Editorial

Metabolic syndrome leading to chronic kidney disease: An emerging threat

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Kidney has always exerted an important role in the field of endocrinology, and "renal endocrinology" still proves to be an area of active research with new dimensions coming forth. Cardio-renal metabolic syndrome (MS), a relatively new entity, has been recognized often, which constitutes the presence of a group of interactive maladaptive factors including MS leading to kidney and heart disease, and is on a rise.

The MS is defined as a syndrome of truncal obesity, insulin resistance, elevated BP, hypertriglyceridemia, and hyperglycemia.[1] which is strongly associated with the potential development of atherosclerotic cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). The prevalence of MS depends on age, ethnic background, and gender, and increases linearly from the age of 20 until age 50, when it plateaus. The recent data show that one-fourth to one-third of the urban population of India has MS[2-4] and has increased to 45.3%.[5,6] MS is highly prevalent among urban Indians compared to their rural counterparts (35.2% vs. 20.6%) and is 1.5–2 times higher in women than in men.[2,7] Interestingly, certain communities in India (e.g. the Punjabi Bhatia community in northern India) tend to have a high incidence of obesity, T2DM, and MS.[8]

Developing countries such as India are major reservoirs for chronic diseases (CDs), especially CVD and chronic kidney disease (CKD), with their incidence rising rapidly.[9,10] India, with the highest incidences of diabetes and hypertension (HT) in the world, is likely to face a catastrophic CKD/end-stage renal disease (ESRD) burden, with 25–40% of its population being at risk.[11] A survey across 10 Asian countries showed that the most common cause of ESRD in 9 out of 10 countries was diabetic nephropathy and develops in 1 out of 3 diabetics worldwide. The remaining 66% of patients die from CVD prior to reaching ESRD, which contributes heavily to the burden of CVD (>30% of the global CD burden).[12] Estimated burdens of CKD in India are often conservative representations of the overall national health burdens due to lack of national renal disease registries.[13]

The association between MS and CKD in different populations varies with odds ratios (OR) ranging from 0.93 to 2.60.[14] Various definitions of MS and adjusted ORs of associated microalbuminuria[14] are as follows. Patients diagnosed to have MS by World Health Organization (WHO) 1998;[15] European Group for the Study of Insulin Resistance (EGIR) 1999;[16] National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) 2001;[17] International Diabetes Federation (IDF), 2005;[18] and American Heart Association (AHA) 2005[19] had adjusted ORs (95% CI) of microalbuminuria for men: 4.44 (2.85–6.91), women: 4.16 (2.57–6.73); men: 2.62 (1.49–4.60), women: 1.80 (0.99–3.29); men: 1.99 (1.31–3.03), women: 2.21 (1.47–3.32); men: 1.51 (0.97–2.35), women: 2.29 (1.51–3.48); and men: 1.64 (1.08–2.50), women: 2.26 (1.52–3.38), respectively. High blood pressure and hyperglycemia came out to be the most powerful predictors of CKD in subjects with MS. Several population-based studies supported the effect of MS on CKD even after adjusting for the influences of diabetes, HT, age, and gender. Latest meta-analysis involving 11 studies (n = 30,146)[20] showed that MS was significantly associated with the development of estimated glomerular filtration rate (eGFR) <60 ml/min

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.93728

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per 1.73 m^2 (OR 1.55; 95% CI 1.34, 1.80). The strength of this association seemed to increase as the number of components of MS increased (trend *P* value <0.02). In patients with MS, the ORs (95% CI) for development of eGFR <60 ml/min per 1.73 m^2 for individual components of MS were: elevated blood pressure 1.61 (1.29, 2.01); elevated triglycerides 1.27 (1.11, 1.46); low high-density lipoprotein (HDL) cholesterol 1.23 (1.12, 1.36); abdominal obesity 1.19 (1.05, 1.34); and impaired fasting glucose 1.14 (1.03, 1.26).

These findings suggest that MS *per se* is an important causative factor for CKD. It is known that CKD is associated with decreased cardiac function, ventricular hypertrophy, and diastolic dysfunction, and increased risk of adverse cardiovascular events.[21] A recent study reported the association between MS, CKD, and left ventricular hypertrophy (LVH), and suspected that the combination of MS and CKD is a strong risk for LVH as well as a strong and independent predictor of subsequent CVD.[22]

The mechanism(s) by which MS might accelerate renal disease remains speculative.[23] One possibility relates to the presence of obesity itself. Obesity has been found to be an independent risk factor for CKD and treating obesity might stabilize renal function[24] or reverse early hemodynamic abnormalities and glomerular dysfunction.[25] Obesity has been associated with a type of focal segmental glomerulosclerosis (FSGS) called "obesity-related glomerulopathy."[26] Hall *et al*.[27] proposed that lipid deposition in the inner medulla increases intrarenal pressure, leading to decreased tubular flow, which results in increased sodium reabsorption in Henle's loop, volume expansion, and the development of systemic HT. Obesity is a risk factor for diabetes and HT, and has been shown to lead to glomerular HT and hyperfiltration.[27] MS is also associated with the release of inflammatory cytokines causing endothelial dysfunction and oxidative stress,[28] resulting in glomerulosclerosis. Insulin resistance also contributes to renal damage by virtue of stimulating the sympathetic nervous system and the rennin–angiotensin–aldosterone system.[29] Dyslipidemia may induce toxic and inflammatory tubulointerstitial injury.[30] With caloric excess, there is fatty acid excess and insulin resistance, leading to hepatic steatosis and steatohepatitis, and ultimately cirrhosis. There is a speculative role of higher fetuin-A levels leading to suppression of adiponectin transcription in adipocytes, which in turn reduces 5' adenosine monophosphate-activated protein kinase (AMPK) in podocytes to promote podocyte foot process effacement and albuminuria.[31]

The rise in MS indirectly may be a major contributor to the general rise in renal disease that has been observed in the past few decades. The public health relevance of the above findings is underscored by the fact that the prevalence of MS and its components is increasing over time, and findings suggest that the CKD burden might rise commensurately. These findings emphasize the need to identify individuals with the constellation of these metabolic risk factors earlier and consider multidisciplinary interventions, particularly lifestyle modifications, to retard the development of CKD.

Studies from developed countries show that mortality risk for CDs can be reduced by 75% through health interventions and the incidence can be reduced by up to 58% through lifestyle interventions.[32] Cost-effective population-based health intervention has shown to give maximum results by modifying three major risk factors – poor diet, lack of physical activity, and tobacco use – and hence should be targeted.

Multiple interventions are required in all the sections of the society to fight this emerging threat of cardio-renal MS. The preventive and primary health care systems come at the forefront, and hence must be strengthened and unified. There is also a desperate need for community awareness and advocacy for lifestyle changes and disease management, increased availability of medical practitioners, and cost-effective practical screening systems for CDs.

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