Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Gender Differences, Hyperuricemia and Brain Natriuretic Factor

Uric acid (UA) is the end product of the metabolism of purine compounds in humans and some primates. UA is produced in the liver from degradation of dietary and endogenously synthesized purine compounds. Hyperuricemia is known to be associated with development of gout and nephrolithiasis.

Reports in recent years described associations between hyperuricemia and both renal diseases, cardiovascular diseases (CVD), including ischemic heart disease, and mortality[1,2]: High serum UA levels are a strong, independent marker of impaired prognosis in patients with moderate to severe congestive heart failure.[3] Hyperuricemia on admission to cardiac care unit was reported to be associated with short-term mortality in myocardial infarction patients.[4] Hyperuricemia is associated with increased long-term mortality and major cardiovascular event rates in patients following acute coronary syndrome.[5] In a recently published meta-analysis, ten studies involving 12,854 acute heart failure patients were identified and analyzed.[6] AHF patients with the highest serum UA levels had increased risk of all-cause mortality (risk ratio [RR] 1.43; 95% confidence intervals [CI] 1.31−1.56) and combined endpoint of death or readmission (RR 1.68; 95% CI 1.33−2.13) after adjusting for potential variables. All-cause mortality and the combined endpoint of death or readmission significantly increased by 11% and 12%, respectively, per 1 mg/ml increase in serum UA. Some studies even showed that elevated serum UA is a marker of CVD risk in healthy populations.[7] Hyperuricemia was also associated with accelerated kidney failure and all-cause mortality in patients with chronic kidney disease.[8]

We showed that UA is a predictor of short-term mortality in elderly patients admitted to department of medicine regardless of the reason for admission.[9] Data of the same cohort four years later revealed that UA was also associated with long-term mortality.[10]

These and other studies support the assumption that hyperuricemia in itself conveys an increased morbidity and mortality risk, therefore should be addressed in a much broader context. The association between elevated UA and increased risk for CVD is undisputable, yet causality in the UA-CVD relationship remains unproven. Thus, there is no definitive answer to the question whether elevated UA is directly and independently involved in the pathophysiology of CVD (as a risk factor) or just an epiphenomenon of increased cardiovascular risk (a risk marker). Difficulties in determining whether UA acts as a risk marker or a risk factor for CVD may be explained by its frequent association and intricate relationship with other cardiovascular risk factors, possibility of reverse causation and conflicting findings from epidemiological and clinical studies undertaken to investigate the association of UA with CVD.[11]

Brain natriuretic peptide (BNP) is a natriuretic hormone released from myocardial cells in response to volume expansion and possibly increased wall stress. The N-terminal fragment, N-proBNP, is also released into the circulation. Serum BNP and N-proBNP are increased in patients with heart failure and are predictors of death and cardiovascular events in asymptomatic patients without heart failure.

In the July issue, Wei and colleagues[12] showed that NT-ProBNP was elevated, in correlation with UA levels. Two hundred sixty patients admitted with unstable angina pectoris (UAP) were divided into four groups according to their UA level. After adjusting for potential confounding factors, elevated UA was significantly related to the increase of NT-ProBNP. This finding was shown solely among males.

Differences between male and female patients regarding cardiovascular risk factors have gained interest for decades. Data from the Whitehall II study first revealed the association between social and economic factors and coronary heart disease (CHD) in the early 1990s.[13] In their cohort of middle-aged, British civil servants, differences in 10-year mortality rates could be explained only in part by traditional risk factors. A complex interplay between circulating sex steroid hormones, their receptors, and sex steroid-independent mechanisms possibly contributes to the overall difference in endothelial function observed between healthy young men and women. Young men have greater vasoconstrictor tone and attenuated endothelium-dependent dilation compared with premenopausal women, and it is this subclinical impairment in endothelial function that likely contributes to the earlier rise in the incidence of CVD in men. However, aging and the concomitant reduction in circulating sex hormones complicates the delineation of sex differences in older adults, and postmenopausal women may lose this cardiovascular “protection” compared with age-matched men.[14]

The explanation for this difference between males and females regarding the association of NT BNP and hyperuricemia in patients with ischemic heart disease remains unclear. Is it related to gender differences in UA metabolism? Could this possibly be related to differences in angiotensin-converting enzyme (ACE) or ACE2 levels? Of note, gender differences in ACE levels gained much interest with the recent COVID-19 pandemia. In two large independent cohorts of patients with heart failure, plasma ACE2 concentrations were higher in men than in women.[15]

Further studies are needed to better understand these interesting findings presented in this article.

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