Effects of Immunosoppressive Therapy on Endothelial Progenitor Cells in Kidney Transplantation

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INTRODUCTION

Endothelial dysfunction contributes to accelerated atherosclerosis in chronic kidney disease (CKD) . Endothelial dysfunction and endothelial regenerative capacity play a key role in the pathogenesis of cardiovascular disease (CVD) also in CKD.

Endothelial Progenitor Cells (EPCs) are bone marrow-derived cells and constitute an endogenous vascular repair system protecting against atherosclerosis. Through different steps (recruiting, mobilization, homing, differentiation) they are able to produce tissue neovascularisation and post-traumatic endothelial regeneration[1,2,3].

Circulating Endothelial cells (CECs) are mature endothelial cells and represent a further differentiative step of EPCs, with loss of markers of early staminality. In response to injury, EPCs, recruitment from the bone marrow, are able to differentiate into mature cells and to restore endothelial integrity.

In CKD, vascular progenitor cell availability and function may be adversely affected by several reason[4] (rise in ADMA levels, chronic inflammatory condition, uremic toxins, secondary hyperparathiroidism, vitamin D deficiency, mobilization factors deficiency [VEGF and SGF-1]). Many pharmacologic strategy seem to improve number and function of vascular progenitor cell (inhibitors of HMG-CoA reductase, RAAS blockers, thiazolidinediones, erythropoietin)[5].

OBJECTIVES

Aim of our study is to evaluate the **number of EPCs and CECs,** through cytofluorimetry analysis, **in kidney transplant recipients (KTR) and healthy blood donors (HBD).** We also investigate possible influences in the number of EPCs and CECs by *different immunosoppressive regimens, glomerular filtration rate (GFR), established cardiovascular risk factors.*

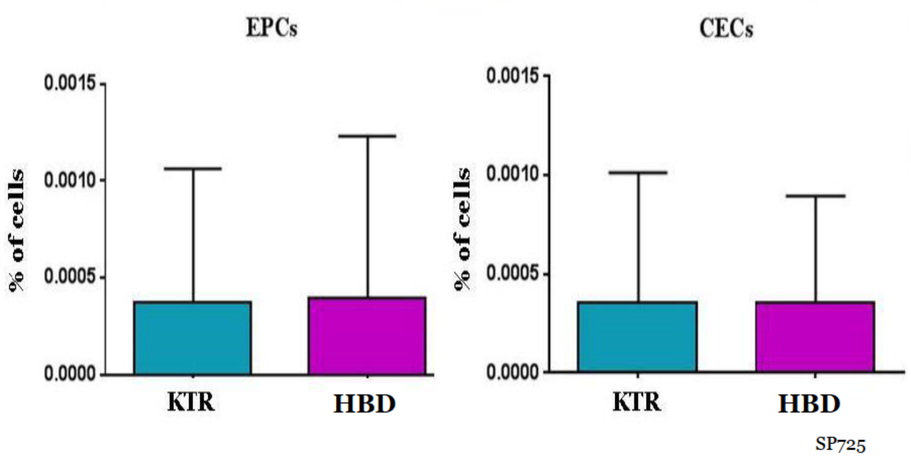
MATHERIALS and METHODS

We considered **51 KTR** and **25 HBD** that met inclusion and exclusion criteria (e.g. 10ml/min≤GFR≤90ml/min; time after transplantation ≥ 3 months; no any type cancer; no recent acute vascular events or acute infections; no chronic inflammatory disease; no graft rejection in the previous 3 months). After local Ethics Committee approval, informed consent was obtained from all participants (KTR and HBD).
The number of EPCs and CECs was determined by detection and counting with sequential gating with Attune® Acoustic Focusing Flow Cytometry staining with **CD14, CD45, CD34, CD133, KDR (VEGFR) antibodies**.

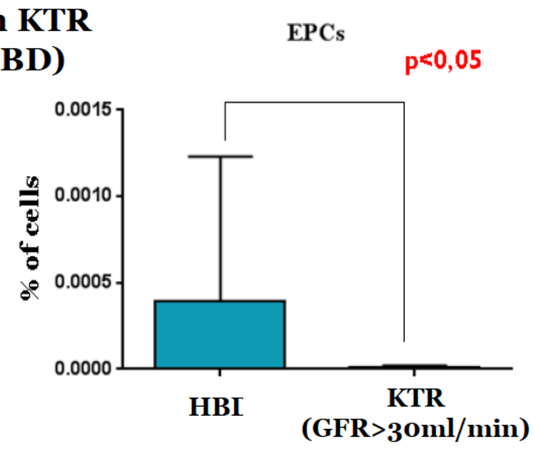
REFERENCES
1. Hristov M. Pharmacol Res 2008; 58: 148–151 2. Hirschi KK. Arterioscler Thromb Vasc Biol 2008; 28:1584–1595 3. Hristov M. Drug Discov Today 2008; 5:e267–e271 4. Herbring K. Kidney Blood Press Res 2006; 29: 24-31
5. Kim EJ. NDT 2010; 25: 1825-1882 6. Krenning G. Am J Physiol Renal Physiol 2009; 296: F1314-F1321

RESULTS

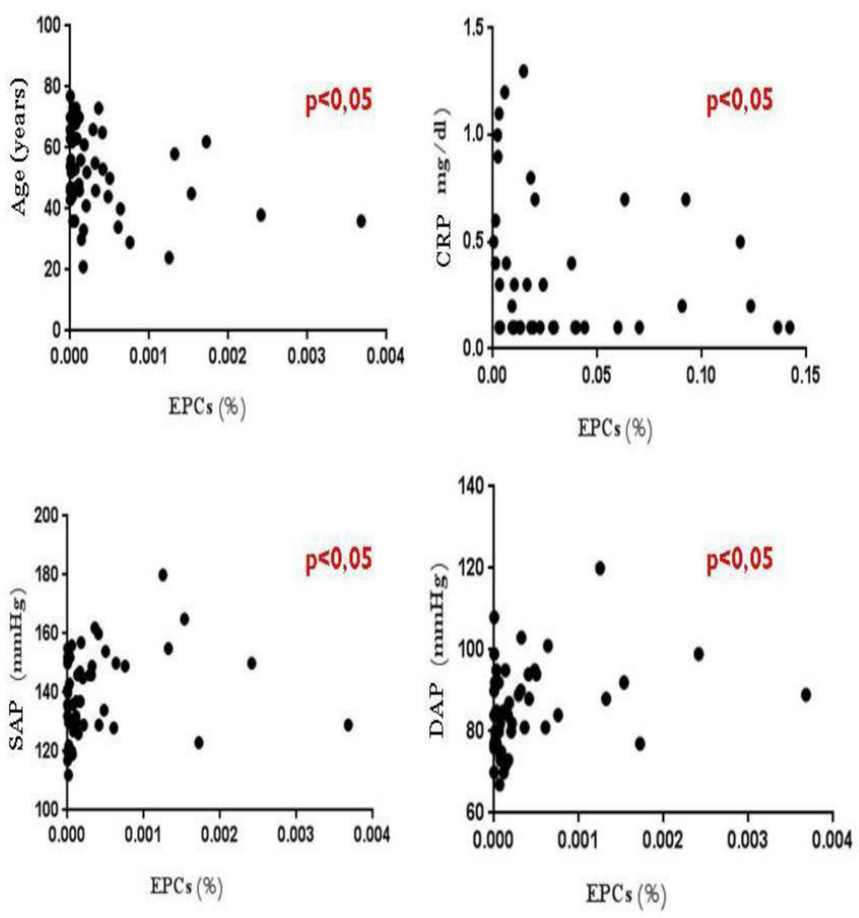
1. No difference in EPCs and CECs between KTR and HBD



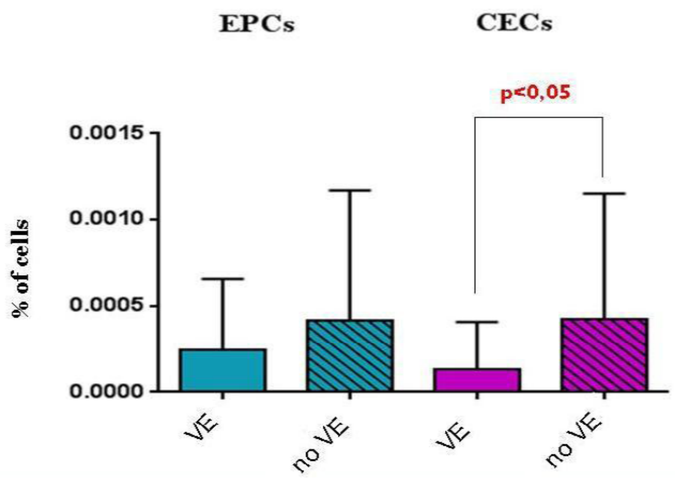
2. EPCs significantly lower in KTR with GFR <30ml/min (vs HBD)



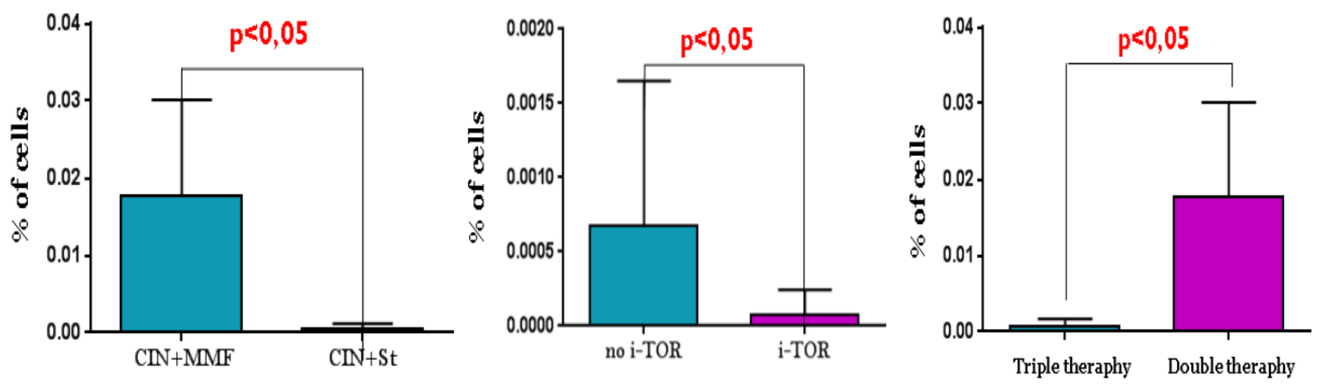
3. Number of EPCs was inversely related with age, systolic and diastolic blood pressure, C-reactive protein



4. CECs resulted significantly and negatively influenced by the presence of a previous vascular event



5. EPCs resulted significantly lower in KTR receiving steroid and in KTR receiving mTOR-i



CONCLUSIONS

We find out **in our KTR population a number of EPCs and CECs comparable with HBD**; notwithstanding the higher CVD risk in KTR renal transplantation seems to keep intact the physiological vascular repair system.

Some factors however result to interfere on EPCs and CECs number in KTR:
- a **GFR<30ml/min** shows a significant negative difference vs HBD, probably due to the progression of the uremic state.
- EPCs value is inversely related to **CRP**, key marker for inflammatory state: a factor for manteinance of vascular damage.
- CECs number is significantly dependent on the presence of **previous CV events**
- **steroid treatment** has a detrimental effect on % number of EPCs.

In summary ***EPCs act as an emerging marker of CV risk***, helping assessing the "*global vascular competence*" and may support clinical decision in *tailoring immunosoppressive therapies* in KTR.

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