disorders in the future. Therefore, it is crucial to identify any early exponents of metabolic disorders.

Despite the wide range of scientific reports suggesting the existence of links between metabolic disorders in PCOS and alterations in miRNA expression, it is difficult to identify miRNAs that clearly could be used as markers of these disorders. Currently, more studies have focused on miRNA involvement in pathological processes underlying PCOS, such as IR, obesity, or dyslipidemias. Although the substantial role of several miRNAs, including miR-222, miR-223, miR-320, and miR-122, in such mild PCOS complications has been postulated by several research teams, there is a risk of low specificity of these miRNAs as markers. Therefore, to increase their clinical usefulness, there is a need for in-depth investigation and determining the pathways regulated. On the other hand, few studies have focused on miRNAs characteristic for more severe metabolic complications, including type 2 diabetes mellitus or NAFLD; hence, this issue is poorly studied. In summary, further research should strive to predict more severe complications of PCOS, including type 2 diabetes mellitus or NAFLD, especially in young patients. Moreover, emphasis should be placed on detection of miRNAs with minimally invasive methods to enhance the clinical utility.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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