

Chronic kidney disease

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Dursun B. Metabolic syndrome and chronic kidney disease. Clin Nephrol Res. 2020;4(2):4-5.

Metabolic syndrome and chronic kidney disease (CKD) have become global public health problems due to their increasing prevalence and their close associations with cardiovascular events. First recognised by Reaven [1] in 1988, metabolic syndrome (previously known as syndrome X) is a complex pathophysiological issue and essentially considered as an assembly of cardiovascular and metabolic risk factors, which include abdominal obesity, dyslipidemia, hypertension and insulin resistance/hyperglycemia components. Over the years, there have been several definitions of metabolic syndrome. In most of the epidemiological studies NCEP-ATP (National Cholesterol Education Program-Adult Treatment Panel III) criteria were used [2]. Lastly, Harmonized (Consensus) Definition incorporating IDF (International Diabetes Federation) and AHA/NHLB (American Heart Association/ National Heart, Lung and Blood Institute) definitions were released requiring any three of the following criteria:

Waist circumference for Europids >94 cm in men and >80 cm in women,

Triglycerides ≥ 150 mg/dL,

HDL cholesterol <40 mg/dL in men and <50 mg/dL in women,

Blood pressure ≥ 130 mmHg systolic ; ≥ 85 mmHg diastolic,

Fasting glucose ≥ 100 mg/dL or use of medication [3].

The frequency of metabolic syndrome is approximately 20-25% of adult population, showing some difference according to race, gender and geographical regions. The frequency of metabolic syndrome is alarmingly high and reaching 50% in obese population. This is especially important in this century, because there is a global epidemic of obesity in developed and emerging economies driven by easy access to high calorie food and sedentary life style. Several studies have shown a clear association between metabolic syndrome and markers of CKD, including reduced glomerular filtration rate, proteinuria, and micro albuminuria. In most of the studies, presence of hypertension and diabetes were the prominent risk factors leading to CKD, at the setting of metabolic syndrome. It was also suggested that as the number of metabolic syndrome components increased, the risk for CKD increased more, especially for those who fulfilled three or more criteria. A meta-analysis including more than thirty thousand people reported that metabolic syndrome was associated with development of an estimated GFR for stage 3 CKD level with odds ratio 1.55, even when diabetes was excluded [4]. Another study including more than seven thousand people that were followed for twenty-one years have shown that those with normal renal function at baseline had an odds ratio of 2.6 for CKD if metabolic syndrome was present [5]. Therefore, in the light of present data, it may be possible to suggest a link between metabolic syndrome and CKD, independent of hypertension, diabetes and ethnic origin. Further studies also identified the role of metabolic syndrome with progression of CKD level. In a cohort of fifteen thousand people, those who reached stage 3-4 CKD level had a hazard ratio of 1.33

for end-stage kidney disease during a 2.3 year follow-up, if metabolic syndrome was present [6]. On the other hand, prevalence of metabolic syndrome is also known to be amplified during both the predialytic and dialytic stages of CKD, suggesting a bi-directional relationship; however, it may be difficult to determine which one incidentally occurred first. Although limited in number, histopathological data also have shown main determinants of CKD such as increased global or segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis and arterial sclerosis in kidney specimens of those with metabolic syndrome.

The main mechanism underlying the pathogenesis of metabolic syndrome-related CKD seems to be obesity-induced insulin resistance and chronic inflammation. From a mechanistically point of view, obesity is also the leading factor for increased glomerular volume and hyper filtration, mesangial expansion and podocyte hypertrophy. Abdominal obesity and concomitant low-grade chronic inflammation are the main reasons for insulin resistance. Expansion of visceral adipose tissue activates macrophages to convert into an inflammatory phenotype. Activated macrophages stimulate the secretion of pro-inflammatory cytokines, especially tumor-necrosis factor alpha (TNF- α) and interleukin-6 (IL-6), which further contributes to insulin resistance. Today, visceral adipose tissue is considered as a component of immune system due to the fact that it secretes immune-regulatory mediators, namely adipokines such as leptin, adiponectin, resistin; as well as IL-6, TNF- α and plasminogen-activator-inhibitor -1 (PAI-1). In metabolic syndrome, deranged metabolism of visceral adipose tissue may stimulate insulin resistance, inflammation and atherosclerotic damage. Adipokines release vasoactive mediators and also activate reactive-oxygen species to further damage endothelial structure and promote vascular re-modeling. Anti-inflammatory adiponectin level may be reduced leading to vascular smooth muscle proliferation and intimal thickening. Hyperinsulinemia activates arterial stiffness mechanisms leading to salt-sensitive hypertension and microvascular damage. Insulin resistance exerts progressive injury on essentially all the components of the kidney, including tubular epithelial, mesangial, podocyte and endothelial cells through proinflammatory cytokine and profibrotic factor production [7,8].

In the medical literature, it is a matter of debate whether metabolic syndrome really exists, but rather it is a constellation of cardiovascular-related risk factors. There is also controversy about the causality between metabolic syndrome and CKD. Based on current evidence, it seems that apart from its individual traits, metabolic syndrome per se is also independently linked to development and progression of CKD. In the setting of metabolic syndrome major pathophysiological manifestations occur due to presence of the cardinal features including abdominal obesity and insulin resistance, both of which further elicit complex kidney injury mechanisms through secretion of inflammatory mediators, adipokines or activation endothelial dysfunction, oxidative stress, renin-angiotensin-aldosterone and sympathetic nervous system. The resultant effects of all these are the increased risk and progression of CKD, as well as increased cardiovascular morbidity and mortality. The awareness of the link between metabolic syndrome and kidney injury may help to focus on preventive

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Received: November 3, 2020, Accepted: November 17, 2020, Published: November 24, 2020,



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and therapeutic interventions to avoid the deleterious effects of these inter-related pathophysiological processes. Further longitudinal trials are needed to establish the precise role of metabolic syndrome in the incidence and progression of chronic kidney disease.

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