Inflammation, Atherosclerosis, Classic Cardiovascular Risk Factors, Biostatistics, Clinical Significance. Where Are We?

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Ischemic heart disease is the main factor associated with morbidity and mortality in Western countries,[1] with the worldwide incidence increasing as the standard of living rises. Study of ischemic heart disease is, therefore, a priority in most industrialized countries.

The last 2 decades have seen important advances in the understanding of the pathophysiology of atherogenesis, in which inflammation plays an essential role in the various phases of the development of atherosclerotic plaque, from the onset of disease up to rupture or fissure, which is what can really lead to the appearance of an acute coronary syndrome. Indeed, back in the 19th century, Virchow proposed calling atherosclerotic disease "endarteritis deformans," linking the inflammation with the atherosclerosis.[2] Since then, great strides have been made in our understanding of the mechanisms of atherogenesis, establishing the irrefutable association of clear causality between the classic risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking) and atherosclerosis. Our eagerness to determine the underlying mechanisms of the association, together with the fact that some patients with ischemic heart disease have no evidence of any of the risk factors mentioned (referred to as the 50% hypothesis) have spurred research. Over the last 20 years researchers have described in great detail the characteristics linking risk factors and atherogenesis: inflammation and thrombosis are the intermediate effectors between the risk factors and diseases such as ischemic heart disease.[3,4] This greater understanding of pathophysiology has led to information about possible markers or risk factors, and as a result to better risk stratification in our patients. It should also lead to the discovery of new therapeutic targets and, consequently, to improvements in prognosis. Many studies have been published describing the association between markers of inflammation (or of anti-inflammation) and atherosclerotic disease, from the points of view of both primary and secondary prevention as well as the risk stratification for an acute coronary syndrome.

Two studies appear in this issue of the *Revista Española de Cardiología* that provide further data on inflammation in patients who are admitted with acute coronary syndromes.[5,6] The study by Gómez García et al[5] estimated the effect of rosuvastatin and metformin on inflammation and oxidative stress in patients with hypertension and dyslipidemia. The study was an open-label, parallel clinical trial that included 48 patients with hypertension and hyperlipidemia, distributed randomly into 3 treatment groups: 16 were treated with rosuvastatin, 10 mg per day; 16 with metformin, 1700 mg per day; and 16 with 10 mg of starch, as a control group. The variables assessed were those related with lipid metabolism, glycemic control, age, weight, the body mass index, and markers of inflammation and oxidative stress (interleukin [IL] 6, tumor necrosis factor alfa [TNFα], glutathione reductase [GSH], glutathione peroxidase [GPx], and superoxide dismutase [SOD]). The authors conclude that rosuvastatin improves the lipid profile and that both drugs reduce inflammation and oxidative stress. The authors question whether the benefits found are due to the improvement in lipid parameters or are secondary to the pleiotropic effects of the drugs used. A multivariate analysis that included the variation in lipid fractions might have helped to clarify this question.

The study by Gonzálvez et al[6] analyzes the prognostic value of TNFα in patients with ST-segment elevation myocardial infarction after a follow-up of 6 months. They provide new details about inflammation in ST-segment elevation myocardial infarction. Their study included 74 patients with ST-segment elevation myocardial infarction, in whom they measured the concentrations of TNFα as well as other parameters related with inflammation (C-reactive protein [CRP], IL-6, and soluble cell adhesion molecules type 1) within 10 h of the onset of symptoms and 48 h later. They found that TNFα concentrations were significantly greater in those patients with ischemic events or heart failure during the follow-up than in those who had no events, and the levels of TNFα at 48 h and CRP on admission were independent predictors of

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cardiovascular events. It is important to highlight a very relevant item in the study by Gonzálvez et al. Those patients who had been revascularized after acute myocardial infarction experienced a high incidence of cardiovascular events. However, as these events are considered "soft," they are not usually taken into account in large clinical trials. As the authors comment, the data are similar to those of other studies in our environment, which obliges us to consider again the importance of secondary prevention with the well-determined norms relating to hygiene and diet and with adequate drugs at an appropriate dose for each patient.

The interest in research on inflammation in the pathophysiology of atherosclerosis derives from the notion that the classic risk factors (smoking, diabetes mellitus, hypertension, and hypercholesterolemia) account for just 50% of cases of ischemic heart disease. This figure was generated in 1975 despite no clear empiric base, and was since perpetuated. However, it was later questioned with the presence of a solid base in certain articles at the beginning of this century[7-9] and was finally refuted with the publication of the INTERHEART study,[10] which determined that around 90% of the risk for acute myocardial infarction can be explained by just 9 easily determinable risk factors, with results valid for all age groups and ethnic races, both in men and in women. Accordingly, the margin that can be explained by the new markers is smaller than initially reported, and large increases in sample sizes are probably required in order to explain modest increases in the prognostic yield. At the same time, the results encourage us even more to treat the classic cardiovascular risk factors adequately. Atherosclerosis is a systemic disease, and its treatment should have a systemic focus as well as the cardiologic focus. Adequate knowledge and treatment of the risk factors is therefore fundamental in order to avoid the clinical development of the disease and, once it becomes established, to undertake good secondary prevention. It is in this light that the results obtained in patients with ST-segment elevation myocardial infarction (PRIAMHO study and the French registry) are very relevant, as well as those from the DESCARTES registry (acute coronary syndrome with non-ST segment elevation).[11-13] Insistence on a healthy diet and adequate pharmacologic treatment in secondary prevention, which have been shown to be important for the reduction of morbidity and mortality in patients with ischemic heart disease, is fundamental.

One feature common to both studies reported in this issue of the *Revista Española de Cardiología*[5,6] is the small size of the sample, which has particular relevance in the clinical study of markers of inflammation. As mentioned earlier, the problem of the inflammatory phenomenon is its systemic character, with the result that isolating the effect of inflammation on another systemic disease requires controlling for many variables, which necessitates a very exhaustive adjustment. Adjustment for multiple variables in a multivariate model requires a large sample size (the figure commonly used is 10 patients per variable introduced into the model). Review articles on inflammation and atherosclerosis have shown that the adjustment of the variables of inflammation in multivariate models is not usually complete, and when it is complete, the impact of the markers of inflammation is not relevant (in some cases even with no statistical significance). Glycemia or renal function, with their known impact on prognosis, or the prior use of such drugs as statins, angiotensin converting enzyme inhibitors, or aspirin (drugs that modulate an acute phase inflammatory response) are not always introduced into the multivariate analysis. If, additionally, we consider that the pathophysiologic of certain markers such as CRP role remains to be determined and that specific anti-inflammatory therapy has shown no benefit in ischemic patients, it is easy to understand why they have not yet been introduced into common clinical practice. Another question concerns the clinical relevance of certain statistically significant results, a problem that is difficult to resolve and that is the subject of discussion in biostatistics forums.

Nevertheless, these observations should not rule out the possible use of markers of inflammation in the prognostic stratification of patients with ischemic heart disease, but rather they should spur further research in this field.[14] Polymorphisms of CRP, which modulate the acute phase response of the molecule, or even a vaccination against particular epitopes of oxidized lipid fractions, may have a role in the future.[15,16] The real mechanisms by which certain markers of inflammation might influence the pathophysiology of atherosclerotic plaque are still unknown. Articles such as those published in this issue of the *Revista Española de Cardiología* preserve our interest in a subject in which many unknowns still remain to be resolved.

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