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Review Article

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The Role of Microparticles in Polycystic Ovarian Syndrome. An Updated Review

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ABSTRACT

Microparticles (MPs) are vesicles of less than 1 μm in diameter (submicron vesicles) shed from plasma membranes to cell activation, injury, and apoptosis response. They consisted of membrane proteins and cytosolic material from the cell they originated. These vesicles are vital mediators of pathological and physiological cellular processes. Polycystic ovary syndrome (PCOS) is a regular endocrine, menstrual and metabolic condition that affects 10-15% of females in their reproductive period. Numerous researches have described the association between low-grade chronic inflammation and PCOS; however, the relation is not well understood. Chronic low-grade inflammation is reflected as a risk factor for cardiovascular disease, atherosclerosis, and endothelial dysfunction, and it is linked to abdominal obesity and insulin resistance (IR). MPs may be useful biomarkers for the early detection of cardiovascular disease and thrombosis in PCOS patients. In March 2020, the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) became pandemic, wreaking havoc on healthcare systems worldwide and the global economy. Obesity, diabetes, and cardiovascular disease have all been linked to COVID-19 increased risk of infection. PCOS patients have recently been identified as an underserved and potentially high-risk demographic for COVID-19 problems. This article tried to review and present recent studies that explored the role of microparticles in polycystic ovarian syndrome.

Key words: *Platelets microparticles, Polycystic ovarian syndrome, Inflammation, Obesity*

INTRODUCTION

Microparticles (MPs), which were once thought to be little more than cell waste, are now being identified as potential biomarkers [1]. They create a phospholipid bilayer with a diameter of 100–1000 nm because of cell activation and apoptosis. Membrane-derived receptors, such as cytokines and chemokines are involved in intracellular signaling and/or migration of lipids, carbohydrates, and genetic material such as mRNA and microRNAs (miRNAs) are all carried by microvesicles [2]. The contents of these cells are determined by the parent cell, the microenvironment, and the events that precede their release [3]. They operate as mediators in cells' physiological and pathological processes by transmitting specific biological information and modifying target cell activity. Because MPs can come from a verse majority of cells, including endothelial cells, leukocytes, platelets, and lymphocytes, they have distinct activities; hence many studies compare microparticles from multiple sources [4, 5].

To measure Endothelial microparticles (EMPs), several techniques depending on the platelet-free plasma preparation and succeeding recognition of cell-surface proteins Platelet endothelial cell adhesion molecule-1 (PECAM), intercellular adhesion molecule 1 (ICAM-1), and E-selectin [6]. Furthermore, measurement of these cell-surface proteins can be accounted for in their soluble form in serum samples to their microparticle-bound form [7].

Membrane remodeling and the production of blebs are the first steps in generating MPs. Increased intracellular calcium levels are required for this process, which results in the redisposition and phosphatidylserine externalization to the outer surface [8]. Calcium-sensitive enzymes are triggered, causing the cytoskeleton filaments to cleave, resulting in the development of blebs on the cell membrane and the release of MPs. In addition, MPs depict their membrane proteins providing the precise cells from which they are derived, which can be utilized to investigate their particular origin [9] as Podocytes, tubular cells, and epithelial cells lining the urogenital tract produce urine microvesicles [10].

In injury situations and stress conditions, MP migrated from cell to extracellular space [11]. Vesicles released by cells into the extracellular space under normal and stressful situations, specialized vesicles, such as lysosomes, endosomes, and transport vesicles, are vital to the homeostasis of cells and proteins molecules shuttling and intercellular communication [12]. Purinergic receptor stimulation, shear stress or apoptosis, and proinflammatory mediators or thrombin can all cause vesicle release [13]. Shiga toxins, lipopolysaccharides, and uremic toxins are examples of bacterium virulence factors [14]. Endothelium-derived microparticles (EMPs) levels are low in healthy people, but they are raised in various disease states, including acute coronary syndrome, myocardial infarction, metabolic syndrome, and obesity [15]. Exogenous phosphatidylserine (PS) is present in EMPs, which also express adhesion molecules such as E-selectin, cadherin, ICAM-1, and integrins [16].

Polycystic ovary syndrome (PCOS) is the three major polycystic ovary syndrome kinds, comprising hyperandrogenemia biochemical or hyperandrogenemia clinical indications, chronic oligo- or anovulation, and polycystic ovarian morphology on ultrasound [17]. PCOS must be diagnosed after the exclusion of other conditions which mimic or cause these three anomalies. In addition to its reproductive squeal, it is now considered a metabolic disorder characterized by defects in secretion and insulin sensitivity, leading to an enlarged risk of type 2 diabetes [18]. Also, patients may have an increased risk of cardiovascular disease, but the mechanisms are not yet fully established.

In March 2020, the new disease (COVID-19) caused by the novel severe acute respiratory syndrome (SARS) coronavirus-2 (SARS-CoV-2) was declared pandemic. COVID-19 can cause severe disease and increased death in high-risk people, although being asymptomatic or moderate in most cases. Pneumonia, severe signs of acute respiratory distress syndrome [2], and multiple organ failure can all occur in COVID-19 patients [19].

Low vitamin D levels, hyper inflammation, and hyperandrogenism are risk factors for severe COVID-19, all of which have been linked to PCOS [20]. Furthermore, there is an increased incidence of numerous cardio-metabolic conditions in PCOS patients, such as type 2 diabetes, obesity, and hypertension, which might considerably upsurge the risk of the COVID-19-related consequences. These significant risk variables intersect for both PCOS and severe COVID-19 cardiometabolic symptoms [21]. Studies of MP are growing fast, and while there is increasing literature in this field, this review presents an update on microparticles, manly platelet-derived MP, as biomarkers for PCOS.

Types of MP

The formation of MP has been detected in cells of the vasculature, including endothelial cells, platelets, erythrocytes, leucocytes, cardiomyocytes, podocytes, and vascular smooth muscle cells [22]. Although MPs come from cells under stress and apoptosis, cell death situations are not essential for the formation of MPs [23]. We can differentiate MPs from other extracellular vesicles, for example, apoptotic bodies or exosomes, depending on content, size, and mechanism of formation [24].

The mechanism of MPs formation is not understood and may vary between different groups of cells. The re-organization of the cytoskeleton appears to represent an essential step in the formation of MPs [25]. This is because the formation of MPs starts with the plasma membrane outward blebbing; according to this, we can conclude that actin filament dynamics appear critical for MP formation from numerous cell types [25].

The externalization of phosphatidylserine (PS) is implicated in MP formation. Phosphatidylserine is an aminophospholipid present only on a healthy cell's plasma membrane inner side [26]. There are three different enzymes: flippases, scramblases, and floppies which regulate asymmetric phosphatidylserine distribution Floppases [27] that have members of "the ATP-binding cassette transporter" (ABC transporter) family, the phosphatidylserine is transported to the outer membrane by ATP-dependent manner [28].

LMPs (leukocyte-derived microparticles) promote inflammation, change endothelial function, accelerate coagulation, promote thrombosis, and generate new blood vessels in susceptible plaques [29]. Platelet-derived MPs (PMPs) include a variety of growth and nutritional factors that promote angiogenesis and neurogenesis, as well as help to recover from brain injury [30]. They can also protect endothelial cells from apoptosis and induce

angiogenesis in vitro and in vivo [31]. Erythrocyte-derived microparticles (ErMPs) are involved in cell-to-cell communication and the generation of adaptations in response to internal and external stimuli, such as exercise [29].

MPs are bioactive molecules that show a significant function in regulating vascular homeostasis and thrombus formation mechanisms [3, 4]. As a result, MPs can be used as indicators and therapeutic targets in the battle against arterial and venous thrombotic disorders [32]. Potential pro-coagulation is a feature of MPs based mostly on PS exposure and tissue factor (TF) expression [33]. MPs have an important role in coagulation activation, arterial and venous thrombosis, and CVD because of this characteristic. In healthy people, platelets produce the majority of the detectable MPs in the blood. MPs from erythrocytes, leukocytes, and endothelial cells, on the other hand, can be detected in blood in lower quantities. In patients with arterial and venous thrombosis, however, significant alterations in MP number, cellular origin, and MP-associated biological functions have been described. MPs have a role in the disease's complications as a result of these circumstances, as MPs increase thrombotic activities as part of a cascade of adverse responses [34].

Proteomic analysis of the antigenic composition of EMP reveals the presence of a wide range of proteins, including metabolic enzymes, proteins involved in adhesion and fusion processes, cytoskeleton-associated proteins, and nucleosomes [35], suggesting that EMPs may serve as messengers or signals of a dysfunctional endothelium. High EMP values are strongly linked to a variety of vascular anatomical and functional problems, such as impaired flow-mediated dilation and increased pulse wave velocity. Endothelial role therapeutic development has been correlated with reducing circulating EMP levels [36].

The anionic phospholipids' expression, particularly PS, and tissue factor (TF), the principal cellular activator of the clotting system, determines the procoagulant characteristics of MPs. The asymmetrical phospholipid membrane distribution loss during MP synthesis outcomes in PS externalization at the cell membrane's outer leaflet [37]. PS boosts the procoagulant potential by increasing the assemblage of calcium-dependent coagulation components on the MP surface, allowing the creation of tenase and/or prothrombinase complexes followed by the synthesis of thrombin. Procoagulant activity is higher in MPs that have both PS and TF. TF is a factor VII/VIIa (FVII/VIIa) receptor that activates factor X (FX) and factor IX (FIX) to ensure blood coagulation. Post-translational alterations have been hypothesized as a method for controlling TF activity on MPs. This shows that TF-expressing MPs from distinct cell types may have variable procoagulant properties [38, 39].

Cardiovascular disease risk factors (CVD) and resulting endothelial dysfunction are related to releasing (MPs) from endothelial cells. The functional condition of parental endotheliocytes appears to be reflected in the pattern of circulating EMPs, and different EMP subtypes cause different pathophysiological responses. Endothelium may produce MP-expressing adhesion molecules, allowing inflammatory cells to be recruited, while MPs from apoptotic endothelial cells (ECs) appear to promote angiogenesis. Other EMPs play a role in the formation and progression of atherosclerosis, and their levels are independent predictors of atherosclerosis and future cardiovascular illnesses [40].

MP and inflammation

MPs vital role in coagulation, thrombosis, atherosclerosis, and angiogenesis. As mentioned before, they are also important in inflammation, malignancy, and infection. In other words, despite they present in the blood of healthy persons, their levels rise significantly in disease states characterized by cell activation and death. This recommends a relationship between MPs and inflammation. The MP's pro-inflammatory potential is well recognized in both in vitro and in vivo research [41, 42].

In platelets, pro-inflammatory stimuli are variable like lipopolysaccharide (LPS), and cytokines, such as erythropoietin and interleukin 6 (IL6), soluble CD40 ligand are considered as strong stimuli for blebbing of membrane and releasing of MPs. Noradrenaline (norepinephrine) and the calcium ionophore A23187 stimulate MP formation from platelet. On the other hand, decreasing MPs formation from platelets is associated with Syk and epoprostenol (a synthetic salt of prostacyclin) [43, 44].

Releasing of MPs from the endothelial cell is enhanced by interleukin-l (IL-1α), C-reactive protein (CRP), tumor necrosis factor (TNF)-α, angiotensin II, high glucose, growth factor deprivation, camptothecin, and reactive oxygen species (ROS). In addition, thrombin, pro-coagulant factors, and plasminogen activator inhibitor-1 (PAI1) promote MP formation from endothelial cells. P-cresyl sulfate, homocysteine, indoxyl sulfate, and p-cresol are considered uraemic toxins associated with the formation of endothelial MPs. On the other hand, suppression of production of MP from endothelial cells occurred by nitric oxide (NO) and statin treatment [45, 46].

The endothelial MPs have oxidized membrane phospholipids on their surface due to this oxidative stress cause adhesion of monocytes to endothelial cells and activation of neutrophils in vitro. Inflammation is triggered by the expression of Leukocyte-derived MPs for adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, which are expressed by stimulated endothelial cells and attract leukocytes to the inflammatory site. The release of cytokines and growth factors into the innermost layer of endothelial cells is caused by this leuko-endothelial adhesion [47].

By expressing Fas ligand (FasL) on their surface, MPs can cause immune-competent cells to die. However, this type of response has the potential to manage excessive inflammation. Leukocyte-derived MPs may be responsible for the downregulation of proinflammatory pathways in the early stages of severe inflammation [48]. This, in turn, gives protection against immunosuppression caused by erythrocyte-derived MPs, which can occur when blood products are stored for lengthy periods. In the early phases of inflammation, these leukocyte-derived MPs contain an endogenous anti-inflammatory protein called Annexin 1 (AnxA1) and produce the anti-inflammatory cytokine transforming growth factor 1 (TGF - 1). They also limit macrophage activation and, consequently, inflammation by suppressing proinflammatory cytokines, including IL-8 and tumor necrosis factor (TNF), in a dose-dependent manner [49]. MP-induced production of proinflammatory cytokines such as IL-1 and IL-6 may occur later in the inflammation process. Of the aforementioned, MPs have an essential role in the inflammation process and vascular function because of modulation of nitric oxide and production of prostacyclin from endothelial cells, and they stimulate releasing of cytokine and induction of tissue factor in endothelial cells, in addition to monocyte chemotaxis and adherence to the endothelium. Additionally, MP can induce, regulate, and even reduce inflammation [50].

Polycystic ovarian syndrome (PCO)

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder, metabolic, and menstrual disorder that affects 10-15% of females of their reproductive age. Stein and Leventhal first talked about PCOS in 1935 when cases presented with many endocrine problems like amenorrhea, hirsutism, and polycystic ovaries [51, 52]. PCOS can be characterized by oligo or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovaries detected by ultrasound (US) examination [52]. PCOS prevalence is between 6% - 10% depending on the examination by the US of National Institutes of Health (NIH) criteria and raised to 15% when dependent on the broader Rotterdam criteria. Also, the prevalence of PCOS is significantly higher in South Asian and black females than in white females [51].

The pathophysiology and etiology are still not completely understood despite the prevalence of PCOS, but it may result from genetic and environmental factors. PCOS has significant clinical effects, like glucose intolerance, hyperinsulinemia, type 2 diabetes mellitus (T2DM), abnormal blood lipid levels, and obesity. PCOS should be suspected if females of the reproductive age present with hyperandrogenism signs: hirsutism, acne, and male pattern baldness. PCOS should be on high of the differential diagnosis if the patient also complains of irregular menstrual cycles and infertility [53, 54]. Patients with PCOS are at very high risk of T2DM, cardiovascular disease, and non-alcoholic fatty liver disease. There is an increase in many markers of inflammation detected in females with PCOS, such as raising in white blood cell (WBC) count, C-reactive protein (CRP), interleukin 6 (IL-6), interleukin 18 (IL-18), and tumor necrosis factor-α (TNF-α) [55, 56].

Numerous studies have described the relationship between PCOS and low-grade chronic inflammation [57, 58]. Chronic low-grade inflammation has been considered a risk factor for endothelium dysfunction, coronary heart disease, and atherosclerosis related to insulin resistance (IR) and obesity [59]. Many studies assumed that hyperandrogenemia also has pro-inflammatory effects and that the inflammatory state in PCOS females is more significant than that resulting from IR and obesity alone [60, 61]. PCOS patients have an uneven ratio of pro-and anti-coagulant factors, resulting in an increased risk of atherothrombotic events and higher levels of pro-inflammatory cytokines involved in systemic and chronic low-grade inflammation. Because inflammation is a lineament of endothelial and hemostatic dysfunction, it may have a role in an increased risk of cardiovascular disease in PCOS patients. Also, subclinical inflammation has been expected to connect to several metabolic complications commonly linked with PCOS [61, 62].

MP in PCOS patients

As previously stated, EMPs are involved in endothelial cell modification, inflammation, coagulation, and angiogenesis; there is a link between elevated EMP levels and cardiovascular and autoimmune diseases, cancer, endocrine and metabolic disorders such as PCOS so EMPs can be used as surrogate markers for endothelial

dysfunction in these conditions. Studies examined MPs produced from variable cell types (platelets, leukocytes, and endothelial cells) and MPs expressing TF to assess their link and correlation with clinical and laboratory investigation in PCOS females [63].

Platelet microparticles (PMPs) are mainly increased in overweight/ obese and normal-weight women with PCOS compared to normal women [64]. In addition, there are increases in the level of total MP, leucocyte MP (LMPs), endothelial MP (EMPs), and annexin-expressing MPs in PCOS cases, unlike normal females [65]. In other meaning, MPs types could be valuable biomarkers for the relationship between thrombosis and cardiovascular disease in PCOS patients, which are potential markers for PCOS related to inflammation and coagulation disorders [66].

PCOS is linked to an increase in PMP levels. The clinical importance of this finding has yet to be determined. High levels of PMP may have a role in the increased CVD risk associated with PCOS, according to one theory. PMPs appear to have a major role in atherosclerosis and thrombosis, according to mounting evidence. Patients with acute coronary syndromes, strokes, and diabetes mellitus are more likely to get them. Unluckily, Females with PCOS are more likely to develop hypertension, diabetes, and cardiovascular problems at a younger age. MPs can affect insulin signaling from adipose tissue through the expression of gluconeogenic genes and protein kinase B [67, 68].

In PCOS patients, MP types could be useful biomarkers for the link between thrombosis and cardiovascular disease. MPs (annexin-positive) levels were increased in PCOS patients, as were LMPs, PMPs, and EMPs, which are putative PCOS markers linked to inflammation and coagulation issues [69].

Markers for COVID-19 in PCO patients

The majority of coronavirus 2019 (COVID-19) cases have mild symptoms, on the other side, the occurrence of respiratory failure, severe illness, and mortality in groups that have high-risk this led to instructed measures for quarantine and stop the economy between different countries in the world due to the saving capacity of health systems and intensive care units [70]. COVID-19 infection is more severe in older adults than younger people, and males than females, according to growing research. Even after correcting for several other factors, the Black, Asian, and Minority Ethnic (BAME) groups are at very high risk of death from COVID-19 infection, according to current mortality [70].

COVID-19 infection is more likely in those with metabolic risk factors such as obesity, diabetes, and cardiovascular disease, according to numerous research [71-73]. In addition, Plasma proteome examination recognized COVID-19 disease biomarkers progression, and the important pathways are platelet degranulation, complement system, and coagulation cascades. There are variable factors, for example, hyperandrogenism, low vitamin D levels, and hyper-inflammation, associated with the degree of severity of COVID-19 infection, all these factors have a direct connection with PCOS [74]. There is a difference in protein expression patterns between females with and without PCOS. In PCOS cases, there are differences in platelet degranulation, such as fibrinogen-gamma chain, fibrinogen, fibronectin, and kallistatin [75, 76]. Also, there are changes in complement factor 1 coagulation factor IX, complement factor H, complement component C9, plasma serine protease inhibitor, and heparin cofactor, which are proteins for complement and coagulation cascade. Those proteins that significantly differ between PCOS and normal individuals contribute a close correlation to each other [77].

Recently, polycystic ovary syndrome (PCOS) patients have been considered potentially high-risk people for COVID-19 infection and its complications; these patients have also been overlooked population from the health care system. PCOS patients are at high risk of numerous problems, such as cardio-metabolic complications, like hypertension, obesity, and type 2 diabetes; these increase the risk for COVID-19 infection and its outcome. The risk of severity of COVID-19 infection and mortality from it is less in younger and female patients. PCOS patients are a subgroup of females at more risk of adverse COVID-19 infection [74, 78].

There is a difference in patterns of protein expression (platelet degranulation and proteins for complement and coagulation cascade) seen in PCOS when we compared them to the normal population, which showed the need for validation of such markers in persons who don't have COVID-19 infection before they can be considered as biomarkers for COVID-19 and its severity. Notably, depending on the indication that COVID-19 [76]. The severity of diseases can be linked to these markerstheir ; detection in a PCOS COVID-19 cases patient may give a false negative of severity, potentially leading to the introduction of unsuitable treatment; on the other hand, the detection of these definite markers in females with PCOS may point to that more intervention is needed, because these patients may have a liability to COVID-19 infection [76].

More study on the overlap between PCOS's severe cardio-metabolic symptoms and COVID-19 infection is needed for clinical practice, especially when PCOS patients receive fragmented care from several healthcare providers. Doctors should inform PCOS patients about the potential dangers of COVID-19 and how it may affect their disease management. Metformin is used to treat patients with PCOS who are obese but do not have T2DM since it can enhance both metabolic and reproductive results. Furthermore, it has antiviral characteristics because it activates the AMP-activated protein kinase (AMPK) pathway, preventing SARS-CoV-2 from infecting host cells and producing changes in the ACE-2 receptor, suggesting that metformin could be used in COVID-19 treatments [79].

On the other hand, Metformin can cause lactic acidosis, especially in severe COVID-19 patients who are dehydrated and have renal impairment. Doctors should encourage females with PCOS who are taking metformin to discontinue using it if they develop COVID-19 symptoms or if they become unstable. It is also suggested for diabetic patients. Because of COVID-19, PCOS patients who also have diabetes should follow the updated guidelines and recommendations for glucose-lowering medications. Because of the risk of diabetic ketoacidosis and dehydration from sodium-glucose co-transporter-2 inhibitors, when COVID-19 is diagnosed, especially in patients with symptoms, glucose-lowering medicines should be halted (SGLT2i) [80].

On the other hand, insulin therapy remains the treatment of choice for very sick diabetic patients, and COVID-19 should be optimized and maintained. In addition, medicines that inhibit dipeptidyl peptidase-4 (DPP4) appear to be well tolerated and can be sustained when necessary (doctors can detect the dose of DPP4 inhibitors according to the condition of the kidney if the renal function is affected or not in severe COVID-19 [81]. Because sulfonylureas raise the risk of hypoglycemia, they should be avoided when COVID-19 infection is severe. Accordingly, hypertension is common in patients with PCOS [82, 83]; the following five antihypertensive categories and their relationship with COVID-19 should be studied and noted: thiazide diuretics, angiotensin-receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE inhibitors), beta-blockers, and calcium-channel blockers. They found no significant increase in the likelihood of COVID-19 positive and severe infection. COVID-19 [84].

Patients with PCOS frequently fall between the cracks of various healthcare systems, especially in the face of the COVID-19 pandemic's tremendous demand on clinical practice. Regardless of the massive challenges that the COVID-19 pandemic has posed to healthcare systems around the world, attention should be focused on maintaining a high standard of care for patients, such as many females with PCOS, and providing significant practical measures for optimal management in the face of this pandemic [85].

CONCLUSION

The low-grade chronic inflammatory state associated with PCOS, type 2 diabetes mellitus, cardiovascular diseases, and obesity is the core component relating these underlining disorders to poor COVID-19 outcomes. Obesity (the main comorbid factor for COVID-19) is found in 30%–70% of PCOS patients, which causes stimulation of the inflammatory response and increases micro particles release, leading to increased COVID-19 mortality. PCOS patients are at an increased risk of COVID-19 infection and should be encouraged to follow infection control measures during the COVID-19 pandemic, and therapy must be tailored for those patients. Finally, additional studies on the molecular mechanisms underlying COVID-19 and PCOS and MPs as valuable biomarkers are warranted.

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