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## Epicardial adipose tissue and coronary artery disease

Obesity accounts for a substantial amount of cardiovascular deaths in the developed world.<sup>1</sup> Unfortunately, it looks as if the better life expectancy observed during the past few decades will be halted by the obesity and diabetes epidemics. Obesity is a powerful risk factor of coronary artery disease (CAD), and recently it has been suggested that epicardial fat may have a role in the development of CAD.

### Visceral fat

Traditionally considered as an inert energy storage compartment, the adipose tissue is now seen as an endocrine organ in its own right. Indeed, it secretes proteins (ie, adipokines), proinflammatory cytokines, chemokines, and acute-phase reactants.<sup>2,3</sup> These molecules are associated with insulin resistance, inflammation, increased oxidative stress, thrombogenesis, and endothelial dysfunction, and are likely to explain the established link between obesity and atherosclerotic disease.<sup>4,5</sup> Of importance, subcutaneous and visceral compartments differ in many respects. Visceral fat pads can be considered to represent "mini-organs" that interact with neighbouring tissues.<sup>6</sup> For example, the mammary fat depot contributes to normal mammary growth, but may also have a role in breast cancer development, both through endocrine, ie, adipokine release in the circulation, and paracrine and autocrine pathways.<sup>7</sup> Similarly, it has been suggested that perivascular fat might interact with the vessel wall and contribute to CAD progression.

### Epicardial fat and CAD

The real function of epicardial adipose tissue in humans is unknown but its small mass, compared with the fat in the organism, suggests that its contribution to systemic metabolism can be only limited. However, this tissue shows avidity for fatty acid uptake and lipogenesis, and may serve both as a local energy source to the myocardium and/or as a scavenger of circulating free fatty acids, which can be damaging to the myocardium.<sup>8</sup> In animal studies, the periaortic administration of interleukin-1 $\beta$  (IL-1 $\beta$ ) or monocyte chemoattractant protein-1 (MCP-1) to porcine coronary arteries resulted in adventitial macrophage accumulation and the development of vascular lesions.<sup>9</sup> Moreover, local application of endotoxin on the adventitia of rat femoral arteries is known to trigger vascular smooth muscle cell migration and the development of intimal lesions.<sup>10</sup> These data suggest that a bidirectional cross-talk exists between perivascular tissues and both the adventitia and the arterial intima.

The activity of the epicardial adipose tissue mimics that of visceral obesity regarding the release of proinflammatory substances. In patients with CAD, the expression of pro-inflammatory cytokines (IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and

MCP-1) was enhanced in the epicardial fat compared with the subcutaneous depot.<sup>11</sup> Lower adiponectin and increased leptin mRNA expression in the epicardial compared with subcutaneous fat, has also been reported in CAD patients.<sup>12</sup> Functional studies in animals have provided evidence that the perivascular adipose tissue can affect arterial tone. It has been shown that the presence of fat surrounding the adventitia attenuates the vasoconstrictor response to various agonists. This effect is mediated by an adventitial- or perivascular adipose tissue-derived relaxing factor (ADRF or PVRF), that is released by a calcium-dependent process and involves tyrosine kinase and protein kinase A intracellular pathways.<sup>13,14</sup> Although these studies suggest a modulatory role of perivascular fat in vascular biology, we know very little at present of the complex vascular regulatory mechanisms involving the adipose tissue. The relationship between local adipokine release and endothelial function is an interesting area that requires investigation, as it may hold key information in this regard. Adiponectin appears to have a modulatory role of vascular function, as it enhances the synthesis of nitric oxide by the endothelium.<sup>15</sup> Moreover, understanding the biology of epicardial adipose tissue is likely to have therapeutic implications. For example, in animal experiments increased adiponectin expression has been shown to directly suppress progression of atherosclerosis.<sup>16</sup> Of practical importance, several pharmacological agents employed in the management of patients with cardiovascular disease, ie, thiazolidinediones, fibrates, and ACE inhibitors are known to beneficially affect adipose tissue biology. Studies using these agents are likely to provide clues as to the importance of the local adipose tissue in atherogenesis, as well as the role of epicardial fat in the context of obesity, particularly visceral obesity.

**In summary, a new avenue has been opened up for research to try to understand the potential pathogenic role of perivascular fat in atherosclerosis. The field is developing rapidly, and we are certain that very exciting findings of potential practical application lie ahead.**

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