Adiponectin & Leptin Roles in Cardiometabolic Control, Diabetes, Aging and Mortality

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A number of different cell types contribute to the cellular architecture of fat tissue. While the fat cell is making important functional contributions to the systemic metabolic well-being, several additional cell types contribute a supportive role to bestow maximal flexibility on the tissue with respect to many biosynthetic and catabolic processes. The adipocyte has morphed into a cell type whose complexity we only start to appreciate. We now understand that: 1) the contributions of the adipocytes depend on their location, e.g. visceral vs. subcutaneous location. In fact, there are many more distinct fat pads in the body that act as "miniorgans" that play major roles in their local microenvironment; 2) we have different types of fat cells, some of them geared for energy storage (white adipocytes), some of them geared towards energy and heat generation (beige or brown adipocytes); under some physiological conditions, adipocytes can de-differentiate into (myo)fibroblasts and adipocyte precursor cells; 3) the ability to store excess calories and thereby acting as an anti-lipotoxic tissue is a key role for adipose tissue; 4) **adipocytes produce hormones** and other signaling molecules that integrate the systemic energy reserves and convey that to the brain and other organs; these adipokines should not be judged in isolation but rather be looked upon as a carefully orchestrated group of multiple different components that act in concert; Understanding the mutual influence of adipokines on each other is an essential part of understanding the endocrinology of the fat cell.

The landmark discoveries of leptin and adiponectin firmly established adipose tissue as a sophisticated and highly active endocrine organ, opening a new era of investigating adipose-mediated tissue crosstalk. Both obesity-associated hyperleptinemia and hypoadiponectinemia are important biomarkers to predict cardiovascular outcomes, suggesting a crucial role for adiponectin and leptin in obesity-associated cardiovascular disease, diabetes, aging and mortality. Normal physiological levels of adiponectin and leptin are indeed essential to maintain proper cardiovascular function and insulin sensitivity. Insufficient adiponectin and leptin signaling results in cardiovascular disorders. However, a paradox of high levels of both leptin and adiponectin is emerging in the pathogenesis of cardiovascular disorders. n particular, both adipokines are required for proper cardiovascular function. Impaired leptin or adiponectin signaling, due to lipodystrophy or genetic mutations, results in an adverse outcome of cardiovascular dysfunction. On the other hand, an oversupply of leptin or adiponectin in circulation, can directly exert a negative cardiovascular impact. The paradoxical increase of adiponectin in this context is likely a reflection of a compensatory response. A combined approach aimed at restoring normal physiological levels of both adipokines is highly likely to elicit a positive cardiovascular disease effect. We propose that an increased ratio of adiponectin-to-leptin can emerge as a highly promising and viable therapeutic goal, not only for cardiovascular disease, but also for diabetes.