Underlying Pathophysiological Mechanisms of Cardiovascular-Kidney Metabolic Syndrome

MECHANISM	MEDIATOR	End-organ Outcome: HEART	End-organ Outcome: KIDNEY
Increased central venous and intra-abdominal pressures	• Increased salt/water retention • Activation of RAAS/SNS	• Acute/chronic HF • Adverse remodeling of heart and lungs	• Renal venous congestion • Reduced GFR
Reduced cardiac output and cardiac index	• Peripheral vasodilation/ reduced vascular resistance • Reduced perfusion pressure	• Activation of RAAS/SNS detrimental to heart • Cardiac ischemia from reduced perfusion	• Reduced renal perfusion • Renal ischemia
Neurohormonal dysregulation • RAAS activation • SNS activation • Adenosine/AVP	• Impaired baroreceptor reflexes • Increased renin secretion • Increased Ang II secretion • Increased aldosterone secretion • Increased ET-1 expression • Oxidative stress	• Myocyte hypertrophy, left ventricular dysfunction • Proinflammation, profibrotic effect • Hypertension	• Arteriolar vasoconstriction • Reduced GFR • Enhanced reabsorption of sodium/water • Proinflammation, profibrotic effect
Oxidative stress	• Increased reactive oxygen species formation • Ang II–enhanced NADPH-oxidase activity • Uremic toxin–mediated cytokine release	• Left ventricular hypertrophy • Accelerated atherosclerosis • Endothelial dysfunction • Inflammation • Fibrosis	• Endothelial dysfunction • Accelerated atherosclerosis • Inflammation • Interstitial fibrosis
Inflammatory mediators	• TNF-α • TWEAK • Members of IL-1 family • IL-6 • CRP	• Atherosclerosis • Inflammation • Left ventricular dysfunction • Cardiac hypertrophy • Myocardial cell death • Fibrosis	• Inflammation • Fibrosis • Atherosclerosis • Glomerular damage by mesangial cell apoptosis
Renal failure–disturbances	• PBUTs (indoxyl sulfate, p-cresyl sulfate) • Chronic inflammatory cytokines • Oxidative stress • FGF-23 • Calcium/phosphate-mediated inflammation • Anemia	• Endothelial dysfunction • Atherosclerosis • Left ventricular dysfunction • Cardiac hypertrophy	• Atherosclerosis • Inflammation • Increased interstitial and perivascular fibrosis

Table adapted from Kumar, et al. 2019.

Ang II, angiotensin II; AVP, arginine vasopressin; CRP, C-reactive protein; ET-1, endothelin-1; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate; IL, interleukin; PBUTs, protein-bound uremic toxins; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TNF- , tumor necrosis factor alpha; TWEAK, tumor necrosis factor alpha–related weak inducer of apoptosis.

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