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Dyslipidemias

Pathophysiology, Evaluation and Management

Humana Press

Contemporary Endocrinology

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To

My wife, Sandeep, for her enduring encouragement, support and love; to my children, Ooshma and Aashima, for providing sparks in my life; to my parents, Anand Swaroop and Shyam Lata, for their nurturing; and to Scott Grundy, for guiding me through my research in lipids and lipoproteins.

Preface

For the last 20 years, there has been a growing recognition worldwide of the importance of managing dyslipidemia for the primary and secondary prevention of atherosclerotic vascular disease, especially coronary heart disease. This has been mainly due to the publication of the guidelines of National Cholesterol Education Program's Adult Treatment Panel and Pediatric Panel from the USA. These guidelines have stimulated generation of similar recommendations from all over the world, particularly Europe, Canada, Australia and Asia. Thus, it is important for the treating physicians and other providers to understand the pathophysiology, epidemiology, clinical evaluation and management of dyslipidemias. This book entitled, "Dyslipidemias: Pathophysiology, Evaluation and Management" has a clinical focus and is aimed at General Internists, Pediatricians, Cardiologists, Endocrinologists, Lipidologists and Geneticists.

A striking feature of this book is the fact that all the authors are at the forefronts of their disciplines, thereby ensuring inclusion of the latest scientific developments in their chapters. These authors have international reputation in their fields and represent global leadership. The authors were chosen by the Editor in view of their scientific contributions, reputation and most importantly not to have any direct conflicts of interests due to their employment in the pharmaceutical industry. A unique feature of this book is that all chapters have been peer-reviewed by an equally qualified group of experts and have undergone extensive revisions. This process has accomplished at least two goals: (a) improved the scientific quality of the chapters and (b) eliminated the bias of the authors, if any. Thus, I thank all the reviewers who provided constructive critiques but also appreciate the efforts of the authors in revising the chapters according to the comments of the peer reviewers. I hope that this book can provide practical guidance to the clinicians to provide the best care and new opportunities to the patients with dyslipidemias. The online version of the book provides useful links for those who seek an in-depth understanding of a particular topic.

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Lipoprotein Physiology

1

Daniel J. Rader and Sumeet A. Khetarpal

Introduction

Lipoproteins evolved due to the need to transport extracellular hydrophobic lipids within an aqueous environment. The two major lipids they transport are triglycerides (TGs) and cholesterol (both esterified and unesterified). Lipoproteins play an essential role in the absorption of dietary lipids, the transport of TGs from the liver to peripheral tissues, and the transport of cholesterol from peripheral tissues to the liver. Lipoproteins contain a core of hydrophobic lipids (TGs and cholesteryl esters, CEs) surrounded by hydrophilic lipids (phospholipids (PLs), unesterified cholesterol) and proteins that interact with body fluids. The plasma lipoproteins are divided into five major classes based on their relative density (Table 1.1): chylomicrons, very low density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs). The proteins associated with lipoproteins are called apolipoproteins (Table 1.2). They serve a number of roles, including the assembly, structure, and function of lipoproteins, the activation of enzymes, and as ligands for cell surface receptors.

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Physiology and Metabolism of ApoB-Containing Lipoproteins

Lipoproteins containing apoB exist to transport hydrophobic lipids within the blood. A major role is the transport of energy in the form of TGs, and another key role is the transport of cholesterol largely in the form of CEs. The intestine produces chylomicrons containing apoB-48 and the liver produces VLDL-containing apoB-100. The role of intestinal chylomicrons is the postprandial transport of (exogenous) dietary fatty acids (within TGs) to tissues that use or store them, whereas a key role of hepatic VLDL is the fasting transport of (endogenous) fatty acids to tissues that use them. In each case, the by-product of lipolysis of the TGs is a remnant lipoprotein—chylomicron remnant or VLDL remnant (also known as IDL)—that contains residual TG as well as cholesterol and is removed from plasma by the liver. In the case of IDL, some of the particles are further converted to LDL before removal. These two related pathways are discussed in greater detail below.

First, however, is a discussion of the key structural protein in both chylomicrons and VLDL, namely apoB. ApoB is one of the largest proteins in the human genome and provides the unique structural and functional features of these lipoproteins. Importantly, there is one single molecule of apoB protein per lipoprotein particle. There is a single *APOB* gene that is expressed in both the enterocyte and the hepatocyte. However, whereas the hepatocyte synthesizes a full-length apoB known as apoB-100 (for 100 %), the

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