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Obesity and kidney disease: differential effects of obesity on adipose tissue and kidney inflammation and fibrosis

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Abstract

Purpose of review—This review provide a perspective by investigating the potential cross-talk between the adipose tissue and the kidney during obesity.

Recent findings—It is well established that excessive caloric intake contributes to organ injury. The associated increased adiposity initiates a cascade of cellular events that leads to progressive obesity-associated diseases such as kidney disease. Recent evidence has indicated that adipose tissue produces bioactive substances that contribute to obesity-related kidney disease, altering the renal function and structure. In parallel, proinflammatory processes within the adipose tissue can also lead to pathophysiological changes in the kidney during the obese state.

Summary—Despite considerable efforts to better characterize the pathophysiology of obesity-related metabolic disease, there are still a lack of efficient therapeutic strategies. New strategies focused on regulating adipose function with respect to AMP-activated protein kinase activation, NADPH oxidase function, and TGF- β may contribute to reducing adipose inflammation that may also provide renoprotection.

Keywords

Nutrient stress; AMPK; HIF1 α ; NADPH oxidase; TGF- β

Introduction

The growing epidemic of obesity particularly in the western world is a major factor in reducing expected life expectancy and is an added serious health and economic burden. The epidemic of obesity is related to the combination of sedentary lifestyle, usually associated

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Conflicts of interest

None

with a high caloric intake and a lack of exercise. A possible scenario is when the energy intake exceeds the storage capacity of white adipose tissue (WAT), ectopic lipid accumulation in ectopic organs is induced [1], promoting metabolic disturbances such as insulin resistance and alteration in the control of glucose and lipid metabolisms, contributing to hyperglycaemia, dyslipidaemia, hypertension, insulin resistance, glucose intolerance, and atherosclerosis [2]. Moreover, central obesity is a major risk factor for diabetes and hypertension which together account for about 70 % of all cases of end-stage renal disease [3]. However, a full understanding of mechanisms involved to the progressive renal disease is still absent.

White adipose tissue is not only a simple fat storage organ but is now recognized as a dynamic tissue involved in the production of adipokines such as leptin, adiponectin, tumor necrosis factor- α (TNF- α), monocyte chemotactic protein-1 (MCP-1), Transforming Growth Factor-beta (TGF- β) and angiotensin II [4, 5]. The balance between these adipokines allows the adipose tissue to regulate the appetite, the food intake, the glucose clearance, and the energy expenditure. The perturbation of this balance during obesity promotes a pro-inflammatory environment and lead to insulin resistance (IR). Obesity-related kidney disease is associated with renal hemodynamic abnormalities, endothelial and podocyte dysfunction, glomerular basement membrane thickening and mesangial expansion, tubular atrophy, interstitial fibrosis and a progressive decrease in renal function (increased albuminuria and decreased glomerular filtration rate (GFR)) leading to end-stage renal disease (ESRD) [6-9]. Assuming that common factors exist between obesity-induced adipose tissue and kidney disease, here, we will discuss the potential crosstalk between both tissues during obesity.

Insulin Resistance in Adipose Tissue and Kidney

As mentioned, adipose tissue is not a passive energy storage but an active tissue able to produce a number of hormonally and metabolic factor, called adipokines. In a healthy state, there is a balance between these adipokines in order to maintain body energy homeostasis. In contrast, during obesity, an excessive caloric intake contribute to adiposity and initiates a cascade of cellular events that leads to progressive obesity-associated diseases [10-12]. In the obese rodent and human, adipose tissue has been demonstrated to be inflamed and to likely contribute to the development of insulin resistance [11, 13]. Insulin resistance is a key metabolic risk promoting chronic kidney disease [14]. Many studies have demonstrated the association between IR/hyperinsulinemia and CKD. This association was even shown before the onset of diabetes [15, 16]. It is known that insulin mediates the mesangial cell growth and modulates the glomerular hemodynamics by stimulating glomerular cells in response to ANGII [17, 18]. Moreover, Cusumano et al. demonstrated a link between hyperinsulinemia and glomerular hypertrophy [19]. In kidney, insulin promotes its effects by binding and activating its two receptors IRS1/2 which in turn activate molecular signaling pathways to promote for example glucose uptake, cell growth or NO production [20]. In pathological conditions like obesity, abnormal modulations of the insulin receptors and signaling have been shown. These alterations were associated with increased levels of many factors such as TNF α (reported below), ANGII, endothelin, free fatty acids, oxidative stress and amino acids (reviewed [21]). More recently, Welsh et al. demonstrated the critical role of insulin signaling in normal kidney function, particularly in podocytes [22]. In that study,

transgenic mice missing insulin receptors in their podocytes were generated. These mice showed normal glomerular histological features at their early age (3 week old). However, later, starting at 5 week old, loss of podocyte foot process structures, clear evidence of albuminuria and increased glomerular matrix were observed [22]. Even though this study demonstrated a clear evidence of the role of insulin in glomerular kidney function, which is the chicken and which is the egg in the development of CKD is still elusive. It might be worth to admit that several mechanisms involved in obesity-related organ dysfunction are concomitant. As previously mentioned, IR is linked to increased levels of ANG II while renal damage progression in obesity is also associated with increased ANG II level. Indeed, Angiotensin II is a crucial mediator in the progression of obesity and diabetes related kidney disease [23-25]. Angiotensin II participates to the hyperfiltration and glomerulosclerosis through hemodynamic and non-hemodynamic effects [26-31]. Many works have demonstrated that insulin can attenuate ANG II effect on the vasculature and *vice versa* [32-35]. Insulin induces vascular relaxation by promoting NO production through the phosphatidylinositol 3-kinase (PIK3-Akt) signaling pathway while ANG II has vasoconstriction effects on the vasculature. The inhibitory effects of ANG II on the insulin action may be mediated by the production of reactive oxygen species (ROS) [33, 36, 37]. In turn ROS act to induce inflammatory cytokines such as MCP-1 or TNF α which can then impair the PI3K-Akt pathway of the insulin signaling [38-41], leading to insulin resistance. Free Fatty Acids (FFA) might also contribute to IR. Increased FFA flux from overwhelmed adipose tissue to nonadipose organs leads the increase of lipid accumulation in ectopic organ such as liver, muscle but also the kidney. This later promotes the impairment of glucose metabolism and insulin sensitivity in these organs. Lennon et al. (2009) demonstrated that the exposition of immortalized human podocytes to the FFA palmitate blocked the effect of insulin on glucose uptake [42]. This adverse effect was associated with an increase of ceramide, a highly lipotoxic molecule, that has been reported to play a role in insulin resistance [43]. In addition, a dysregulation of the insulin receptor as well as the impairment of glucose GLUT4 transporter to the cell surface were observed [42]. We have previously shown that lipid accumulation occurs in the kidney after a high fat caloric exposure, leading to insulin resistance associated with impairment of tubular cell structure and inflammation as well as fibrosis. In that study, the central energy sensor, AMPK, appears to play a beneficial role [44].

Thus, there is a strong evidence in support of the important role of IR as a driver of the renal disease. However, is IR critical to the progression of the disease is still under debate and needs more investigations.

Inflammation-related to obesity in Adipose Tissue and kidney

As previously mentioned, insulin resistance (IR) is a common adverse process related to the development of obesity and its related metabolic syndrome [11, 45, 46]. Rapid expansion of adipose tissue results in an aberrant production of pro-inflammatory adipokines that leads to a state of low-grade inflammation [47]. Evidence of macrophage infiltration into adipose tissue have been reported in obese human and experimental models [48-50]. Among the large number of pro-inflammatory adipokines, TNF- α has been recognized as one of the most critical mediators of adipose tissue inflammation and IR development. It has been

demonstrated that TNF- α knockout mice were protected from obesity-induced IR [39]. In patients, the correlation between circulating TNF- α and IR has also been reported [51, 52]. In an experimental model of obesity using a co-culture system, Suganami et al. (2005) postulated a paracrine loop involving free fatty acids and TNF- α between macrophages and adipocytes, generating a vicious cycle that maintains or even increases the chronic inflammatory state [53]. Increased TNF- α level is usually associated with the increased production of monocyte chemoattractant protein-1 (MCP-1), a chemokine produced by adipocytes and macrophages, which has been reported to be increased with excessive fat storage [54, 55]. Both these pro-inflammatory adipokines are upregulated while anti-inflammatory adipokines such as adiponectin are down-regulated. MCP-1 is also now recognized as a key mediator of adipose tissue inflammation and IR development. Many studies have demonstrated its effects on macrophage recruitment into the adipose tissue [56, 57]. In contrast, the deficiency of MCP-1 or its receptor was shown to induce a reduction of macrophage infiltration in the adipose tissue and to improve IR in obese experimental models [56, 58].

On the other hand, it has been clearly demonstrated that adiponectin (also called Acrp30), is one of the most abundant adipokines produced by the adipocytes and it is down-regulated in obesity [59-62]. Adiponectin is an insulin-sensitizing factor and has anti-inflammatory effects. Reduced plasma adiponectin level has been inversely correlated with IR in obese patients [63, 64]. The roles of adiponectin in obesity-related disease has been extensively investigated using transgenic mice or pharmacological globular Acrp30 compound [65-70]. While deficiency in adiponectin was associated with insulin resistance, globular adiponectin transgenic mice or treatment with exogenous gAcrp30 showed beneficial effect regarding insulin resistance and glucose tolerance [65, 66, 68]. Adiponectin is an important regulator of lipid and glucose metabolism and a key link between TNF- α , MCP-1, and insulin resistance. As already noted, TNF- α plays a critical role in the induction of IR as suggested by the protection of TNF- α KO mice against IR induction [39, 40]. The infusion of TNF- α in rat was reported to induce rapid changes in adipocyte gene expression, favouring pro-inflammatory cytokine production along with a reduction of adiponectin. These changes were associated with the increase of lipolysis leading to the rise of plasma FFA and the induction of IR [71].

While increased TNF- α level is usually associated with a decreased adiponectin level, a potential role of AMPK has also been considered in the insulin resistance process. Effects of adiponectin are tightly linked to the activation of AMP-activated protein kinase (AMPK) [60, 72]. AMPK is an ubiquitous heterotrimeric enzyme that is considered to be the master energy sensor in all eukaryotic cells [73]. As a cellular energy sensor, its activity is highly linked to the change in the intracellular AMP/ATP ratio. Increase of the AMP/ATP ratio stimulates AMPK activity whereas a reduction of the AMPK/ATP ratio results in its inhibition [74]. Hence its activation results in a change of energy utilization involving the stimulation of energy-producing pathways and reduce energy-requiring cell processes in order to restore energy balance[75]. Metabolic stress conditions such as obesity modulate the activity of AMPK. Steinberg et al. (2006) demonstrated that TNF- α could suppress AMPK activation through the TNF receptor 1 (TNFR1), suppressing fatty acid oxidation and promoting IR in skeletal muscle. This negative effect of TNF- α on AMPK activation was

prevented in transgenic TNFR1 and 2 KO mice or after treatment with exogenous TNF- α neutralizing antibody [76]. The mechanisms involved in the inhibition of AMPK activation by TNF- α is still unclear. However, Steinberg et al. showed that this process might involve the upregulation of protein phosphatase 2C (PP2C) by TNF- α with the subsequent suppression of AMPK activation. Hence, TNF- α treatment showed a decrease of AMPK activation along with an elevated PP2C activity in WT mice but not in the transgenic ob/ob TNFR-/- mice. This change was associated with a reduction of the fatty acid oxidation and an increase of diacylglycerol (DAG) and triacylglycerol (TAG) in skeletal muscle [76]. DAG is known to be involved in insulin resistance through the activation of the protein kinase C [77]. In contrast, the activation of AMPK was shown to reduce TNF- α action and positively regulate insulin signalling. Shibata et al. showed that the AMPK activation by 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR), a potent AMPK activator, could inhibit the effect of TNF- α to induce IR in 3T3L1 adipocytes [78]. Similarly, in human adipose tissue, AMPK activation reduced level of TNF- α and increased adiponectin level, improving insulin sensitivity [79]. A similar link has been observed regarding AMPK activation and MCP-1 level. Increased level of MCP-1 by human adipocytes was accompanied by a decrease of adiponectin and AMPK activation which was prevented by the treatment with AICAR [80].

While adipose tissue has a clear role in obesity, excessive fat deposition has been also reported to induce lipid accumulation in ectopic sites, especially in liver and muscle. Indeed, non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease associated with insulin resistance [81]. In muscle, lipid accumulation has been related to impaired glucose and insulin metabolism as well as mitochondrial function [82-86]. While the impact of lipid accumulation in liver and muscle is widely investigated, less is known regarding other organ such as kidney. More recently, studies showing ectopic lipid deposition in kidney have emerged, suggesting the role of fat accumulation in the development of chronic kidney disease (CKD) [44, 87-89]. It has been reported that adipose tissue of patients with end-stage renal disease exhibits higher amount of pro-inflammatory cytokines TNF- α and MCP-1 and an increase of macrophage infiltration [90]. Even though it is well-known that patients with renal disease are more susceptible to develop IR [91, 92], the direct link between adipose tissue dysfunction, insulin resistance and kidney disease in obesity is becoming more apparent. One likely explanation is the decreased adiponectin level associated with reduced insulin sensitivity leads to the increase of pro-inflammatory process in the kidney [93]. Studies have shown the correlation between elevated expressions of pro-inflammatory cytokines or chemokine (TNF- α , IL-6, IL-1 β , MCP-1) in adipose tissue with renal inflammation (increased TNF- α , MCP-1, IL-6 and infiltrated macrophages) in rodent models of obesity [94, 95].

We have previously identified that low levels of circulating adiponectin correlate with low grade albuminuria in obese African Americans and that the adiponectin KO mouse developed low grade albuminuria without obesity [60]. Adiponectin was found to have a protective effect on podocytes primarily via stimulating the enzyme AMPK. In another study, we demonstrated an early reduction of AMPK activity in a model of High-Fat Diet (HFD)-induced kidney disease [87]. This was associated with reduced plasma adiponectin level, increased renal inflammation and increased plasma insulin level. Interestingly, the

decrease of AMPK activity was associated with the up-regulation of MCP-1. Indeed, renal MCP1 was increased as early as 1 week after HFD at the gene expression and protein level, in the renal tissue, and in the urine. The role of MCP-1 and its receptor CCR2 has been receiving greater recognition for its role in mediating chronic kidney disease [96, 97]. MCP-1 was found to regulate nephrin expression via CCR2 in human podocytes and mice lacking MCP-1 had resistance to diabetes induced albuminuria [98]. Studies in mesangial cells demonstrated a marked stimulation of MCP-1 secretion by palmitate, suggesting that exposure of circulating saturated fatty acids, such as palmitate, may be a trigger of MCP-1 production in the setting of HFD and obesity. We also showed that the early increase in MCP-1 could contribute to the subsequent recruitment of macrophages and enhancement of pro-inflammatory factors such as TNF- α [87]. Importantly, we demonstrated that AMPK activation is able to completely inhibit MCP-1 stimulation both *in vivo* with HFD and *in vitro* in response to palmitic acid.

The mechanism by which AMPK activation inhibits MCP-1 in renal cells is unclear, but is likely due to inhibition of NF κ B activation. AMPK has been recently shown to affect the proteolysis of I κ B in endothelial cells and regulate NF κ B [99]. AMPK also seems to play a prominent role in regulating macrophage infiltration and activation. The overall numbers of macrophages infiltrating the kidney with high fat diet was completely normalized with AMPK activation [44]. A role for AMPK in regulating macrophage activation has been highlighted recently [100]. The use of metformin, another AMPK activator, showed similar data in a murine model of HFD-induced renal injury [101]. In another study, activation of AMPK by metformin prevented the decreased urinary sodium excretion and increased blood pressure induced by angiotensin II [102]. In turn, low adiponectin level has been reported to contribute to the development of obesity-related hypertension [103]. Finally, we showed that AMPK activation is a key regulator of lipid storage in kidney. Indeed, our results revealed a significant lipid accumulation in vacuolated proximal tubular cells along with impaired brush border, increased nitrotyrosine and NOX4 levels suggesting tubular dysfunction. These changes were prevented with AMPK activation [44]. The regulation of Nox4 and NADPH oxidase activity has now been demonstrated in podocytes and proximal tubular cells. We previously found that high glucose-induced stimulation of Nox4 can be blocked by adiponectin or AMPK activation. Similarly, NADPH oxidase activity by angiotensin II was completely blocked by adiponectin and AMPK activators [104]. The regulation of Nox by AMPK is also likely due to its effects on NF- κ B activation [99].

Adipose and kidney matrix accumulation

Hypoxia-inducible factor 1 α (HIF-1 α), a key mediator of hypoxia, has been also reported to act in adipose tissue fibrosis. As mentioned previously, an excessive metabolic challenge in adipose tissue induces a hypoxia in the tissue that leads to the initiation of inflammation, and in turn, to fibrosis. Halberg et al. demonstrated that local adipose tissue hypoxia results on the stabilization of the transcription factor HIF-1 α that is an important driving force to induce fibrosis [105].

However, the mechanisms underlying adipose tissue fibrosis are still unclear.

The kidney is susceptible to fibrosis with a high fat diet and obesity. Renal fibrosis is marked by progressive tissue scarring leading to glomerulosclerosis and tubulointerstitial fibrosis [106]. TGF- β is the major driver of matrix synthesis, inhibition of matrix degradation and stimulator of myofibroblast activation and has been considered as the major mediator of chronic fibrosis in kidney disease. Recent studies demonstrate that with diet-induced obesity there is induction of TGF- β in the kidney in association with upregulation of ECM molecules, including fibronectin, type IV and type I collagens [87]. Inhibition of TGF- β as an interventional agent results in reduced matrix accumulation in diabetes, puromycin nephropathy, UUO, anti-GBM disease, and hypertensive renal disease [107-110]. Many therapeutic approaches have been tested to inhibit TGF- β such as the administration of neutralizing anti-TGF- β [107, 109, 111, 112], soluble TGF- β receptor [113], or small-interfering RNA for TGF- β type II receptor [114] in experimental model of chronic kidney disease.

Similar to adipose tissue, Smad3 has emerged as a key receptor-regulated phospho-Smad that has been tightly linked to matrix accumulation. It has been reported that deletion of Smad3 protects against diabetic kidney disease, hypertensive kidney disease, and obstructive nephropathy [115]. Smad4 is a co-Smad that mediates all Smad mediated signalling and has emerged as a necessary co-factor to initiate transcription of Smad3 targeted genes. Deletion of Smad4 in tubular epithelial cells, tubulointerstitial fibroblasts and mesangial cells protects cells against TGF- β induced matrix stimulation. Recently, we have found several interactions between the AMPK pathway and TGF- β . TGF- β 1 gene stimulation by high glucose has been found to be regulated by the USF family of transcription factors. Upon exposure to high glucose USF1 translocated to the nucleus, however this nuclear translocation is blocked by AMPK activation. Similar findings were noted with Smad4 in that nuclear translocation stimulated by elevated glucose or TGF- β 1 itself was blocked by AMPK activation (AJP in submission).

However, the role of fibrosis and TGF- β likely has potent effects in many organs outside the kidney, especially in obesity. In obesity-induced adipose tissue dysfunction, increased ECM has been demonstrated in rodent and in human WAT [105, 116] even though the role of ECM of adipose tissue has received limited attention to date. Nevertheless, Khan et al. demonstrated that adipose tissue exhibited an increased collagen content in the ECM, and especially collagen VI, a predominant component of adipose matrix, in obese mice as well as in Asian Indian patients [117]. The role of collagen VI was then evaluated by the use of a genetic *ob/ob* mice model with collagen VI disruption. These mice presented an improved fasting blood glucose, insulin sensitivity and lipid metabolism along with an altered level of many key fibrotic genes in adipose tissue. Luminican, involved in the epithelial-mesenchyme transition during fibrosis, was downregulated while decorin, an antagonist of TGF- β -induced fibrosis, was up-regulated [117]. TGF- β , itself, was downregulated in the mice with collagen VI deletion. This was associated with a reduced activation of downstream TGF- β signalling mediators, Smad2 and Smad3. These changes were accompanied by a decrease of adipose tissue inflammation [117]. Therefore, the decreased levels of TGF- β and its downstream mediators suggest a potential role of TGF- β in adipose tissue fibrosis.

A more recent study demonstrated the crucial role of TGF- β and Smad3 in regulating glucose and energy homeostasis using a Smad3 KO mice [118]. Obesity was found to correlate with circulating TGF- β 1 levels in mice and humans. Upon exposure to diet-induced obesity there was an increase in adipose tissue TGF- β and increased Smad3 phosphorylation. Interestingly when mice were treated anti- TGF- β neutralizing antibody (1D11) the mice had less weight gain, less insulin resistance and the WAT had features of brown fat, with increased UCP1 and mitochondrial biogenesis [118]. The Smad3 KO mice on the high fat diet exhibited an increase of insulin sensitivity, a reduced adipocyte size, reduced pro-inflammatory cytokines and macrophage infiltration in adipose tissue as compared to WT mice on the high fat diet.

Orphan G-Protein-coupled receptors in kidney and adipose tissue

More recently, orphan G-protein-coupled receptors (GPCRs) have been pointed as playing a role in the progression of obesity-related disease. These receptors function as receptors for short chain fatty acids (SCFAs), such as acetate and propionate. The source of FA can be diverse. They can come from the digestion and lipolysis of triglycerides in the liver and adipose tissue or be obtained from food intake. The GPCRs are expressed in many tissues such as in pancreas, adipose tissue and kidney. In pancreas, the orphan GPCRs, especially the GPR40, have been found to interact with the insulin signaling [119]. A recent study showed that an acute exposure of FFA stimulated insulin release from the beta cells while a chronic stimulation by FFA impaired the beta-cell insulin secretion and lead to lipotoxicity [120]. In that study, transgenic GPR40 knockout mice were protected from hyperinsulinemia, and glucose intolerance [121]. It is thus easy to figure out that excess food intake, and especially fat food, lead to an increase of FFAs that in turn promote abnormal response in their orphan GPCRs, promoting impaired insulin secretion. In adipose tissue, GPR43 and GPR41 have been identified. Their exact role is not fully elucidated. Xiong et al. (2004) found that the activation of GPR41 by short chain fatty acids (SCFA) induced leptin expression in both a mouse adipocyte cell line and mouse adipose tissue in primary culture [122]. The increased level of circulating leptin was also measured in mice after acute oral administration of propionate, a well-known SCFA, ligand of the GPCRs [122], therefore suggesting that SCFA via specific GPC Receptor could play a role in cellular signaling pathway and regulate metabolic factor such as leptin. In another study, increased expression of GPR43 but not GPR41 was demonstrated in adipose tissue from mice fed a high-fat diet [123]. Moreover, the inhibition of GPR43 in 3T3-L cells by specific siRNA was found to significantly reduce lipid accumulation after stimulation with the SCFA, propionate [123]. The role of GPR43 activation in inhibition of lipolysis was then confirmed using an *in vitro* model of adipocytes isolated from GPR43 knockout mice [124]. Furthermore, in vivo, activating GPR43 by SCFA resulted in a reduced level of plasma FFA, reinforcing the role of GPR43 in inhibit lipolysis and reduce plasma FFA [124]. In kidney, the evidence for a role of GPCR has been reported. Indeed, GPCR were detected in distal tubular cells and in macula densa, suggesting sensory role in the regulation of the tubuloglomerular feedback by regulating the renin release [125]. A more recent study reported opposite effects of the GPCR functions [126]. In this study, the olfactory receptor78 (Olfr78) and the GPR41 knockout mice models were used to determine the role of the SCFA and their receptors in regulation of renal vascular tone and release of renin. Both Olfr78 and GPR41 were detected

in renal vasculature [126]. However, while Olfr 78 KO mice presented a lower blood pressure associated with a lower plasma level of renin, the contrast was observed in GPR41 KO mice. That study revealed that Olfr78 activation promotes an increase of blood pressure while the activation of GPR41 contributes to the hypotensive effect of propionate. This opposite effect may act to buffer blood pressure modulation. The role of these receptors in IR is uncertain. However, SCFAs released in bloodstream can modulate diverse cellular signaling such as the renal RAS system which may in turn promote impairment of insulin signaling. Clearly, further investigations are needed to delineate the exact role of these orphan G-protein-coupled receptors.

Conclusion

Thus, it is becoming increasingly clear that there is an important cross-talk between adipose tissue and the kidney, especially in obesity-related kidney disease, although similar cross-talk is likely important with diabetes and possibly hypertension-associated kidney disease as well. The use of systemic AMPK activation is likely to have profound effects on adipose tissue which could contribute to the reduced inflammation and fibrosis observed in the kidney. Nevertheless, there are likely kidney specific effects of AMPK activators as well. In addition, use of systemic anti-inflammatory and anti-TGF- β antibodies likely also have profound effects on adipose tissue which are beneficial systemically and for improvement in renal structure and function. In future studies, further understanding and elucidation of key pathways linking adipose tissue to the kidney will suggest improved treatment approaches which will likely have widespread application and implications for progressive CKD of many etiologies.

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Key points

- Obesity is as a serious health issue particularly in the western world increasing related complications such as metabolic syndrome.
- Adipose tissue is now considered as an endocrine organ producing biologically active molecules that contribute to the onset of obesity-related disease.
- Excess lipid accumulation may lead to lipotoxicity and may be the major driver of organ dysfunction such as kidney injury.
- The central energy sensor, AMPK, appears to play a key role in obesity-related metabolic disease.
- Increased knowledge of the link between adipose tissue and kidney in a context of obesity will allow for novel therapeutic approaches to prevent obesity-induced kidney injury.