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Belma Turan
Naranjan S. Dhalla *Editors*

Diabetic Cardiomyopathy

Biochemical and Molecular Mechanisms

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Diabetic Cardiomyopathy

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This book is dedicated to Prof. S.K. Gupta for his outstanding leadership in promoting cardiovascular research and education throughout the Indian continent. In his capacity as Head of the Department of Pharmacology at the All India Institute of Medical Sciences, Dr. Gupta established the National Center for promoting health and family welfare. He has published more than 250 research papers and seven books, mostly on the role of herbal drugs in the prevention and treatment of cardiovascular diseases, and trained more than 150 postgraduate students. As Dean and Director General of The Institute of Clinical Research, he initiated and promoted a comprehensive education program for clinical research throughout India.

Dr. Gupta has been heavily engaged in promoting the scientific basis for the practice of cardiology as well as young investigators and is currently serving as President of the India Section of the International Academy of Cardiovascular Sciences. This book, presenting molecular and cellular aspects of cardiac dysfunction during the development of diabetic cardiomyopathy, pays a special tribute to Prof. Suresh Gupta for his distinguished services.

Preface

Diabetes has long been recognized as a disease of high blood sugar, and there has been a continuous search for the exact reason for its development. In the middle of the nineteenth century, autopsies of patients with diabetes mellitus showed damaged pancreases. The first evidence for the link between diabetes and the pancreas was provided in 1889 by O. Minkowski and J.V. Mering, who depancreatized a dog and demonstrated the development of polyuria, which was undistinguishable from diabetes. This disease is known as a disorder of carbohydrate metabolism resulting from insufficient production of insulin by pancreas (type 1 diabetes) or an ineffective response of cells to insulin (type 2 diabetes). In 2005, the World Health Organization had estimated that more than 180 million people worldwide suffer from diabetes mellitus and indicated that this figure is likely to double within the next 20 years. Among the 3.8 million deaths each year associated with diabetes, about two thirds are attributable to cardiovascular complications. In fact, diabetes is now considered to be a major metabolic risk factor for the occurrence of heart disease.

Metabolic syndrome has been used to describe a cluster of disorders such as diabetes and is believed to be an indicator of risk for heart disease, stroke, and other cardiovascular abnormalities. This term dates back to the late 1950s, but came into common usage in the 1970s to describe the association of various risk factors with diabetes, particularly insulin resistance, which is the cornerstone of this syndrome. Some individuals are genetically predisposed to developing insulin resistance; however, both obesity and sedentary lifestyle are conditions that promote metabolic syndrome and result in developing type 2 diabetes, heart disease, kidney disease, and stroke. It should be noted that cardiovascular dysfunction is the leading cause of mortality in diabetic individuals, primarily because of the development of cardiac abnormality, diabetic cardiomyopathy, as defined by A. Grishman and his coworkers in 1972. Diabetic cardiomyopathy is a clinical condition in which ventricular dysfunction is diagnosed in diabetic patients in the absence of coronary atherosclerosis and hypertension. Several mechanisms involved in the development of cardiomyopathy in diabetic patients have been postulated, including alterations in

intracellular cation homeostasis and glucose metabolism, as well as enhanced oxidative stress. It is becoming clear that cardiovascular complications in diabetes result from multiple parameters including glucotoxicity, lipotoxicity, fibrosis, and mitochondrial uncoupling.

Diabetic cardiomyopathy is associated with both type 1 (insulin-deficient) and type 2 (insulin-resistant) diabetes and is characterized by early-onset diastolic and late-onset systolic dysfunctions, including depressions in diastolic compliance, contractility, and rate of myocardial relaxation. Diabetic cardiomyopathy was initially classified as a dilated cardiomyopathy with prominent left ventricular enlargement and depressed systolic function; however, during the past two decades, diastolic left ventricular dysfunction was also indentified as a manifestation of this disorder. Because discovering the nature of diabetic cardiomyopathy and its complications has been generally considered to help in designing effective therapeutic strategies to curb this epidemic problem in society, this book was aimed to provide a comprehensive approach to understanding diabetes and its complications as well as various strategies for its prevention and treatment. This book is a compilation of review articles devoted to the study of diabetic cardiomyopathy with respect to biochemical and molecular mechanisms of hyperglycemia. The wide range of topics covered here are of interest to basic research scientists, clinicians, and graduate students who are devoted to the study of the pathogenesis of diabetes-induced cardiovascular dysfunction. Furthermore, some chapters are directed toward increasing our understanding of novel ways for the prevention and treatment of cardiomyopathy. The 25 chapters in this book are organized into three sections.

The first section discusses general aspects of the metabolic derangements in diabetic cardiomyopathy, including metabolic alterations and substrate utilization in the heart, metabolic alterations and cardiac remodeling, role of diet in the development of metabolic syndrome in the heart, and the effects of hyperglycemia in terms of biochemical and structural alterations in the heart. This section also has chapters on the role of hyperglycemia in cardiovascular complications and their possible prevention with antioxidant treatment protocols. It is generally well accepted that diabetes is associated with increased oxidative stress. In fact, chronic hyperglycemia has been shown to cause oxidative stress, leading to cardiac complications, including hypertension, left ventricular hypertrophy, dilated cardiomyopathy, and myocardial infarction. Furthermore, significant increases in oxidants have been shown to trigger a cascade of pathological events including contractile dysfunction. Oxidative stress and imbalance between endogenous reactive oxygen species as well as antioxidant systems are involved in the etiology of diabetes-induced downregulation of heart function. There is also a close relationship between impaired insulin signaling and alteration in heart function via depressed endogenous antioxidant defense mechanisms. In addition, there is some evidence for sex-related differences in diabetes-induced cardiovascular pathologies, particularly the role of estrogen, which can exert protective effects against diabetes through modulation of altered Ca^{2+} dynamics and reduction of oxidative damage to the heart.

In the second section, several cellular mechanisms of diabetic cardiomyopathy are discussed, indicating that diabetic cardiomyopathy is a multifactorial and

complex problem. Included are alterations in cardiac energy metabolism showing reduced glucose uptake and increased free fatty acid oxidation, resulting in mitochondrial uncoupling, impaired Ca^{2+} homeostasis, and depressed contractile activity. The use of PPAR-α agonist to reduce fatty acid oxidation and physical exercise to induce mitochondrial adaptation has been claimed to prevent diabetes-induced cardiac dysfunction. It should be emphasized that the diabetic heart is almost dependent on the metabolism of fatty acids as there occurs an increase in the myocardial uptake of fatty acids and an increase in its oxidation as well as a reduction in glucose oxidation. Such changes result in a decrease in ATP production per mole of oxygen and an increase in mitochondrial uncoupling, leading to an unfavorable energetic state together with an overproduction of reactive oxygen species. On the other hand, diabetes has long been reported to rapidly induce contractile dysfunctions associated with altered Ca^{2+} handling in isolated ventricular myocytes. Because miRNAs play a fundamental role in gene expression, alterations of a large number of miRNAs in chronic diabetes are closely associated with the development of heart disease. In a chronic neonatal rat model of diabetes demonstrating cardiomyopathy, 14 miRNAs were upregulated and 28 miRNAs were downregulated. In addition, miR223 was consistently upregulated in the insulin-resistant heart, and miR223 overexpression-induced GLUT4 protein expression in cardiomyocytes was found to be necessary for increased glucose uptake.

Several authors have contributed to the formulation of the seven chapters in the third section of this book, which demonstrate the prevention and treatment of diabetes using appropriate diet, proper supplements including antioxidants, angiotensin inhibitors, and some other drugs. Indeed, different epidemiological, experimental, and clinical investigations have demonstrated a close correlation between diet and increased risk of developing diabetes-induced cardiovascular complications. For example, the increased consumption of refined and simple carbohydrates, fats, red meats, and low fiber as well as low intake of specific minerals and vitamins have been shown to impair insulin response and increase plasma glucose levels and thus produce damage to the macro- and microvasculature. Some investigators have also highlighted the beneficial effects and impact of nutritional interventions on the developing fetus and described the role of epigenetics and maternal nutrition on the risk of developing diabetes and cardiovascular complications. In summary, the text covers a broad range of topics related to general aspects of diabetes, particularly diabetic cardiomyopathy, including pathophysiology, complications, management, and various treatment options.

We are taking this opportunity to offer our sincere thanks to all the eminent authors for their extraordinary contributions. The time and efforts of both Dr. Vijayan Elimban and Ms. Eva Little of the Institute of Cardiovascular Sciences at St. Boniface Hospital Research, University of Manitoba, are gratefully acknowledged. Our gratitude is also extended to Ms. Rita Beck and the staff at the Springer Media, New York, for their understanding of problems associated with the preparation of this book.

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