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Review

Metabolic syndrome and renal disease

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ABSTRACT

The metabolic syndrome (MetS) is a cluster of risk factors including insulin resistance, dyslipidemia and hypertension which are also relevant for the development of chronic kidney disease (CKD). It has proven difficult to elucidate whether the renal dysfunction in MetS is due to the MetS itself or the individual risk factors. For example, obesity – which is also part of the MetS – may enhance the risk of renal dysfunction development probably through mechanisms associated with renal hyperfiltration, hyperperfusion and focal glomerulosclerosis. Insulin resistance also promotes kidney disease by worsening renal hemodynamics. In patients with MetS, tubular atrophy, interstitial fibrosis, and arteriolar sclerosis indicating the presence of vascular damage, have also been described. As yet, there has been little evidence that preventing or treating symptoms of the MetS protects patients from renal impairment.

1. Introduction

Metabolic syndrome (MetS) is a condition characterized by the presence of at least 3 of the following: abdominal obesity, increased blood pressure (BP), impaired glucose tolerance or diabetes, dyslipidemia [elevated levels of triglycerides (TG) and low concentration of high-density proteins (HDL)] [1]. Other abnormalities have also been reported including the presence of proinflammatory and prothrombotic state [2] as well as an altered oxidative/antioxidant ratio [3]. The increase in oxidative stress markers is proportional to the number of risk factors for the MetS which are present [4,5].

There are several widely accepted definitions of MetS. They have been issued by the National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATP III) [6], World Health Organization (WHO) [7] and the International Diabetes Federation (IDF) [8]. They differ slightly in criteria of diagnosis of the MetS. The third definition underlines for the first time the importance of abdominal adiposity as a risk factor for the development of MetS. Recently, a unified MetS definition prepared by the International Diabetes Federation (IDF), the National Heart, Lung, and Blood Institute (NHLBI), the World Heart Federation (WHF), the International Atherosclerosis Society (IAS), and the American Heart Association (AHA) has been published in order to eliminate confusion regarding the identification of patients with MetS [9].

MetS is associated with an increased risk of renal injury, cardiovascular disease (CVD), development of type 2 diabetes (T2DM), fatty liver disease, polycystic ovary syndrome, sleep-disordered breathing as well as all-cause and CVD mortality [10–14]. However, it has proven difficult to elucidate whether the renal dysfunction seen in MetS is due to the syndrome itself or to the individual risk factors. In patients with MetS, tubular atrophy, interstitial fibrosis, and arterial sclerosis indicating the presence of vascular damage, have also been described. As yet, there is little evidence that preventing or treating symptoms of the MetS protects patients from renal impairment [15–17].

2. Search strategy

We searched using the electronic databases [MEDLINE (1966–May 2011), EMBASE and SCOPUS (1965–May 2011), DARE (1966–May 2011)]. Additionally, abstracts from national and international cardiovascular meetings were studied. Where necessary, the relevant authors of these studies were contacted to obtain further data. The main data search terms were: dialysis, dyslipidemia, hemodialysis, hypertension, kidney disease, metabolic syndrome, microalbuminuria, obesity and renal impairment.

3. MetS and kidney disease

Being very common in developed countries, MetS is also emerging as a public health problem in developing countries [10]. The risk of

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developing MetS in patients with chronic kidney disease (CKD) can be predicted by racial origin. According to Eckel et al. [18], the prevalence of MetS ranges from 8% in French males to 60% in female Native Americans. Others demonstrated that the prevalence of the MetS ranged from 11.0% in Chinese individuals to 41.6% in Native Indians [19] and was very high (about 80% individuals with at least 2 components of MetS) in Pacific Islanders and Maoris [20,21]. However it is worth to emphasize that the number of patients diagnosed with MetS depends on the definition used [22].

According to the National Health and Nutrition Examination survey (NHANES III), the MetS is independently associated with CKD in the general population and in non-diabetic adults [1,23]. Johnson et al. [20] reported that MetS in patients with CKD correlated with oxidative stress and reduced adiponectin levels, which in turn significantly increased the risk of future cardiovascular events. The presence of MetS also seems to be a strong predictor of subsequent adverse cardiovascular (CV) events. Johnson et al. [20] also confirmed the earlier observation [24] that the prevalence of MetS was gradually rising with the decrease in creatinine clearance (18% of patients with creatinine clearance >90 mL/min, 21% of those with 45–89 mL/min and 33% of patients with <45 mL/min). The greater prevalence of MetS in patients in more advanced stages of CKD suggests that the MetS is an independent predictor of CKD development and progression [20].

CKD is associated with a poorer quality of life and a shorter life expectancy and is becoming a global public health challenge [25,26]. Hoehner et al. [27] observed that after adjusting for social, demographic, and comorbidity factors, patients with 1 or more risk factors for the MetS were more likely to develop albuminuria. Moreover, on the basis of NHANES III data obtained from over 6000 subjects from the general population in the USA, Chen et al. [28] demonstrated a significant correlation between the number of MetS traits and both albuminuria and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. Also, Palaniappan et al. [29] showed a higher risk for microalbuminuria in men and women with the MetS. These data support the importance of MetS in the development of CKD.

In a cross-selectional study [27] of an American Indian population, the risk of microalbuminuria in individuals with 3 or more MetS traits was 2.3-fold increased when compared with patients without MetS. In US adults, MetS was associated with 2.60-fold increase in the risk of CKD and 1.89-fold increase in microalbuminuria [27]. In a large cohort survey of patients with type 2 diabetes mellitus [30], both MetS and microalbuminuria had strong adverse effects on the GFR, and that this effect was even more pronounced in the presence of both factors. This finding has been challenged since the presence of the MetS also predicts the new onset of CKD in patients with T2DM independently of albuminuria [31,32]. Indeed, Athyros et al. [32] demonstrated that the association between MetS and low GFR was lost after adjustment for albuminuria. Of course, the differences in the prevalence of MetS between studies may depend on the definition used [28–32].

MetS was an essential predictor of CKD in Japanese [33] and Korean [1] populations. Some studies show differences in MetS prevalence in patients with CKD, depending on criteria used for the diagnosis. For example, Young et al. [34] estimated that the MetS when diagnosed on the basis of 2 criteria was present in 69.3% of patients on chronic hemodialysis (HD), but when 3 criteria were used, it was found in 31.7% of such patients [34,35].

According to Yu et al. [36] the effect of the MetS on CKD depends on age and gender, since MetS appeared to be a risk factor for CKD only in men under the age of 60 years and in postmenopausal women. This might have been due to the presence of androgenic milieu, since neither the MetS nor its individual components were associated with CKD in men over the age of 60 years and in premenopausal women [36]. This observation suggests that MetS may not be of key importance in the development of CKD in older men who have other risk factors such as atherosclerosis [36].

Using the WHO criteria, the MetS was present in 30% of CKD patients, especially in older subjects and those on peritoneal dialysis (PD) [37]. The age-specific prevalence of MetS was also seen in the NHANES III survey where the MetS was present in 10.7% of men and 18.0% of women aged 20–39 years and in 39.7% of men and 46.1% of women aged 60 years and older [37].

Gender-dependent differences in the susceptibility to kidney disease may be due to the beneficial vascular actions of estrogens as well as the negative effects of androgens [36,38]. The progression of renal disease in premenopausal women has been shown to be slower than in men [38]. This protection is lost at the beginning of the menopause, but the introduction of estradiol replacement treatment results in the recovery of the nephroprotective effects of estrogens. Animal studies have demonstrated that the attenuation of proteinuria in aging rats with the MetS after estradiol replacement therapy results from the increase in renal blood flow and GFR [39]. A sharp increase in MetS occurrence in women has also been attributed to higher prevalence of hypertension in women with aging [36], which is, in turn, associated with an increased risk of CKD [40].

In contrast, a strong positive correlation between MetS and the risk of CKD in Korean population irrespective of age and gender has been reported [1]. This has also been seen in the Chinese population aged 40 and more where the risk of developing CKD in conjunction with the MetS was also independent of age, sex and other risk factors for CKD [41]. Chen et al. [26] also found a relationship between the MetS and CKD in the general adult population of China that was independent of age, sex and CKD risk factors such as alcohol intake, smoking, body mass index (BMI) and lack of physical activity. Indeed, the greater the number of MetS components was, the more pronounced was the risk of CKD. Due to the fact that eGFR decreased in conjunction with the increase in the number of MetS components, it was suggested that each MetS component may be independently associated with decreased eGFR and increased risk for CKD [1]. Johnson et al. [20] suggested that the influence of the MetS on patient outcomes in severe CKD, might depend on the interplay between individual risk factors for the MetS such as hypertension, BMI and serum cholesterol concentration [20].

4. CKD, high BP and hypertension

MetS is frequently associated with type 2 diabetes and hypertension. The PAMELA population study (Pressioni Arteriose Monitorate E Loro Associazioni) revealed that high normal BP values and hypertension were present in 80% of individuals with MetS [42,43]. Such a high prevalence of high BP in patients with MetS may explain the frequent occurrence of subclinical organ damage manifested by left ventricular hypertrophy, arterial stiffening and increased urinary protein excretion [42,43]. According to studies insulin resistance and central obesity have been indicated to be the main factors involved in hypertension pathophysiology in the MetS [44]. Clinical studies have revealed that MetS plays an important role in the increased salt sensitivity of BP [45–47]. Salt sensitivity of BP increased progressively with a higher number of MetS risk factors [48]. The precise mechanism of salt-induced BP elevation is not well-studied, however it was suggested that it was due to impaired renal sodium excretion [45,49]. Study results demonstrated that renal function curve of obese hypertensive patients is identical to that of salt-sensitive-type hypertensives, which confirms the observation that obese hypertensive patients have greater depressor response to salt restriction on a low-salt diet in comparison to lean hypertensive patients [46]. Several factors such as hyperinsulinemia, kidney compression, sympathetic overactivity, increased activity of the renin-angiotensin (RA) system, and aldosterone excess in plasma induce abnormal natriuresis and increased salt sensitivity of BP in MetS [45].

Obesity is thought to be responsible for 65–75% of the risk for essential hypertension [50]. Obesity increases renal sodium reabsorption by