Atherosclerosis 284 (2019) 262–263

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Correspondence

Reply to: "The "cholesterol paradox" in patients with mastocytosis"

ARTICLE INFO

Keywords:
Systemic mastocytosis
Mast cells
Atherosclerosis
Cardiovascular risk
Cholesterol
Low-density lipoprotein
High-density lipoprotein
Lipoproteins
Risk factors

To the Editor,

We read with interest the Letter to the Editor "*The "cholesterol paradox" in patients with mastocytosis*" by Feminò and Feminò [1] and we would like to thank the authors for their vision on our recently published data [2]. In our paper, we have found a significantly higher prevalence of cardiovascular events in patients with systemic mastocytosis (SM), which is a disease characterized by the accumulation of mast cells in one or more organs, compared to matched control subjects. Remarkably, we observed significantly lower circulating total and LDL cholesterol levels in patients with SM compared to the controls. An interesting point has been raised by the authors with respect to that specific finding, and we would like to take the opportunity to address that here.

In their letter, Feminò and Feminò suggest that these low total and LDL cholesterol levels may actually have been causal to the higher prevalence of cardiovascular disease events that we observed in the SM patient group. To substantiate their hypothesis, the authors cite a study in which low cholesterol levels were associated with atrial fibrillation [3], and subsequently postulate that low LDL levels may lead to a potential increase in circulating lipopolysaccharides (LPS), which cannot sufficiently be cleared by lipoproteins such as LDL. This may result in an increased inflammatory state that could lead to enhanced mast cell activation. Although we cannot provide data regarding circulating LPS concentrations in our patients with SM and the controls, we would like to argue that this is a rather unlikely mechanism for the increased in cardiovascular events in our study. First of all, although LDL cholesterol levels were significantly lower in our patients with SM compared to the controls, these were still within a normal range, whereas the study Feminò and Feminò refer to shows that an increased risk in atrial fibrillation only occurs when LDL levels are lower than 90 mg/dL (~2.3 mmol/L), which is below the values in our patients with SM. Of note, in our study we analyzed the prevalence of acute cardiovascular events, which consisted of cerebrovascular events, coronary heart disease events and peripheral artery disease in the patients with SM, but did not include atrial fibrillation or heart failure. Second, in patients with SM, mast cells numbers are elevated, and can be triggered by a number of potential activators, which leads to a high circulating tryptase concentration (59 ± 9 pg/mL (mean ± sem) in our patient population), which is actually one of the parameters to diagnose SM. Bacterial components such as LPS activate mast cells via Toll-like receptors (TLRs) such as TLR4, which indeed results in cytokine release, however, it does not lead to active degranulation of the mast cell [4]. Only upon active degranulation, tryptase but also chymase, both mast cell specific proteases, are released from mast cells. This suggests that in patients with SM other mast cell activation pathways are involved besides via TLRs.

There are actually other more likely reasons for the enhanced incidence of cardiovascular events in the mastocytosis patient group, which are supported by both experimental and clinical data. For example, systemic mast cell degranulation has been shown to enhance atherosclerotic plaque development and leads to destabilization of advanced atherosclerosis *in vivo* [5]. Both tryptase and chymase have been shown to contribute to atherosclerotic plaque destabilization in experimental models [6,7], suggesting that these proteases are actively involved there. In addition, the amount of degranulated mast cells in the plaque as well as the circulating tryptase concentrations associated with the incidence of future acute cardiovascular events [8]. Given the fact that the amount and thickness of the plaques did not differ between our patients with SM *versus* the controls, it is quite likely that the enhanced prevalence of cardiovascular events in the patients is due to accelerated plaque destabilization caused by mast cell mediators in our patients. This may have subsequently resulted in plaque rupture or

DOI of original articles: https://doi.org/10.1016/j.atherosclerosis.2019.01.019, http://dx.doi.org/10.1016/j.atherosclerosis.2017.11.030

https://doi.org/10.1016/j.atherosclerosis.2019.02.018
Received 4 February 2019; Accepted 22 February 2019
Available online 02 March 2019
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erosion and the observed acute cardiovascular events. Finally, mast cell proteases have been shown to modify and degrade lipoproteins and apolipoproteins [9–11], which may have caused the lower total and LDL cholesterol levels in patients with SM.

Although these data from the literature can explain our main findings in patients with SM, we do agree with the authors that further research into the pathology of the disease is required, and should aim at the elucidation of the underlying mechanisms leading to the increased prevalence of cardiovascular disease events in patients suffering from SM. For example, more in-depth visualization of plaque stability may identify patients at risk for an acute cardiovascular event and may also shed more light on the exact mechanisms via which mast cells contribute to cardiovascular disease.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

[1] R. Feminò, G. Feminò, The “cholesterol paradox” in patients with mastocytosis, Atherosclerosis (2019 Jan 26), https://doi.org/10.1016/j.atherosclerosis.2019.01.019 pii: S0021-9150(19)30032-2. [Epub ahead of print].
[2] S. Indhirajanti, P.L.A. van Daele, S. Bos, M.T. Mulder, I. Bot, J.E. Roeters van Lennep, Systemic mastocytosis associates with cardiovascular events despite lower plasma lipid levels, Atherosclerosis 268 (2018) 152–156.
[3] X. Li, L. Gao, Z. Wang, B. Guan, X. Guan, B. Wang, X. Han, X. Xiao, K.B. Waleed, C. Chandran, S. Wu, Y. Xia, Lipid profile and incidence of atrial fibrillation: a prospective cohort study in China, Clin. Cardiol. 41 (2018) 314–320.
[4] S.J. Galli, N. Borregaard, T.A. Wynn, Phenotypic and functional plasticity of cells of innate immunity: macrophages, mast cells and neutrophils, Nat. Immunol. 12 (2011) 1035–1044.
[5] I. Bot, S.C. de Jager, A. Zernecke, K.A. Lindstedt, T.J. van Berkel, C. Weber, E.A. Biessen, Perivascular mast cells promote atherogenesis and induce plaque destabilization in apolipoprotein E-deficient mice, Circulation 115 (2007) 2516–2525.
[6] X. Zhi, C. Xu, H. Zhang, D. Tian, X. Li, Y. Ning, L. Yin, Tryptase promotes atherosclerotic plaque haemorrhage in ApoE-/- mice, PLoS One 8 (2013) e60960.
[7] I. Bot, M. Bot, S.H. van Heiningen, P.J. van Santbrink, I.M. Lankhuizen, P. Hartman, S. Gruener, H. Hilpert, T.J. van Berkel, J. Fingerle, E.A. Biessen, Mast cell chymase inhibition reduces atherosclerotic plaque progression and improves plaque stability in ApoE$^{-/-}$ mice, Cardiovasc. Res. 89 (2011) 244–252.
[8] S. Willems, A. Vink, I. Bot, P.H. Quax, G.J. de Borst, J.P. de Vries, S.M. van de Weg, F.L. Moll, J. Kuiper, P.T. Kovanen, D.P. de Kleijn, I.E. Hoefer, G. Pasterkamp, Mast cells in human carotid atherosclerotic plaques are associated with intraplaque microvessel density and the occurrence of future cardiovascular events, Eur. Heart J. 34 (2013) 3699–3706.
[9] S.D. Nguyen, K. Maaninka, J. Lappalainen, K. Nurmi, J. Metso, K. Öörni, M. Navab, A.M. Fogelman, M. Jauhiainen, M. Lee-Rueckert, P.T. Kovanen, Carboxyl-terminal cleavage of apolipoprotein A-I by human mast cell chymase impairs its anti-inflammatory properties, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 274–284.
[10] J. Wang, S. Sjöberg, T.T. Tang, K. Oörni, W. Wu, C. Liu, B. Secco, V. Tia, G.K. Sukhova, C. Fernandes, A. Lesner, P.T. Kovanen, P. Libby, X. Cheng, G.P. Shi, Cathepsin G activity lowers plasma LDL and reduces atherosclerosis, Biochim. Biophys. Acta 1842 (2014) 2174–2183.
[11] K. Maaninka, S.D. Nguyen, M.I. Mäyränpää, R. Plihtari, K. Rajamäki, P.J. Lindsberg, P.T. Kovanen, K. Öörni, Human mast cell neutral proteases generate modified LDL particles with increased proteoglycan binding, Atherosclerosis 275 (2018) 390–399.

Ilze Bot
Division of BioTherapeutics, Leiden Academic Centre for Drug Research, Leiden University, Leiden, the Netherlands

Monique T. Mulder
Department of Internal Medicine, Laboratory Vascular Medicine, Erasmus MC, Rotterdam, the Netherlands

Swasti Indhirajanti
Department of Internal Medicine, Franciscus Gasthuis & Vlietland, the Netherlands

Paul L.A. van Daele
Department of Internal Medicine, Division Immunology, and Department of Immunology, Erasmus MC, Rotterdam, the Netherlands

Jeanine E. Roeters van Lennep[*,1]
Department of Internal Medicine, Laboratory Vascular Medicine, Erasmus MC, Rotterdam, the Netherlands
E-mail address: j.roetersvanlennep@erasmusmc.nl.

[*] Corresponding author. P.O. Box 2040, 3000 CA, Rotterdam, the Netherlands.
[1] Visiting address: Doctor Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.