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Metabolic syndrome and hypertension: A dangerous cocktail for older women?

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Cardiovascular disease (CVD) remains the leading cause of death for men and women despite substantial progress in medical and surgical treatment[1]. Since the life expectancy in women is greater than that of men, the resulting burden of CVD in older women is a major public health issue. With the rising rate of obesity, it is anticipated that the incidence and prevalence of hypertension will continue to increase in both men and women during the next decades. Despite the proven efficacy of antihypertensive drugs, dietary and behavioral modification, and the overwhelming evidence supporting the increased risk of CVD in hypertensive subjects, why is it that hypertension remains a major public health issue worldwide?

The lack of an adequate answer to this key question is a consequence of the complex nature of the hypertensive phenotype and the interplay across various factors that influence the management of hypertension. One potential explanation is that comorbid conditions may exert an important role through their synergistic effects on CVD risk or their influence on the management of hypertension. Among comorbid conditions, type 2 diabetes is associated with a 2- to 3-fold increased risk of CVD. The underlying insulin resistance is known to cluster with other metabolic derangements including dyslipidemia and higher levels of inflammatory cytokines. In 1988, Gerald Raeven[2] described the concept of the metabolic syndrome (MS) as a cluster of hypertension, insulin resistance or glucose intolerance, abdominal obesity, and atherogenic dyslipidemia resulting in a prothrombotic and proinflammatory state[3]. MS is highly prevalent in the US [25% to 35% depending on the chosen definition[4]] and is associated with a 2- to 4-fold increased risk of CVD and mortality[5] and a 5-fold increased risk of type 2 diabetes[6]. Could the co-existence of hypertension and MS be a deadlier cocktail for CVD risk than either condition alone in older women?

In the current issue of the journal, Rossi and colleagues[7] attempted to address this question in postmenopausal women and demonstrated that the prevalence of MS was associated with an unfavorable CVD risk profile. Specifically, subjects with MS showed increased plasma levels of C-reactive protein and endothelial dysfunction assessed noninvasively by flow-mediated dilation than non-MS subjects. In addition, hypertensive postmenopausal women with MS needed, on average, one more antihypertensive drug than similar women without MS to control

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blood pressure, and the antihypertensive treatment was less effective in the presence of MS. The limited sample size of this study precluded the examination of possible effects of ethnicity or age on the observed relation. In addition, the authors did not provide data to differentiate the effects of visceral from peripheral adiposity, the former being more prevalent in older people and may be more relevant to insulin resistance and MS.

However, these findings reiterate the importance of comorbidity as a potential effect modifier of an antihypertensive treatment regimen on the overall CVD risk profile. Among comorbid conditions, obesity is central to both MS and hypertension. Adipocytes produce several hormones that influence appetite, weight regulation, glucose and fatty acid metabolism, cytokines production, among others. Under ideal weight conditions, adipocyte-derived adiponectin facilitates fatty acid oxidation via AMP-activated protein kinase, thereby reducing plasma levels of free fatty acids. In addition, fatty acid binding protein-4 (another hormone produced by adipocytes) and free fatty acids activate nuclear factor kappa B and increase the production of inflammatory cytokines. The presence of overweight/obesity shifts the balance towards unfavorable CVD risk profile. The fact that 70% of participants in the paper by Rossi et al[7] were overweight/or obese and that the average body mass index among MS patients was 30 kg/m^2 supports this concept and underscores the importance of maintaining a normal weight.

What are the clinical implications of the current study? Although the study by Rossi et al[7] examined intermediate factors and not CVD hard endpoints such as stroke, myocardial infarction, and heart failure, one could presume that the coexistence of MS and hypertension would lead to a more than an additive effect on those endpoints. An important message is that clinicians should not only monitor body weight but also encourage their patients to maintain a healthy weight, especially in the presence of hypertension. In addition, an aggressive management of hypertension, overweight/obesity in the presence of MS would appear to be appropriate in such patients. Lastly, it is essential to curb the obesity epidemic through multi-factorial interventions including a healthier diet, physical activity, and surgical intervention where appropriate, among other measures.

Despite those clinical and public health implications arising from the current study[7], it remains uncertain whether the co-existence of MS and hypertension among postmenopausal women affects the bottom line. The lack of comparative data on mortality and major hard endpoints limits the utility of these findings. Since MS subjects used more antihypertensive agents than subjects without MS, it possible that poor compliance as it is expected with an increasing number of drugs among MS subjects could partially account for the poor treatment effect in the MS group. Furthermore, a differential compliance in lifestyle factor recommendations and inter-group difference in genetic predisposition, severity of hypertension, and other factors between the two groups may have played a role in these findings. In light of these limitations, it remains important to examine in future studies whether there is a synergistic effect between MS and hypertension on the risk of CVD and mortality and to quantify the magnitude of such effect in postmenopausal women. Such confirmation would call for a focus on global CVD risk appraisal and an aggressive management of underlying comorbidity.

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References

1. Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117:e25–146. [PubMed: 18086926]
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–1607. [PubMed: 3056758]
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497. [PubMed: 11368702]
4. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Prevalence of the metabolic syndrome among U.S. adolescents using the definition from the International Diabetes Federation. Diabetes Care 2008;31:587–589. [PubMed: 18071007]
5. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683–689. [PubMed: 11315831]
6. Ford ES, Li C, Sattar N. The Metabolic Syndrome and Incident Diabetes: Current State of the Evidence. Diabetes Care 2008;31:1898–1904. [PubMed: 18591398]
7. Rossi R, Nuzzo A, Origliani G, Modena M. Metabolic syndrome affects cardiovascular risk profile and response to treatment in hypertensive postmenopausal women. Hypertension. 2008xx:xx