Summary

Lipoproteins play a central role in atherosclerosis, the leading cause of death in patients with diabetes mellitus. Diabetic dyslipidemia largely results from hepatic overproduction of very low density lipoproteins, stimulated by a high flux of nonesterified fatty acids from adipose tissue to the liver. The dyslipidemia is characterized by high plasma triglyceride, low levels of high density lipoproteins, and small, dense low density lipoproteins—all of which contribute to the atherogenic state in diabetes.

Atherosclerosis is accelerated by multiple other factors in diabetes in addition to lipoprotein abnormalities. For example, the accumulation of advanced glycosylation endproducts in arterial tissue may produce chronic inflammatory responses. Even in this milieu, epidemiologic data and clinical trials suggest that intensive treatment targeting lipoproteins can markedly reduce diabetic cardiovascular risk. Recognizing that average or “normal” lipoprotein levels predict adverse outcomes in diabetic patients, the health care provider should use dietary, lifestyle, and pharmacologic treatment to make lipoprotein parameters considerably better than average.

INTRODUCTION

Atherosclerosis is the most common serious complication of diabetes mellitus. An estimated 60–75% of people with diabetes will die of an atherosclerotic event such as myocardial infarction or stroke. Cardiovascular events are 2–4 times more common in diabetic versus nondiabetic people (1,2).

Because lipoproteins play a central role in atherogenesis, an important question to be addressed in this chapter is the manner and the degree to which altered lipoproteins—diabetic dyslipidemia—may contribute to the elevated risk of diabetes. However, an equally important issue is the degree to which lipoproteins contribute to atherosclerotic cardiovascular events among all persons in the developed, industrialized world. Regardless of diabetic status, atherosclerotic risk is 3–10 times higher than in undeveloped societies (3–5). In recent clinical trials, low density lipoprotein (LDL) cholesterol levels typical of undeveloped societies have been achieved, and marked risk reduction has been the rule. Lipoproteins in diabetes do carry special risk, but even more they offer...
opportunity to reduce diabetes-associated risk. Reduction of cardiovascular events in diabetes may be gained by treating lipoproteins to targets that are considerably better than average level in the developed world.

With these goals in mind, this chapter will review fundamental concepts of lipoprotein metabolism and atherogenesis, address the special features of dyslipidemia in diabetes, and then emphasize aspects of evidence-based practical treatment.

**FUNDAMENTALS OF LIPOPROTEIN METABOLISM**

**General Properties and Physical Chemistry of Lipids**

Phospholipids form the essential bilayer structure of cell membranes and participate in many specialized lipid functions. Cholesterol, which is present in most membranes of the cell, increases the “stiffness” or viscosity of the phospholipid bilayer and makes it less permeable to water and small organic molecules. Membranes do not self-assemble with exactly the proper ratios of cholesterol to phospholipids for ideal function; instead, multiple gene products function in overlapping systems to actively maintain membrane homeostasis. There is considerable evidence that these systems all fail in the lipid-rich core of atherosclerotic plaques, and vascular cells may die there from overaccumulation of cholesterol that disrupts critical membrane functions.

Fatty acids supply most of the fuel used by skeletal muscle, heart muscle, and many other tissues. The transport or storage of large quantities of fatty acids is made more efficient by esterification to form triglyceride. Likewise, cholesterol is esterified to form cholesteryl ester for transport or storage. These lipid esters are insoluble in water, leading to their efficient nonaqueous packing in oily droplets in cells or in the oily core of lipoproteins. Moreover, esterification reactions also represent cellular defense mechanisms, preventing the overaccumulation of cholesterol or fatty acids that could disrupt membrane structure and function. Cholesteryl ester and triglyceride are nontoxic owing to their sequestration in oily droplets and their minimal presence in cell membranes.

**Lipoproteins and Apolipoproteins**

For circulatory transport, cholesterol, cholesteryl ester, triglyceride, and phospholipid are packaged together with specific proteins (apolipoproteins) in spherical pseudomicellar structures, the plasma lipoproteins. The surface monolayer of amphiphilic phospholipid molecules provides an aqueous-oily interface that allows the particle to dissolve in water. Plasma lipoproteins are separable into distinct classes on the basis of their equilibrium...