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REVIEW

Manifestation of renal disease in obesity: pathophysiology of obesity-related dysfunction of the kidney

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Abstract: Albuminuria in individuals whose body mass index exceeds 40 kg/m^2 is associated with the presence of large glomeruli, thickened basement membrane and epithelial cellular (podocyte) distortion. Obstructive sleep apnea magnifies glomerular injury as well, probably through a vasoconstrictive mechanism. Insulin resistance from excess fatty acids is exacerbated by decreased secretion of high molecular weight adiponectin from adipose cells in the obese state. Adiponectin potentiates insulin in its post-receptor signaling resulting in glucose oxidation in mitochondria. Recent studies of podocyte physiology have concentrated on the structural and functional requirements that prevent glomerular albumin leakage. The architecture of the podocyte involves nephrin and podocin, proteins that cooperate to keep slit pores between foot processes competent to retain albumin. Insulin and adiponectin are necessary for high-energy phosphate generation. When fatty acids bind to albumin, the toxicity to proximal renal tubules is magnified. Albumin and fatty acids are elevated in urine of individuals with obesity related nephrotic syndrome. Fatty acid accumulation and resistin inhibit insulin and adiponectin. Study of cytokines produced by adipose tissue (adiponectin and leptin) and macrophages (resistin) has led to a better understanding of the relationship between weight and hypertension. Leptin, is presumably secreted after food intake to inhibit the midbrain/ hypothalamic appetite centers. Resistance to leptin results in excess signaling to hypothalamic sympathetics leading to hypertension. Demonstration of the existence of a cerebral receptor mutation provide evidence for a role in hypertension of a central nervous reflex arc in humans. Further understanding of obesity-related renal dysfunction has been accomplished recently using experimental models. Rapid weight loss following bariatric surgery may reverse renal pathology of obesity with restoration of normal blood pressure.

Keywords: glomerulomegaly, podocyte hypertrophy, obesity, albuminuria, adiponectin, insulin, leptin

An association of body mass index (BMI) with risk of kidney disease was summarized from the Boston University Framingham study as a single unit increase of BMI accounting for a 20% increase of kidney disease over 20 years of follow up.[1] A recent study from Copenhagen involving 20,000 women and 17,000 men aged 30–80 years found that for each 10% increase in BMI, the systolic blood pressure was 2.0–6.0 mm Hg higher along with an increase in diastolic pressure of 1–3 mm Hg.[2] Visceral adipose was quantified by CT scan in a study from Laval University, Quebec.[3] A significant correlation between mass of visceral adipose and level of blood pressure was noted. Kidney donors who were obese, or who became obese during an 11 year follow up

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at the University of California, San Francisco were found to have higher blood pressure than nonobese kidney donors even though proteinuria and nitrogen waste products in the plasma were not different[4]

When obesity is accompanied by persistent proteinuria of greater than 1 gm/day, findings at light microscopy include focal, segmental and global sclerosis. As lesions progress, individuals may become dependent upon renal replacement therapy. Since obese individuals do relatively well from earlier stages of chronic kidney disease through the stage of hemodialysis, this group is an important component of individuals awaiting kidney transplantation. Investigators from the Department of Nephrology, University of Vienna have concluded from a review of 50,000 patients in the Austrian Dialysis Transplantation Registry that cardiovascular mortality was significantly decreased for BMI 30–35 kg/m^2 compared to less than 30 kg/m^2.[5] Individuals with obesity-related renal failure that is not complicated by accelerated hypertension or profound insulin resistance do well on hemodialysis because of residual function in their large kidneys, in contrast to smaller people with diminutive kidneys. Many patients have been overweight since adolescence. Although elevations of blood glucose and blood pressure may not have occurred until many years later, official statistics may label the cause as hypertensive nephrosclerosis or diabetic nephropathy. It is reasonable to assume that if obesity promotes pathologic renal changes or accelerates damage from other entities that loss of excess body weight would ameliorate such changes, as well as having a beneficial effect on glucose metabolism and blood pressure.

Proteinuria in obesity is associated with changes in structure of the epithelial cell of the glomerulus (podocyte): changes in pathophysiology of the glomerulus are better understood than those of the proximal tubule

Anatomical studies of the renal glomerulus correlate with the physiology of obesity

Investigators from the Autonomous University of Barcelona described a distinct obesity-related change in the renal glomerulus.[6] Extremely obese individuals (BMI > 40 kg/m^2) undergoing renal biopsy during bariatric surgery were compared with a group of age-matched patients studied at the time of elective nephrectomy. Twenty-four hour protein excretion was statistically different: 100–340 in the bariatric group vs 100–120 mg/day ($p = 0.01$) in the non-obese group. Fasting blood sugar levels also were different 88–117 vs 85–99 mg/dl ($p = 0.02$), respectively.

Light microscopic changes noted in the bariatric group, but not the nephrectomy group, included large glomeruli (glomerulomegaly), podocyte hypertrophy along with increased mesangial cellularity and extracellular matrix. On electron microscopy, only in the bariatric group were fusion of adjacent podocytes containing lipids and cytoskeletal filaments aligned parallel to the basement membrane found. From the pathology and nephrology departments of Nagasaki and Hiroshima Universities, histologic findings in an overweight population included glomerular basement membrane thickening when proteinuria was 100–2000 mg/day.[7] Earlier stage obese patients reported from University Hospital, Patras, Greece with urine albumin below 30 mg/day were also found to have basement membrane thickening on renal biopsy.[8]

In the aforementioned study by the Barcelona group, the largest glomeruli were found in those extremely obese patients who also had clinically apparent sleep apnea.[6] The kidney dysfunction of obesity may in part be due to altered physiology accompanying sleep apnea, a frequent comorbidity in these patients. Obesity is actually the best-documented risk factor for obstructive sleep apnea (OSA)[9] OSA is now a well-recognized cause of systemic hypertension in a portion of affected patients, and the severity of OSA appears to positively correlate with the degree of risk for hypertension.[10]

An increased prevalence of proteinuria in obese patients with OSA was initially recognized at the University of Wisconsin.[11] This group of investigators studied 34 obese patients with OSA documented by formal sleep study and 34 patients whose sleep studies were negative for the disorder. Patients who had diabetes mellitus, arterial hypertension, hematuria, bacteriuria/pyuria, or a serum creatinine greater than 1.2 were excluded from participation. Statistical analysis between the two groups revealed no difference in age, weight (mean 112.7 kg in patients with OSA versus 109.2 kg in controls), height, or percentage above ideal body weight. Proteinuria (defined as 1+ or more on urinary dipstick) occurred in 47% of the patients with OSA versus 29% of the control group, and high-grade proteinuria (3 to 4+ on dipstick; 3+ equating to >300 mg/dl and 4+ equating to >2000 mg/dl) was found in six patients with OSA but in none of the controls. Four patients able to be followed for 3 years, had improvement in proteinuria after therapy for OSA.

Investigators from the Medical College of Georgia, Augusta[12,13] observed nocturnal urinary protein excretion to be 16.2 ± 5.5 microgram/min in 9 healthy control subjects, 29.3 ± 9.5 microgram/min in 12 obese subjects without OSA on sleep study, and 94.0 ± 13.8 microgram/min in 14 obese patients with documented OSA. Patients with known renal disease, diabetes mellitus, elevated serum creatinine, abnormal urine sediment, or uncontrolled hypertension were excluded in this study. More recently, a group at the University of Athens,[14] studied microalbuminuria in hypertensive patients with OSA versus hypertensive patients without OSA by formal polysomnography. Participants were matched for age, sex, smoking status, BMI, 24-hour pulse pressure, with exclusion if impaired glucose metabolism and chronic kidney disease were detected. This group demonstrated that albuminuria was greater by 57% in hypertensive patients with OSA as compared with those without OSA. This group demonstrated that the number of apneas plus hypopneas per hour of sleep (AHI) as well as 24-hour pulse pressure were independent predictors of albuminuria in their multivariable linear regression model. Since albuminuria is a well-validated sign of diffuse endothelial dysfunction, these investigators hypothesized that such vascular dysfunction observed in OSA may engender the increased rate of cardiovascular morbidity and mortality seen in the disease. The pathophysiologic mechanism underlying the increased rate of proteinuria in OSA is incompletely understood.

Prospective studies of biopsy-proven focal glomerulosclerosis demonstrate higher levels of proteinuria and more rapid progression of renal dysfunction when compared to the findings of the Barcelona investigators. The study group from Columbia University, in New York[15] followed 71 patients whose renal biopsies were denoted "obesity- related glomerulopathy", 50 with "pure" focal sclerosis, and 50 with "mixed" findings. Chronic renal dysfunction occurred in 3.6% of the glomerulopathy group, 42% of the "pure" focal sclerosis group, and 4.0 % in the "mixed" group suggesting the mixed findings group was similar to the obesity-related glomerulopathy patients. As oxygen requirements of the medulla are higher than that of the cortex, it has been suggested that juxtamedullary nephrons would be more susceptible to hypoxemia and more likely to benefit from loss of weight.[12] The most striking degree of glomerulomegaly observed in obese patients biopsied at the University of Texas, Houston was more evident in the cortex.[16] Thus, while hypoxemia may be important in "pure" focal sclerosis of juxtamedullary nephrons, the role of hypoxemia in the increased glomerular size of obesity may be limited to individuals with superimposed sleep apnea.[6]

The presence of an inflammatory cascade contributing to mesangial expansion would be expected to accelerate sclerosis in obesity. Investigators at the Hospital of St. Etienne, University of Lyon studied the effect of obesity on 162 patients with IgA nephropathy (95 patients were lean, 67 were obese).[17] Baseline renal biopsy in the 67 obese patients showed higher grades of glomerular, tubulointerstitial, and vascular pathology in association with higher levels of proteinuria compared to controls. At the 20-year follow up, 60 % of the obese group had become dialysis dependent as opposed to 10 % of the non-obese patients. A major mechanism in obesity-related inflammation is a deficiency in adiponectin, a protein secreted by adipose tissue. Adiponectin inhibits Tumor Necrosis Factor alpha, which activates Nuclear Factor kappa B (NFkB). Since NFkB initiates gene sequences for inflammation cascades, a deficiency of adiponectin has profound consequences for the pathophysiology of obesity-related inflammation.[18]

Table 1 compares the glomerulopathies of obesity, diabetes, and focal sclerosis. Loss of creatinine clearance is associated with mesangial cell proliferation, matrix expansion and progressive scarring to different degrees in these three causes of proteinuria.

Mechanisms of proteinuria in obesity-related glomerulopathy

Studies from Indiana University have focused on renal tubular handling of sodium in obesity and insulin resistance. Increased insulin levels promote proximal tubular absorption of sodium with decreased delivery to the distal tubule (macula densa), causing a feedback reflex that results in greater perfusion of the glomerulus.[20] Increased proximal tubular resorption of

Table 1 Pathology in proteinuria of obesity, type 2 diabetes, focal sclerosis

	Glomerulus	Podocyte	Basement membrane	Mesangium
Obesity	Glomerulomegaly	Fusion, linear deposits	Thickened 2+	Increased 2+
Type 2 diabetes	No Change	Fusion	Thickened 3+	Increased 4+
Focal sclerosis	Epithelial Hyperplasia[19]	Fusion	Thickened 4+	Increased 3+

sodium is enhanced by hyperinsulinemia but countered by proximal tubular sodium wasting due to elevated levels of leptin seen in obesity.[21] Higher aldosterone levels of obese compared with non-obese individuals also enhance tubular sodium resorption at a distal site in the collecting duct.[22] On balance renal tubular resorption response to insulin appears more potent than the mixed response to leptin/aldosterone in obesity. The same relationship between BMI, aldosterone and sodium balance has also been demonstrated in normotensive subjects.[23]

Increased filtered solute load due to turnover of the increased fat plus muscle content of extreme obesity along with increased plasma volume can be expected to enlarge glomerular capacity.[24] Studies from Hopital Lapeyronie, Montpellier found glomerular filtration rate (GFR) increased in obese patients. Increased GFR associated with obesity and glomerulomegaly correlated with urinary excretion of urea and protein. This was supported by use of BUN as a marker for protein intake.[25] Hyperinsulinemia of obesity was related to increased perfusion of muscle[26] consistent with observations of increased perfusion of the nephron.[20] Animal studies have demonstrated glomerulomegaly with high fat diet. When the obese Zucker rat lost weight as a result of a low calorie diet, there was a decrease in proteinuria associated with improvement in glomerulopathy.[27]

A human study from Hospital Universitario 12 de Octobre, Madrid found that a decrease in BMI from 33 to 31.6 kg/m^2 was associated with a fall in 24-hour urine protein from 2.8 to 1.9 grams/day. The investigators studied patients with Type 2 diabetes, hypertensive nephrosclerosis, focal sclerosis, mesangial glomerulonephritis, and reflux nephropathy. The control group consisted of ten obese patients on their usual diet, who gained 2 kg in 5 months. The diet group was allowed 500 kilocalories less than their usual daily intake, resulting in a loss of 3.6 kg in 5 months. These combined data generated a positive correlation between weight loss or gain and urine protein decrease or increase ($p < 0.01$, $r = 0.62$) for the 30 study patients.[28] Mechanisms described from Rabin Medical Center, Tel Aviv University have included hemodynamic alterations involving expanded plasma volume, increased renal plasma flow (RPF), increased GFR, and increased filtration fraction (GFR/RPF). Another mechanism is increased capillary filtration pressure.[29] When gastric reduction surgery was used to cause loss of fat but not muscle in 8 obese individuals (BMI = 48.0 kg/m^2) compared with 9 controls of normal body mass index (22.1 kg/m^2), there was a weight loss of 48 kg over 12–17 months for a change in BMI of 15.9 kg/m^2 as opposed to no change. GFR fell significantly from 144 to 110 ml/min in the obese group versus a value of 90 ml/min in the control group, which did not change. Renal plasma flow fell significantly from 803 to 698 ml/min versus a control of 610 ml/min. Filtration fraction fell significantly from 0.178 to 0.158, versus control of 0.149. Systolic pressure fell from 143 to 133 mm Hg versus control of 120 mm Hg.[29]

The cellular physiology of the podocyte has become the focus of much new research. These epithelial cells have interconnected architectures with close-fitting foot processes that require a large amount of energy to function as a filtration barrier for albumin and fats, not only to preserve resources, but also to protect the proximal tubule from injury. This energy comes from oxidation of glucose and fatty acids. A key step is phosphorylation of the kinase of adenosine monophosphate whose activation is promoted by metformin.[30] Glucose enters the podocyte through the glucose transporter protein complex (GLUT). Pioneering studies have identified cooperation of insulin and adiponectin in glucose transport across the podocyte cell membrane. From the University of Bristol and from University College, London, the filtration barrier protein, nephrin, was found to be critical for movement of GLUT proteins across the cytosol for attachment to the cell surface membrane.[31] Without nephrin, there is no quick energy for maintaining a barrier to loss of nutrients as a meal is being digested. Studies from the University of California at San Diego, Thomas Jefferson University, Philadelphia, and Baylor University, Houston have produced convincing evidence that adiponectin cooperates with insulin in the work of nephrin by co-activating adenosine monophosphate kinase (AMPK), a step just before oxidation of long-chain fatty acids is begun in mitochondria,[32] Table 2.

Insulin resistance occurs in obesity due to a deficiency of active insulin receptors, an inhibition of oxidation of fatty acids related to a deficiency of adiponectin and inefficient secretion of insulin by beta cells associated with higher levels of leptin (Table 3). Normal feedback inhibition of insulin secretion by insulin itself retains intermittent or

Table 2 Glomerular filtration barrier: Nephrin is assisted by oxidation of glucose fatty acid

	Glucose transport	Fatty acid disposal
Insulin	+	+*
Adiponectin	+	+*
Leptin	?	?
Resistin	?	–

Note: *Promoted by metformin/acetyl L-carnitine.

Table 3 Adiponectin, leptin and resistin interact with insulin in liver, pancreas, and kidney

	Hepatic gluconeogenesis	Hepatic glycogenolysis	Glucose/ fatty acid disposal	Pancreatic beta cell function	Renal tubular Na resorption/wasting
Insulin	Inhibits***	Inhibits	Activates*	Inhibits	+/–
Adiponectin	Inhibits***	Inhibits	Activates*	?	?/?
Leptin	?	?	?	Inhibits**	+ indirect/+ direct
Resistin	Activates	?	Inhibits**	Inhibits	?

Notes: *Promoted by metformin/acetyl L-carnitine. **Promoted by aldosterone. ***Promoted by acetyl L-carnitine.

pulsatile secretion in contrast with inhibition of beta cell function by leptin. In combination with excess glucose the oscillation of calcium in the cytosol is inhibited, resulting in loss of pulsatile secretion, followed eventually by loss of adequate insulin non-pulsatile secretion.[33] Adiponectin assists insulin in the liver by decreasing gluconeogenesis and glycogenolysis. Failure to process fatty acids due to a deficiency of adiponectin leads to their accumulation, which is in itself another cause of insulin resistance at the level of phosphfructokinase in the glycolytic cycle.[34] The apparatus for post-receptor propagation of the insulin signal after binding to its receptor exists within muscle, adipose, and glomerular epithelial cells (podocytes) and can be inhibited by elevated levels of aldosterone.[35] Aldosterone also promotes the generation of NADPH oxidase which inhibits the phosphorylation of AMPK at the last step before mitochondrial generation of high energy phosphate.[36] Without a fundamental collaboration of nephrin, adiponectin and insulin, there would be insufficient energy to maintain the foot processes in correct position to occlude the slit pore. If protein and lipids were to appear in the glomerular filtrate, they would quickly damage the proximal tubule, particularly with the elevated concentrations seen in the nephrotic syndrome.

The cytocellular components actin and podocin utilize energy to position the community of foot processes. Occupation of the receptor for advanced glycated end products inhibits confluence of foot processes by inhibiting mitochondrial energy production.[37] Since the unoccupied receptor is found precisely at the places where the foot processes must come together, inhibition of free movement with glycated end-products would have pathological consequences. Studies of the receptor for advanced glycated end products at Albert Einstein School of Medicine[37] and Columbia University both in New York have brought the greatest clarity to mechanisms.[38] It is now appreciated that the AGE carboxymethyl lysine has a higher potential for cardiovascular cytotoxicity than carboxyethyl lysine[39] or methyl glyoxal[40] but there is no study as yet available pinpointing a pathological AGE for the podocyte. The receptor for advanced glycated end products is found precisely where endothelial injury and inflammation combine to initiate atherosclerosis and diabetic vascular pathology.[41] The diabetes complications observed in survivors of insulin deficiency for greater than 50 years were limited to large vessel rather than microvascular disease.[39] Diabetic congenital complications are related to a malformation of the aortopulmonary outflow tract.[40] The current hypothesis is that carboxymethyl lysine has a major impact on the inflammatory cascade due to its generation in the setting of oxidative stress.

Studies of the renal proximal tubule are not yet specific to obesity-related glomerulopathy

Investigators from Shinshu University and the National Cancer Institute, Bethesda have focused on proximal tubular toxicity of fatty acids present in a model of nephrotic syndrome with hyperlipidemia.[42] In their mouse model, although high concentrations of albumin were not toxic, 16-carbon fatty acid (palmitic) bound to albumin caused severe injury to proximal tubular cells. In this model, the peroxisome proliferator activated receptor alpha (PPAR alpha) was found to be highly protective. In view of this finding, studies of pharmaceutical agents that activate renal PPAR alpha such as clofibrate are warranted. Using clofibrate these investigators found that in the nephrotic mouse successful elimination of excess fatty acid by increased beta-oxidation in mitochondria was associated with protection of the proximal tubule. However, the investigators warned that an increased generation of reactive oxygen species by mitochondria was detected. This would be of concern in the insulin resistant obese patient due to formation of advanced glycated end products. No proximal tubular site has yet been identified for injury related deposition of AGE at its receptor.

Accumulation of fatty acids in muscle and liver has its own toxicity. Carnitine is essential for transportation of long-chain fatty acids from cytoplasm to mitochondria. Deficiency of carnitine is associated with insulin resistance, hypertension and loss of the beneficial effects of adiponectin. Replacement of acetyl carnitine among type 2 diabetic patients studied at the Mario Negri Institute for Pharmacological Research in Bergamo[43] restored insulin sensitivity and normal blood pressure as well as both total and high molecular weight adiponectin. Removal of excess fatty acids permits enzymes of glycolysis[44] and gluconeogensis[45] to return to normal function.

Experiments from Massachusetts General Hospital, Indiana University Medical Center and Victoria, Australia demonstrate that impaired uptake of albumin by the proximal tubule in streptozotocin-treated (ie, insulinopenic) diabetic rats is reversible with insulin.[46] This malfunction was identified earlier in the course of diabetes than glomerular albumin leakage. There is no similar report as yet in the insulin resistant animal with diabetes-induced albuminuria.

Obesity carries with it a glomerular leak, relative insulin resistance, and increased fatty acids (reflected in the circulating triglycerides). If the obese insulin resistant animal model or patient were to respond entirely to insulin, there would be no proximal tubular toxicity. If however, the insulin resistant animal or patient were to respond in a similar manner to the insulinopenic STZ rat, then failure to correct the glomerular lesion entirely, while reversing tubular leakage, might result in greater toxicity to the proximal tubule. In many glomerular diseases duration of renal function is predicted by tubulointerstitial rather than glomerular pathology. We can conclude based upon current knowledge that insulin resistance has toxic potential on the podocyte through advanced glycated end-products and impaired metabolism of fatty acids. An increased concentration of fatty acids in the plasma and glomerular filtrate is toxic to proximal tubules when absorbed across the cell membrane in the presence of insulin, particularly when bound to albumin. In cultured human renal proximal tubular epithelial cells, aldosterone can increase expression of collagen III and IV that gives it a potential role in tubulointerstitial fibrosis by promoting tubular epithelial-mesenchymal transition and collagen synthesis.[47] This combination of profibrotic effects in tubular as well as mesangial cells can contribute to tubulointerstitial fibrosis with glomerular scarring. Type 2 diabetic kidney disease may well be another example of glomerular disease in which outcome is predicted by degree of tubulointerstitial inflammation/scarring

Hypertension of obesity may be exacerbated by altered levels of adipokines secreted by white adipose tissue

Adiponectin is the adipokine with highest concentration in the circulation

Adiponectin is secreted by white adipose tissue. Levels are higher in lean individuals who benefit from the effects of adiponectin in assisting insulin, which decreases gluconeogenesis. Low, intermediate and high molecular weight (HMW) forms of adiponectin are found in the circulation. Levels of HMW adiponectin fall with obesity. Studies from Munich, Maastricht and Leuven have further concluded that there is a decrease in concentration of HMW adiponectin in hypertensives with normal BMI.[48] In Osaka decreased levels of HMW adiponectin were noted to be associated with ischemic heart disease[49] in lean individuals. In Denver the only factor found to increase adiponectin in the lean children with chronic renal insufficiency was a decreased creatinine clearance.[50] The other adipokines that are cleared by the kidney are leptin and resistin,[51] factors that do not promote the function of insulin as adiponectin does (Table 4).

An important intracellular form of insulin resistance is inhibition of mitochondrial fatty acid oxidation associated with adiponectin deficiency and/or increased levels of resistin. As fatty acids accumulate, insulin resistance is magnified. The energy generated by fatty acid oxidation at the slit pore membrane maintains a filtration barrier for albumin and lipids. The point in the renal glomerulus where this activity occurs is referred to as the slit-pore or zona occludens of the community of podocytes. This is the very same anatomic point at which advanced glycated end products bind to their specific receptors. Adiponectin and leptin also both affect endothelial surfaces of vessels. HMW adiponectin is considered protective. Since leptin has both a sympathetic effect to constrict vessels without going through endothelium

Table 4 Factors in blood levels of insulin and adipokines

	Obese	Lean	Renal dysfunction
Insulin	Increased	Decreased	Increased
Adiponectin	Decreased	Increased	Increased
Leptin	Increased	Decreased	Increased
Resistin	Increased	Decreased	Increased

and an indirect endothelial effect on nitric oxide release[52] that dilates vessels with the potential for increased fluid leakage, it is not considered renoprotective.

Investigators from Melbourne divided 34 obese hypertensive patients into an insulin resistant (n = 19) and an insulin sensitive (n = 15) group by measuring multiple insulin and norepinephrine levels during an oral glucose tolerance test and evaluating the area under the curve.[53] At baseline norepinephrine levels were higher and clearance of norepinephrine was lower in the insulin-resistant group. With 12 weeks of life style modification, body weight fell by 8 kg in both study groups. Leptin levels fell significantly more in the insulin-resistant group. With weight loss and fall in leptin, a significant fall in level of norepinephrine was seen only in the insulin-resistant group. Thus, from this study we can conclude that in the absence of weight loss, treatment of blood pressure can be expected to be more difficult in the insulin resistant group.

Leptin levels are higher when there is an excess of white adipose

Leptin may also be secreted by muscle and placenta, leading to obstetrical difficulties such as pregnancy-induced hypertension, intrauterine growth retardation, and pre-eclampsia according to studies from Portland, Oregon.[33] To gain further insight into the relationship between leptin levels and blood pressure control, investigators from the Athens School of Medicine worked with non obese study subjects.[54] They measured circulating levels of leptin and soluble leptin receptor of 494 (272 males, 222 females) individuals (BMI < 30 kg/m^2). 180 subjects were normotensive and 314 had high blood pressure. Of the 314 hypertensive patients, 166 had fixed, 82 had white coat (abnormal in clinic, normal on ambulatory monitoring), and 66 had masked (normal in clinic, abnormal on ambulatory monitoring) blood pressure elevations. Leptin levels were significantly higher and soluble leptin receptor levels were significantly lower in individuals with fixed or masked hypertension when compared with subjects with normal blood pressure or white coat hypertension.

It has been hypothesized that increased concentrations of insulin and leptin may activate obesity related high blood pressure by stimulation (Table 5) of the central sympathetic nervous system (hypothalamus or nucleus tractus solitarius in midbrain).

The intermediate step between leptin and the midbrain sympathetic centers involves two transmitters known as neuropeptide Y and melanocortin. A mutation of the receptor for melanocortin is being studied in families with early-onset obesity followed at Addenbrooke's Hospital, Cambridge.[55] There were two groups of study patients with obesity. The first group had a greater than 50% incidence of hypertension due to a functioning melanocortin signal through an intact receptor. The second had a less than 25% incidence of high blood pressure despite extreme obesity. In addition to lower blood pressure while awake there were slower heart rates with lower outputs of norepinephrine along with evidence for intact parasympathetic heart rate variation. Blood pressure and heart rate increased and heart rate variation decreased with an experimental agonist of the dysfunctional receptor. Raising leptin concentrations to achieve satiety does not result in weight loss and could conceivably exacerbate hypertension in obese patients.

The locus of the leptin post-receptor signal in mid brain, the melanocortin site, has been studied by investigators from the University of Mississippi[56] Medical Center. The Sprague-Dawley rat treated with STZ develops insulin deficiency hyperglycemia, hyperphagia and a slow heart rate. Intracerebral ventricular infusion of leptin reverses this clinical problem. An antagonist to the melanocortin receptor blocks leptin's reversal of these acute insulin deficiency findings. An agonist to the melanocortin receptor eliminated the need for leptin but could only sustain the effect for several days unlike leptin, which appeared to permanently replace insulin. Thus, the

Table 5 Mechanisms of hypertension in obesity

	CNS sympathetic stimulation	Vasodilates	Vasoconstricts
Insulin	+	+*	+ CNS
Adiponectin	–	+	?
Leptin	+	+	+
Endothelial dependant		+	–
Nonendothial dependant		–	+ CNS
Resistin	?	?	?

Note: *Promoted by metformin.
Abbreviations: CNS, central nervous system.

receptors for leptin and melanocortin represent an area of active investigation for both satiety and elimination of excess fuel via heat dissipation by brown adipose tissue.[57]

Another hypothesis suggests direct stimulation of the renin/angiotenin/aldosterone system by a combination of excessive leptin and deficient adiponectin[58] from white adipose tissue in the obese patient[33,59] (Table 6). Other possible mechanisms include the release by white adipose tissue of the oxidative derivative form of linoleic acid[60] and a releasing factor stimulating the secretion of mineralocorticoids by the adrenal cortex.[61] Small studies have shown that addition of spironolactone to renin angiotensin system blockade may reduce proteinuria and retard renal progression in chronic kidney disease patients.[62] Eplerenone, another aldosterone antagonist, has been shown to reduce albuminuria in patients with type 2 diabetes.[63] It is not known whether aldosterone receptor blockade will be effective or of reasonable price for future clinical studies.

Resistin inhibits insulin in liver and possibly muscle and podocyte

Rodents secrete resistin from white adipose tissue (adipokine), however, humans secrete resistin from macrophages. Resistin increases with obesity and diminished renal function. Insulin resistance results from elevated levels of gluconeogenic enzymes and inhibition of mitochondrial generation of energy (inhibition of AMP kinase). Circulating resistin exists in several oligomeric forms. The roles of the different oligomers are not yet known. The endoplasmic reticulum is the locus for removal of some forms of resistin.[64]

Experimental animal models may clarify obesity-related kidney pathology

Mouse model

The obesity gene (ob) codes for leptin and is absent in the ob/ob mouse resulting in a phenotype of hyperphagia and physical inactivity. This obese animal model does not exhibit the renal pathology of obesity seen in other animal models theoretically due to an absence of leptin. The db gene controls the central nervous system receptor for leptin binding. Absence of this db gene encodes the CNS leptin receptor and renders the db/db mouse susceptible to high leptin obesity. This animal model exhibits glomerular pathology similar to that seen in obesity and type 2 diabetes. Investigators from the University of Pennsylvania Renal Electrolyte-Hypertension Division[65] used an antibody to Transforming Growth Factor beta (TGF beta) to protect the kidney of the db/db mouse from its expected pathology. Because leptin has homology with Interleukin 6, it was hypothesized that leptin might stimulate an inflammatory cascade, involving TGF beta. Thus blockade at this level might be protective.

Use of mouse models for type 1 (Akita) and type 2 diabetes mellitus (db/db) have demonstrated that hyperglycemia[66] and advanced glycation end-products[67] promote detachment, necrosis, and apoptosis of podocytes via enhanced expression of NADPH oxidase resulting in generation of reactive oxygen species. Studies of type 2 diabetic patients from the Pima nation in Arizona have demonstrated that a decreased number of podocytes can be detected prior to other changes in the glomerulus.[68] It is possible that loss of podocyte nephrin will be understood as the transition step from an obesity-related to a diabetes-induced pathogenesis of proteinuria.[69]

Table 6 Obesity-related hypertension: Role of central nervous and adrenal mechanisms

A. Central nervous system: sympathetic stimulation
1. Increased insulin via renin-angiotensin-aldosterone system
2. Increased leptin via renin-angiotensin-aldosterone system
B. White adipose
1. Local renin-angiotensin-aldosterone system
2. Mineralocorticoid releasing factors stimulating adrenal secretion
3. Oxygenated fatty acid (linoleic) stimulating adrenal secretion
4. Absence of vasodilatory effect of adiponectin

Mouse angiogenesis model

Investigators from Denver, Ashikawa, and London have reviewed prior studies that employed the STZ diabetic rat (model of Type 1 Diabetes) and the db/db mouse (model of Type 2 Diabetes).[70] In both models, hyperglycemia was associated with an increased capacity of the podocyte and proximal tubular cell to synthesize vascular endothelial growth factor (VEGF) A, which activates receptors on the capillaries of both glomerulus and proximal tubule leading to neovascularization similar to that observed in the retina.

Current epidemiological studies indicate a rapid increase in the prevalence of obesity in pre-adolescence[71] and in adolescence.[72] Even Type I diabetic patients may develop obesity. Obesity can begin so early in childhood that Type 2 diabetes is possible before the age of 21 years. Information acquired from the study of obesity with or without insulin resistance will be useful in the study of the risk for blindness and kidney failure.

Vitamin D receptor deficient mouse: model for hyperreninemia

An experimental mouse model lacking the vitamin D receptor has been used to demonstrate an inhibition of renin secretion by juxtaglomerular cells following exposure to 1,25 dihydroxy vitamin D.[73] Research from the University of Chicago and Northwestern has demonstrated that the interaction between vitamin D and renin is independent of the concentration of serum calcium or parathyroid hormone. Current appreciation of a high incidence of vitamin D deficiency in obesity has been supported by a demonstration of diminished capacity to respond to ultraviolet light or to oral supplementation in obese compared with lean subjects studied at Boston University School of Medicine.[74] However, universal supplementation of Vitamin D without appropriate monitoring could be injurious by calcium phosphate deposition and has not been demonstrated to be renoprotective at present.

Active mineralocorticoid receptor mouse model

The Dahl salt-sensitive rat expresses elevated levels of blood pressure and aldosterone with salt in the diet. The mineralocorticoid receptor is activated under these conditions, but can be inhibited with eplerenone. In studies from the University of Tokyo Graduate School of Medicine, a mouse model has been developed that has spontaneous activation of the mineralocorticoid receptor even with low levels of aldosterone. Renal pathology includes podocyte injury with increased mesangial matrix.[75] There is ongoing research in blocking activation of the mineralocorticoid receptor for preservation of renal function.

Integrin/kinase deficient mouse model

Integrin has been identified at the unique location on the foot process cytoskeleton that is central to orientation of the slit pore. Integrin linked kinase appears to be responsible for changes in slit pore conformation. A mouse model lacking a functional integrin linked kinase exhibits proteinuria before any anatomical abnormalities are discernable. This critical link between structure and function has been hypothesized to contribute to nephrosis.[76] Transforming Nuclear Factor alpha promotes adhesion and expression of endothelial adhesion molecules. Deficiency of adiponectin is a stimulus to adhesion. When human aortic endothelial cells were used, vascular adhesion molecule (VCAM-1), endothelial leukocyte adhesion molecule (E-selectin), and intracellular adhesion molecule (ICAM-1) even in the presence of Transforming Nuclear Factor alpha were inhibited by adiponectin in a concentration-dependent proportion.[77]

Mouse model for obesity and diabetes (KKA/T)

Polyunsaturated fatty acids have been demonstrated to diminish urine albumin excretion, inhibiting expression of the inflammatory marker monocyte chemoattractant protein without an effect on GFR or blood pressure.[78] In a meta analysis of 17 trials evaluating urinary protein excretion changes with administration of omega 3 fatty acids, it was concluded that urine protein excretion was diminished significantly (19%) over a median of 9 (range 1.5–48) months. Results in the diabetes group were more impressive than in the IgA nephropathy patients.[79] Use of the Wistar rat hypertension model (abdominal aortic banding) has demonstrated limitation of left ventricular hypertrophy and heart failure by omega 3 fatty acids. High fat diet appeared to negate this benefit.[80]

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