Adipokines as a link between obesity and chronic kidney disease

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1Biomedical and Lifestyle Diseases Unit, College of Health and Biomedicine, Victoria University, St Albans, Victoria, Australia; 2School of Medical Sciences, The Bosch Institute, The University of Sydney, New South Wales, Australia; and 3Department of Physiology, The University of Melbourne, Parkville, Victoria, Australia

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Briffa JF, McAinch AJ, Poronnik P, Hryciw DH. Adipokines as a link between obesity and chronic kidney disease. Am J Physiol Renal Physiol 305: F1629–F1636, 2013. First published October 9, 2013; doi:10.1152/ajprenal.00263.2013.—Adipocytes secrete a number of bioactive adipokines that activate a variety of cell signaling pathways in central and peripheral tissues. Obesity is associated with the altered production of many adipokines and is linked to a number of pathologies. As an increase in body weight is directly associated with an increased risk for developing chronic kidney disease (CKD), there is significant interest in the link between obesity and renal dysfunction. Altered levels of the adipokines leptin, adiponectin, resistin, and visfatin can decrease the glomerular filtration rate and increase albuminuria, which are pathophysiological changes typical of CKD. Specifically, exposure of the glomerulus to altered adipokine levels can increase its permeability, fuse the podocytes, and cause mesangial cell hypertrophy, all of which alter the glomerular filtration rate. In addition, the adipokines leptin and adiponectin can act on tubular networks. Thus, adipokines can act on multiple cell types in the development of renal pathophysiology. Importantly, most studies have been performed using in vitro models, with future studies in vivo required to further elucidate the specific roles that adipokines play in the development and progression of CKD.

Keywords: adipokines; obesity; chronic kidney disease; leptin; adiponectin

THE MAIN FUNCTIONS of the kidney are to reabsorb nutrients, excrete wastes, regulate blood volume and pressure, and secrete hormones (17). In a healthy individual, the proximal tubule of the kidney is able to reabsorb the majority of protein that enters the glomerular filtrate, with only traces being excreted in the urine (51). In kidney disease, the filtration and reabsorption of protein are altered, leading to a loss of protein in the urine (proteinuria) (24, 61, 73). Importantly, an increase in proteinuria is associated with an increase in renal damage (nephropathy) (24).

Obesity rates in the Western world are increasing rapidly, which mirrors the increase in comorbidities such as nephropathy (24). Obesity-related pathologies increase the health, economic, and social costs associated with this disease (13). Importantly, the numbers of obese patients with end-stage renal disease (ESRD) have significantly increased worldwide in the last 10 years (40). In the obese state, there are two main cellular targets that are associated with proteinuric renal disease. These are 1) structural changes to the glomerulus allowing more protein to enter the filtrate (73) and 2) the proximal tubules are unable to endocytose the increase in protein load (64). Thus, both the glomerulus and proximal tubules are sites of dysfunction in proteinuric nephropathy.

Adipocytes are able to secrete a number of bioactive proteins, termed “adipokines” (50, 71), with dysregulation in the production and secretion of a number of adipokines occurring in the obese state (63). Many of these molecules have been shown to alter renal cell function in vitro, which could increase the risk of developing kidney damage associated with obesity (45, 68).

Clinical Diagnosis, Progression, and Pathogenesis of Chronic Kidney Disease

Chronic kidney disease (CKD) is the result of a decrease in the kidneys’ ability to function (41, 61). The average glomerular filtration rate (GFR) is ~90–120 ml/min (46), with a reduction in GFR being associated with kidney disease (46). Recent research has supported the inclusion of albuminuria as an indicator for CKD either in the presence or absence of a decrease in GFR (33, 46). Consequently, CKD stages 1 and 2 indicate kidney damage with either a reduction in GFR (33, 46) and/or albuminuria. CKD stages 3–5 are associated with a significant drop in GFR to below 60 ml/min, which is associated with albuminuria (33, 41, 46). CKD stage 5 is associated with severe albuminuria and reduced GFR in addition to interstitial fibrosis (33), with dialysis and renal replacement required. It is estimated that 5–10% of the adult population in the Western world has an estimated GFR (eGFR) similar to those observed in CKD stages 3–5 (41).

There is a strong correlation between obesity and hypertension, both of which are risk factors for CKD. In the initial stages of obesity-related hypertension, there is afferent arteriole vasoconstriction, which is caused by an increase in solute delivery to the distal tubules, detected by cells of the macula.
denotes (60), which activates tubuloglomerular feedback. However, in the obese state, there is an increase in Na+ retention by the kidney (14, 27, 34, 64). The increase in Na+ retention is caused by increased renal sympathetic nervous system (SNS) activation, activation of the renin-angiotensin system (RAS), and altered intrarenal physical forces (2, 27, 57). However, the main factor contributing to the changes in Na+ retention is caused by an increase in the extracellular matrix mass of the kidneys, which compresses the loop of Henle, decreasing blood flow to the vasa recta and increasing Na+ reabsorption in the loop of Henle (2, 27), resulting in renal vasodilation, increasing GFR and activating the RAS. Current data suggest that adipose tissue contains all components of the RAS and is capable of producing both angiotensinogen and ANG II, which increases their plasma levels (2, 27, 57). Therefore, the adipose tissue surrounding the kidneys of obese individuals may be contributing to the increase in RAS proteins that are observed in the obese state. Increased RAS activation further compounds the increase in Na+ and water retention, resulting in an expansion of the extracellular matrix driving hypertension (27). Ultimately, the kidney attempts to compensate for the increase in Na+ retention by increasing renal plasma flow, increasing GFR, and causing hypertension (2, 27), resulting in glomerular hyperfiltration. Glomerular hyperfiltration is caused by the decrease in Na+ and Cl− delivery to the macula densa cells of the distal tubules, as a result of their increased reabsorption in the loop of Henle (60). This switches off the tubuloglomerular feedback mechanism, reducing afferent arteriole vasoconstriction, resulting in an increased GFR (60) to normalize solute delivery to the distal tubule. Persistent glomerular hyperfiltration ultimately causes glomerular sclerosis and renal failure (2).

Proteinuria and albuminuria are hallmark characteristics of renal damage. The increase in protein filtration through the glomerulus is primarily due to basement membrane thickening (77, 79), which is further compounded with an impairment of the protein endocytic pathway by proximal tubule cells (PTCs), which are unable to remove excess proteins from the glomerular filtrate (73). Exposure to elevated levels of protein in the renal tubule has been linked to the enhancement of proinflammatory and profibrotic changes in the tubulointerstitium in vivo (79). Specifically, exposure to high levels of albumin induces the production of proinflammatory, profibrotic, and vasoactive factors in vitro (79). For example, the profibrogenic cytokine transforming growth factor (TGF)-β is increased in the glomerular filtrate, which upregulates extracellular matrix production, leading to basement membrane thickening (79). Exposure of renal cells to elevated protein increases the secretion of collagen types I, III, and IV, resulting in tubulointerstitial fibrosis and also leading to basement membrane thickening (77). Despite our understanding of the pathophysiological changes in albuminuria, in general, the molecular and cellular targets that are altered in obesity-related nephropathy are not as well understood; however, studies in vivo have supported the role of adipokines in the pathogenesis of obesity-related renal disease.

Adipose Tissue as an Endocrine Organ

Adipose tissue has been identified to secrete >50 adipokines, including cytokines, chemokines, hormone-like factors, and other signaling mediators (5). These adipokines can activate many signal transduction pathways that are essential for the maintenance of energy homeostasis and metabolism (50, 71). Adipokines have various roles in vivo, including lipid metabolism, inflammation, atherosclerosis, insulin resistance, the immune-stress response, vascular homeostasis, and cell adhesion and migration (39). Analysis of adipokine function in vitro has provided an indicator for the molecular mechanisms linking obesity and renal disease.

Increases in body mass index are tightly associated with an increased risk in the development of obesity-related CKD (24). Studies in vivo in obese animals as well as in healthy animals injected with higher concentrations of adipokines have characterized the roles of leptin, adiponectin, resistin, and visfatin in obesity-related renal pathophysiology. These adipokines are associated with renal dysfunction by increasing the risk of developing albuminuria by altering GFR and potentially by modulating renal tubule function. In vitro studies have typically focused on the glomerulus, with altered adipokines acting on specific cell types within this region of the nephron. Recent research in our laboratory (12) has also demonstrated that leptin can alter proximal tubular function, which may exacerbate the pathophysiological changes in the obese. This review will specifically focus on leptin, adiponectin, resistin, and visfatin as links between obesity-related CKD and renal failure.

Adipokines and CKD

Leptin. Leptin is a 16-kDa peptide product of the obese (ob) gene and is predominantly secreted by white adipose tissue (3, 28, 42) but, under some circumstances, may be produced in other tissues (the gastric mucosa, placenta, bone marrow, mammary epithelium, skeletal muscle, pituitary, hypothalamus, and bone marrow) (3, 28, 42). Leptin is filtered across the glomerulus and is taken up by the scavenger receptor megalin in the proximal convoluted tubules (28). Megalin processes leptin from the filtrate, with negligible levels of leptin in the urine (56). Low leptin in the urine is evident even in situations when serum leptin is elevated, such as obesity (18, 47). In nonobese individuals, the serum level of leptin is ~5.5 ng/ml, with 9.5% being transferred from the blood to the filtrate (26). In nonobese individuals, the renal clearance of leptin is ~0.0595 µg/ml (59.5 ng/ml) (26). The glomerular concentration of leptin in obese individuals has not been measured; however, obese individuals have ~5–10 times higher serum levels of leptin than normal individuals (26), with another group (48) determining that the maximum plasma leptin level observed in the obese is likely to be 200 ng/ml. Interestingly, individuals with CKD also present with hyperleptinemia, at levels up to 490 ng/ml (19).

The major physiological role of leptin is to regulate hunger and satiety (21); it does this by crossing the blood-brain barrier and inhibiting neuropeptide Y neurons in the arcuate nucleus of the basomedial hypothalamus (10, 21, 70, 80). Leptin also acts on the ventromedial hypothalamus, where it activates the SNS and increases circulating epinephrine and norepinephrine levels (70, 80). Although the effect of leptin on the basomedial hypothalamus is diminished in obesity, its effects on the ventromedial hypothalamus remain the same (70, 80). Typically, obese individuals have an increased sympathetic output (70), with a study (38) in dogs showing that renal denervation ameliorates obesity-associated hypertension. Animal studies (8, 32) have shown that lean animals acutely infused with leptin have no changes in blood pressure and an increased Na+
excretion and urine output. The ability of leptin to increase natriuresis is caused by a decrease in Na\(^+\)/K\(^+\) transport in the tubules, with work by Beltowski et al. (8) identifying that acute leptin exposure decreases Na\(^+\)/K\(^+\)-ATPase activity. Several studies have now demonstrated that acute leptin infusion stimulates the release of nitric oxide (NO) in endothelial cells and blood vessels (74), with NO being shown to decrease Na\(^+\) reabsorption in the tubules by decreasing Na\(^+\)-K\(^+\)-ATPase (58). Therefore, acute leptin exposure in the kidney may increase NO expression in an attempt to regulate obesity-associated hypertension. However, chronic leptin exposure further compounds hypertension in the obese by increasing Na\(^+\) retention (7) and/or decreased NO production (7). Beltowski et al. (9) identified that hyperleptinemia causes NO deficiency primarily due to increased renal oxidative stress, which inhibits the protective role of NO in increasing Na\(^+\) excretion (9).

Leptin predominantly binds to the leptin receptor (Ob-R) in most tissues, which is capable of activating downstream signal transduction pathways (3). The long isoform of the leptin receptor (Ob-Rb) has been shown to activate JAK/STAT (10) and MAPK pathways (3, 6). However, leptin can activate a number of cell signaling pathways in a cell-specific manner, and, thus, the effect of altered levels of leptin on the kidney is an emerging area of research. In vitro, leptin can alter glomerular cell size via activation of the MAPK pathway through ERK1/2 (15, 45). Specifically elevated levels of leptin cause hypertrophy in glomerular mesangial cells via activation of phosphoinositide 3-kinase and ERK1/2 (Fig. 1) (45). Glomerular mesangial hypertrophy increases the amount of filtered protein and albumin reaching the PTCs activating fibrotic and inflammatory pathways (77, 79). In addition, exposure to elevated leptin results in an accumulation of collagen and an upregulation of TGF-β1 secretion from glomerular endothelial cells in vitro (78). In vivo, increased TGF-β1 could cause thickening of the basement membrane, leading to the development of glomerulosclerosis (Fig. 1) (78). However, the direct link between leptin and TGF-β1 secretion in the glomerulus in vivo has not been demonstrated. In vitro, TGF-β has been shown to increase collagen synthesis, which could cause extracellular matrix accumulation and, ultimately, fibrosis (79). However, others (44) have shown that elevated leptin induces the expression of matrix metalloproteinase-2 in mesangial cells without altered expression of collagen types I and IV. Importantly, in vivo, Wolf et al. (78) demonstrated that leptin infusion into rats for 3 wk caused an increase in collagen type IV expression in the glomerulus. Despite the obvious differences between in vitro and in vivo experimentation, the study by Wolf et al. (78) may not represent a true pathophysiological condition as the levels of leptin that were infused were significantly higher than those detected in obesity. Conversely, in PTCs, acute leptin exposure reduces cellular metabolic activity by the activation of the mammalian target of rapamycin and also reduces the protein content per cell (Fig. 1) (12). Research by Hama et al. (28) identified that megalin is the sole receptor for leptin reuptake in the kidney, with histological sections of kidneys from rats that were infused with a radioactive labeled leptin showing that leptin uptake occurs in the proximal convoluted tubule, which lacks Ob-R. Importantly, research by Zou et al. (82) identified that another megalin ligand, vitamin D-binding protein, is able to cause regulated intramembrane proteolysis of megalin with the cytosolic fragment translocating to the nucleus, which may be able to activate signal transduction pathways. Recently, another group (66) has determined that megalin is trafficked to the endocytic recycling compartment in L2 rat yolk sac cells for proteolytic

![Diagram of a normal glomerulus and proximal tubule](image_url)

**Diagram A:** A normal glomerulus and proximal tubule in the nephron with key cells identified. **Diagram B:** Changes in the plasma concentrations of each adipokine observed in obesity. The effects that these changes in adipokine levels have on the structure of the glomerulus and proximal tubule cells are shown. All of these adipokines in obesity lead to changes in the glomerular filtration rate (GFR) and/or an increase in albuminuria or proteinuria. These changes are characteristic of chronic kidney disease. AMPK, AMP-activated protein kinase.
processing and the modulation of cellular gene expression for the activation of signal transduction pathways. Research from our laboratory (12) has shown that leptin alters signaling-mediated expression in opossum kidney cells, a cell line that has characteristics of the proximal tubule and appears to lack protein expression of Ob-R. Therefore, we speculate that in the proximal tubule, leptin signaling may occur via megalin. To add to our knowledge in this area, long-term exposure to leptin results in the activation of apoptotic pathways in PTCs (30), which is absent after acute exposure to leptin (12, 15). Recently, we (12) have also demonstrated that acute exposure to leptin activates ERK1/2 and mammalian target of rapamycin phosphorylated at serine residue 2481. These few studies clearly highlight a need for further research into leptin-megalin signaling pathways so that potential targeted molecules can be identified for future therapeutics.

Leptin is linked to the development of CKD in the absence of obesity, as patients with ESRD have an estimated 4- to 7.5-fold increase in plasma leptin concentration (hyperleptinemia) compared with healthy control subjects (19, 55, 67). However, this finding has only been investigated in ESRD patients undergoing hemodialysis and may be an artifact of the dialysis itself. To investigate if the identified hyperleptinemia in ESRD patients is caused by hemodialysis or by altered leptin excretion or production, Dagogo-Jack et al. (19) investigated this association in ESRD patients undergoing continuous ambulatory peritoneal dialysis. They determined that hyperleptinemia is still observed in patients undergoing continuous ambulatory peritoneal dialysis, suggesting that the hyperleptinemia may be the result of terminal renal failure (19). Interestingly, Sharma et al. (67) identified in patients with renal insufficiency that leptin uptake by the kidneys is diminished. These data, taken together, suggest that in ESRD, hyperleptinemia may be the result of altered leptin production as well as terminal renal failure. However, the mechanism for this link is poorly understood, and, as such, future studies are required to further investigate this association.

Adiponectin. Adiponectin is a 30-kDa plasma protein that is predominantly secreted by adipose tissue (63, 68). Physiological plasma concentrations of adiponectin are between 5 and 30 \( \mu \text{g/ml} \) (63, 68), which constitute 0.01% of total plasma protein (63). In healthy individuals, both a low- and high-molecular-weight isofrom of adiponectin are detected in the urine in trace amounts, with the low-molecular-weight isofrom being the most abundant form of urinary adiponectin (69, 76). Adiponectin has a number of functional roles, including acting as a cardioprotective protein, improving insulin sensitivity, and acting as a vascular protective agent via the suppression of ROS production (68). Secreted adiponectin exists in many stable complexes of different molecular weights (23). Adiponectin levels are negatively correlated with percent body fat, with adiponectin levels decreasing significantly in obesity (1, 68, 81). Adiponectin binds to two receptors that have varied distributions and different affinities to the molecular weight complexes of adiponectin. Adiponectin receptor (AdipoR)1 is abundantly expressed in skeletal muscle and moderately expressed in other tissues, including the brain and heart (37, 68); in the kidney, AdipoR1 is located in the glomerulus and proximal tubule (68). AdipoR2 is predominantly expressed in the liver (37); however, AdipoR2 has also been identified in PTCs (69). Adiponectin binding to both AdipoR1 and AdipoR2 increases the activation of the downstream signaling mediator AMP-activated protein kinase (AMPK) (1, 68), a key regulator of energy homeostasis. Adiponectin also activates the downstream signaling mediator peroxisome proliferator-activated receptor-\( \alpha \) as well as the MAPK pathway in vitro (43).

Hypoadiponectinemia has been associated with renal dysfunction and CKD. Research by Doumatey et al. (22) identified an inverse relationship between circulating adiponectin levels and renal function, which was further supported by Sharma et al. (68), who identified that adiponectin is an independent predictor of moderate CKD. Specifically, adiponectin can be used as a predictor of eGFR and CKD (22), with circulating adiponectin being negatively associated with eGFR (Fig. 1) (22). A potential mechanism for this has been identified in mice with hypoadiponectinemia. These mice exhibit podocyte fusion with adiponectin treatment improving the glomerular podocyte foot processes via activation of AMPK, which down-regulates podocyte NADPH oxidase (Nox)4 production (Fig. 1) (68). Importantly, these mice exhibit albuminuria (45), clearly demonstrating a link between hypoadiponectinemia and kidney dysfunction.

AdipoR1 is localized to the podocytes, which suggests that at the molecular level, altered adiponectin receptor activity may lead to obesity-related dysfunction (68). Importantly, adiponectin has been shown to downregulate Nox4 production in podocytes (68), which is an important mediator in oxidative stress. Furthermore, research by Sharma et al. (68) demonstrated that the low adiponectin levels in obesity cause an upregulation of podocyte production of Nox4, which suggests that the role for AdipoR1 may be by the modulation of oxidative stress associated with renal damage. Interestingly individuals with established kidney disease and patients with type 2 diabetes mellitus (DM) have a significant increase in the urinary excretion of both the low- and high-molecular-weight isoforms of adiponectin (69, 76). The cause of this association was determined by von Eynatten et al. (76), who identified that glomerular adiponectin is diminished in diabetic nephropathy, which is caused by glomerular sclerosis. Importantly, AdipoR1 and AdipoR2 have been identified in vitro in PTCs (HK2 cells) (69), with adiponectin treatment increasing AMPK activation and decreasing the secretion of monocyte chemotactic protein (MCP)-1 (a mediator of inflammation) (69). Research by Declèves et al. (20) further identified significant increases in urinary excretion of MCP-1 and \( \text{H}_2\text{O}_2 \) after only 1 wk of high-fat feeding in vivo that proceeded albuminuria, identifying that MCP-1 and \( \text{H}_2\text{O}_2 \) are involved in the onset of inflammation in the kidney. Importantly, treatment with an AMPK activator prevented the increase in urinary MCP-1 and \( \text{H}_2\text{O}_2 \), which also prevented the decrease in adiponectin levels associated with obesity, suggesting that adiponectin is the main modulator of these inflammatory proteins via AMPK activation (20). Therefore, hypoadiponectinemia results in tubular inflammation by decreasing tubular AMPK activation, resulting in an accumulation of MCP-1. Despite this finding, limited research exists on the effect hypoadiponectinemia has on the tubules, with most studies investigating patients with normal adiponectin levels who have kidney disease and DM. As elevated glucose, which is observed in DM, may alter tubular function independently of obesity, future studies are required to clarify the specific roles that AdipoR1 and AdipoR2 play in the tubules, including the effect that obesity has on the downstream signaling targets of these receptors.
While obesity is typically associated with hypo adiponectinemia, in contrast to this, adiponectin levels have been demonstrated to increase in type I diabetic patients with diabetic nephropathy and later stages of CKD (35, 53). To help possibly explain the rationale for this increase, a recent study by Martínez Cantarin et al. (52) identified that elevated adiponectin in ESRD is caused by an increased production of adiponectin from adipose tissue. Despite the generally protective actions of adiponectin on health, interestingly, elevated adiponectin is a predictor for mortality in patients with CKD stages 3 and 4 (53); however, the mechanisms behind this observation remain unclear. Future studies are therefore required to determine why adiponectin levels rise in CKD stages 3 and 4 and how adiponectin is a predictor of mortality in these patients.

Resistin. Resistin is a 12.5-kDa adipokine that is predominantly produced by macrophages, with lower levels released from adipocytes (4, 54). Resistin circulates in the blood in two forms (minor and major) (59), with increasing resistin levels associated with adiposity (54). The minor form of resistin has a significantly increased bioactivity compared with the major form, indicating that it is the major active form of the molecule (59). The pathophysiological role that high resistin levels has in obesity has been poorly investigated. Resistin levels are linked to the albumin-to-creatinine ratio as well as GFR (4, 54), with increased resistin levels associated with a decrease in GFR (Fig. 1). This may be due to the activation of inflammatory pathways, with elevated resistin levels being associated with an enhanced inflammatory response (4), which is likely to be due to the activation of macrophages in CKD, the primary source of resistin production (4, 54).

Several studies (36, 49, 75) have investigated the role that resistin plays in the development of cardiovascular disease (CVD), where high resistin levels correlate with increased endothelin (ET)-1 expression. ET-1 is a potent vasoactive factor that causes endothelial dysfunction in CVD and has also been linked to obesity-related hypertension. A study by Jung et al. (36) identified macrophages that infiltrated atherosclerotic aneurysms secreted resistin and that resistin increases ET-1 and causes vascular smooth muscle cell infiltration. In vitro experiments have also shown that resistin significantly increases the expression of MCP-1 and VCAM (75). Physiological levels of ET-1 are responsible for the maintenance of normal renal function (62). A study (29) in transgenic mice overexpressing ET-1 in the kidney developed glomerulosclerosis and tubulointerstitial fibrosis in an aging-induced manner and have noted decreases in GFR. These studies, taken together, suggest that in obesity, there is an increase in macrophage invasion in the endothelium of the kidney, which increases renal expression of ET-1 and MCP-1, causing inflammation, with the increase in ET-1 causing endothelial dysfunction, ultimately resulting in glomerulosclerosis and tubulointerstitial fibrosis, suggesting a role for ET-1 in the development of CKD. However, such studies have not been carried out looking at obesity-related changes to macrophage infiltration and ET-1 levels in the kidney. Currently, the specific molecular targets in the nephron that are activated after exposure to elevated resistin is unknown, and further studies are required to characterize the specific role that resistin has in macrophage infiltration and inflammation in the kidney.

Visfatin. Visfatin (also known as pre-B cell colony-enhancing) is an adipokine that was first identified in 2005 (25), with the gene discovered in 1994 (65). Visfatin is a 52-kDa protein, which makes it one of the largest adipokines (23). Adipocytes are the primary source of visfatin, with leucocytes, hepatocytes, and skeletal muscle also producing the adipokine at lower levels (50, 72). The estimated physiological plasma concentration of visfatin is 15 ng/ml (23), with plasma concentrations of visfatin increasing with adiposity (71, 72). Controversy exists between the classification of visfatin as an adipokine, with some researchers suggesting that it should be classified as a marker of inflammation (50, 71), as elevated visfatin levels in obesity are potentially caused by renal failure or inflammation (50). Nonetheless, visfatin has been shown to increase the production of the inflammatory cytokines TNF-α, IL-6, and IL-1β as well as increasing ROS generation (50). Currently, the role that visfatin plays in the kidney in vivo is not well understood; however, after renal transplantation, visfatin levels are positively correlated with proteinuria and the production of markers of inflammation (50). Analysis of visfatin in cultured glomerular endothelial cells in vitro has determined that visfatin stimulation causes a significant increase in superoxide production via lipid raft clustering (11). As superoxide production increases oxidative stress, it alters the permeability of the cell (11), suggesting that visfatin may activate oxidative stress pathways leading to renal pathology (Fig. 1).

In vitro visfatin administration at levels associated with obesity have been shown to upregulate components of the intrarenal RAS (31). Specifically, in glomerular mesangial cells, exposure to elevated visfatin resulted in increased renin mRNA expression in addition to increased mRNA and protein expression of angiotensinogen (31). As the RAS plays an important role in the regulation of GFR (31), any changes in renin or angiotensinogen levels are likely to alter GFR (31), contributing to nephropathy (Fig. 1). Song et al. (71) identified that glomerular mesangial cells in vitro express visfatin protein in normal glucose conditions, with minimal visfatin secretion from these cells. Interestingly, high glucose (30 mM) conditions significantly increase mesangial visfatin production and secretion (71). The increase in visfatin production under high glucose conditions could contribute to the increased influx of glucose into mesangial cells, accelerating the progression of diabetic nephropathy (71). Furthermore, there is a correlation between plasma visfatin levels and the severity of DM (16, 71). However, the role that visfatin plays in obesity-related CKD is poorly understood. Future studies should investigate the effect that elevated visfatin has on the glomerulus and proximal tubules, specifically, the downstream signaling mediators it activates under physiological and pathophysiological conditions, to characterize the effect of visfatin in CKD and diabetic nephropathy.

Conclusions

Obesity rates worldwide are increasing rapidly, with obesity being associated with a number of pathologies, including CKD. CKD is the result of a decrease in the kidney’s ability to function and is associated with albuminuria and proteinuria. Both albuminuria and proteinuria cause basement membrane thickening and fibrosis in the glomerulus (77, 79), and, in the tubules, it activates the tubuloglomerular feedback mechanism, resulting in glomerular hyperfiltration and hypertrophy, lead-
ing to renal fibrosis and progressive nephropathy (64). Our understanding of the roles that adipokines play in obesity and CKD is an emerging field of research. The link between adipokines and changes in glomerular filtration have been observed; however, for most adipokines, the molecular mechanism(s) have not been determined. Most research has been performed on leptin, with elevated levels of leptin resulting in glomerular mesangial hypertrophy (77, 79) and basement membrane thickening (78) in vivo in addition to leptin-mediated changes in the metabolic activity of PTCs leading to tubular apoptosis (12, 15, 30). These changes to the nephron structure would result in an increase in proteinuria and albuminuria as well as the activation of fibrotic pathways in tubular cells.

Studies investigating a number of other adipokines have been more limited. Hypoadiponectinemia in the obese state increases the production of ROS, leading to oxidative stress in the podocytes (68), which is likely to alter GFR. Importantly, adiponectin may also play a role in tubular inflammation (69), which may further compound the development of nephropathy. However, research into the roles that resistin and visfatin play in obesity-related nephropathy is limited, with both adipokines being associated with declining GFR. Currently, the mechanism behind the role of resistin in declining GFR is unknown. Interestingly, glomerular mesangial cells have been shown to secrete visfatin under high glucose conditions (71), with visfatin being shown to increase angiotensinogen protein expression, which may increase RAS activation, which would alter GFR (31).

Overall, there appears to be an emerging link between adipokine dysregulation in obesity and the development of CKD. Largely, these studies have demonstrated that adipokines can alter glomerular function, with emerging research also identifying a tubular link. More extensive mechanistic studies in vivo are required to clarify the role(s) that these adipokines play in CKD and other obesity-related pathologies. Furthermore, the characterization of the molecular downstream signaling targets in altered renal cells is essential in developing effective therapeutics for obesity-related nephropathy.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS


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