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Editorial

C-reactive protein, metabolic syndrome, and end organ damage

Cardiovascular diseases (CVDs) persist as unyielding medical challenges and public health care burdens globally. Although the incidence of classic CVD risk factors has diminished over the last decade, there has been a concomitant elevation in nontraditional risk factors, stemming predominantly from our increasingly obesogenic lifestyles and the preponderance of diabetes. Accordingly, the prevalence of cardiometabolic diseases has achieved epidemic proportions.

The metabolic syndrome was coined to describe the clustering of cardiometabolic risk factors in a single individual. This disease plagues about a quarter of the world's adult population [1] and is currently believed to be the principal driving force behind future developments of diabetes and CVD [1-4] as well as premature cardiovascular and all-cause morbidity and mortality [1,2]. Because of its multifactorial foundation, the specific etiology of the metabolic syndrome continues to elude us; and advances in the understanding of this disease are now both timely and imperative.

Underscoring the debilitating nature of the metabolic syndrome is the proactive efforts of the World Health Organization, the National Cholesterol Education Program (NCEP), the European Group for the Study of Insulin Resistance, and the International Diabetes Federation to define a unified set of clinically relevant criteria for easy and early identification of individuals who have or are predisposed to this disease. Although these definitions do somewhat differ, the core abnormalities mostly concur and include abdominal obesity, atherogenic dyslipidemia, hypertension, dysglycemia, insulin resistance, a prothrombotic state, and a proinflammatory state. More importantly, all of the definitions stress the value of prevention strategies. Avoidance of a sedentary lifestyle and responsible diet regulation are irrevocably the best deterrence, but both are doubtful to be 100% effective. Resultantly, many at-risk patients will likely have to resort to pharmacologic treatments highlighting the importance of deciphering the foundation of these derangements.

C-reactive protein (CRP) is recognized as a key player in the pathogenesis and prediction of cardiovascular risk [2,3,5,6]. Although it has also been associated with several metabolic disorders [2,3,7,8], there have been surprisingly few studies directed at delineating the CRP–metabolic syndrome relationship per se. In Ford's [9] cross-sectional analysis of participants of the Third National Health and Nutrition Examination Survey, persons with the metabolic syndrome tended to have elevated levels of this pentraxin. Similarly, 2 other groups have independently reported that, at least in women, baseline high-sensitivity CRP (hsCRP) rose significantly with culmination of components of the metabolic syndrome [3,10]. This phenomenon has been mirrored in moderately hypercholesterolemic men [2] and in patients with histories of myocardial infarction [11], with both sets of investigators concluding that hsCRP added prognostic CVD and diabetes risk information beyond that provided by the presence of the metabolic syndrome.

In this issue of the journal, Zhao and colleagues [12] performed a cross-sectional study on a relatively large cohort of Chinese patients (1082) hailing from the Chongqing area of China. All of the subjects were admitted for minor medical conditions, and none had a prior history of cardiovascular or major disease [12]. Participants were classified as having the metabolic syndrome (619 of 1082) if they fulfilled the criteria established by the NCEP Adult Treatment Panel III (ATP-III) [13], whereas *target organ damage* was defined by the presence of cardiac hypertrophy, thickening of the carotid arterial wall, and renal impairment. Upon correlating these factors to fasting hsCRP levels, the authors confirmed previous reports of a positive association between hsCRP concentrations and increased metabolic disorders [2,3,9-11]. Furthermore, it was evident that elevated hsCRP and metabolic syndrome comorbidity is solidly indicative of target organ damage. These findings add to the growing evidence of a robust relationship between an inflammatory element of CVD with the metabolic syndrome and lends further credence to the notion that CRP levels should be considered a criterion for defining the metabolic syndrome.

Despite the high and increasing prevalence of the metabolic syndrome in China [14], there is surprisingly little data available on this disease in Chinese patients. Based on a modified version of the NCEP ATP-III definition, a fairly recent cross-sectional survey involving 15 540 Chinese adults from China categorized 9.8% of the men and 17.8% of the women as presenting with the metabolic syndrome [14]. In a demographically similar albeit smaller cohort (1458 men and 1831 women), CRP levels were highly associated with the metabolic syndrome in the middle-aged and elderly [15].

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The Zhao et al report [12] reinforces the epidemiological findings of the 2 earlier studies but more notably provides evidence for a previously uninvestigated pathological arm in the dynamics of the metabolic syndrome and baseline CRP.

Target organ damage is predictive of cardiovascular risk and, by extrapolation, the metabolic syndrome. Although these injuries are often silent, detection is possible with routine clinical tests. Zhao and colleagues [12] used left ventricular mass index (LVMI), carotid intima-media thickness (CIMT), and urinary albumin excretion (UAE) as surrogates of left heart hypertrophy, atheroma development, and diabetic nephropathy, respectively. Left ventricular mass index was estimated by normalizing to body surface area and height. Because obesity was an influential factor in this study as per waist circumference and waist-to-hip ratios, it may have been more appropriate for LVMI to be calculated against height alone. In addition, although CIMT is often used as a marker of early atherosclerosis, supplementary ultrasound information such as plaque density, extent of stenosis, and carotid blood flow velocity would have made the vascular aspect of the data more substantial and solid. Finally, certain factors such as recent intense physical activity, fever, increased hyperglycemia, and elevated blood pressure can yield false-positive UAE results. Hence, rather than the single UAE measurement, the investigators should probably have considered taking the mean UAE value of multiple samples. Notwithstanding the critique, Zhao and colleagues may be the only group to date that has attempted to collate hsCRP levels and multiple target organ damage data with the metabolic syndrome in a relatively large patient cohort. Therein lies the impact of this work, although it is admittedly difficult to resist the temptation of pondering over how the final findings may have differed or been alternately interpreted should a different definition had been applied to the study cohort.

C-reactive protein has been repeatedly touted as an active contributor of all of the integral phases of atherogenesis—endothelial dysfunction, vascular remodeling, and atherothrombosis [6]. Like almost all of the cardinal features of the metabolic syndrome, LVMI, CIMT, and UAE are independently allied with raised hsCRP levels. Zhao and colleagues [12] have in this present project taken these observations to the next notch by demonstrating concurrent positive correlation of LVMI, CIMT, and UAE values with hsCRP levels in the presence of the metabolic syndrome and consequently suggest that CRP is vital to the pathophysiology of this complex malady.

Elevated LVMI, CIMT, and UAE are considered to be the eventualities of generalized endothelial damage along the vascular tree. Loss of endothelial integrity reduces nitric oxide and prostacyclin influences and escalates endothelin-1 activity, thereby producing a milieu that promotes increased blood pressure, reduced blood flow, and cell proliferation, events that can act alone or in concert to raise LVMI, CIMT, and UAE. In vitro evidence indicates that CRP can further aggravate this deleterious situation via multiple pathways in several cell types (see references in [6]). It can inhibit endothelial nitric oxide synthase transcription, translation, activity, and bioactivity as well as reduce prostacyclin secretion and enhance endothelin-1 and interleukin-6 release. C-reactive protein is also supportive of the detrimental endothelial effects of the receptor for advanced glycation end products and oxidized low-density lipoprotein (via lectin-like oxidized low-density lipoprotein receptor [LOX-1]). Furthermore, CRP promotes endothelial cell apoptosis, retards endothelial cell progenitor cell angiogenesis, and possesses antifibrinolytic as well as prothrombotic properties. As briefly mentioned by Zhao et al [12], CRP in addition induces endothelial cell adhesion molecule expression, promotes monocyte-macrophage differentiation, and encourages smooth muscle migration and proliferation. Together, these observations are in line with the notion that inflammation is the crux of atherosclerosis and obesity, both of which are foci of the metabolic syndrome.

A noteworthy finding, and perhaps an anomaly, of the Zhao et al [12] cohort is the striking difference between the reported hsCRP levels with that of the Ye et al [15] cohort that comprised participants of similar demography with comparable clinical features. In the former, the median hsCRP concentrations were 2.42 and 1.13 mg/L, respectively, for those with and without the metabolic syndrome. Both of these hsCRP concentrations correspond to what is considered medium risk for Western populations. In contrast, subjects in the Ye et al study [15] had a median hsCRP level of 0.68 mg/L, which correlates to low risk for Western populations. To the best of our knowledge, except for one other study on healthy Taiwanese Chinese men, the current literature indicates that hsCRP levels in persons of Chinese origin tend to be in the <1 mg/mL range (see references in [15]). Two previous reports noted that the metabolic syndrome was more prevalent in northern Chinese and urban populations. However, geography is unlikely to account for the higher hsCRP levels reported by Zhao et al [12], with the collection and processing procedures more likely to be at the root of this disparity. Because the fasting durations before blood sampling are not provided and there is no information on the rigidity of this protocol, it can only be speculated that different satiety statuses may have contributed to the higher-than-expected hsCRP levels. Duplicate analysis of blood samples cannot account for normal fluctuations of hsCRP levels, so it would have been prudent to average the hsCRP values of 2 blood samples drawn over a fortnight under optimal conditions. Different assay sensitivity is also plausible, but the system exploited is well recognized and unlikely to be responsible for the divergent hsCRP readings.

That the Zhao et al study [12] was a cross-sectional, single-center investigation precludes interpretations about the sequential changes in CRP levels with the progression of target organ damage in patients with the metabolic syndrome. Despite its limitations, this work reiterates the need for prospective studies to confirm if elevated CRP

levels are causal or just biomarkers of target organ damage in the metabolic syndrome. Regardless of the outcome, a better comprehension of how these individual factors interact could identify particularly high-risk groups of patients who may benefit from more aggressive therapy that can curtail both the tide of target organ damage and the progression of the metabolic syndrome. This is a timely global issue that must now be urgently addressed.

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References

[1] International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome. http://wwwidforg/webdata/docs/IDF_Meta_def_finalpdf, 2006 Accessed 6th June 2007.
[2] Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414-9.
[3] Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. Circulation 2003;107:391-7.
[4] Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (syndrome X). Diabetes 1992;41:715-22.
[5] Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.
[6] Verma S, Devaraj S, Jialal I. Is C-reactive protein an innocent bystander or proatherogenic culprit? C-reactive protein promotes atherothrombosis. Circulation 2006;113:2135-50 [discussion 50].
[7] Frohlich M, Imhof A, Berg G, Hutchinson WL, Pepys MB, Boeing H, et al. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes Care 2000;23:1835-9.
[8] Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972-8.
[9] Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 2003;168:351-8.
[10] Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes Care 2002;25:2016-21.
[11] Aguilar D, Fisher MR, O'Connor CM, Dunne MW, Muhlestein JB, Yao L, et al. Metabolic syndrome, C-reactive protein, and prognosis in patients with established coronary artery disease. Am Heart J 2006;152:298-304.
[12] Zhao Z, Nie H, He H, Yan Z, Liu D, Luo Z, et al. High-sensitivity C-reactive protein predicts target organ damage in Chinese patients with metabolic syndrome. Metabolism 2007;56:1612-9.
[13] 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;285:2486-97.
[14] Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF, et al. Prevalence of the metabolic syndrome and overweight among adults in China. Lancet 2005;365:1398-405.
[15] Ye X, Yu Z, Li H, Franco OH, Liu Y, Lin X. Distributions of C-reactive protein and its association with metabolic syndrome in middle-aged and older Chinese people. J Am Coll Cardiol 2007;49:1798-805.