

Overview: Obesity: What Does It Have to Do with Kidney Disease?

CHRISTINE K. ABRASS

Department of Medicine, University of Washington School of Medicine, VA Puget Sound Health Care System, Seattle, Washington



Christine Abrass, MD

Obesity has become a national epidemic, with ~65% of Americans currently above ideal body weight (1,2). It is widely recognized that obesity contributes to morbidity and mortality from diabetes, heart disease, stroke, and some cancers, yet the important role that it plays in progression of kidney disease is rarely mentioned. It is the goal of this *Frontiers* to raise awareness of the importance of obesity to

chronic kidney disease. In each decade of the last two, the number of people with end-stage kidney disease has doubled, and it is estimated that 600,000 people will require dialysis treatment by 2010 (3). Moreover, it is estimated that 20 million people in the United States have either persistent proteinuria or substantial kidney damage (3,4). Although these numbers represent all forms of kidney disease, hypertension and type 2 diabetes account for the largest proportion. Obesity is mechanistically tied to renal disease associated with hypertension and type 2 diabetes. This *Frontiers* reviews several key aspects of the relationship of obesity to chronic kidney disease.

Obesity is the phenotypic hallmark of the metabolic syndrome (also referred to as the dysmetabolic syndrome, the insulin resistance syndrome, and syndrome X), which is characterized by insulin resistance, hyperinsulinemia, and dyslipidemia. The metabolic syndrome contributes to the development of type 2 diabetes, hypertension, and cardiovascular disease (5). Concerns about the epidemic of obesity have fueled research. Considerable progress has been made in defining central control of food intake (6,7), adipose tissue as an

endocrine organ and the factors that it senses and secretes (8), and the feedback control between the central nervous system and fat that regulates body weight (9,10). In addition to adverse consequences to the health of obese individuals, obesity during pregnancy has been linked to future risk for the development of type 2 diabetes and hypertension in the offspring when they reach adulthood (11,12). Because this has such important implications for generations to come, understanding and preventing metabolic syndrome is of immediate importance.

At the annual meeting of the American Society of Nephrology in November 2003, Randy Seeley and Barbara Hansen reviewed the central mechanisms that control satiety and food intake and the body's sensing of adipose mass and weight determination in animals and humans (8,9,13). A large body of evidence convincingly concludes that genetic and epigenetic factors determine set points and that each of us is programmed to defend that weight. These data explain why it is so difficult to lose weight and why most individuals who do, regain it in a relatively short time, yet these data fail to explain the obesity epidemic. Why is the set point shifting? There is growing agreement that environment is driving the epidemic (2). Modern lifestyles encourage overconsumption of energy and discourage expenditure of energy. Minor (<100 kcal/d) gaps in the balance of energy consumption and expenditure lead to gradual but steady weight gain (2,8). Although each of us has some control over the environmental aspects of our own life, our mother's nutritional status influenced the establishment of our set point, and as obesity becomes more common, through this effect, it will have a growing impact on our children and future generations (12,14). Thus, modification of this epidemic is crucial to health and to the development of kidney disease today and for the future.

There are many pathways by which the metabolic syndrome, which is characterized by obesity, insulin resistance, hyperinsulinemia, and dyslipidemia, might contribute to renal disease. These relationships are outlined in Figure 1. Most reviews indicate that insulin resistance with the compensatory increase in insulin secretion is the fundamental abnormality of the metabolic syndrome. This concept is supported by studies of normoglycemic, first-degree relatives of individuals with type 2 diabetes who have insulin resistance and hyperinsulinemia (15), and in Pima Indian children, in whom insulin resistance precedes the development of obesity and diabetes (16). Because obesity also aggravates insulin resistance and both genetic and epigenetic factors have been implicated in the patho-

Correspondence to Dr. Christine K. Abrass, Department of Medicine, University of Washington School of Medicine, VA Puget Sound Health Care System, 1660 S. Columbian Way, Seattle, WA 98108. Phone: 206-277-3242; Fax: 206-277-3436; E-mail: cabrass@u.washington.edu

1046-6673/1511-2768

Journal of the American Society of Nephrology

Copyright © 2004 by the American Society of Nephrology

DOI: 10.1097/01.ASN.0000141963.04540.3E

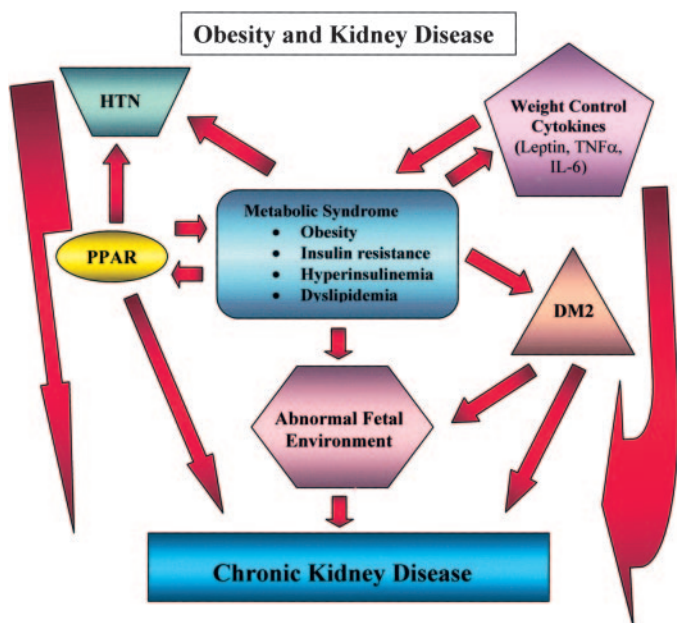


Figure 1. Obesity and kidney disease. Diagram shows relationships between components of the metabolic syndrome and the development of renal disease. DM2, type 2 diabetes mellitus, HTN, hypertension.

genesis of the metabolic syndrome, there may be various primary defects that lead to its development. The contribution of dyslipidemia typical of the metabolic syndrome (elevated triglycerides, intermediate-sized LDL particles, and low HDL) to the development of progressive renal disease has been reviewed extensively in other settings (17–21); thus, although very important, it is not included in this article.

For many years, it has been known that obesity is associated with focal and segmental glomerulosclerosis, yet the degree of the association and its pathogenesis were unknown (reviewed in reference 22). Recently, its incidence has increased in association with increased obesity (22). There have been many clues that insulin resistance/hyperinsulinemia contributes to this association. Nearly 30 y ago, Stout *et al.* (23) first posited that hyperinsulinemia might contribute to vascular injury by stimulated smooth muscle proliferation in the media of vessels. In studies of rats with streptozotocin-induced diabetes, typical nephropathy develops only in those that have poor glycemic control and also are treated with insulin (24). Zatz and Brenner (25) showed that in contrast to insulin-deficient animals, insulin-treated diabetic rats have increased intraglomerular pressures and that angiotensin converting enzyme inhibitors reverse this effect and protect against glomerular injury (26). Kreisberg (27) showed that insulin sensitizes cells to the contractile effects of angiotensin II, providing the link between insulin and angiotensin II-mediated injury. Abrass *et al.* (24) showed that insulin treatment of normal rats was associated with glomerular hypertrophy, new expression of interstitial collagens, and glomerulosclerosis. Experiments of mesangial cells in culture confirmed the direct role of insulin in mediating the changes in extracellular matrix synthesis (28,29). Recently,

Cusumano *et al.* (30) confirmed a link between hyperinsulinemia and glomerular hypertrophy before the onset of diabetes in rhesus monkeys. Although treatment of diabetes with exogenous insulin is necessary to improve glycemic control, considerable data show that hyperinsulinemia can mediate glomerular injury. Thus, hyperinsulinemia associated with obesity may contribute to the growing rates of ESRD, despite the slowed rate of progression in individual patients through improved glycemic control. These seeming paradoxes may be resolved through new understanding of the mechanisms of induction and cellular consequences of insulin resistance.

In this *Frontiers*, Susan Bagby (31) reviews the clinical significance of obesity and its contributions to the development of renal disease and strategies for management. She briefly reviews new concepts related to fetal origins of acquired insulin resistance and the contribution to adult disease. Obesity-associated gestational diabetes influences pancreatic development *in utero* and the development of insulin resistance, hypertension, and type 2 diabetes in the offspring when they reach adulthood (12,32) (Table 1). Growing interest in the environmental impact on the genome through epigenetic modifications will undoubtedly lead to new insights into the epidemic of obesity that the United States has witnessed over the past three decades.

Brent Wisse (33) reviews the feedback loop between adipose tissue and the central nervous system that controls body weight regulation (34,35). Cytokines that participate in feedback control, including leptin, adiponectin, angiotensin II, TNF- α , IL-6, and others, have been postulated to contribute to vascular injury and glomerulosclerosis (36). A commentary by John Sedor and Jeff Schelling addresses the specific application of these concepts to the kidney (37). This will raise potential avenues for future research to define the link between obesity and renal disease.

The role of peroxisome proliferator-activated receptors (PPAR) in the pathogenesis of obesity and insulin resistance has received considerable attention. PPAR play important roles in regulation of cellular cholesterol and triglyceride metabolism with direct effects on insulin sensitivity (38–40). Not only can agonists of these receptors improve insulin sensitivity and aid in the treatment of diabetes, but also there is evidence that fundamental abnormalities in this system may underlie the development of insulin resistance and obesity (38,39). Correction of these abnormalities has prevented the development of obesity and type 2 diabetes in animals. Agonists for these receptors, by modifying cellular lipid metabolism and direct effects on mesangial matrix synthesis, can prevent or reverse diabetic glomerulosclerosis (41–43). Youfei Guan (44) reviews the details of the role of these receptors in the metabolic syndrome and the kidney.

Hypertension and associated abnormalities in the renin-angiotensin system have long been known to contribute to the rate of progression of renal disease. Recent data indicate that the subset of individuals who have hypertension, who are nondippers and have elevated insulin levels and microalbuminuria, are the ones who develop significant renal and vascular disease (45–47). The relationship of this risk to obesity and

Table 1. Diabetes: Fetal origins of adult disease^a

Maternal	Fetal	Adult	Offspring
Mild hyperglycemia	Asymmetric macrosomia, ↑ insulin, ↑ IGF-1	Type 2 diabetes, normal pancreatic mass	↑ Risk for type 2 diabetes
Gestational diabetes	Islet hypertrophy and hyperplasia	Impaired glucose tolerance, impaired insulin secretion, ↑ risk for breast cancer	
Severe hyperglycemia	Asymmetric microsomia, ↓ insulin, ↓ IGF-1	Type 2 diabetes, ↑ pancreatic mass	↑ Risk for type 2 diabetes
Poorly controlled diabetes	↓ Insulin receptors, degranulation of β cells	Insulin resistance, ↑ insulin, cardiovascular disease and renal disease	
Protein restriction Intrauterine growth retardation	Reduced nephron number, ↓ insulin, ↓ pancreatic mass, ↓ β cells	Type 2 diabetes, women are insulin resistant, hypertension	↑ Risk for type 2 diabetes

^a Fetal exposure to nutritional disturbances affects pancreatic development and influences the insulin response in adulthood that becomes manifest as diabetes. Furthermore, these offspring have an increased rate of gestational diabetes, which in turn increases the risk for future development of type 2 diabetes in their offspring. In this manner, obesity may play a role in escalating the incidence of obesity and its associated diseases, including renal disease.

abnormalities in lipids, insulin resistance, and function of the PPAR system has recently been elucidated (48). In the final article in this series, Jim Sowers and colleagues review these relationships (49).

How does microalbuminuria fit into this scenario? Is it a manifestation of the metabolic syndrome? It is well recognized that the presence of microalbuminuria in patients with diabetes predicts future development of overt diabetic nephropathy. There is also substantial evidence that this risk is genetically determined and has led to searches for a nephropathy gene. As careful studies have included normal populations, 15% of “normal” individuals have microalbuminuria. Furthermore, among hypertensive individuals, those with hyperinsulinemia have microalbuminuria and an increased rate of chronic kidney and cardiovascular disease (50–52). As shown in Figure 2, the presence of insulin resistance/hyperinsulinemia may define the subset of normal, obese, hypertensive, and diabetic individuals with an increased risk for developing progressive kidney disease. The presence of microalbuminuria may be a surrogate marker for insulin resistance and the risk for progression from any renal insult or injury. In the effort to identify individuals who are at risk for renal disease with early intervention to prevent progression, these relationships deserve further study.

Obesity and its contribution to chronic kidney disease are of utmost importance to all of us. As nephrologists, we must face its contribution to the growth in our dialysis population. We must recognize the risk of obesity to future generations and particulate in strategies for prevention. The impact of the obesity epidemic and its consequences will likely touch us personally as we and the world population age.

Acknowledgments

I acknowledge support from the Medical Research Service of the Department of Veterans Affairs and the National Institutes of Health.

Microalbuminuria: Relationship to the Metabolic Syndrome

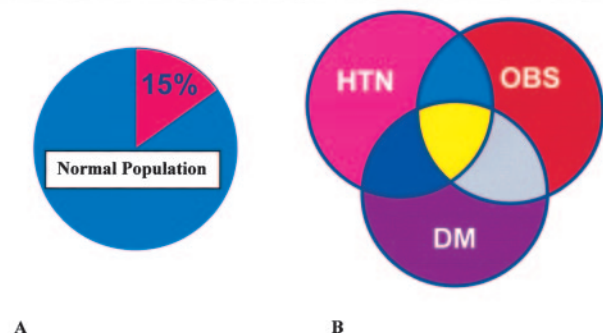


Figure 2. Microalbuminuria: Relationship to the metabolic syndrome. (A) Fifteen percent of the normal population has microalbuminuria. (B) Shows overlap of subsets of individuals who have obesity (OBS; 15 to 20%), hypertension (HTN; 5 to 40%), and diabetes (DM; 15 to 40%) and have microalbuminuria (yellow). This group is at increased risk for cardiovascular disease and renal disease, which is usually associated with insulin resistance/hyperinsulinemia.

References

- Marx J: Cellular warriors at the battle of the bulge. *Science* 299: 836–849, 2003
- Hill JO, Wyatt HR, Reed GW, Peters JC: Obesity and the environment: Where do we go from here? *Science* 299: 852–855, 2003
- Hostetter TH, Lising M: National Kidney Disease Education Program. *J Am Soc Nephrol* 14: S114–S116, 2003
- Hostetter TH: Prevention of the development and progression of renal disease. *J Am Soc Nephrol* 14: S144–S147, 2003
- DeFronzo RA, Ferrannini E: Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14: 173–194, 1991

6. Woods SC, Chavez M, Park CR, Riedy C, Kaiyala K, Richardson RD, Figlewicz DP, Schwartz MW, Porte D Jr, Seeley RJ: The evaluation of insulin as a metabolic signal influencing behavior via the brain. *Neurosci Biobehav Rev* 20: 139–144, 1996
7. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG: Central nervous system control of food intake. *Nature* 404: 661–671, 2000
8. Seeley RJ, Woods SC: Monitoring of stored and available fuel by the CNS: Implications for obesity. *Nat Rev* 4: 901–909, 2003
9. Bodkin NL, Alexander TM, Ortmeyer HK, Johnson E, Hansen BC: Mortality and morbidity in laboratory-maintained Rhesus monkeys and effects of long-term dietary restriction. *J Gerontol* 58: B212–B219, 2003
10. Korner J, Aronne LJ: The emerging science of body weight regulation and its impact on obesity treatment. *J Clin Invest* 111: 565–570, 2003
11. Catalano PM: Obesity and pregnancy—The propagation of a vicious cycle? *J Clin Endocrinol Metab* 88: 3505–3506, 2003
12. Holemans K, Aerts L, Van Assche FA: Lifetime consequences of abnormal fetal pancreatic development. *J Physiol* 547: 11–20, 2003
13. Hansen BC: Introduction: Calorie restriction: Effects on body composition, insulin signaling and aging. *J Nutr* 131: 900S–992S, 2001
14. Barker DJP: The fetal origins of type 2 diabetes mellitus. *Ann Intern Med* 130: 322–323, 1999
15. Axelsson M, Smith U, Eriksson JW, Taskinen M-R, Jansson P-A: Postprandial hypertriglyceridemia and insulin resistance in normoglycemic first-degree relatives of patients with type 2 diabetes. *Ann Intern Med* 131: 27–31, 1999
16. Odeyeye OE, de Courten M, Pettitt DJ, Ravussin E: Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes* 46: 1341–1345, 1997
17. Dominquez JH, Tang N, Xu W, Evan AP, Siakotos AN, Agarwal R, Walsh J, Deeg M, Pratt JH, March KL, Monnier VM, Weiss MF, Baynes JW, Peterson R: Studies of renal injury III: Lipid-induced nephropathy in type II diabetes. *Kidney Int* 57: 92–104, 2000
18. Grone EF, Walli AK, Grone HJ, Miller B, Seidel D: The role of lipids in nephrosclerosis and glomerulosclerosis. *Atherosclerosis* 107: 1–13, 1994
19. Keane WF: The role of lipids in renal disease: Future challenges. *Kidney Int* 57: S27–S31, 2003
20. Samuelsson O, Mulec H, Knight-Gibson C, Attman P-O, Kron B, Larsson R, Weiss L, Wedel H, Alaupovic P: Lipoprotein abnormalities are associated with increased rate of progression of human chronic renal insufficiency. *Nephrol Dial Transplant* 12: 1908–1915, 1997
21. Abrass CK: Cellular lipid metabolism and the role of lipids in progressive renal disease. *Am J Nephrol* 24: 46–53, 2004
22. Praga M: Obesity—A neglected culprit in renal disease. *Nephrol Dial Transplant* 17: 1157–1159, 2002
23. Stout RW, Bierman EL, Ross R: Effect of insulin on the proliferation of cultured primate arterial smooth muscle cells. *Circ Res* 36: 319–327, 1975
24. Abrass CK, Raugi GJ, Gabourel LS, Lovett DH: Insulin and insulin-like growth factor I binding to cultured rat glomerular mesangial cells. *Endocrinology* 123: 2432–2439, 1988
25. Zatz R, Brenner BM: Pathogenesis of diabetic microangiopathy. The hemodynamic view. *Am J Med* 80: 443–453, 1986
26. Zatz R, Dunn BR, Meyer TW, Anderson S, Renke HG, Brenner BM: Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. *J Clin Invest* 77: 1925–1930, 1986
27. Kreisberg JI: Insulin requirement for contraction of cultured rat glomerular mesangial cells in response to angiotensin II: Possible role for insulin in modulating glomerular hemodynamics. *Proc Natl Acad Sci U S A* 79: 4190–4192, 1982
28. Abrass CK, Spicer D, Raugi GJ: Induction of nodular sclerosis by insulin in rat mesangial cells in vitro: Studies of collagen. *Kidney Int* 47: 25–37, 1995
29. Abrass CK, Spicer D, Raugi GJ: Insulin induces a change in extracellular matrix glycoproteins synthesized by rat mesangial cells in culture. *Kidney Int* 46: 613–620, 1994
30. Cusumano AM, Bodkin NL, Hansen BC, Iotti R, Owens J, Klotman PE, Kopp JB: Glomerular hypertrophy is associated with hyperinsulinemia and precedes overt diabetes in aging rhesus monkeys. *Am J Kidney Dis* 40: 1075–1085, 2002
31. Bagby SP: Obesity-initiated metabolic syndrome and the kidney: A recipe for chronic kidney disease? *J Am Soc Nephrol* 15: 2775–2791, 2004
32. Van Assche FA, Holemans K, Aerts L: Long term consequences for offspring of diabetes during pregnancy. *Br Med J* 60: 173–182, 2001
33. Wisse BE: The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. *J Am Soc Nephrol* 15: 2792–2800, 2004
34. Wisse BE, Campfield LA, Marliss EB, Morais JA, Tenenbaum R, Gougeon R: Effect of prolonged moderate and severe energy restriction and refeeding on plasma leptin concentrations in obese women. *Am J Clin Nutr* 70: 321–330, 1999
35. Wisse BE, Schwartz MW: Role of melanocortins in control of obesity. *Lancet* 358: 857–859, 2001
36. Wolf G, Chen S, Han DC, Ziyadeh FN: Leptin and renal disease. *Am J Kidney Dis* 39: 1–11, 2002
37. Schelling JR, Sedor JR: The metabolic syndrome as a risk factor for chronic kidney disease: More than a fat chance? *J Am Soc Nephrol* 15: 2773–2774, 2004
38. Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznajdman ML, Lambert MH, Xu HE, Sternbach DD, Kliever SA, Hansen BC, Willson TM: A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. *Proc Natl Acad Sci U S A* 98: 5306–5311, 2001
39. Wang Y-X, Lee C-H, Tiep S, Yu RT, Ham J, Kang H, Evans RM: Peroxisome-proliferator-activated receptor δ activates fat metabolism to prevent obesity. *Cell* 113: 159–170, 2003
40. Norris AN, Chen L, Fisher SJ, Szanto I, Ristow M, Jozsi AC, Hirshman MF, Rosen ED, Goodyear LJ, Gonzalez FJ, Spiegelman BM, Kahn CR: Muscle-specific PPAR γ -deficient mice develop increased adiposity and insulin resistance but respond to thiazolidinediones. *J Clin Invest* 112: 608–618, 2003
41. Guan Y, Breyer MD: Peroxisome proliferator-activated receptors (PPARs): Novel therapeutic targets in renal disease. *Kidney Int* 60: 14–30, 2001
42. Baylis C, Atzpodien E-A, Freshour G, Engels K: Peroxisome proliferator-activated receptor γ agonist provides superior renal protection versus angiotensin-converting enzyme inhibition in a rat model of type 2 diabetes with obesity. *J Pharmacol Exp Ther* 307: 854–860, 2003
43. McCarthy KJ, Routh RE, Shaw W, Walsh K, Welbourne TC, Johnson JH: Troglitazone halts diabetic glomerulosclerosis by

- blockade of mesangial expansion. *Kidney Int* 58: 2341–2350, 2000
44. Guan Y: PPAR family and its relationship to renal complications of the metabolic syndrome. *J Am Soc Nephrol* 15: 2801–2815, 2004
 45. Bianchi S, Bigazzi R, Valtriani C, Chiapponi I, Sgherri G, Baldari G, Natali A, Ferrannini E, Campese VM: Elevated serum insulin levels in patients with essential hypertension and microalbuminuria. *Hypertension* 26: 681–687, 1994
 46. Christlieb AR, Krolewski AS, Warram JH, Soeldner JS: Is insulin the link between hypertension and obesity. *Hypertension* 7: 1154–1157, 1985
 47. Ferrannini E, DeFronzo RA: The association of hypertension, diabetes, and obesity: A review. *J Nephrol* 1: 3–15, 1989
 48. Sowers JR: Insulin resistance and hypertension. *Mol Cell Endocrinol* 74: C87–C89, 1990
 49. El-Atat FA, Stas SN, McFarlane SI, Sowers JR: The relationship between hyperinsulinemia, hypertension and progressive renal disease. *J Am Soc Nephrol* 15: 2816–2827, 2004
 50. Bigazzi R, Bianchi S, Baldari D, Sgherri G, Baldari G, Campese VM: Microalbuminuria in salt-sensitive patients. A marker for renal and cardiovascular risk factors. *Hypertension* 23: 195–199, 1994
 51. Kuusisto J, Mykkanen L, Puorala K, Laakso M: Hyperinsulinemia microalbuminuria: A new risk indicator for coronary heart disease. *Circulation* 91: 831–837, 1995
 52. Redon J, Miralles A, Pascual JM, Bald'o E, Robles RG, Carmena R: Hyperinsulinemia as a determinant of microalbuminuria in essential hypertension. *J Hypertens* 15: 79–86, 1997