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Metabolic syndrome, microalbuminuria and chronic kidney disease

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The metabolic syndrome is defined by a constellation of risk factors, including abdominal obesity, impaired glucose tolerance in association with hyperinsulinaemia, insulin resistance, dyslipidaemia characterized by low high-density lipoprotein (HDL)-cholesterol and high triglyceride levels, and hypertension. The World Health Organization (WHO) and the Adult Treatment Panel (ATP) III of the National Cholesterol Education Program have developed clinical criteria for metabolic syndrome (1). Metabolic syndrome has gained a great deal of attention because it is considered a precursor to type 2 diabetes mellitus (DM) and also increases cardiovascular disease (CVD) risk, even with levels of glycaemia below that used to define diabetes (1). The connections between chronic kidney disease (CKD) and CVD are increasingly evident. Indicators of CKD, albuminuria (micro- or macro-) and loss of glomerular filtration rate (GFR) are independently associated with increased CVD risk in the general population, as well as high-risk subgroups (2,3). These connections are exceedingly complex and include a number of shared traditional risk factors (notably diabetes and hypertension), development of non-traditional risk factors (anaemia, hyperparathyroidism with disordered mineral metabolism, high levels of homocysteine and others) and more severe atherosclerosis.

Microalbuminuria It is defined as urinary albumin excretion of 30 - 300 mg/day (20 - 200 ug/mt.) or albumin creatinine ratio in untimed urine specimen of 30 mg/g. Microalbuminuria in type I DM is the earliest sign of overt nephropathy of these who have microalbuminuria within 10 years of the onset of DM, most will progress to overt proteinuria while in type-II DM progression of microalbuminuria to overt nephropathy occurs in 20-40% of patients. Microalbuminuria is a clinical criterion for metabolic syndrome by the WHO classification (1). The frequency of microalbuminuria increases across the spectrum from those with normal glucose tolerance (5-10%), to metabolic syndrome (12-20%), to type 2 diabetes (25-40%) (4). Enough evidence has been garnered confirming the association between microalbuminuria and each of hypertension (5) and central obesity (6). Also, studies confirm the association of microalbuminuria with salt sensitivity, the

absence of nocturnal drops in both systolic and diastolic blood pressure, dyslipidemia, and left ventricular hypertrophy (7).

More importantly, microalbuminuria is now established as a modifiable predictor of CVD and CVD mortality (5). Evidence has been garnered that microalbuminuria is a marker of generalized endothelial dysfunction and consequently a risk factor for CVD (8). In recent studies, this endothelial dysfunction has been characterized by the presence of transmembrane leakiness (9). It is presently unclear whether transmembrane leakiness should be viewed as the culminating event of different atherogenic factors acting in concert to promote endothelial dysfunction or whether it should be considered as the underlying substrate that enhances the atherogenicity. For one, the increase in vascular permeability can promote the penetration of atherogenic lipoprotein particles in the arterial wall. One possible explanation is that endothelial dysfunction might promote increased penetration of atherogenic lipoprotein particles in the arterial wall, but glucose control, insulin resistance, procoagulant stage, and adhesion molecules have all been implicated in the pathogenesis. In addition, microalbuminuria has also been associated with alterations in hemodynamic and vascular responses. This is exemplified by studies that have demonstrated that the compensatory vasodilation seen after relief from prolonged ischemia or infusion of vasodilators such as nitroglycerin is blunted in people with microalbuminuria (9).

In summary, microalbuminuria is a signal from the kidneys conveying the abnormalities in endothelial function and vascular response. It can be seen as a early marker of generalized endothelial dysfunction, althrosclerosis increased cardiovascular disease risk and progressive renal failure. More importantly microalbumniuria represents the stage of nephropathy at which treatment is often successful in preventing progressive renal disease. In this light, the reduction of microalbuminuria should be implemented as a therapeutic goal to reduce overall CVD and CKD risk (10).

Chronic kidney disease (CKD) as per position statement from Kidney Disease: Improving Global Outcomes (KDIGO) 2005 has been defined as GFR < 60 ml.mt. (11). There has been on alarming growth of the prevalence of CKD and end stage renal disease (ESRD) over the last decade, in concert with a striking increase in the burden of diabetes, the leading cause of ESRD. Furthermore US Renal Data Support System (USRDS) 15th annual report projects that by the year 2030, ESRD population will increase by 460,000 new cases annually and the prevalent population will reach 2.24 million, with two thirds of these numbers having diabetes as the primary cause of renal disease (12,13).

In parallel with the growth in kidney disease, the prevalence of obesity/insulin resistance and impaired glucose

metabolism has been rising rapidly, currently meeting the epidemic proportions (14). The prevalence of diagnosed and undiagnosed diabetes constitute a major portion of the insulin resistant population is estimated at 8% of adult population (15). An even greater number of patients have cardiometabolic syndrome (24%) (12).

In India, conservative estimates put the annual incidence of ESRD in India around 100 per million of the population this would mean approximately 100,000 new patients every year for a population of 1 billion. Diabetic nephropathy is the commonest cause of ESRD in persons over 40 years of age accounting for 34% of ESRD cases. The fate of ESRD patients in this country is quite dismal, with a majority (65.7%) not receiving any form of RRT or stopping the treatment due to lack of resources. Only 12.8% undergo renal transplantation, 16.3% receive maintenance hemodialysis for varying periods of time and 5% continuous ambulatory peritoneal dialysis (16).

The prevalence of metabolic syndrome in Indian population has been reported to be 11-40 % (17). If metabolic syndrome per se is the cause of CKD as has been shown in recent studies then a substantial population is going to have ESRD in near future. This burden of ESRD can neither be borne by individuals nor the state. Hence it is important to address the issue of CKD in metabolic syndrome so that preventive steps can be taken.

The two most important causes of ESRD viz. diabetes and hypertension are closely associated with excess body weight, but obesity is still not listed as a cause of ESRD in USRDS report.

Obesity and Kidneys

Obesity is the phenotypic hallmark of metabolic syndrome. 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 II Diabetes and hypertension in the offspring when they reach adulthood, thus risking the kidneys of next generation.

Obesity related glomerulopathy

Nephrotic syndrome associated with obesity was reported 3 decades ago. The prevalence of obesity related glomerulopathy which causes CKD has increased 10 fold over last 15 years as a consequence of the spread of obesity epidemic (18). Increased incidence of higher body mass index (BMI) and ESRD in Japanese men has been shown after adjusting for comorbid conditions (19).

In experimental animals a number of structural changes viz expansion of bowman's space, increased bowman's capsule surface area and glomerular tuft area, endothelial and mesangial cell proliferation and basement membrane thickening have been shown in early obesity (20). In human beings kidney biopsy from obese individuals showed glomerulomegaly in all, focal segmental glomerulosclerosis in 80% and increased mesangial matrix and cellularity in 45% of

individuals (21). Obesity has also been shown to accelerate the course of idiopathic glomerular disease, such as IgA nephropathy (18). The clinical course of obesity related glomerulopathy appears to be progressive. After a mean follow up of 27 months 14% of patients reached renal end point i.e. doubling of serum creatinine (21).

Renal hemodynamic changes in obesity

The elegant renal physiological studies of Chagnac et al (22) in obese patients have demonstrated that values of GFR and renal plasma flow (RPF) exceeded those of lean controls by 50% and 30% respectively. This results in increased filtration fraction, an indirect indicator of glomerular hypertension. Glomerular hyperperfusion, hyperfiltration and hypertension lead to stretching of the glomerular capillary wall, injury to endothelial and epithelial cell and transudation of macromolecular in the mesangium. This leads to mesangial expansion and sclerosis. This supported with experimental data has been proposed to contribute to progression of nephropathy.

Effect of weight loss on renal function

Obesity related glomerular hyperfiltration ameliorates after weight loss. In a study of 17 morbid obese individuals (BMI-48 kg/m^2) who lost 48 kg and 1 year with BMI decreasing to 32 kg/m^2 after gastroplasty, augmented GFR, RPF and albuminuria improved substantially after weight loss (23). The decreased albuminuria was not solely due to decrease in GFR as evidenced by decrease in the fractional albumin clearance. The decrease in fractional albumin excretion after weight loss could be due to improvement in glomerular hemodynamics or it could also be the result of improvement of generalised endothelial cell dysfunction and thus a better integrity of the systemic capillary network. Whether these improvements in general hemodynamics and endothelial dysfunction translates in prevention of nephropathy is yet to be established.

Pathophysiology of kidney involvement in metabolic syndrome

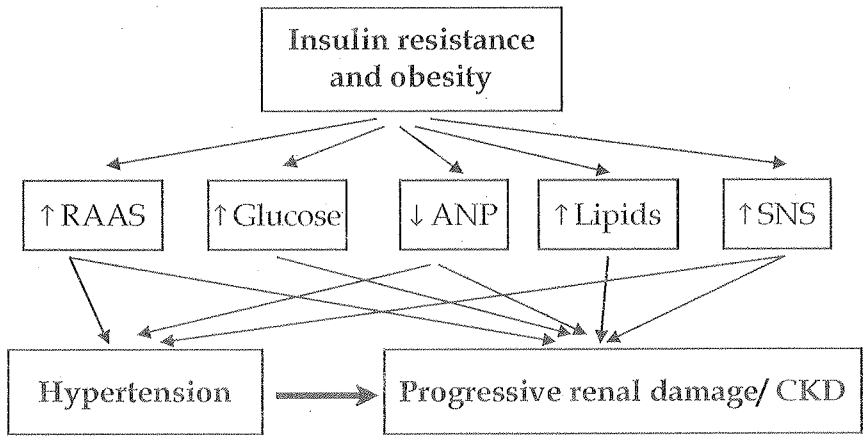
Kidney involvement in metabolic syndrome per se occurs due to interplay between number of mediators as shown in Fig.1.

Renin angiotensin aldosterone system (RAAS): Adipose tissue, especially visceral type, possesses a local RAAS, which has more significant local paracrine as well as systemic effects than the subcutaneous fat In insulin resistance/hyperinsulinemia, which is frequently associated with visceral obesity, RAAS activity is increased. In addition to the increased adipose tissue RAAS activity, systemic RAAS effects are also enhanced in the insulin-resistant/ hyperinsulinemic state, despite a state of sodium retention and volume expansion.

Sympathetic nervous system (SNS): Both animal and human studies suggest that increased SNS activity, where vascular

Figure 1

Pathophysiology of Chronic Kidney Disease



RAAS : renin angiotensin aldosterone system SNS : sympathetic nervous system
ANP : natriuretic peptide

and renal INS actions are selectively preserved, may be another mediator of hypertension in insulin resistance/ hyperinsulinemia state via stimulating renal sodium reabsorption with subsequent volume expansion and increasing cardiac output (9). In the Normative Aging Study, SNS activity was elevated with hyperinsulinemia and correlated with BMI (24).

Natriuretic peptide system: The natriuretic peptide system consists of the atrial natriuretic peptide(ANP), the brain natriuretic peptide (BNP), and the C-type natriuretic peptide (CNP), each encoded by a separate gene. They are synthesized predominantly in the heart, brain, and kidneys and work via specific receptors, namely NPr-A, NPr-B, and NPr-C.(3) The natriuretic peptides have a protective role on the development of hypertension due to their natriuretic and vasodilator effects as well as due to their inhibitory effect on the SNS and the RAAS. In obesity/ hyperinsulinemia, over expression of NPr-C receptor and lower levels and function of ANP with a possible role for a promoter variant at position -55 in the NPr-C gene, have been reported, contributing to increased sodium retention (7).

Dyslipidemia: It enhances renal dysfunction through filtered lipoproteins, damaging glomerular and tubular cells, in addition to enhancing endothelial dysfunction and atherosclerosis and participating in the deleterious renal functional and structural changes, eventually leading to nephron damage.

Dysglycemia: It is not only involved in the aforementioned renal changes, but it

also exerts a direct toxic effect on nephrons through glycosylation of glomerular proteins

Functional and Structural Changes, Compensatory Responses, and Late Nephronal Damage: Insulin resistance/ hyperinsulinemia state is accompanied by increased EC proliferation and intrarenal lipid and hyaluronate deposition in the matrix and inner medulla . These depositions increase intra-renal pressure and volume in the tightly encapsulated kidney, leading to parenchymal prolapse and urine outflow obstruction, which result in slow tubular flow and subsequently increased sodium reabsorption, especially in the loop of Henle . This leads to inappropriately small natriuretic response to saline load at mean and glomerular pressure, often referred to as "impaired pressure natriuresis" (6,7).

These functional and structural changes in the kidney provoke compensatory lowered renal vascular resistance, elevated kidney plasma flow, glomerular hyperfiltration, and stimulation of RAAS, despite volume expansion. Neurohumoral factors like Ang II, sympathetic system, and cytokines are synergistically involved in these compensatory mechanisms. For instance, AngII, in addition to its systemic effects on BP, directly contributes to increased glomerular capillary pressure through vasoconstriction of the efferent arterioles and upregulation of renal injury response. These alterations with the hypertension associated with the insulin-resistant state help overcome the increased tubular reabsorption and maintain sodium balance. The persistence of these compensatory responses, increasing glomerular wall stress, in the presence of hypertension, dyslipidemia and dysglycemia, will precipitate gradual nephron loss, glomerulosclerosis and eventually ESRD. This glomerulosclerosis in the hyperinsulinemic/insulin-resistant kidney is peculiar and characterized by lower rate of nephrotic syndrome, fewer lesions of segmental sclerosis and a greater glomerular size compared with the idiopathic variety (25).

Clinical evidence of CKD in metabolic syndrome

Theoretically as discussed above metabolic syndrome per se can and should lead to CKD. But the evidence was not so convincing because of the effect of overlapping variables which constitute this syndrome. Epidemiological studies have linked the metabolic syndrome with an increased incidence of microalbuminuria, few studies have evaluated its relationship with CKD (26,27).

In National Health and Nutrition Examination survey (NHANES III) prevalence of metabolic syndrome was 24.7%. There was a graded increase in the prevalence of CKD with more number of risk factor 0.9% with 1 risk factor to 9.2% with 5 factors. The prevalence of microalbuminuria also increased for 4.9% with 1 risk factor to 20.1% with 5 risk

factors. The multivariate-adjusted odds ratio of CKD and microalbuminuria in participants with metabolic syndrome 2.60 and 1.89 respectively (27). The cross sectional study however does not prove whether the syndrome is a cause or a consequence of reduction of kidney function and also whether the association is independent of future development of diabetes and hypertension.

The Atherosclerosis Risk in Communities Study (ARIC), a large prospective, community-based longitudinal study has demonstrated that the metabolic syndrome, absent diabetes, is associated with an increased risk for incident CKD, defined as progression to estimated GFR<60ml/min per 1.73 m^2 over a 9-yr period. The risk was independent of potential confounding factors such as age, gender, race, education, BMI, alcohol and tobacco use, coronary heart disease, and physical activity. There were graded relations among the number of clinical traits of the metabolic syndrome, HOMA-insulin resistance, and fasting insulin levels and the risk for CKD, suggesting a pathophysiologic basis for these findings. Moreover, the increased risk for CKD was evident even after adjusting for hypertension (a potential cause and consequence of kidney disease) and incident diabetes, another known mediator of CKD. The association between metabolic syndrome and CKD in nondiabetic individuals remained robust even after accounting for the subsequent development of diabetes and hypertensionIn sum, these findings suggest that the metabolic syndrome directly contributes to the development of CKD (28).

Future directions In view of the emergence of evidence linking CKD with metabolic syndrome further work is required to address the issue whether weight reduction, exercise and other measures to improve insulin sensitivity as well as interventions that target biochemical components of metabolic syndrome result in the reduction of the risk of CKD. This would help in preventing a large number of individuals from progressing to ESRD.

References

1. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C (2004) for the conference participants. Definition of metabolic syndrome : report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on scientific issues related to definition. *Circulation* **109**: 433-438.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C (2004). Chronic kidney Disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* **351**: 1296-1305.
3. Hillege HL, Fidler V, Diercks GF et al (2002). Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin Excretion predicts

cardiovascular and noncardiovascular mortality in General population. *Circulation* **106:** 1777-1782

4. Tuttle KR (2005). Renal manifestations of the metabolic syndrome. *Neph Dial Transplant* **20:** 861-64.
5. Palaniappan L, Carnethon M, Fortmann SP (2003). Association between microalbuminuria and the metabolic syndrome : NHANES III. *Am J Hypertens* **16:** 952-958.
6. Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM (1998). Mijcroalbuminuria is associated with insulin resistance in nondiabetic subjects : The insulin resistance atherosclerosis study. *Diabetes* **47:** 793-800.
7. El-Atat FA, Stas SN, Mcfarlane SI, Sowers JR (2004). The relationship between hyperinsulinemia, hypertension and progressive renal disease. *JASN* **15:** 2816-2827.
8. Yudkin JS (1996). Hyperinsulinemia, insulin resistance, microalbuminuria and the risk of coronary heart disease. *An Med* **28:** 433-438.
9. Castro JP, EI-Atat FA, McFarlane SI, Aneja A, Sowers JR (2003). Cardiometabolic syndrome: pathophysiology and treatment. *Curr Hypertens Rep* **5:** 393-402.
10. Mangrum A, Bakris GL (1997). Predictors of renal and cardiovascular mortality in patients with non-insulin-dependent diabetes : a brief overview of microalbuminuria and insulin resistance. *J Diabetes Complications* **11:** 352-357.
11. Levey AS,Eckardt K, Tsukamoto Y, Levine A et al (2005). Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International* 67; 2089.
12. Ford ES, Giles WH, Dietz WH (2002). Prevalence of the Metabolic Syndrome among US adults : Findings from the Third National Health and Nutrition Examination Survey. *JAMA* **287:** 356-359.
13. U.S. Renal Data System. USRDS 2003 15th Annual Data Report : Atlas of end-stage renal disease in the United States. Bethesda (MD) : National Institute of Health, National Institute of Diabetes and Digestive and Kidney Diseases 2003.
14. Sowers JR (2003). Recommendations for special populations : Diabetes mellitus and the metabolic syndrome. *Am J Hypertens* **16:** 41S-45S.
15. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD (1998). Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care* **21:** 518-524, 10.
16. Sakhuja V, Sud K (2003). End stage renal disease in India and Pakistan: Burden of disease and management issues. *Kidney Int* 63 (supp.83); s115-s118.
17. Cameron JS, Shaw JE, Zimmet PZ (2004). The metabolic syndrome : prevalence in worldwide populations : *Endocrine Metabolic clinics of N America* **33:** 351-375.
18. Bonnet E, Deprele C, Sassolas A, Moulin P, Alamartine E, Berthezene F, Bertoux F (2001) Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* **37:** 720-727.
19. Iseki K, Ikemiya, Kinjo K, Inoue T, Iseki C, Takishita (2004). Body mass index and risk

of development of end stage renal disease in a screened cohort. *Kidney Int.* **65**: 1870-1876.

20. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE (2001). Functional and structural changes in the kidney in the early stages of obesity. *JASN* **12**: 1211-1217.

21. Kambham N, Markowitz S, Valeri AM, Lin J, D'Agati VD (2001). Obesity-related glomerulonephropathy : an emerging epidemic. *Kidney Int* **59**: 1498-1509.

22. Chagnac A, Weinstein T,Korzets A, Ramadan E, Hirsch J., Gafter U (2000). Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* **278**: F817-F822.

23. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Yaacov O (2004). The effects of weight loss on renal function in patients with severe Obesity. *J Am Soc Nephrol* **14**: 1480-1486.

24. Word KD, Sparrow D, Landsberg L, Young JB, Weiss ST (1993). The influence of obesity, insulin and sympathetic nervous system activity on blood pressure. *Clin Res* **4**: 168A-168A.

25. Bagby SP (2004). Obesity initiated metabolic syndrome and the kidney : a recipe for chronic kidney disease? *JASN* **15**: 2775-2791.

26. Fujikawa R, Okubo M, Egusa G, Kohno N (2001). Insulin resistance precedes the appearance of albuminuria in non-diabetic subjects : 6 years follow up study. *Diabetes Res Clin Pract* **53**: 99-106.

27. Chen J, Muntner P, Hamm LL, Jones DW, Batuman V, Fonseca V, Whelton PK, He J (2004). The metabolic syndrome and chronic kidney disease in U.S.adults. *Ann Intern Med* **140**: 167-174.

28. Kurella M, Lo J.C. and Chertow GM (2005). Metabolic Syndrome and the risk for chronic kidney disease among nondiabetic adults. *J Am Soc Nephrol* **16**: 2134-2140.