Review

Obesity and renal disease: A possible role of leptin

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ABSTRACT

Obesity is one of the most frequently encountered medical problems of our time. Among the complications of this pathologic entity, renal disease is an important issue and its pathophysiologic mechanisms are a challenge for the physician, since a variety of etiologic factors are implicated in its genesis. For example, hypertension, hyperlipidemia and insulin resistance affect renal function, each one in a different way. Obesity seems to be a state in which kidneys demonstrate morphological and functional alterations, while hormonal and growth factors play a significant role. Among them, leptin, a recently discovered cytokine, has undergone extended investigation and has proven to be a factor that contributes to renal disease, mainly through mechanisms that involve activation of the TGF-β system resulting in glomerulopathy and related clinical symptoms. Experiments in animals have revealed interesting aspects as far as the role of leptin in kidney function. Understanding the underlying mechanisms of obesity- related glomerulopathy may become a valuable aid in handling an obese patient with renal disease and associated problems.

Key words: Glomerulopathy, Insulin resistance, Leptin, Obesity, TGF-β

INTRODUCTION

The prevalence of obesity in the Western world has dramatically increased over the past two decades, a phenomenon which is mainly attributed to the change in dietary habits and lifestyle in general. Obesity is defined as BMI (body mass index) >30kg/m^2, while a BMI >25kg/m^2 characterizes a person as overweight.

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A variety of medical problems develops in obese patients and is related to many organ systems, including the kidneys. Hypertension, for example, has multiple causes, including absolute weight and its distribution, high sodium intake, hyperinsulinemia, increased sympathetic activity, hemodynamic changes, increase in plasma catecholamines, renin and aldosterone and rise in T3, due to the consumption of carbohydrates, which in turn stimulate b-adrenergic receptors, increasing the vascular sensitivity to catecholamines. Insulin resistance and diabetes mellitus are frequently encountered in obese patients and are responsible for kidney damage, known as diabetic nephropathy. Hyperlipidemia and coronary artery disease are also well known sequela of

obesity which, through a cascade of biochemical, mechanical and hemodynamic reactions, dysregulate normal kidney functions.[1] Finally, in obesity-induced sleep apnea, hypoxemia, hypercapnia and systemic venous hypertension activate the sympathetic nervous system, increasing the tone of the glomerular efferent arterioles and the secretion of renin and angiotensin. The resulting hypertension leads to imbalanced capillary hemodynamics and disrupts the function of the kidneys of obese patients.[2] It is evident that obesity can result in renal disease through mechanisms such as those described above. Yet obesity per se, even in the absence or elimination of related pathophysiologic processes, does have an impact on the kidney and recent data support this view.[1,3]

RENAL EFFECTS OF OBESITY

The renal effects of obesity are divided into two categories, morphological and functional.

Morphological changes: Experiments in obese animals indicated expansion of Bowman's capsule, cell proliferation in the glomeruli, thickening of glomerular and tubular basement membrane and increase in the mesangial matrix in many glomeruli as well as the kidney size. Studies of renal structure in obese patients have indicated either normal findings or obesity related glomerulopathy (ORG), which includes focal segmental glomerulosclerosis (FSGS), glomerulomegaly, mesangial hyperplasia and minimal foot process fusion, with FSGS and glomerulomegaly being most often encountered. Changes that resemble diabetic nephropathy, such as focal mesangial sclerosis or focal glomeruli and tubular basement membrane thickening, are also observed, probably reflecting preexisting DM or glucose intolerance, though most patients reported with ORG have no other underlying conditions.[2,3]

Compared with idiopathic FSGS, ORG has a lower percentage of glomeruli affected by segmental sclerosis, mainly in perihilar regions, reflecting milder and more slowly evolving disease. Additionally, ORG has a milder foot process effacement, probably suggesting a different mechanism of podocyte injury and almost 100% incidence of glomerulomegaly. Glomerulomegaly may be the only manifestation of ORG without co-existing FSGS and, along with renal hypertrophy, is responsible for increased kidney weight observed at autopsy in obese patients. Another entity under the term ORG is focal glomerular basement membrane thickening or focal mesangial sclerosis. Despite the co-existence of DM or glucose intolerance in some patients with the above morphological changes, the cases are distinguishable from typical diabetic nephropathy, which demonstrates both diffuse mesangial sclerosis and glomerular basement membrane thickening. Additionally, juxtaglomerular apparatus hyperplasia has been observed histologically in obese patients with renal involvement, even without a history of hypertension.[3]

Functional changes: Experiments in obese animals showed significant glomerular hyperfiltration and a rise in renal plasma flow (RPF), blood pressure, plasma renin and insulin levels. The functional changes that occur in the kidneys of obese patients include increase in GFR, RPF, nephritic range proteinuria or sub-nephrotic proteinuria. Their course of progression is indolent and less frequently progresses to end-stage renal disease.[2]

In contrast to idiopathic FSGS, obese patients have a lower incidence of nephrotic syndrome, higher serum albumin, lower serum cholesterol and less edema. The above are mainly attributed to the preservation of tubular function in reabsorbing and catabolizing the filtered protein and to the less severe podocyte injury observed in ORG.[3]

THE ROLE OF HORMONES

In the pathophysiology of renal disease in obesity, hormonal and growth factors play important roles. The increase in GFR and RPF in obese patients has a complex etiology. Apart from the increased protein consumption that results in a rise in GFR, insulin resistance increases efferent arteriolar pressure since insulin directly reduces noradrenaline-induced efferent arteriolar constriction. Subsequently, the transcapillary pressure gradient increases causing hyperfiltration. Additionally, the role of insulin is mediated through stimulation of synthesis of IGF-1 and IGF-2, both of which promote glomerular hypertrophy.[3]

The contribution of leptin: Leptin, the product of the obesity (ob) gene, is a recently discovered cytokine produced by adipocytes. In lean humans leptin circulates in the blood mostly in the bound form, while it is free in obese humans. Leptin reaches the hypothalamus through the blood brain barrier and exerts its actions, by decreasing appetite and increasing metabolism. Although the short-length variant receptor of this cytokine exists in all tissues, only the full-length variant receptor in the hypothalamus has been found to mediate the actions of leptin. The signal transduction which takes place after leptin binds to the hypothalamic receptors includes a decrease in neuropeptide Y (NPY) and alterations in melanocortin release that affect feeding behavior and cause satiety. The cytokine levels demonstrate diurnal variation, rising during the night and causing less desire to eat.[4]

Obese patients have markedly elevated leptin mRNA expression in subcutaneous tissue. They show resistance to endogenous leptin because of defective transport across the blood brain barrier, resulting in hyperleptinemia. Consequently, appetite and body weight increase. The high insulin levels of obese patients directly stimulate the production of leptin mRNA. Other factors, such as puberty, female gender, IL-1, TNF-a and corticosteroids, increase leptin secretion, while menopause, senescence, fasting and exercise decrease it. On the other hand, leptin reduces insulin secretion and enhances hematopoiesis, angiogenesis, thermogenesis, diuresis and natriuresis. Leptin is mainly cleared by the kidney. In end-stage renal disease, leptin levels rise because of impaired clearance and/or increased synthesis. Particularly when co-existent with the abovementioned factors, like obesity, inflammation and steroid treatment, renal failure is characterized by hyperleptinemia that is probably responsible for the low eating drive observed in these patients.[4] In obese patients who are at risk for developing glomerulosclerosis, leptin levels are elevated and possibly play a role in the genesis of ORG. Animal testing showed that leptin induces proliferation of glomerular endothelial cells, enhances glomerular TGF-β1 expression and increases collagen type IV mRNA production. These factors result in focal glomerulosclerosis, glomerular and mesangial glucose uptake and proteinuria. Furthermore, leptin is associated with adrenergic activation, rise in arterial pressure and tachycardia, contributing to obesity related hypertension and indirect kidney damage.[2,5]

The leptin receptor is a member of the gp130 family of cytokine receptors. It has a large extracelleular domain, a single transmembrane domain and a cytoplasmic tail, varying in length in the different isoforms. There are at least 6 slice variant ob-receptors[R(a-f)]. Among them, the ob-Ra variant transports leptin across the blood brain barrier and the ob-Rb variant represents a receptor with a long intracellular domain, necessary for intracellular signal transduction. The long isoform of the ob-receptor is expressed in the brain, particularly in the arcuate hypothalamic nuclei. In the peripheral tissues, the long splice variant ob-Rb has been detected only in the adrenals and kidneys. In the kidneys, ob-Rb has been found in the inner zone of the medulla and the pyramid, in association with collecting tubules and ducts.[6,7]

Experimental data: Two models in mice have been studied with regard to serum leptin concentration and response to exogenous leptin administration, both of which have significantly increased amount of fat. The first is the obese diabetic db/db mouse which lacks the functional full-length ob-Rb receptor of leptin because of gene insertion and point mutation and which demonstrates resistance to the action of leptin and marked hyperleptinemia. The second is the obese ob/ob mouse which has undetectable leptin levels because of mutation in the ob gene.

Db/db mice do not respond to exogenous leptin administration, while ob/ob mice normalize their metabolic status after injection of leptin. They reduce food intake, increase energy expenditure, correct hyperinsulinemia and abnormal glucose tolerance, reduce NPY and increase MSH.

Obese mice of the db/db congenic strain show long-term hyperglycemia due to severe insulin resistance. The hyperglycemia in the fed state persists despite secretion of insulin and increase in pancreatic b-cells. There is also evidence of mesangial matrix expansion, a hallmark of diabetic nephropathy. Mice deficient in leptin (ob/ob) have variable

obesity-diabetes. Those with high insulin (>10 IU/L) are markedly obese and have a greatly increased number of b-cells. Those with low insulin (<1 IU/L) have diminished adiposity, show atrophy of the islets and evidence of increased b-cell neogenesis from the ductal epithelium.[8-10]

The db/db mouse is characterized by hyperinsulinemia, hyperglycemia, increased corticosterone and extreme obesity. It is a model of genetic diabetes that develops abnormalities in renal morphology and function that resemble those of human diabetic nephropathy. Since it exhibits increase in albuminuria and mesangial matrix production, it has been used to study progressive diabetic renal disease.[11] A short form of the leptin receptor has been found by reverse transcription PCR in the kidney and mesangial cells of db/db mice that lack the long isoform of the receptor. The rise in leptin levels, as occurs in db/db mice, may transmit a signal through the short form of the leptin receptor, which activates the intraglomerular TGF-β system and contributes to the glomerulosclerosis of obesity or type II diabetes. Both cultured glomerular endothelial cells and mesangial cells from db/db mice possess the Ob-Ra receptor. In glomerular endothelial cells, leptin stimulates cell proliferation, TGFβ1 synthesis and type IV collagen production. In mesangial cells, leptin up-regulates the synthesis of TGF-β type II receptor and increases 2-deoxy-D-glucose uptake and type I collagen production in the renal cortex, via phosphatidylinositol 3-kinase dependent pathways. It appears that a paracrine interaction takes place in which glomerular endothelial cells secrete TGF-β, which evokes a response from mesangial cells.[12] The up-regulation of TGF-β type II receptors occurs as a consequence of hyperglycemia in the hyperinsulinemic diabetic mouse and leads to increased gene expression and subsequent production of the extracellular matrix proteins fibronectin and type IV collagen.[11]

The db/db mouse shows mesangial matrix expansion and glomerular basement membrane thickening as occurs in human disease. The mouse becomes hyperglycemic by 8 weeks of age and develops overt proteinuria by 16 weeks. When compared with the non-diabetic model, db/db shows increased kidney weight, mesangial matrix fraction in both inner and outer cortices, thickening of glomerular basement membrane with irregular distortions and multifocal foot process effacement of podocytes, slightly increased size of mesangial cells and no difference in the number of mesangial cells in the glomerulus. Furthermore, db/db mice demonstrate elevated TGF-β1 mRNA expression in glomerular and tubular compartments, not in the medulla, but the fractional expression of TGF-β1 protein is less than that of the mRNA in the glomerulus, probably because hyperinsulinemia inhibits translation of TGF-β1 mRNA to protein. In contrast, type I diabetic animals show an increase in both TGF-β1 mRNA and protein in the glomerulus.[10,11,13]

Another protein, Smad 3, is found in the nuclei of glomerular and tubular cells in diabetic mice. When TGF–β binds to its receptors, Smad 3 is phosphorylated and translocates into the nucleus where it regulates the transcription of TGF-β target genes, like plasminogen activator inhibitor PAI-1 and type I collagen, as well as other extracellular matrix proteins. The nuclear accumulation of Smad 3 and the nuclear protein binding to the Smad binding element (SBE) increase in parallel with the mesangial matrix expansion and glomerular hypertrophy in the db/db mouse.[14]

It is significant that leptin deficiency in ob/ob mice increases their susceptibility to endotoxic shock, while hyperleptinemic db/db mice are more resistant to lipopolysacharide toxicity and show reduced levels of TNF-a, something that may be attributed to high levels of free leptin cross reacting with other cytokine receptors.[15,16] Additionally, ob/ob mice show phenotypic abnormalities in macrophages, such as elevated mitochondrial production of superoxide and hydrogen peroxide, increased expression of IL-6 and COX-2 and increased COX-2 dependent production of PGE-2, while db/db mice show impaired NK cell function and production of IL-2.[17] The above may contribute to obesity related pathophysiology.

Leptin adminstered I.V. increases noradrenaline turnover and sympathetic nervous system activity to thermogenic brown adipose tissue, as well as in the kidney and adrenals. The effects include natriuresis, insulin sensitization, vascular vasodilatation and angiogenesis. Leptin given to normotensive animals

produces a significant elevation in sodium excretion. In contrast, hypertensive animals are refractory to the natriuretic effect of leptin and obese animals also show attenuated response. Leptin may be a potential salt excretory factor in conditions of normal blood pressure and may function pathophysiologically in obesity and hypertension.[6]

Other contributing factors: Apart from leptin, angiotensin II plays a role in the development and progression of nephropathy. It is mainly related to glomerular capillary hypertension and mesangial cell hypertrophy. Particularly when increased levels of angiotensin II are combined with hyperinsulinemia, as occurs in obesity, the significance may be more profound as far as kidney function is concerned. In addition, evidence exists that nephropathy is more severe in obese women. Estrogens cause deposition of apolipoproteins A-IV and B and increase in glomerular expression of desmin and type IC collagen, with subsequent kidney damage.[5]

CONCLUSIONS

Apart from the various effects that obesity exerts on the human body, it may be particularly harmful to the renal system and lead to progressive damage through a variety of mechanisms. Obesity related glomerulopathy covers a wide range of morphological and functional changes in the kidneys that include glomerulosclerosis, glomerulomegaly, glomerular cell proliferation, mesangial matrix expansion, thickening of glomerular and tubular BM as well as increase in RPF and GFR and variable proteinuria.

Hormonal factors have been found to play important roles in the development and progression of renal disease in obese patients. Among them, leptin, a recently discovered cytokine known as the "satiety" hormone, correlates with the levels of adiposity and regulates the eating desire through central effects on the hypothalamus. Leptin imbalance, either in terms of leptin resistance or leptin deficiency, defined at the molecular level as defective leptin receptor and gene, respectively, proves to be harmful for renal function in an obese patient.

Obesity is a state of disequilibrium among the multiple homeostatic mechanisms of the human body, including the renal system. The best therapeutic approach is weight reduction and correction of the underlying pathology before irreversible damage is established. Therapy with ACE inhibitors has proven to be effective, while leptin remains a promising field for investigation. Today the proper physical and psychological approach remains the key that will help an obese patient to achieve health balance.

REFERENCES

1. Glassock R, 2002 Glomerular, Vascular and Tubulointerstitial Genetic Diseases. Nephrology Self Assessment Program 1: 8-10.
2. Henegar J, Bigler S, Henegar L, Tuagi S, Hall J, 2001 Functional and structural changes in the kidney in the early stages of obesity. Am J Soc Nephrol 12: 1211-1217.
3. Kambham N, Markowitz G, Valeri A, Lin J, D'Agati V, 2001 Obesity-related glomerulopathy: An emerging epidemic. Kidney Int 59: 1498-1509.
4. Stenvinkel P, 1999 Leptin and its clinical implications in chronic renal failure. Miner Electrolyte Metab 25: 298-302.
5. Adelman R, 2002 Obesity and renal disease. Curr Opin Nephrol Hypertens 11: 331-335.
6. Villarreal D, Reams G, Freeman RH, Taraben A, 1998 Renal effects of leptin in normotensive, hypertensive and obese rats. Am J Physiol 275: 2056-2060.
7. Vaisse C, Halaas JL, Horvath CM, Darnell Jr JE, Stoffel M, Friedman JM, 1996 Leptin activation of Stat3 in the hypothalamus of wild-type and ob/ob mice but not db/db mice. Nat Genet 14: 95-97.
8. Bunger L, Forsting J, McDonald KL, et al, 2003 Long-term divergent selection on fatness in mice indicates a regulation system independent of leptin production and reception. FASEB J 17: 85-87.
9. Cohen P, Zhao C, Cai X, et al, 2001 Selective deletion of leptin receptor in neurons leads to obesity. J Clin Invest 108: 1113-1121.
10. Sharma K, McCue P, Dunn S, 2003 Diabetic kidney disease in the db/db mouse. Am J Physiol Renal Physiol 284: 1138-1144.
11. Cohen P, Sharma K, Guo J, Eltayeb BO, Ziyadeh FN, 1998 The renal TGF-beta system in the db/db mouse model of diabetic nephropathy. Exp Nephrol 6: 226-233.
12. Wolf G, Chen S, Han DC, Ziyadeh FN, 2002 Leptin and renal disease. Am J Kidney Dis 39: 1-11.
13. Han DC, Isono M, Chen S, et al, 2001 Leptin stimulates type I collagen production in db/db mesangial cells: glucose uptake and TGF-beta type II receptor expression. Kidney Int 59: 1315-1323.
14. Hong SW, Isono M, Chen S, Iglesias-De La Cruz MC,

Han DC, Ziyadeh FN, 2001 Increased glomerular and tubular expression of transforming growth factor-beta1, its type II receptor, and activation of the Smad signaling pathway in the db/db mouse. Am J Pathol 158: 1653-1663.
15. Madiehe A, Mitchell T, Harris R, 2003 Hyperleptinemia and reduced TNF-a secretion cause resistance of db/db mice to endotoxin. Am J Physiol 284: 763-770.
16. Faggioni R, Fuller J, Moser A, Feingold KR, Grunfeld C, 1997 LPS-induced anorexia in leptin deficient (ob/0b) and leptin receptor-deficient (db/db) mice. Am J Physiol 273: 181-186.
17. Zhao Y, Sun R, You L, Gao C, Tian Z, 2003 Expression of leptin receptors and response to leptin stimulation of human natural killer cell lines. Biochem Biophys Res Commun 300: 247-252.