seems to be associated with adverse outcome in manifest CAD when measured with a commercially available assay. This information, in a large epidemiological study, may help to better understand the complex pathophysiological role of adiponectin in health and disease.

References

Renate Schnabel
Johannes Gutenberg-University Mainz
Langenbeckstraße 1
Mainz
Germany
Email: schnabelr@gmx.de

doi:10.1093/eurheartj/ehn258
Online publish-ahead-of-print 17 June 2008

Vascular endothelial growth factor protein levels and gene expression in peripheral monocytes after stenting: a randomized comparative study of sirolimus-eluting and bare-metal stents

With great interest, we read the article by Kochiadakis et al.1 dealing with the relationship between monocyte vascular endothelial growth factor (VEGF) gene expression, VEGF serum level, and in-stent late luminal loss following stenting in stable coronary artery disease (CAD) patients. The authors demonstrate that the VEGF serum level 1 month after stenting was significantly lower in patients who received a sirolimus-eluting stent (SES) compared with those who received a bare-metal stent (BMS). Furthermore, monocyte VEGF gene expression 1 month after stenting positively correlated with in-stent luminal loss after 6 months. This is an important study as it (i) highlights clearly detectable systemic effects of SES and (ii) underscores the usefulness of circulating monocytes as diagnostic tools.2

Kochiadakis et al. suggest that the lower VEGF level in the SES group can be attributed to the decreased VEGF gene expression of their circulating monocytes probably resulting in reduced VEGF protein production. Monocytes are certainly attractive indicators for drug-influenced gene regulation because of their easy accessibility. However, although serving as bioreactors and reservoirs for (paracrine) cytokines and chemokines during tissue repair and remodelling, monocytes/macrophages may not be regarded as important contributors to the VEGF concentration in human blood. Indeed, thrombocytes were shown to be the major source of VEGF in serum samples following its release during the in vitro clotting process.3 Elevated VEGF levels indicate local inflammation and are closely related to the presence of atherosclerotic risk factors.4 In contrast, the reduced VEGF serum level as well as the reduced VEGF monocyte level following SES implantation may rather reflect a systemic effect of rapamycin on cellular VEGF production.

Sirolimus-eluting stent-related reduction in VEGF serum levels may not only be beneficial, as proposed by Kochiadakis et al.1 Previously, it was shown that VEGF inhibition is associated with enhanced endothelial dysfunction and apoptosis.5 Likewise, the use of the VEGF inhibitor bevacizumab (Avastin®) is potentially associated with increased cardiovascular complications.2 Therefore, decreased VEGF levels following SES implantation may reflect a reduced stimulus for endothelial regeneration and may therefore be causally linked with the elevated risk for SES-related late stent thrombosis.6

A recent study highlighted the positive correlation between maximal circulating monocyte count after coronary stenting with in-stent neointimal volume after 6 month follow-up.7 Although this publication is cited by Kochiadakis et al. as an argument that monocytes contribute to neointima formation, the authors did not provide monocyte count data themselves. It would be interesting to see whether the absolute monocyte count did differ in the two study groups following stent implantation. Instead, the authors suggest that the higher monocyte VEGF gene expression in the BMS group reflects monocyte activation after stent implantation, leading to inflammatory reactions which trigger pathophysiological mechanisms and ultimately restenosis.

Further investigation of functional aspects of monocytes such as adhesion or chemotaxis may be a clue to get a clearer picture of the link between monocyte activation and potential consequences for neointima formation following coronary stenting.

References

Frauke S. Czepluch
Department of Cardiology
Cardiovascular Research Institute Maastricht (CARIM)
University of Maastricht
P. Deybelaan 25, PO Box 5800
6202 AZ Maastricht
The Netherlands
Vascular endothelial growth factor protein levels and gene expression in peripheral monocytes after stenting: a randomized comparative study of sirolimus-eluting and bare-metal stents: reply

We thank the authors for their interest in our work. We have read their comments carefully and are pleased to have the opportunity to reply.

Czepluch et al. correctly state that other factors apart from monocytes, such as platelets, also make an important contribution to vascular endothelial growth factor (VEGF) concentrations in human blood, and that the reduced VEGF serum levels following sirolimus-eluting stent (SES) implantation may reflect a systemic effect of rapamycin on cellular VEGF production. This possibility was explicitly mentioned in our manuscript, together with the hypothesis that a reduction in VEGF serum levels may be attributed to parallel effects of rapamycin, e.g. anti-inflammatory properties. Indeed, we did not go into the subject in detail, as this was not the aim of our study. Moreover, our results, showing that there is no correlation between serum levels of VEGF and in-stent restenosis, did not provide the motivation to research the origin of serum VEGF changes further.

We certainly agree with the authors’ comment that decreased VEGF levels following SES implantation may reflect a reduced stimulus for endothelial regeneration and may be related to stent thrombosis. Although not proven, the inhibition of VEGF expression by SES could affect and delay re-endothelialization, creating conditions favourable for acute stent thrombosis. We also wished to indicate a possible implication of the above hypothetical mechanism in the case of the patient in the SES group who suffered from an acute myocardial infarction post-stenting. However, this unique case among the small number of participants of our study did not allow us to draw any further inferences. Further research efforts could focus on that direction.

We do not dispute that it would be interesting to look at the monocyte counts. On the other hand, the aim of our study was to investigate the link between angiogenic factors and restenosis as these are reflected through VEGF gene expression in monocytes and not the number of monocytes, since this is already known from previous reports to be correlated with late luminal loss. Besides, monocyte activation and their VEGF gene expression do not depend on the absolute number of monocytes. Nonetheless, we concur that future studies should focus on the functional aspects of monocytes, such as adhesion or chemotaxis, in order to obtain a clearer picture of the pathophysiology of neointima formation following coronary stenting.

Corrigenda

doi:10.1093/eurheartj/ehn316


On page D24, in Figure 18, the placement of fluorine groups and stereochemistry in the chemical structure of AZD6140 were incorrectly shown. The correct figure is reprinted below.


Regrettably, on page 187, in the list of author names, the name of Dr Kiotsekoglou was incorrectly quoted as ‘Kiotsekolgou’.