Excess body weight, a burgeoning problem worldwide, is a major risk factor for cardiovascular disease. Diabetes affects >180 million people around the world, and the number of patients is anticipated to increase to 300 million by 2025. Recent data indicate that diabetes prevalence in adults has increased since 1980 virtually in every country of the world; the end-result is a near quadrupling of the number of adults worldwide with diabetes.

Within this escalating healthcare problem of monumental proportions, obesity-associated type 2 diabetes accounts for 90% to 95% of all diagnosed diabetes cases in adults. In fact, diabetes and insulin resistance are powerful predictors of cardiovascular morbidity and mortality, and each is an independent risk factor for death in patients with heart failure. Yet, the complex mechanisms underlying the deleterious impact of diabetes on the heart and the vasculature are poorly characterized.

Diabetes-associated cardiovascular diseases arise by a variety of mechanisms. Atherosclerotic disease often emerges in multiple vascular beds. Also, patients with diabetes are often hypertensive. Obesity is associated with a proinflammatory state marked by chronic elevations of systemic adrenergic activity, dyslipidemia, and hyperglycemia. Circulating levels of a variety of bioactive molecules are perturbed. Clearly, the underlying pathophysiology is complex.

Constant and unremitting metabolic stress on the heart leads over time to progressive deterioration of myocardial structure and function, and heart failure is a typical end-result. Sadly, current therapies are insufficient to arrest the progression of heart failure, and developing new therapies will require greater understanding of molecular mechanisms underlying pathological cardiac remodeling. This suggests that therapeutic interventions early in the disease, targeting specific metabolic and structural derangements, may be required. This is especially relevant as rigid control of hyperglycemia, however central to treatment, has not fulfilled hopes of meaningful morbidity and mortality benefit. Recent and ongoing research into mechanisms of metabolic control, insulin resistance, and diabetes-associated derangements portend novel therapies designed to benefit the rapidly expanding cohort of patients with diabetes, a benefit with tremendous societal impact.

In light of these realities, we have assembled thought leaders from around the world to review recent developments in the complex biology of obesity-associated diabetes and cardiovascular diseases. In so doing, we present a compendium of 10 articles that touch on all critical aspects of this complex and fascinating biology.
of epigenetic mechanisms contributing to macrovascular disease in diabetes. The authors highlight the recent identification of chromatinized changes associated with perturbed gene expression relevant to atherosclerosis in endothelial cells, smooth muscle, and circulating immune cells. Their review also discusses challenges associated with pharmacological targeting of epigenetic networks to restore dysregulated gene expression.

Bhupathiraju et al., in an article entitled “Epidemiology of Obesity and Diabetes and Their Cardiovascular Complications,” discuss the “diabesity” epidemic. They point to sex-related differences, as well as racial and ethnic disparities, in the prevalence and trends of obesity and diabetes. The authors discuss a wide range of contributing factors, including the obesogenic diet, marked by increased portion sizes of calorie-laden foods. They also highlight the contributions of limited access to healthy food choices, agricultural policies, physical activity, and sleep patterns.

Cardiac myocytes rely heavily on fatty acid oxidation as a predominant source of fuel; in the context of insulin resistance, where glucose utilization is suppressed, fatty acid catabolism is enhanced. Schulze et al., in an article entitled “Lipid Use and Misuse by the Heart,” discuss diabetes-associated alterations in fatty acid oxidation within cardiac myocytes. The authors also review evidence for intracellular accumulation of lipids, including some species of lipid that may contribute to cardiac dysfunction. The authors go on to discuss preclinical and clinical data suggesting that efforts to deplete toxic lipids may have therapeutic relevance.

Ortega et al., in an article entitled “Obesity and Cardiovascular Disease,” discuss the complex relationship between obesity and cardiovascular disease. They discuss how the extent, distribution, and duration of obesity affect cardiovascular events. The authors go on to discuss the “fat but fit” paradigm, the notion of an obese and yet metabolically healthy phenotype. Finally, they review and discuss the obesity paradox in cardiovascular disease.

Beckman et al., in their contribution entitled “Vascular Complications of Diabetes,” highlight the fact that diabetes promotes disease in nearly all blood vessel types and sizes. They discuss the fact that patients with diabetes are at substantially increased risk for both microvascular and cardiovascular adverse events. Indeed, the authors remind us that vascular complications are responsible for most of the morbidity, hospitalizations, and mortality in patients with diabetes. Indeed, once cardiovascular disease develops, diabetes exacerbates disease progression and worsens outcomes.

Fuster et al., in their section entitled “Obesity-Induced Changes in Adipose Tissue Microenvironment and Their Impact on Cardiovascular Disease,” discuss the role of adipose tissue in obesity-associated diabetes and cardiovascular disease. The authors highlight the concept of obesity-driven adipose tissue dysfunction and the associated inflammatory state. Adipose tissues secrete many biologically active molecules termed “adipokines,” and several of these are capable of promoting the proinflammatory state of diabetes. The authors provide a thorough overview of this biology.

Shah et al., in their article entitled “Molecular and Cellular Mechanisms of Cardiovascular Disorders in Diabetes,” point to the importance of the toxic accumulation of reactive oxygen species in accelerated atherosclerosis. Whereas reactive oxygen species signaling is fundamental to many normal cellular events, excessive reactive oxygen species synthesis or diminished reactive oxygen species removal, can be toxic. The authors organize their discussion by categorizing these events as either hyperglycemia-induced mechanisms or insulin resistance–related mechanisms.

Standl et al., in a section entitled “Heart Failure Consideration of Antihyperglycemic Medications for Type 2 Diabetes,” point to the remarkable growth of new antihyperglycemic medications that has occurred in recent years. The authors discuss these agents, noting that some seem to be particularly beneficial with respect to heart failure–related effects; others pose no significant harm. Finally, the authors discuss the agents where the cardiovascular effects, good or bad, are less apparent.

In many instances, obesity is the proximal trigger that culminates ultimately in diabetes and cardiovascular disease. Eckel et al., in a piece entitled “Treatment of Obesity: Weight Loss and Bariatric Surgery” discuss the roles of lifestyle changes, pharmacotherapy, and surgical approaches in the treatment of obesity. In each case, the authors review the relative efficacies and roles of the intervention.

As in all living cells, intermediary metabolism provides energy substrates essential to fuel cardiac myocytes and their contractile function. Taegtmeyer and Abel (in press) discuss mechanisms by which a shifted metabolic milieu or intrinsic changes can impair the performance of the heart in obesity and diabetes. The dysregulated metabolic state touches the heart at multiple levels. Their review focuses on consequences of altered insulin signaling, altered mitochondrial metabolism, altered redox state, and additional mechanisms that disrupt cardiac function, with the ultimate goal of optimizing the treatment of diabetic patients with heart failure.

We have been fortunate to work with a panel of thoughtful leaders to assemble a compendium of review articles that spans molecular mechanisms, cell biology, clinical medicine, and epidemiology—and across multiple cell types and tissues. The world faces an epidemic of diabetes-driven cardiovascular disease, and elucidation of underlying pathophysiological mechanisms is urgently required. Looking to the future, it has been suggested that the thrombocardiologist of the 21st century (Eugene Braunwald, personal communication). It is our fervent hope that these authoritative review articles will help to stem the tide.

Disclosures

None.

References


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Obesity, Diabetes, and Cardiovascular Diseases: A Compendium
Philipp E. Scherer and Joseph A. Hill

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