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Editorial

Epicardial adipose tissue: The new target for statin therapy

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In this issue of International Journal of Cardiology Parisi et al. published an interesting study aimed at investigating the effect of statins on epicardial adipose tissue (EAT) [1]. Patients with calcified aortic sclerosis ($n = 193$) undergoing aortic valve surgery were divided into two groups: treated ($n = 87$) and not treated ($n = 106$) with statins. Among statin-treated patients, 82% received atorvastatin (40 mg/day), 11% rosuvastatin and 7% pravastatin for a period of 3–72 months. Maximum EAT thickness at systole was measured by standard transthoracic echocardiography. In addition, EAT biopsies were obtained from 31 patients and secretion of multiple adipokines and growth factors was measured ex vivo. Finally, the effect of atorvastatin added to the medium on secretory profiles of EAT and subcutaneous adipose tissue (SAT) samples collected from patients not receiving statins was examined as well.

It has been demonstrated that EAT thickness is significantly lower in statin-treated patients. In multivariate model, statin use and dyslipidemia were the only independent factors determining EAT diameter; both together explained 16% of EAT size variability and 96% of this value was attributed to statin use. In addition, EAT samples collected from statin-treated patients secreted less adipokines, chemokines and adipose tissue-derived growth factors than EAT samples of non-statin users. Finally, atorvastatin applied ex vivo reduced the secretion of most these adipokines by EAT explants which was not observed in SAT samples [1].

Epicardial adipose tissue is a specific visceral adipose tissue depot localized between the myocardium and visceral layer of pericardium [2]. EAT is in the close contact with myocardium and coronary vessels which allows for bidirectional humoral communication. EAT-derived factors may reach myocardium and/or coronary arteries by both paracrine and vasocrine manner. “Healthy” EAT is beneficial for the heart as it secretes antiinflammatory adiponectin. However, under pathological conditions EAT becomes dysfunctional, that is its beneficial functions are impaired. Diseases such as obesity, type 2 diabetes, metabolic syndrome, ageing and chronic kidney disease are associated with enhanced secretion of proinflammatory, proliferation-promoting and pro-coagulant EAT-derived factors such as tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein (MCP-1), interleukins 1β and 6, resistin and leptin. Although all of these adipokines are secreted by other adipose tissue depots as well, EAT-derived factors may be particularly detrimental promoting atherosclerosis locally in coronary arteries [2]. Many clinical studies have demonstrated that EAT diameter/volume correlates with and/or predisposes to coronary artery disease, atrial fibrillation, heart failure, aortic stenosis, coronary artery calcifications and all-cause mortality [2]. Consequently, EAT size emerges as a novel cardiovascular risk factor and a target for therapy.

Although the study of Parisi et al. was not prospective, the results strongly suggest that statins decrease EAT size and reduce EAT inflammation. This observation is consistent with several previous studies. In hyperlipidemic postmenopausal women [3], 12-month treatment with atorvastatin (80 mg/day) reduced EAT volume by 3.4% whereas pravastatin (40 mg/day) had no significant effect (−0.8%). In that study atorvastatin had also more marked effect than pravastatin on plasma lipids. Similarly, in patients with atrial fibrillation atorvastatin (80 mg/day) administered for 3 months decreased EAT volume by 5.9% whereas placebo had no effect [4]. In patients with coronary artery disease undergoing percutaneous coronary intervention, treatment with atorvastatin (20 mg/day) or simvastatin combined with ezetimibe (each at 10 mg/day) reduced EAT size by 10% and 5.2%, respectively [5]. The effect of atorvastatin on EAT size was more marked although both treatments reduced LDL cholesterol to a similar extent. Although antiinflammatory effect of statins in the adipose tissue has been demonstrated in many experimental studies, the study of Parisi et al. is the first one in which such effect was observed in human EAT both in vivo and ex vivo.

The mechanism through which statins reduce EAT size are unclear at present. Statins have been demonstrated to inhibit adipogenesis [6]. In retroperitoneal adipose tissue of rats with the metabolic syndrome, atorvastatin reduced the expression of sterol regulatory element-binding protein-1c involved in fatty acid synthesis and increased the activity of AMP-stimulated protein kinase involved in fatty acid oxidation [7]; consequently, atorvastatin reduced adipocyte diameter and retroperitoneal fat size. In addition, according to some studies statins may induce insulin resistance in the adipose tissue [8]. Impaired insulin signaling results in reduced glucose uptake and triglyceride synthesis as well as in the increase in lipolysis ultimately leading to reduced adipocyte size.

An interesting finding is that atorvastatin reduced adipokine secretion specifically in EAT but not in SAT. Epicardial adipose tissue is

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characterized by smaller adipocytes and better blood supply which may results in better statin penetration to the tissue. In addition, EAT collected from patients with AS could be shifted toward the proinflammatory phenotype. It is possible that antiinflammatory effect of statins is more marked in “activated” or “inflamed” EAT than in “healthy” quiescent SAT.

It is generally appreciated that hydrophilic statins such as prava- or rosuvastatin are quite liver-specific and have less effects on extrahepatic tissues than lipophilic drugs such as atorvastatin. Therefore, the interesting question appears if all statins have similar or divergent effects on EAT. The results presented by Parisi et al. cannot answer this question because most patient were treated with atorvastatin and only atorvastatin was used in the ex vivo experiments. Nevertheless, it has been demonstrated, for example, that only atorvastatin but not pravastatin increases the level of endogenous antiinflammatory gasotransmitter, hydrogen sulfide, in perivascular adipose tissue most likely due to better penetration of lipophilic atorvastatin to the adipocytes [9]. As mentioned previously, atorvastatin appears more effective in reducing EAT size than either pravastatin or simvastatin [4,5]. More studies are needed to compare the effects of different statins on EAT volume under both experimental and clinical settings.

Despite these unresolved issues, the results presented by Parisi et al. indicate that epicardial adipose tissue is a new target for statin therapy, and statin's effect on EAT size and phenotype may be strongly involved in beneficial cardiovascular outcomes in statin-treated patients. Due to close proximity of EAT and coronary vessels, measuring EAT volume may become important in assessing/predicting efficacy of statins in cardiovascular pathologies.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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