High-Sensitivity C-Reactive Protein, Obesity, and Subclinical Atherosclerosis
Implications of JUPITER From the MESA Study

Giovanni Targher

There is a growing body of evidence suggesting that elevated plasma high-sensitivity C-reactive protein (hs-CRP) levels are associated with obesity, metabolic syndrome, and adverse cardiovascular disease (CVD) outcomes.\(^1\)\(^-\)\(^3\)

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The recent results of Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial\(^4\) demonstrated that the treatment with rosuvastatin, 20 mg daily, as compared with placebo, was associated with a 44% reduction in the cumulative incidence of major CVD events among 17,802 middle-aged healthy men and women with low levels of low-density lipoprotein cholesterol (ie, <130 mg/dL) but elevated hs-CRP (ie, hs-CRP \(\geq\)2 mg/L). The benefits of rosuvastatin were consistent in all subgroups evaluated.\(^4\)

Overall, the results of JUPITER trial are consistent with the notion that achieving very low levels of low-density lipoprotein cholesterol and hs-CRP can enhance the benefits of statin therapy in the primary prevention of CVD. However, the results of JUPITER trial raise some important questions about the primary prevention of CVD. Should indications for statin therapy be expanded? How should measurements of hs-CRP be used? In addition, because the JUPITER trial did not include people with low levels of hs-CRP, it remains debatable whether hs-CRP is just a marker or does indeed participate in CVD pathogenesis.

I believe that the results of the Multi-Ethnic Study of Atherosclerosis (MESA), reported by Blaha et al\(^5\) in this issue of the journal, are timely and clinically important given the heated discussions about the obesity epidemic, the use of hs-CRP measurement for cardiovascular risk prediction and therapy decisions, and the JUPITER trial.

The MESA investigators conducted a stratified analysis assessing the relationships between obesity, high hs-CRP (as defined by JUPITER), and subclinical atherosclerosis in a population-based sample of 6,760 men and women who were aged 45 to 84 years and free of clinical CVD. The presence of subclinical atherosclerosis was detected by the noninvasive measurement of coronary artery calcium using computed tomography and the measurement of carotid-artery intima-media thickness using ultrasonography. Participants were stratified into 4 groups: nonobese/low hs-CRP, nonobese/high hs-CRP, obese/low hs-CRP, and obese/high hs-CRP. For secondary analyses, similar study groups were constructed stratifying by the Adult Treatment Panel III–defined metabolic syndrome in place of obesity. Interestingly, in a subsequent analysis, the investigators identified a subpopulation of 2,083 MESA participants who fit JUPITER eligible criteria (retaining the low hs-CRP group for this analysis because JUPITER enrolled only those with high hs-CRP): men \(\geq\)50 years old and women \(\geq\)60 years old who had low-density lipoprotein cholesterol \(<\)130 mg/dL, triglycerides \(<\)500 mg/dL, and creatinine \(<\)2 mg/dL; were not on lipid-lowering therapy; and were free of diabetes and CVD.

The main results of the MESA study were that a plasma hs-CRP level \(\geq\)2 mg/L, in the absence of obesity (or metabolic syndrome), was mildly associated only with carotid intima-media thickness and not with coronary artery calcium, after adjusting for demographic variables and other potential confounders. In contrast, obesity (or the metabolic syndrome) was consistently associated with both measures of subclinical atherosclerosis independently of hs-CRP status. When obesity (or the metabolic syndrome) and high hs-CRP were both present, there was no evidence of multiplicative interaction. Notably, almost identical results were observed among the 2,083 JUPITER-eligible individuals.\(^5\)

These findings clearly indicate that obesity (or the metabolic syndrome) is the strongest correlate of both coronary artery calcium and carotid intima-media thickness and that a high hs-CRP (as defined by JUPITER) is not associated with coronary artery calcium, which has already been demonstrated to be a better predictor of subsequent CVD events than carotid intima-media thickness in the entire MESA cohort.\(^6\)

However, I believe that it would be interesting if future statistical analyses of the MESA cohort also examined the impact of a different cutpoint for hs-CRP on subclinical atherosclerosis (for example, a hs-CRP level >3 mg/L).\(^7\) In addition, these findings further support the importance of obesity as a major modifiable risk factor for CVD, suggesting the possibility that the adverse effects of obesity on atherosclerosis could be largely mediated by hypertension, dyslipidemia, and other obesity-associated comorbidities, including nonalcoholic fatty liver disease.\(^8\)

Obviously, the cross-sectional nature of the findings derived from MESA does not allow any definite conclusions to be drawn about causality. Thus, one might be more seriously

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interested in knowing whether hs-CRP ≥2 mg/L, in the absence of obesity, is or not associated with an increased risk of incident CVD events. Interestingly, in a second part of the article, the investigators present an exploratory events analysis for the subpopulation of JUPITER-eligible individuals (but not for the entire MESA cohort) to confirm the prognostic significance of their findings. During a median follow-up of 5.8 years, 117 subjects developed incident CVD events (ie, myocardial infarction, angina, resuscitated cardiac arrest, stroke or death). In summary, the CVD events analysis showed essentially the same trends as those seen for subclinical atherosclerosis analysis, although it is important to note that this event analysis was largely underpowered to draw a meaningful conclusion and needs to be verified in a larger prospective cohort of individuals.

Additional research is, therefore, urgently needed to further elucidate the mechanisms underlying the interrelationships among obesity, metabolic syndrome, and high hs-CRP and to determine the individual and joint impact of these associations on the incidence of major CVD events.

At this point, I believe that the current recommendations for measurement of plasma hs-CRP in asymptomatic adults without clinical CVD remain reasonable: measurement of hs-CRP is not recommended for risk assessment in asymptomatic adults who are at either low risk or high risk, whereas a measurement of hs-CRP is reasonable in those at intermediate risk (10% to 20% 10-year risk), as estimated on the basis of standard CVD risk scores.6

References

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