International Journal of Impotence Research (2005) 17, 288–290
 0955-9930/05 $30.00
www.nature.com/ijir

Circulating endothelial progenitor cells in subjects with erectile dysfunction

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Erectile dysfunction (ED) is often the first clinical sign of endothelial dysfunction and may precede overt cardiovascular diseases. Bone marrow-derived endothelial progenitor cells migrate into the peripheral circulation to promote endothelial repair. The number of circulating progenitor cells is reduced in patients with cardiovascular risk factor. The objective of our study was to determine the number of these cells in patients with ED both with and without cardiovascular risk factors. These subjects have lower number of circulating progenitor cells, confirming the existence of an endothelial dysfunction and supplying the evidence that ED may be the first symptom of an endothelial damage.
International Journal of Impotence Research (2005) **17,** 288–290. doi:10.1038/sj.ijir.3901311
Published online 24 February 2005

Keywords: circulating endothelial progenitor cells; erectile dysfunction

Introduction

Erectile dysfunction (ED) frequently affects men with underlying cardiovascular diseases (CVD). Epidemiological studies show that ED and CVD share common risk factors such as hypertension, diabetes, smoking, and hyperlipidemia. Common denominator of these clinical situations is an endothelial dysfunction, characterized by a disturbance in the endothelial monolayer that triggers the atherosclerotic process.[1]

Recently, it has been demonstrated that injured endothelial monolayer is regenerated by circulating bone marrow-derived endothelial progenitor cells (EPCs).[2] These cells have the capacity to migrate into the peripheral circulation and to differentiate into mature endothelial cells, thus providing a circulating pool of cells that may contribute to ongoing endothelial repair.

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Received 29 November 2004; revised 15 December 2004; accepted 27 December 2004

The number of circulating EPCs is reduced in patients with overt CVD or with risk factors for CVD and negatively correlates with Framingham cardiovascular risk factors score.[1] Furthermore, healthy subjects with endothelial dysfunction have a reduced number of circulating EPCs.[1] Therefore, the reduction in circulating EPCs has been suggested to play a role in the atherosclerosis disease progression.

The mobilization of stem cells from the bone marrow is dependent on local activity of endothelial nitric oxide synthase (eNOS).[3] Nitric oxide (NO) is generated mainly by vascular cells of the bone marrow stroma, and acts in a paracrine manner to induce mobilization of EPCs, therefore increasing the number of these cells in the circulation.[4]

In this study, we show that patients with ED, with or without cardiovascular risk factors, have a reduced number of circulating EPCs.

Patients and methods

After approval by local ethics committee of the University of Padova, 28 consecutive patients with ED and 22 controls gave informed consent and were enrolled in this study. The patients were aged 35–50

years (mean ± s.d., 45.3 ± 6.2), and had a history of 6–12 months of ED, defined as the consistent inability to obtain and/or maintain an erection for satisfactory sexual intercourse. ED was assessed by an International Index of Erectile Function (IEEF-5) value <21. ED was confirmed in all patients with Nocturnal Penile Tumescence and Rigidity Monitoring (NPTRM) carried out with the RigiScan Plus Rigidity Assessment System (Dacomed, USA) performed in two consecutive nights.[5] Based on clinical history and biochemical blood exams, 13 of 28 patients had cardiovascular risk factors (three smoking, four hypertension, five hypercholesterolemia, and one smoking and hypertension). The remaining 15 patients were considered free of cardiovascular risk factors. Controls were aged 35–50 years (mean ± s.d., 44.8 ± 8.2), with a normal erectile function (IEEF-5 > 21) and without cardiovascular risk factors, based on clinical history and biochemical blood exams.

Blood samples were taken from each subject in heparinized tubes and evaluated by flow cytometry within 6 h as described previously.[6] Briefly, analysis was performed on 100 µl of peripheral blood incubated with fluorescein isothiocyanate-labeled monoclonal antibodies against human CD34 (Becton Dickinson) and allophycocyanin-labeled monoclonal antibodies against human AC133 (Miltenyi Biotec). These markers allow isolation of circulating PC by flow cytometric analysis.[6] The number of circulating PC is expressed as absolute number/ml. Before applying flow cytometry analysis on the patients, control samples were studied in triplicate, on different days, and at different hours of the day to validate the test. These data confirmed the validity of the analysis.

Results

The number of PCs in peripheral blood of patients affected by ED were significantly reduced with respected to controls (862.4 ± 345.1 *vs* 1903.5 ± 558.6, $P<0.001$) (Figure 1). Mean PC values were not different between ED patients with (793.4 ± 310.1) and without (922.3 ± 372.8) cardiovascular risk factors.

Discussion

The results of this study demonstrate that in patients affected by ED, the number of circulating PCs is significantly reduced. Although this finding was expected in ED patients with cardiovascular risk factors,[1] a reduction in the number of circulating PCs in ED patients without any cardiovascular risk factor is very intriguing. These data suggest the existence in these subjects of an endothelial damage,

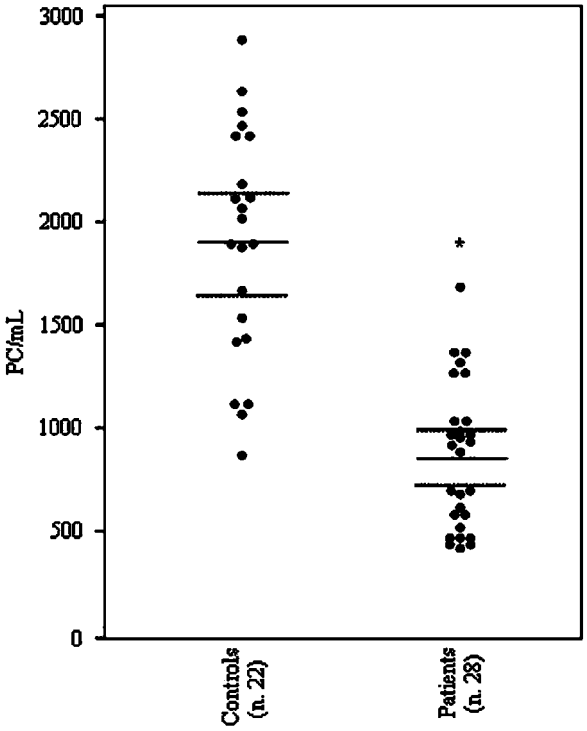

Figure 1 Individual determinations of PCs numbers (PC/ml) in controls and subjects with ED. Continuous and dashed lines indicate the mean value and the 95% confidence intervals, respectively. Mean ± s.d. are as follows: controls, 1903.5 ± 558.6 PC/ml (range 910–2839 PC/ml, 95% CI 1655.8–2151.2 PC/ml); ED patients, 862.4 ± 345.1 PC/ml (range 445–1721 PC/mL, 95% CI 728.6–996.2 PC/mL). *$P<0.001$ *vs* controls.

confirming recent studies reporting that ED may represent the first clinical manifestation and a reliable predictor of peripheral vascular diseases.[7] Indeed, an intact and functioning endothelium is fundamental in maintaining the vascular mechanisms of arterial relaxation and venous constriction and therefore a normal erectile function. Reduced numbers of circulating EPCs are observed in patients with cardiovascular risk factors and in healthy subjects with endothelial dysfunction.[1]

In conclusion, our study shows for the first time that patients with ED, both with and without cardiovascular risk factors, have a lower number of circulating EPCs probably as a result of a generalized endothelial dysfunction.

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