Spironolactone as Add-On Therapy to Chlorthalidone Improves Endothelial Function, Arterial Stiffness and Insulin Resistance in European and African American Patients with Essential Hypertension – A Double-Blind Placebo-Controlled Randomized Study

[1]Dudenbostel T, [1]Whigham T. Jr., [2]Pisoni R., [3]Acelajado MC, [1]Calhoun DA

[1]Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, USA; [2]Division of Nephrology, Department of Medicine, Medical University of South Carolina, Charleston, SC, USA; [3]Department of Medicine, University of South Alabama, Mobile, AL, USA

Diuretics have been shown to have a neutral effect on cardiovascular (CV) biomarkers like arterial stiffness and endothelial function despite their blood pressure (BP) lowering effect. Thiazide diuretics generally have harmful effects on glucose metabolism, however, the effect of mineralocorticoid receptor antagonists on insulin resistance in essential hypertension (eHTN) is only partially elucidated. We hypothesized that chlorthalidone (CHT) in combination with spironolactone (SPL) results in better arterial compliance then CHT therapy alone through additional improvement of glucose metabolism parameters.

Methods: This double-blind placebo-controlled randomized single center study aimed to identify SPL add-on therapy to CHT treatment alone on CV risk markers such as BP, 24-h ambulatory blood pressure monitoring (24-H ABPM), aortic BP (aBP), augmentation index (AIx), pulse wave velocity (cfPWV), flow- mediated dilation (FMD), fasting glucose, plasma insulin levels and insulin sensitivity (by homeostasis model assessment: HOMA-IR). A total of 34 patients (21.7% male, 40% white) were randomized to either CHT 25 mg + Placebo or CHT 25 mg + SPL 25 mg once daily. At baseline and after 3 months office BP, 24-H ABPM, markers of arterial stiffness, FMD, fasting glucose, plasma insulin levels and HOMA-IR.

Results: The study showed statistically significant improvements after three months in patients treated with CHT+ SPL in clinic BP, 24-hour ABPM, FMD, markers of arterial stiffness, and glucose metabolism. In detail, clinic SBP (131.5±14.6 to 119.1±14.3 mmHg (P = 0.034), aortic SBP (122±13 vs 113±13.7 mm Hg, p = 0.048), 24-H ABPM SBP (151.5±15.1 to 131.7 ±10.4 mm Hg, p=0.0049, 24-H ABPM DBP 83.2±6.1 to 74 ±9.3 mm Hg, p=0.032, 24-H ABPM. Fasting plasma glucose, plasma insulin levels decreased and insulin sensitivity (by homeostasis model assessment: HOMA-IR) improved with SPL as compared to CHT alone (p<0.001), AIx (28±9 versus 25.4± 6.9 %) and cfPWV (9±2 vs 7.5±1.8 m/s) in the CHT+SPL group. Endothelial function improved significantly in the CHT +SPL group as compared to the control group (5.5 ± 1.7 to 8.8 ± 2.7 (p = 0.004)).

Conclusion: These results suggest that SPL as add-on therapy to CHT improves BP, markers of arterial compliance, and glucose metabolism in patients with eHTN, while CHT only therapy may have unfavorable effects. Treatment with SPL additional to CHT may represent a novel approach to improve unfavorable metabolic disturbances and CV risk markers.