Role of Neopterin in Cardiovascular Medicine

To the Editor:

It is with great interest that we read the excellent review of biomarkers in cardiovascular medicine by Martin-Ventura et al. They reviewed the biomarkers most commonly reported in the existing literature and assessed their links with atherogenic mechanisms, atheromatous plaque disruption, endothelial dysfunction, inflammation, oxidative stress, and thrombosis. In their scholarly review, however, the authors do not mention neopterin, a marker of macrophage activation which over the last few years has gained particular importance due to its role in cardiovascular risk stratification.

Neopterin is a pteridine derivative, produced by activated macrophages stimulated by interferon gamma. Studies by our group and others have shown that neopterin can be a useful prognostic marker in the risk stratification of patients with coronary artery disease. The serum concentration of neopterin has been shown to correlate with the presence of vulnerable atheromatous plaques and acute coronary syndrome.

High neopterin levels predict risk in patients with chronic stable angina, and in hypertensive patients without obstructive coronary disease, diabetics and patients undergoing coronariography. Moreover, neopterin predicts the rapid progression of coronary disease in patients with chronic stable angina. As this marker predicts cardiovascular events independently of the extension and severity of the coronary disease, it is reasonable to suggest that high neopterin concentrations identify patients with a “vulnerable phenotype.”

Given the scientific evidence accumulated in the literature over recent years, we believe that neopterin should be considered as a promising
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prognostic marker that may find a practical application in the clinical setting.

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With regards the diurnal variation of the biomarkers in vascular disease, we are completely in agreement with the comments made by Domínguez et al. As they correctly mention, the relationship between circadian and seasonal rhythms and coronary disease has been known for many years.
The variability of the plasmatic concentration of the proteins involved in the genesis of vascular damage has also been discussed by many authors. Amongst these studies it would be relevant to mention the noticeable contributions of Dominguez et al regarding circadian rhythm of PCR, CD40L, melatonin, interleukin 6, VCAM-1 and MMP-9, amongst others, and cardiovascular disease.5-8 Some of the proteins mentioned by them, such as PCR and CD40L have higher serum concentrations in the light phase (9.00) than in the dark phase (2.00), whilst other such as VCAM-1 show a higher serum concentration in the dark phase. For obvious reasons, the majority of clinical studies are carried out using blood samples taken in the morning and from patients who have not eaten. Although all these studies are without doubt very important for understanding the implication of the diverse biomarkers in the circadian and seasonal rhythm of cardiovascular events, their extrapolation to clinical practice is not easy, as these same authors demonstrate.

With regards the comments about the role of neopterin in cardiovascular disease from Avanzas et al,2 we agree about the importance of the role that neopterin can have as a biomarker in coronary disease, as well as other biomarkers that we haven’t mentioned due to lack of space (eg, PAPP-A or cystatin C, previously reviewed by this same team). The contributions from the authors, in particular Prof. Kaski, regarding the role of the determination of serum neopterin in particular in acute coronary syndrome, are well known by all of us with interest in plasmatic biomarkers and cardiovascular disease. The studies by authors since their initial description in 1997,10 have made an important contribution to involving neopterin, a protein produced by macrophages activated by the interferon-gamma, as a prognostic marker in risk stratification in patients with coronary disease. Recently it has also been shown that serum concentration of neopterin can be predictive of dysfunction of the left ventricle in patients with stable chronic angina.11 The authors studies have been widely acknowledged in the relevant literature and this year three excellent articles, focused on current, interesting subjects.12-14 Despite not mentioning it in our review, we hope that our comments have helped to place neopterin on the list of available biomarkers and that our respected authors do not have to ever have to say again “Neopterin: still a forgotten biomarker.” 15

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