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**Human Wharton's Jelly Umbilical Cord-Mesenchymal Stem Cells (HWJUC-
MSC)'s Exosomes Ameliorate Endothelial Dysfunction, Vascular Remodeling,
and Angiogenesis via HIF-1 α -independent Pathway in Prolonged Kidney
Ischemia/Reperfusion Injury**

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Objectives : This study aimed to explore the effects of HWJUC-MSC exosomes on endothelial dysfunction, vascular remodeling, and angiogenesis in prolonged renal I/R

Methods : Male 16-20 weeks Wistar rats (n=25) were equally grouped into 5: sham-operated (SO), I/R group, and 3 groups treated with low-, medium-, and high-dose of exosomes. I/R and exosome groups were subjected to bilateral renal pedicle clamping for 45 minutes, followed by reperfusion. Exosomes were injected via tail vein on day-1 after clamping. After 21 days, all rats were sacrificed. Serum creatinine was obtained for functional analysis. Wall thickness of intrarenal arteries was assessed by Sirius Red staining followed by quantitative analysis using ImageJ software. Expression of renal eNOS, ET-1, ETaR, ETbR, VEGF, CD34, and HIF-1 α was measured using RT-PCR. Immunohistochemistry of CD34+ as a marker of vascular progenitor cells was performed to qualitatively assess abundance and localize angiogenesis. One-Way ANOVA with post hoc LSD was used to analyze the data.

Results : The high-dose exosome group showed the highest reduction of serum creatinine compared to other groups (p<0.05). Exosome groups had lower wall thickness compared to the I/R group (p<0.01). Kidney expression of eNOS and ETbR was significantly higher in high-dose exosome group compared to I/R group (p=0.03 and p<0.01 respectively). Lower ET-1 (p=0.03) and ETaR (p=0.01) expression was observed in high-dose exosome group compared to SO and I/R groups. Moreover, expression of angiogenic factors, VEGF and CD34, was higher in high-dose exosome group compared to I/R group (p=0.01 and p=0.03 respectively). Nevertheless, there was no difference of HIF-1 α expression among those groups.

Conclusions : Exosomes derived from HWJUC-MSC significantly attenuate endothelial function, vascular remodeling, and enhance angiogenesis via HIF-1 α independent manner in prolonged renal I/R.