Obesity and Insulin Resistance in Resistant Hypertension: Implications for the Kidney

Akhilesh Rao, Vishwam Pandya, and Adam Whaley-Connell

There is recognition that the obesity epidemic contributes substantially to the increasing incidence of CKD and resistant hypertension (HTN). The mechanisms by which obesity promotes resistance are an area of active interest and intense investigation. It is thought that increases in visceral adiposity lead to a proinflammatory, pro-oxidative milieu that promote resistance to the metabolic actions of insulin. This resistance to insulin at the level of skeletal muscle tissue impairs glucose disposal/utilization through actions on the endothelium that include vascular rarefaction, reductions in vascular relaxation, and vascular remodeling. Insulin resistance derived from increased adipose tissue and obesity has system-wide implications for other tissue beds such as the kidney that affects blood pressure regulation. The additional autocrine and paracrine activities of adipose tissue contribute to inappropriate activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system that promote kidney microvascular remodeling, stiffness, and sodium (Na^+) retention that in turn promote HTN and in the CKD patient, resistance. In this review, we will summarize the important mechanisms that link obesity to CKD as they relate to resistant HTN.

Key Words: Obesity, Insulin resistance, Hypertension, Endothelial dysfunction, RAAS

INTRODUCTION

Despite attempts to curb the growing obesity epidemic, about one-third of the US adult population is obese.[1] In this regard, obesity has been directly or indirectly implicated with various health problems including type 2 diabetes (T2D), hypertension (HTN), and dyslipidemia, with an annual estimated expenditure of approximately 150 billion USD. Of this total, the direct costs to the Centers for Medicare and Medicaid Services account for approximately half of this expenditure.[2] The development of RHTN and CKD related to obesity compounds these costs and contributes substantially to the health care burden related to obesity.[3] The prevalence of RHTN increases with increasing albuminuria and declining estimated glomerular filtration rate (eGFR) to about 48% in those with albumin/creatinine ratio ≥300 mg/g and 33% in those with eGFR ≤45 mL/min/1.73 m^2.[4] Understanding the mechanisms by which obesity contributes to RHTN can provide insight into future therapeutic strategies. In this regard, the metabolic derangements associated with obesity and increases in visceral adiposity promote alterations in the vasculature and the kidney that lead to RHTN and CKD.[5] In this context, CKD prevalence is rising and is estimated to be around 13% of the US population, a finding that parallels the increased prevalence of obesity and T2D.[6,7] Data from the National Health and Nutrition Examination Survey and the National Kidney Foundation Kidney Early Evaluation Program have shown parallel rises in the prevalence of obesity, insulin resistance (IR), and CKD supporting an important role for obesity.[8–10]

The presence of obesity, T2D, and HTN are 3 critical cardiovascular risk factors that contribute significantly to the morbidity and mortality observed in the CKD patient. A number of studies have suggested that there exists a survival advantage for those with obesity in advanced stages of CKD.[11] However, this benefit is attenuated when the obese individual also has HTN, dyslipidemia (low high-density lipoprotein, high triglycerides), and IR.[12] It is believed that increased visceral adipose tissue derived from overnutrition confers a proinflammatory milieu with oxidative stress and ultimately IR.[13,14] It is resistance to the metabolic actions of insulin that leads to reductions in bioavailable nitric oxide (NO), coupled with blunting of the normal endothelial vasodilatory response. In skeletal muscle, this leads to reductions in glucose disposal, and in the kidney, it contributes to sodium (Na^+) retention.[15,16] IR is one mechanism that contributes to the risk of RHTN, and it is highest among obese individuals[17] and in those with CKD. Obesity is also characterized by a state of increased adiposity, especially perivascular adipose tissue. Increases in perivascular adipose tissue is associated with various paracrine and autocrine activities that are involved in vascular inflammation, oxidant stress, and stiffness that lead to the development of atherosclerosis and HTN.[18,19]

The combined presence of both obesity and IR then contributes to inappropriate activation of the sympathetic nervous system (SNS) and the renin-aldosterone-angiotensin system (RAAS) and involvement of adipokines, oxidative stress, and inflammatory pathways that lead to endothelial dysfunction and HTN.[20] Data derived from individuals with stage 3 to 5 CKD suggest that increased indices for IR and inflammation (eg, hsCRP levels) are associated with endothelial dysfunction and atherosclerosis as measured by an increase in brachial artery flow-mediated dilation and carotid artery intima-media thickness, respectively.[13] Furthermore, observational data

From Division of Nephrology and Hypertension, Department of Internal Medicine, University of Missouri-Columbia School of Medicine, Columbia, MO; and Harry S. Truman Memorial Veterans Hospital.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Akhilesh Rao, MD, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Missouri-Columbia School of Medicine, Five Hospital Drive, DC043.00, Columbia, MO 65212. E-mail: raoak@health.missouri.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.12.004

support the prevalence of microalbuminuria increases with the degree of IR and HTN.[21,22] This complex interrelationship between obesity, IR, and high blood pressure can have dramatic implications for the kidney, and the combination of both in the CKD patient contributes substantially to RHTN.

PATHOPHYSIOLOGY OF TREATMENT RESISTANT HYPERTENSION IN OBESITY

There are numerous genetic, environmental, dietary, and behavioral interactions that play a role in the development of HTN in obese individuals. Importantly, the presence of adipocyte dysfunction leads to systemic IR and inappropriate activation of the SNS and the RAAS with local paracrine/autocrine and inflammatory pathways that promote HTN and kidney injury and contribute to overall morbidity and mortality (Fig 1).[23] The combination of obesity, IR, and HTN is often referred to as the metabolic syndrome, now increasingly recognized as the cardiorenal metabolic syndrome that is present in about 25% of the US adult population and 30% of US children and adolescents.[3,24–26]

Insulin Resistance

Understanding the pathways that mitigate IR is important to unravel the importance of RHTN in the CKD patient. IR is a systemic condition indicating a failed response of cells to the metabolic actions of insulin. Resistance to insulin can occur in traditional insulin-sensitive skeletal muscle, adipose, and liver tissue because of an increased hydrolysis of triglycerides within the fat cells and intramyocellular lipids leading to an increased accumulation of lipid metabolites. The accumulation of diacylglycerol (DAG) is a critically important impairment in insulin signaling.[27] Under normal conditions, insulin binds to the insulin receptor leading to phosphorylation of the insulin receptor substrate-1 (IRS-1) that in turn phosphorylates phosphatidylinositol 3-kinase (PI3-K). This attracts protein kinase B/Akt which then phosphorylates the mammalian target of rapamycin (mTOR)-rapamycin-insensitive companion of Tor (Rictor) complex.[28] It has been shown in humans that induction of skeletal muscle IR is associated with increased accumulation of DAG and in turn an inhibition of insulin-stimulated IRS-1 tyrosine phosphorylation and Akt phosphorylation.[29,30]

Activation of PI3-K generates phosphatidylinositol (3,4,5)-triphosphate (PIP3) and phosphoinositide-dependent protein kinase (PDK) 1 and PDK2 that are crucial for Akt activation. mTOR is a Ser/Thr protein kinase belonging to the PI3-K family that exists in 2 distinct complexes called complex (mTORC) 1 containing regulatory associated protein of Tor (Raptor) and complex 2 (mTORC2) that contains Rictor. mTORC2 phosphorylates and activates Akt thereby enhancing insulin signaling. mTORC1 has ribosomal protein S6 kinase (S6K) as its substrate and is involved in promoting lipogenesis, regulating cell growth, and providing feedback inhibition of IRS-1, thereby inhibiting insulin signaling. In contrast, mTORC2 and PDK1 through Akt suppress the Foxo1 forkhead transcription factor that promotes gluconeogenesis. Inactivation of the PI3-K-Akt insulin signaling pathway is key to the development of cell and tissue-level IR.[31] Impaired PI3-K signaling in IR contributes to HTN by not only altering the vasodilatory effect of insulin but also by an enhancement of kidney Na^+ reabsorption. Sodium proton exchanger type 3 (NHE3) and Na-K-ATPase activities in the proximal tubules are increased in IR leading to Na^+ retention and contributing to HTN.[32]

Under normal conditions, insulin engagement of the PI3-K/Akt pathway promotes endothelial NO release to result in vasodilatation.[33] However, impairments in this pathway lead to reductions in bioavailable NO, resulting in a severely impaired endothelial vasodilatory response.[34] Reductions in bioavailable NO are directly related to the development of endothelial dysfunction, arterial stiffness, and kidney disease.[35,36] In fact, alterations in insulin actions in the kidney under conditions of obesity have been implicated in altering tubuloglomerular feedback and promoting Na^+ retention,[37] raising the possibility of kidney arteriole endothelial dysfunction as one of the potential causes for HTN or even RHTN in CKD. Other indirect effects of insulin in the kidney include activation of the intrarenal RAAS,[38] endothelin-1 production by the endothelial cell (leading to vasoconstriction and mesangial cell proliferation),[39] Na^+ retention, and oxidative stress.[40,41] Individuals with IR are noted to have lower eGFR, higher blood urea nitrogen, serum creatinine, and systolic blood pressure.[42] Thus, alterations in insulin's effect on the vasculature and in the kidney are a key mechanism for endothelial dysfunction, Na^+ homeostasis, and HTN.[16,43,44]

CLINICAL SUMMARY

- Obesity contributes to the development of insulin resistance and hypertension (HTN).
- In the CKD patient, it is thought that the combined actions of obesity and insulin resistance contribute to a particularly resistant form of HTN.
- The obese condition is characterized by increases in autocrine and paracrine actions of visceral adipocytes including increased renin-aldosterone-angiotensin system activity and impaired insulin metabolic signaling.
- Alterations in insulin-dependent metabolic pathways contribute to impairments in vascular tone and remodeling and Na^+ homeostasis that contribute to resistant HTN.

Role of Adipokines and Chemokines in Obesity and Insulin Resistance

It is increasingly recognized that visceral adipose tissue is an endocrine organ. Visceral adipose tissue releases adipokines that have a role in fat metabolism, insulin sensitivity, and regulating vascular tone.[45] In this context, adiponectin is a 30-kDa plasma protein that along with leptin and interleukin (IL)-6 are predominant adipokines involved in IR and HTN.[46] Data suggest that increases in abdominal obesity are associated with decreased expression of adiponectin.[47,48] Adiponectin's role in the insulin signaling pathway is mediated by its binding to its receptors