Adiponectin Regulation in Cardiovascular Disease
Is Diseased Fat Showing Its True Color?

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Adipose tissue can release a plethora of factors termed adipokines. The large family of adipokines includes chemokines, cytokines, lipid factors, and growth factors. Adiponectin, the first cloned protein hormone from adipose tissue, is a metabolically active and anti-inflammatory adipokine. Adiponectin mainly circulates in different oligomeric isoforms, including high molecular weight adiponectin, that exerts different biological effects. Expression of adiponectin is suppressed by proinflammatory factors, reactive oxygen species, and hypoxia, whereas peroxisome proliferator activated receptor γ agonists stimulate the production of adiponectin in adipocytes. Adiponectin can improve insulin sensitivity, dampen inflammatory responses in macrophages, and induce the polarization of M2 macrophages. Adiponectin is negatively associated with obesity and insulin resistance, both well-established comorbidities in cardiovascular disease (CVD).

The role of adiponectin in CVD itself is debatable because high levels of adiponectin have been associated with decreased CVD risk in asymptomatic individuals, whereas it can also predict poor prognosis in patients with established CVD.

See accompanying article on page 2151 in the September 2014 issue

From an historical perspective, adipose tissue was regarded as mere energy storage facilities. However, it is now appreciated that adipose tissue is an active tissue type, with important metabolic and endocrine functions. Classically, 2 types of adipose tissue have been identified, white and brown adipose tissue. White adipose tissue is mainly responsible for the release of adipokines, whereas the main function of brown adipose tissue is to generate heat. Brown adipose tissue is prominent in newborns and hibernating mammals and rapidly declines with age. Only recently, evidence was provided that active brown adipose tissue exists in adults. It is mainly found in the subclavicular and neck area, but also small brown fat depots located close to the heart have been identified. A key finding has been the discovery of 2 distinct types of brown fat, classical brown fat (derived from embryogenesis) and inducible brown fat (also referred to as beige fat). Neuronal control is a key regulator in induction (browning) and activation of brown adipose tissue, but also brain natriuretic peptide (BNP) released from the heart can mediate this process. It was only recently discovered that not only white but also brown adipose tissue expresses adiponectin.

In carotid intima–media thickness studies, higher levels of adiponectin were associated with reduced intima–media thickness in healthy subjects. Also, genetic variation within the adiponectin gene promoter is directly associated with carotid intima–media thickness in healthy subjects, suggesting a causal link between adiponectin and atherosclerosis. In CVD, causality testing of new biomarkers is appreciated because causal biomarkers may also be targeted for treatment at the same time. However, genetic variation within the adiponectin gene promoter was not associated with plasma levels of adiponectin, suggesting that plasma levels of adiponectin may not reflect tissue adiponectin. These findings suggest that adiponectin regulation is more complicated than originally thought. The study of Antonopoulos et al in the September 2014 issue of Arteriosclerosis, Thrombosis, and Vascular Biology indeed shows that interpretation of adiponectin regulation in plasma and adipose from heart disease patients is complex and dependent on different processes involved in CVD progression.

The main focus of the study was on the effect of systemic inflammation on adiponectin regulation in patients with CVD. Plasma adiponectin levels were determined in a cross-sectional study containing healthy subjects, patients with coronary artery disease with different stages of heart failure, and heart failure patients without coronary artery disease. It is evident that compared with healthy subjects, adiponectin levels are only elevated in patients with severe heart failure, independent of CAD. Recent data support the idea that plasma adiponectin levels are fluctuating before and after percutaneous coronary intervention on ST-segment–elevation myocardial infarction, suggesting that adiponectin responds to the acute phase of CVD. This suggests that levels of systemic adiponectin in patients may vary depending on the time of sampling after presentation.

Apart from well-established predictors of adiponectin, brain natriuretic peptide (BNP) appeared the strongest independent predictor of adiponectin, whereas inflammation was not correlated to circulating adiponectin levels in diseased patients. BNP and adiponectin were measured at a single time point, giving rise to the question of what comes first. The authors elegantly show in an experimental setting that BNP and not inflammatory substances, added to the medium, indeed causes diseased fat cells to release adiponectin. These findings suggest that adiponectin release in coronary artery disease is regulated by BNP rather than inflammation, also in the absence of clinical heart failure. In healthy adipose however, adiponectin release is controlled by inflammation. This
proof of concept was further substantiated in healthy individuals, where induction of low-grade inflammation resulted in reduced adiponectin levels, independent of BNP.

Despite the novel and interesting concept, some limitations of the study should be taken into account. Different patient groups have been studied, patients undergoing percutaneous coronary intervention or coronary artery bypass grafting, who may differ in syntax scores, risk factor profiles, and stability of CVD, all affecting circulating adiponectin levels. In addition, the model resembling mild inflammation, Salmonella Typhi vaccination, was administered in healthy patients who were on average 30 years younger than the patients with CAD. Besides, the model most likely does not reflect the chronic inflammatory process involved in atherosclerosis.

Still, the study by Antonopoulos et al. provides the reader with an interesting novel concept of variability in adipocyte responsiveness in healthy and diseased adipose tissue. Furthermore, it is clearly established that cardiac-derived BNP is the critical denominator of adiponectin responses in patients with severe CVD (Figure). It is intriguing to speculate that in CVD BNP may affect fat composition by browning of adipocytes, thereby possibly altering adiponectin release. In fact, it has been established that natriuretic peptides can promote a favorable fat distribution profile (with decreased visceral fat, increased lower body fat, and improved insulin sensitivity) and induce the browning of adipocytes. It is of high interest to determine whether the diseased adipose tissue from patients with CVD contains brown fat deposits, either consisting of classical or inducible brown fat, that may directly affect morphological and functional differences compared with healthy adipose tissue.

Whether or not adiponectin is a valuable biomarker for the prognosis of CVD remains elusive because this study provides circulating adiponectin levels at a single time point only. As mentioned earlier, adiponectin circulates in different isoforms, depends on type of CVD, stability of CVD, and other biomarker levels and may also depend on the fat type they are excreted from. This interesting study raises many questions of which we eagerly await the answers.

Disclosures

None.

References


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