Endothelial Progenitor Cell Dysfunction in Polycystic Ovary Syndrome: Implications for The Genesis of Cardiovascular Diseases

Yu-Hsun Kao, Ph.D.1,2#, Wan-Chun Chiu, Ph.D.3#, Ming-I Hsu, M.D.4, Yi-Jen Chen, M.D., Ph.D.2,5*
1. Department of Medical Education and Research, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
2. Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan
3. School of Nutrition and Health Sciences, Taipei Medical University, Taipei, Taiwan
4. Department of Obstetrics and Gynecology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
5. Division of Cardiovascular Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan

Abstract
Polycystic ovary syndrome (PCOS), the most common endocrine disorder affecting women of reproductive age, is characterized by hyperandrogenism and insulin resistance. Women with PCOS have a higher risk for cardiovascular diseases (CVDs) and endothelial dysfunction. The mechanisms underlying these risks are unclear. Human peripheral blood contains circulating endothelial progenitor cells (EPCs) derived from bone marrow that have the ability to proliferate and differentiate into mature endothelial cells, which may contribute to vessel homeostasis and repair. PCOS is associated with insulin resistance, hyperinsulinemia, and dyslipidemia, which may result in EPC dysfunction. In this review, we summarize the potential mechanisms of EPC dysfunction in PCOS, which possibly result in a higher genesis of CVDs in PCOS-affected subjects.

Keywords: Polycystic Ovary Syndrome, Progenitor Cells, Cardiovascular Disease, Endothelial

PCOS and CVDs
PCOS-affected women have a number of reproductive and metabolic abnormalities. Previous studies of PCOS women with body mass index (BMI)-matched controls have proposed several CVD risk factors related to PCOS (17, 18). PCOS is frequently associated with obesity, elevated blood pressure, and dyslipidemia (19, 20); all of which are important risk factors for CVDs. PCOS patients have increased non-traditional risk factors for CVDs, such as elevated homocysteine (21-23), C-reactive protein (24), plasminogen activator inhibitor-1 (25), and fibrinogen (26) levels. In addition, our previous study has found evidence of a widening QRS complex (a biomarker for heart failure) on elec-

Received: 16 Apr 2012, Accepted: 1 Sep 2012
* Corresponding Address: Division of Cardiovascular Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
Email: a9900112@ms15.hinet.net
# The first two authors equally contributed to this manuscript.
trocardiogram in PCOS patients (27).

Through a calcium score analysis, PCOS patients had increased prevalence of coronary artery disease (CAD) independent of BMI and age. Shroff et al. have reported a correlation between CAD and PCOS using coronary artery calcium and inflammatory markers (28). Therefore, PCOS is an important risk factor for CAD. PCOS patients also have an increased risk of cerebrovascular diseases (29). Increased carotid intimal-medial thickness and carotid atherosclerotic plaque index scores have been reported in PCOS patients (30, 31). Asymmetrical dimethyl-L-arginine (ADMA) is an endogenous nitric oxide synthase (NOS) inhibitor, which can induce atherosclerosis and serve as an independent marker for cardiovascular morbidity (32). PCOS women have elevated ADMA (33), which may induce endothelial dysfunction in these patients. The above findings suggest that CVD risk, as reflected by endothelial dysfunction, is increased in PCOS patients. Table 1 summarizes the clinical evidence of PCOS in CVDs.

**EPC dysfunction contributes to CVDs**

EPCs play critical roles in endothelial function and the genesis of atherosclerosis (34, 35). Bone marrow-derived peripheral EPCs can home to sites of vessel growth, where they proliferate and differentiate into mature endothelial cells for neovascularization (10). Aging, diabetes, hypercholesterolemia, and stroke are associated with impaired neovascularization, which may be caused by EPC dysfunction (36, 37). Peripheral EPCs isolated from CAD patients are significantly declined, revealing an impaired migratory response (38). Similarly, decreased EPCs may result in a poor outcomes after ischemic stroke (39).

Circulating EPC numbers and function were significantly reduced in diabetic patients with peripheral artery disease (PAD), and the severity of carotid stenosis was negatively correlated with the EPC number in these patients (40). In addition, angiotensin II and oxidative stress possibly contribute to reduced EPC number and function through activation of the AT1a receptor (41). Therefore, EPCs significantly contribute to the pathophysiology of CVDs.

**Potential EPC disorders in PCOS**

Endothelial dysfunction is a common finding in PCOS patients (13, 42). EPCs have been shown to play a critical role in regulating endothelial function (43-45). According to recent studies, PCOS patients have reduced EPC numbers and impaired EPC function along with increased central arterial stiffness. Our studies have reported the presence of hyperinsulinemia and insulin resistance in PCOS patients (46, 47), which may result in EPC dysfunction through increased reactive oxygen species and impaired insulin signaling (48). When EPCs from insulin-resistant Zucker fatty rats were exposed to tumor necrosis factor-α, there was increased apoptosis and decreased AKT phosphorylation in the EPCs, which suggested that inflammation could induce EPC dysfunction. In addition, our studies found that hyperglycemia significantly modulated peroxisome proliferator-activated receptor and cardiac inflammation (49, 50), which were effects that have been shown to impair EPC function (51). Since PCOS is associated with a hyper-inflammatory status, inflammation-related EPC dysfunction could contribute to increased CVDs in PCOS patients. According to Gallagher et al. diabetic mice have an approximately 50% reduction in circulating EPCs compared to non-diabetic controls (52). PCOS is frequently combined with obesity, which can induce inflammation and oxidative stress, thus resulting in (42) EPC dysfunction. Oxidized low-density lipoprotein has been shown to impair EPC migration and endothelial NOS. Therefore, dyslipidemia from PCOS can also produce EPC dysfunction.

The prevalence of insufficient vitamin D is higher in PCOS patients (53). Vitamin D dysregulation and deficiency is correlated with CVDs and affects EPCs (54, 55). Therefore, administration of vitamin D may have beneficial effects on CVD risk factors in PCOS patients (56-58). Accordingly, vitamin D deficiency may reduce the EPC number and function in PCOS patients as a result of developing CVDs. Various environmental chemical toxicants have also been implicated in endocrine disruption that may be associated with PCOS. PCOS patients have a higher blood level of bisphenol A (BPA), an estrogenic endocrine-disrupting chemical used to produce plastics (59). Since chemical toxicants increase CVDs and are known to affect EPCs (60, 61), it is possible that chemical toxicants may reduce the EPC number and function in PCOS patients, thus increasing CVDs.
Conclusion

PCOS is an independent marker of long-term cardiovascular risk and plays an important role in the pathophysiology of CVDs. EPCs maintain endothelial repaired capacity in mature blood vessels. Impaired EPC number and function will produce endothelial dysfunction and CVD progression (Fig 1). Therefore, EPC dysregulation may contribute to the genesis of CVDs in PCOS patients.

Acknowledgements

The present work was supported by grants from Taipei Medical University, Wan Fang Hospital (100TMU-WFH-02-3 and 99TMU-WFH-03-4). There is no conflict of interest in this article.

References

1. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004; 89(6): 2745-2749.
2. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. J Clin Endocrinol Metab. 1998; 83(9): 3078-3082.
3. Asunciòn M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected caucasian women from Spain. J Clin Endocrinol Metab. 1998; 83(9): 3078-3082.
4. Asgharnia M, Mirblook F, Soltani MA. The prevalence of polycystic ovary syndrome (PCOS) in high school students in Rasht in 2009 according to NIH criteria. Int J Fertil Steril. 2011; 4(4): 156-159.
5. Cibula D, Čifková R, Fanta M, Poledne R, Zivyň J, Skibová J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. Hum Reprod. 2000; 15(4): 785-789.
6. de Groot PC, Dekkers OM, Romijn JA, Dieben SW,
EPC Dysfunction in PCOS

Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum Reprod Update. 2011; 17(4): 495-500.

7. Moran LJ, Cameron JD, Strauss BJ, Teede HJ. Vascular function in the diagnostic categories of polycystic ovary syndrome. Hum Reprod. 2011; 26(8): 2192-2199.

8. Asahara T, Masuda H, Takahashi T, Kalka C, Pastore C, Silver M, et al. Bone marrow origin of endothelial progenitor cells responsible for postnatal vasculogenesis in physiological and pathological neovascularization. Circ Res. 1999; 85(3): 221-228.

9. Asahara T, Takahashi T, Masuda H, Kalka C, Chen D, Iwaguro H, et al. VEGF contributes to postnatal neovascularization by mobilizing bone marrow-derived endothelial progenitor cells. EMBO J. 1999; 18(14): 3964-3972.

10. Takahashi M, Masuda H, Chen D, Silver M, Kearney M, et al. Ischemia- and cytokine-induced mobilization of bone marrow-derived endothelial progenitor cells for neovascularization. Nat Med. 1999; 5(4): 434-438.

11. Gharakhani M, Nghab N, Marzie F. Is reducing ovarian volume in polycystic ovarian syndrome patients after administration of metformin associated with improving cardiovascular risk factors. Int J Fertil Steril. 2011; 5(2): 90-95.

12. Alexandraki K, Protopogerou AD, Papaioannou TG, Piperi C, Mastorakos G, Lekakis J, et al. Early microvascular and macrovascular dysfunction is not accompanied by structural arterial injury in polycystic ovary syndrome. Hormones (Athens). 2006; 5(2): 126-136.

13. Paradisi G, Steinberg HO, Hempfling A, Cronin J, Hook G, Shepard MK, et al. Polycystic ovary syndrome is associated with endothelial dysfunction. Circulation. 2001; 103(10): 1410-1415.

14. Kelly CJ, Speirs A, Gould GW, Petrie JR, Lyall H, Connell JM. Altered vascular function in young normal-weight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001; 87(2): 742-746.

15. Ono F Jr, Palomba S, Cascella T, De Simone B, Di Biase S, Russo T, et al. Early impairment of endothelial structure and function in young normal-weight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2004; 89(9): 4588-4593.

16. Diamanti-Kandarakis E, Alexandraki K, Protopogerou A, Piperi C, Papamichael C, Aessopos A, et al. Metformin administration improves endothelial function in women with polycystic ovary syndrome. Eur J Endocrinol. 2005; 152(5): 749-756.

17. Guzik DS. Cardiovascular risk in PCOS. J Clin Endocrinol Metab. 2004; 89(8): 3694-3695.

18. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: Results from the National Institutes of Health—National Heart, Lung, and Blood Institute sponsored Women’s Ischemia Syndrome Evaluation. J Clin Endocrinol Metab. 2008; 93(4): 1276-1284.

19. Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, Chrousos OP. Pathophysiology and types of dyslipidemia in PCOS. Trends in Endocrinol Metab. 2007; 18(7): 260-285.

20. Ben Salem Hachmi L, Ben Salem Hachmi S, Bouzid C, Younis N, Smida H, Bouguerra R, et al. Hypertension in polycystic ovary syndrome. Arch Mal Coeur Vaiss. 2006; 99(7-8): 687-690.

21. Badawy A, State O, El Gawad SS, El Aziz OA. Plasma homocysteine and polycystic ovary syndrome: the missed link. Eur J Obstet Gynecol Reprod Biol. 2007; 131(1): 68-72.

22. Salehpour S, Manzor-al-ajdad O, Samani EN, Abadi A. Evaluation of homocysteine levels in patients with polycystic ovarian syndrome. Int J Fertil Steril. 2011; 4(4): 168-171.

23. Salehpour S, Broujeni PT, Samani EN. Leptin, ghrelin, adiponectin, homocysteine and insulin resistance related to polycystic ovary syndrome. Int J Fertil Steril. 2008; 2(3): 101-104.

24. Boulman N, Levy Y, Leiba R, Shachar S, Linn R, Zinder O, et al. Increased C-reactive protein levels in the polycystic ovary syndrome: a marker of cardiovascular disease. J Clin Endocrinol Metab. 2004; 89(5): 2160-2165.

25. Lin S, Huiya Z, Bo L, Wei W, Yongmei G. The plasminogen activator inhibitor-1 (PAI-1) gene −844 A/G and −675 4G/5G promoter polymorphism significantly influences plasma PAI-1 levels in women with polycystic ovary syndrome. Endocrine. 2009; 36(3): 503-509.

26. Manneras-Holm L, Baghaei F, Holm G, Janson PO, Ohlsson C, Lonn M, et al. Coagulation and fibrinolytic disturbances in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2011; 96(4): 1068-1076.

27. Huang JH, Tsai JC, Hsu MI, Chen VJ. Cardiac conductive disturbance in patients with polycystic ovary syndrome. Gynecol Endocrinol. 2010; 26(12): 883-888.

28. Shroff R, Kerchner A, Maifeld M, Van Beek EJ, Jagasia D, Dokras A. Young obese women with polycystic ovary syndrome have evidence of early coronary atherosclerosis. J Clin Endocrinol Metab. 2007; 92(12): 4609-4614.

29. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. Clin Endocrinol. 2000; 52(5): 595-600.

30. Talbott EO, Guzik DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zbrowski JV, Remsberg KE, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler Thromb Vasc Biol. 2000; 20(11): 2414-2421.

31. Vryonidou A, Papatheodorou A, Tavridou A, Terzi T, Loi V, Vatalas IA, et al. Association of hyperandrogenemic and metabolic phenotype with carotid intima-media thickness in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005; 90(5): 2740-2746.

32. Heuting D, Schulz H, Nickel I, Kleinjein J, Kaltwasser P, Westphal S, et al. Asymmetrical dimeth-
ylarginine, inflammatory and metabolic parameters in women with polycystic ovary syndrome before and after metformin treatment. J Clin Endocrinol Metab. 2008; 93(1): 82-90.
33. Boulman N, Levy Y, Leiba R, Shachar S, Linn R, Zinder O, et al. Increased C-reactive protein levels in the polycystic ovary syndrome: a marker of cardiovascular disease. J Clin Endocrinol Metab. 2004; 89(5): 2160-2165.
34. Xiao Q, Kiechl S, Patel S, Oberhollenzer F, Weger S, Mayr A, et al. Endothelial progenitor cells, cardiovascular risk factors, cytokine levels and atherosclerosis - results from a large population-based study. PLoS One. 2007; 2(10): e975.
35. Fadini GP, Agostini C, Sartore S, Avogaro A. Endothelial progenitor cells in the natural history of atherosclerosis. Atherosclerosis. 2007; 194(1): 46-54.
36. Dickling G, Salam A, Mohammad A, Hussain MS, Scozzafava J, Nasser AM, et al. Circulating endothelial progenitor cells and age-related white matter changes. Stroke. 2009; 40(10): 3191-3196.
37. Georgescu A, Alexandru N, Constantinescu A, Titoencu I, Popov D. The promise of EPC-based therapies on vascular dysfunction in diabetes. Eur J Pharmacol. 2011; 669(1-3): 1-6.
38. Vasa M, Fichtlscherer S, Aicher A, Adler K, Urbich C, Martin H, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. Circ Res. 2001; 89(1): e1-7.
39. Sobrino T, Hurtado O, Moro MA, Rodríguez-Yañez M, Castellanos M, Brea D, et al. The increase of circulating endothelial progenitor cells after acute ischemic stroke is associated with good outcome. Stroke. 2007; 38(10): 2759-2764.
40. Fadini GP, Sartore S, Albiero M, Baesso I, Murphy E, Menegolo M, et al. Number and function of endothelial progenitor cells as a marker of severity for diabetic vasculopathy. Arterioscler Thromb Vasc Biol. 2006; 26(9): 2140-2146.
41. Endtmann C, Ebrahimiann T, Czech M, Affo A, Laufs U, Fritz M, et al. Angiogenesis in the polycystic ovary syndrome: a marker of severity for diabetic vasculopathy. Arterioscler Thromb Vasc Biol. 2006; 26(9): 2140-2146.
42. Camina E, Ori F, Palomba S, Longo RA, Cassella T, Colao A, et al. Endothelial dysfunction in PCOS: role of obesity and adipose hormones. Am J Med. 2006; 119(4): 356-361.
43. Zampetaki A, Kirtop J, Xu Q. Vascular repair by endothelial progenitor cells. Cardiovasc Res. 2008; 78(3): 413-421.
44. Sen S, McDonald SP, Coates PT, Bonder CS. Endothelial progenitor cells: novel biomarker and promising cell therapy for cardiovascular disease. Clin Sci (Lond). 2011; 120(7): 263-283.
45. Masuda H, Asahara T. Post-natal endothelial progenitor cells for neovascularization in tissue regeneration. Cardiovasc Res. 2003; 58(2): 390-398.
46. Liang SJ, Hsu CS, Tseng CR, Chen CH, Hsu MI. Clinical and biochemical presentation of polycystic ovary syndrome in women between the ages of 20 and 40. Hum Reprod. 2011; 26(12): 3443-3449.
47. Hsu CS, Wu CH, Chiu WC, Lee CT, Chang CJ, Hsu MI. Obesity and insulin resistance in women with polycystic ovary syndrome. Gynecol Endocrinol. 2011; 27(5): 300-306.
61. Biemann R, Navarrete Santos A, Navarrete Santos A, Riemann D, Knelangen J, Blüher M, et al. Endocrine disrupting chemicals affect the adipogenic differentiation of mesenchymal stem cells in distinct ontogenetic windows. Biochem Biophys Res Commun. 2012; 417(2): 747-752.

62. Glueck CJ, Morrison JA, Goldenberg N, Wang P. Coronary heart disease risk factors in adult premenopausal white women with polycystic ovary syndrome compared with a healthy female population. Metabolism. 2009; 58(5): 714-721.

63. Sharpless JL. Polycystic ovary syndrome and the metabolic syndrome. Clin Diabetes. 2003; 21(4): 154-161.

64. Talbott EO, Zborowski JV, Sutton-Tyrrell K, McHugh-Pemu KP, Guzick DS. Cardiovascular risk in women with polycystic ovary syndrome. Obstet Gynecol Clin North Am. 2001; 28(1): 111-133.